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Jean-Jacques Soghomonian
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The Basal Ganglia

Novel Perspectives on Motor and Cognitive Functions

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The Basal Ganglia

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To Allison and Emilie

Preface

Descriptions of the deep brain structures that have come to be called the "basal ganglia" can be traced back as far as 350 years based on recorded anatomical observations, notably those published in 1664 by the English anatomist Thomas Willis. Yet, for much of this time, the basal ganglia have held a certain enigmatic quality in terms of their functions. The conception held late into the twentieth century that the basal ganglia were associated largely with motor control or coordination had a few roots. Basal ganglia ablation studies in animals that began in the nineteenth century showed dramatically marked motor symptomatology. In clinical neurology, features such as dystonia, dyskinesia, and chorea, manifesting in neurodegenerative disorders with known involvement of the basal ganglia structures, reasonably reinforced the prominence of the motor-centered view.

Pioneering work in neurobiology conducted in the 1960s and 1970s began the sea of change in the contemporary understanding of the basal ganglia. Progress was made possible thanks to the advent of novel investigative methods that permitted more precise analysis of anatomical pathways and the discovery of various neuronal phenotypes throughout the basal ganglia. On another front, anatomical and physiological studies carried out in the late 1970s and early 1980s led to the concept of parallel, segregated basal ganglia circuits, while other studies led to the concept of a ventral, "limbic" basal ganglia, and, at a more cellular level, other studies led to the concept of a direct and indirect pathway. These advances have been documented in several reviews and volumes.

By the 1980s, there was early convergence of data from neuroscience and neuropsychology, broadening the conceptual framework of the basal ganglia to include functions of cognition, emotion, and motivation. While the inertia in the motor-centered world of the basal ganglia did not fade overnight, studies from diverse avenues of neuroscience, enabled by novel research techniques, began to reveal a complex neural architecture and functional diversity. As a complex system of interface between intention and action, the role of the basal ganglia has encroached into processes traditionally associated with the cerebral cortex and hippocampus such as language, memory, reinforcement, and associative learning. Its role in the sequencing of learned associations was brought to bear on multiple functional domains.

This also highlighted its importance in neurocognitive, neuropsychiatric, and neurodegenerative motor disorders.

Over the last two decades, the intensification of neuroscience efforts combined with astonishing advances in imaging, genetic, and molecular methods has led to further demystify the basal ganglia and to revise its role in motor and non-motor functions. It is now established that the basal ganglia can be subdivided into several anatomical and functional territories that share different connectivity with cortical and subcortical centers. These advances combined with a more detailed understanding of the cellular and molecular organization have provided the framework for novel integrative and computational models of the basal ganglia.

Yet, even with all the progress in understanding the basal ganglia, perspective of its functions as currently understood is neither readily present nor easily articulated in the general arena of behavioral neuroscience. This volume presents many of the recent developments relating to neural architecture and functional circuitry of the basal ganglia; the role of the basal ganglia across many of the neurobehavioral domains—motor and cognitive function, emotion, and motivation, etc.; and the manifestations of these basal ganglia-mediated functions in various motor, cognitive, and neuropsychiatric disorders. The volume assembles contributions from eminent basal ganglia researchers and covers perspectives across subdisciplines of neuroscience while being grounded in cognitive neuroscience and neurobiology. In addition to the basal ganglia and neuroscience research community, the volume should be of interest to practitioners in neuropsychology, neurology, neuropsychiatry, and speech-language pathology.

Boston, MA Jean-Jacques Soghomonian

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Abbreviations

AC	Adenylyl cyclase
ac	Anterior commissure
AC5/6	Adenylyl cyclase 5/6
ACA	Anterior cingulate area
AcbC	Core of the nucleus accumbens
AcbSh	Shell of the nucleus accumbens
ACC	Anterior cingulate cortex
ACd	Dorsal anterior cingulate cortex
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACv	Ventral anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
AHC	Alternating hemiplegia of childhood
AI	Anterior insular
AID	Dorsal agranular insular cortex
AIMs	Abnormal involuntary movements
AIv	Ventral agranular insular cortex
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AMPAR	Glutamate AMPA receptor
Amyg	Amygdala
AP-1	Activator protein 1
A-PE	Aversive prediction error
arc	Activity-regulated cytoskeleton-associated protein
ATP1A3	ATP1A3 gene
aVITE model	Adaptive VITE model
BAC	Basal amygdaloid complex
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor

BEC	Blood ethanol concentration
BF	Basal forebrain
BG	Basal ganglia
BLA	Basolateral amygdala
BOLD	Blood oxygen level-dependent
BP	Bipolar disorder
BST	Bed nucleus of the stria terminalis
CA1	Hippocampal CA1 cells
CA1 region	Cornu ammonis area 1
CalDAG-GEFI	Calcium- and DAG-regulated guanine exchange factor-1
CalDAG-GEFII	Calcium- and DAG-regulated guanine exchange factor-2
cAMP	Cyclic adenosine monophosphate
cARTWORD model	Conscious ARTWORD
Caudate (DL)	Dorsolateral caudate
Caudate (VM)	Ventromedial caudate
CB1	Cannabinoid-type receptor 1
CBM	Assumed cerebello-cortical input to the IFV stage
cBmg	Caudal part of the magnocellular basal amygdaloid nucleus
cBpc	Caudal part of the parvicellular basal amygdaloid nucleus
cc	Corpus callosum
Cd	Caudate
cdm-GPi	Caudodorsomedial globus pallidus (internal segment)
CeA	Central nucleus of the amygdala
CEN	Central executive network
ChAT	Choline acetyltransferase
CHI	Striatal aspiny cholinergic interneurons
ChIN or ChINs	Cholinergic interneurons
CIE	Chronic intermittent ethanol exposure
cl-SNr	Caudolateral substantia nigra pars reticulata
CM	Central medial thalamic nucleus
CogEM model	Cognitive-emotional-motor model
CP or CPu	Caudate-putamen
CPvm	Ventromedial part of caudate-putamen
CQ	Competitive queuing
CR	Conditioned response
CRE	CREB responsive elements
CS or CS+	Conditioned stimulus
CSF	Cerebrospinal fluid
CS-US	Conditional stimulus-unconditional stimulus
D1	Dopamine D1 receptor

D1-M4-SP-DYN-GABA-MSPN	Direct pathway striatal neurons
D1-MSPN	Direct pathway striatal neurons
D1 or D1R	Dopamine D1 receptor
D2-M1-ENK-GABA-MSPN	Indirect pathway striatal neurons
D2-MSPN or D2-MSPS	Indirect pathway striatal neurons expressing the dopamine D2 receptor
D2 or D2R	Dopamine D2 receptor
D3 or D3R	Dopamine D3 receptor
DA	Dopamine
DA2D	Dopamine receptor 2D
DA-ACh	Dopamine-acetylcholine
DAergic projection	Dopaminergic projection
DAergic R-PE	Dopamine-mediated reward-prediction error
DARPP-32	Dopamine- and cAMP-regulated neuronal phosphoprotein
dARTSCAN model	Distributed ARTSCAN
DAT	Dopamine transporter
DAT KO	Dopamine transporter knockout
DBS	Deep brain stimulation
DCN	Deep cerebellar nuclei
DID	Mouse protocol called “drinking in the dark”
DIRECT model	Direction-to-rotation effector control transform model
DIVA model	Directions-into-velocities of articulators model
DL	Dopamine lesions
DLL	Long-lasting disinhibition
DLO	Dorsolateral orbital cortex
DLPFC	Dorsolateral prefrontal cortex
DLR	Diencephalic locomotor region
DLS	Dorsolateral striatum
DMN	Default mode network
DMS	Dorsomedial striatum
DOPAergic	Dopaminergic
dopamine D1	Dopamine D1 receptor
dopamine D2	Dopamine D2 receptor
Drd1a or drd1a	Dopamine D1a receptor
Drd2-EGFP	Dopamine D2 receptor promotor combined with enhanced green fluorescent protein
DREAM	Downstream regulatory element antagonistic modulator
DRN	Dorsal raphe nucleus
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV

dSPNs	Direct pathway spiny projection neurons
DVV	Desired velocity vector
DV	Difference vector
DYT1	Early-onset primary dystonia
DYT11	Myoclonus dystonia
DYT12	Rapid-onset dystonia parkinsonism
DYT4	Whispering dysphonia
EA	Extended amygdala
EC	Entorhinal cortex
EC50	Half-maximal effective concentration
eCBs	Endogenous cannabinoids/endocannabinoids
EEG	Electroencephalogram
Egr-1	Early growth response 1
EP or EPN or ENP	Entopeduncular nucleus
EPm	Medial part of the entopeduncular nucleus
EPSC	Excitatory postsynaptic current
EPSP	Excitatory postsynaptic potential
ERK	Extracellular signal-regulated kinase
ERK1/2	Extracellular signal-regulated kinases 1 and 2
fcMRI	Functional connectivity magnetic resonance imaging
FDA	Food and Drug Administration
FEF	Frontal eye fields
FLETE model	Factorization of length and tension model
fMRI	Functional magnetic resonance imaging
FOG	Freezing of gate
fr	Fasciculus retroflexus
FR1	FR1 schedule of reinforcement
FR2	Frontal area 2
Fra-1	fos-like antigen
FS or FSI or FSIN	Fast-spiking interneurons
GABA	Gamma aminobutyric acid
GABA-SI	GABAergic striatal interneurons
Glu or GLU	Glutamate
GluA2-flip	Glutamate AMPA receptor GluA2 subunit
GluN1	Glutamate NMDA receptor subunit 1
GluN2A	Glutamate NMDA receptor subunit 2A
GluN2B	Glutamate NMDA receptor subunit 2B
GO	Scaleable basal ganglia gating signal
GPCR	G protein-coupled receptors
GPe	External (lateral) segment of the globus pallidus

GPi	Internal (medial) segment of the globus pallidus
G-protein	G protein-coupled
Gq	Gq protein-coupled receptors
GRK	G protein-coupled receptor kinases
GRK6	G protein-coupled receptor kinase 6
GTPγS	GTPγS binding
Gu2A-flip	Specific splicing variant of the GluA2 subunit ("GluA2-flip")
Gαolf	G protein-coupled receptor olfactory
H-ABC	Hypomyelination with atrophy of basal ganglia and cerebellum
HDB	Horizontal nucleus of the diagonal band
HFS	High-frequency stimulation
Hipp or HPC	Hippocampus
HPLC	High-performance liquid chromatography
HTT	Huntingtin gene
IC50	Half-maximal inhibitory concentration
ICeA	Lateral part of the central amygdala nucleus
IEG	Immediate-early genes
IGT	Iowa gambling task
IL	Infralimbic cortex
IN	Inertial force vector
IP3	Inositol phosphate 3
IPSCs	Inhibitory postsynaptic currents
iSPNs	Indirect pathway spiny projection neurons
ISR	Immediate serial recall
IT	Inferotemporal cortex
ITa	Anterior inferotemporal cortex
ITA	Inferotemporal cortex
ITp	Posterior inferotemporal cortex
IVTA	Lateral part of the ventral tegmental area
Kir2	Potassium channel, inward rectifying
L	Lateral thalamic nucleus
L-DOPA or levodopa	L-3,4-Dihydroxyphenylalanine
LFP	Local field potential
LH	Lateral hypothalamus
LH_gus	Gustatory-responsive lateral hypothalamic cells
LH_in	Lateral hypothalamic input cells
LHb	Lateral habenula
LI	Latent inhibition
LID	L-DOPA-induced dyskinesia
LIP	Lateral intraparietal cortex
LIST PARSE model	Laminar integrated storage of temporal patterns for associative retrieval, sequencing, and execution
lisTELOS model	List telencephalic laminar objective selector

LO	Lateral orbital cortex
LPD	Left-side onset Parkinson's disease
LPO	Lateral preoptica area
LTD	Long-term depression
LTF	Long-term facilitation
LTM	Long-term memory
LTP	Long-term potentiation
LTSI	Low-threshold-spiking interneurons
l-VAmc	Lateral ventral anterior nucleus of thalamus pars magnocellularis
LVF	Left visual field
M1/M1R	M1-type muscarinic acetylcholine receptor
M4R	M4-type muscarinic acetylcholine receptor
mAChR	Muscarinic acetylcholine receptor
mAHPs	Medium after-hyperpolarization potentials
MAPK	Mitogen-activated kinase
MCMCT	Michigan complex motor control task
MD	Mediodorsal thalamic nucleus
MDD	Major depressive disorder
MDmc	Magnocellular subnucleus of mediodorsal nucleus of the thalamus
mdm-GPi	Dorsomedial globus pallidus (internal segment)
MDpl	Parvocellular subnucleus of mediodorsal nucleus of the thalamus
MdSNs	Medium densely spiny neurons
MEA	Midbrain extrapyramidal area
MEK1/2	Mitogen-activated protein kinase kinase 1/2
mEPSC	Miniature excitatory postsynaptic current
mGluR	Metabotropic glutamate receptor
MGP	Medial globus pallidus (Gpi)
MHb	Medial habenula
mIPSCs	Miniature inhibitory postsynaptic currents
MLR	Mesencephalic locomotor region
MO	Medial orbital cortex
MOR	Mu opioid receptor
MORB	Medial orbitofrontal
MOTIVATOR model	Matching objects to internal values triggers option revaluations model
MOVO	Medial orbital and ventral orbital cortices
mPFC	Medial prefrontal cortex
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRaphe	Median raphe nucleus
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
mSN	Medial part of the substantia nigra

MSN or MSNs or MSPNs	Striatal medium spiny neurons
mTOR	Mammalian target of rapamycin
mTORC1	mammalian target of rapamycin complex 1
m-VAmc	Medial ventral anterior nucleus of thalamus pars magnocellularis
NA	Noradrenaline
NAc or NAcc or Nac	Nucleus accumbens
NAcc-C	Accumbens nucleus core
NAcc-Sh	Accumbens nucleus shell
nAChR	Nicotinic acetylcholine receptor
Narp	Neuronal activity-regulated pentraxin
nbM	Nucleus basalis of Meynert
NMDA	N-methyl-d-aspartate
NMDAR	Glutamate NMDA receptor
NO	Nitric oxide
non-NE	Non-noradrenergic
NOS	NO synthase
nptx2	nptx2 gene
NR2A	Glutamate NMDA receptor 2A subunit
NR2B	Glutamate NMDA receptor 2B subunit
oBST	Oval portion of the bed nucleus of the stria terminalis
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
OFPV	Outflow force-plus-position vector
OPV	Outflow position vector
ORB	Orbital frontal
OT	Olfactory tubercle
P or SP	Neuropeptide substance P
PAG	Periaqueductal gray matter
PC	Paracentral thalamic nucleus
PD	Parkinson's disease
PE	Prediction error
pERK	Phosphorylated extracellular signal-regulated protein kinase
PET	Positron emission tomography
PF of Th	Parafascicular nucleus of the thalamus
PFC	Prefrontal cortex
PIVC	Parieto-insular vestibular cortex
PKA	Protein kinase A
PKC	Protein kinase C
PL	Prelimbic cortex
PLC	Phospholipase C
PLd	Dorsal prelimbic cortex
PLT	Persistent low-threshold
PLv	Ventral prelimbic cortex
pm-MD	Posteromedial mediodorsal nucleus of the thalamus

PNR-THAL	Pallidal or nigral input-receiving regions of the thalamus
PP-1	Protein phosphatase 1
PPC	Posterior parietal cortex
PPN or PPTN	Pedunculopontine nucleus
PPV	Perceived position vector
PS	Population spike
PSE	Point of subjective equality
pThr34-DARPP32	Thr-34-phosphorylated DARPP32
Pu	Putamen
PV	Paraventricular thalamic nucleus
rBmg	Rostral part of the magnocellular basal amygdaloid nucleus
rCBF	Regional cerebral blood flow
RDP	Rapid-onset dystonia parkinsonism
Rhes	ras homolog enriched in striatum
RHIN	Rhinal cortex
rl-GPi	Rostrolateral globus pallidus internal
RLi	Rostral linear nucleus of the raphe
RMP	Resting membrane potential
rm-SNr	Rostromedial substantia nigra pars reticulata
RMTg	Rostromedial tegmental nucleus
R-O	Response-outcome
Rp-cAMPS	Phosphodiesterase-resistant analogue of cAMP
RPD	Right-side onset Parkinson's disease
RPE or R-PE	Reward prediction error
RPM	Rotations per minute
RRA	Retrorubral area
RT-PCR	Real-time polymerase chain reaction
RVF	Right visual field
S6	Ribosomal protein S6 (pS235/236)
sAHPs	Slow after-hyperpolarization potentials
SC	Superior colliculus
SCZ	Schizophrenia
SD	Striosomes
SEF	Supplementary eye fields
sEPSCs	Spontaneous excitatory synaptic currents
Ser	Serine
SFV	Static force vector
Shp-2	Tyrosine phosphatase Shp-2
shRNA	Short hairpin RNA
SI	Substantia innominata
siRNA	Silencing RNA
SMA	Supplementary motor area
SN	Substantia nigra
SNc	Pars compacta of the substantia nigra
SNr	Pars reticulata of the substantia nigra

SOPT	Speed of processing training
SP	Substance P
SPECT	Single photon emission computed tomography
SPNs	Spiny projection neurons
S-R	Stimulus-response
SSI	Somatostatin-containing interneurons
SSM	Speech sound map
STEP	Striatal-enriched protein tyrosine phosphatase
STm	Medial part of the subthalamic nucleus
STN	Subthalamic nucleus
STN-DBS	Deep brain stimulation of the subthalamic nucleus
STN-HFS	High-frequency stimulation of the subthalamic nucleus
Sub	Subiculum
TANs or TAN	Tonically active neurons
tDCS	Transcranial direct current stimulation
TELOS	Telencephalic laminar objective selector
TH-IR	Tyrosine hydroxylase immunoreactivity
Thr	Threonine
TMS	Transcranial magnetic stimulation
TPV	Target position vector
TRAP	Translating ribosome affinity purification
TS	Tourette syndrome
TTX	Tetrodotoxin
TUBB4A	*TUBB4A* gene
US	Unconditioned stimulus
V4	Prestriate cortical area
VA	Ventral anterior nucleus of the thalamus
VEGF	Vascular endothelial growth factor
VGluT1	Vesicular glutamate transporter 1
VGluT2	Vesicular glutamate transporter 2
VI-30s	Variable interval schedule of reinforcement-30 seconds
vlPAG	Ventrolateral periaqueductal gray
VITE model	Vector integration to endpoint
VL	Ventrolateral thalamic nucleus
Vl-GPi	Ventrolateral globus pallidus (internal segment)
Vlm	Ventrolateral nucleus of thalamus pars medialis
VLo	Ventrolateral nucleus of thalamus pars oralis
VLO	Ventrolateral orbital cortex
vl-SNr	Ventrolateral substantia nigra pars reticulata
vmPFC	Ventromedial prefrontal cortex
VO	Ventral orbital cortex
VP	Ventral pallidum
vPAG	Ventral periaqueductal gray
VPd	Dorsal part of the ventral pallidum
VPm	Medial part of the ventral pallidum

vPMC	Ventral premotor cortex
VPv	Ventral part of the ventral pallidum
VPvl	Ventrolateral part of the ventral pallidum
VPvm	Ventromedial part of the ventral pallidum
VS	Ventral striatum
VTA	Ventral tegmental area
WM	Working memory
ΔJunD	Transcription factor ΔJunD
32 kDa	Dopamine- and cAMP-regulated phosphoprotein, 32 kDa
6-OHDA	6-Hydroxydopamine
A2a receptor	Adenosine A2a receptor
ATP1 α3	Sodium/potassium-transporting ATPase subunit alpha-3

Chapter 1
Introduction: Overview of the Basal Ganglia and Structure of the Volume

Jean-Jacques Soghomonian and Vinoth Jagaroo

1.1 Why a Volume on the Basal Ganglia?

The functions of the basal ganglia have made for an enduring topic in the history of neuroanatomy, neuroscience, and neurology. While still somewhat enigmatic, the understanding of the basal ganglia in the current time of the early twenty-first century—in the decades of neuroscience and systems biology—is marked by a number of key insights. Particular contributions, starting with some formative descriptions of basal ganglia circuitry in the 1960s and 1970s, critically reshaped the understanding of these structures (and accounts of them are given by other chapters in this volume). The notion of the basal ganglia as set of structures subserving the "single domain" of motor function/motor coordination has long faded into history. The basal ganglia have been notably reconceptualized to include their broader roles in cognition, emotion, and motivation, especially as a complex system of interface between intention and action. Advances in neuroscience research tools, namely novel histological tracing and tagging methods, refinements in single cell recording, optogenetics, and, of course, functional neuroimaging, have had a fair share of impact on basal ganglia research. These methods have contributed to broaden and deepen our understanding of motor and non-motor functions of the basal ganglia. Its functional anatomical organization has gained clarity with updated characterizations of its relationships with cortical and subcortical systems, including thalamic nuclei and the cerebellum. New insights into the functional properties of basal

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ganglia neurons and neural networks have expanded our conceptual grasp of the notion of parallel circuits subserving different functions; and, quite interestingly, how different features of the same functional domain, be that a cognitive or motor domain, can be differentially expressed within basal ganglia circuitry. In addition, the significance of the molecular and neurochemical compartmentalization of the basal ganglia has been updated thanks to recent research combining genetic, neurochemical, and molecular tools. Basal ganglia research has also seen the development of new conceptual models, some based on neural network/computational modeling, and others derived through comprehensive theoretical integration of neuroscience data. Altogether, these developments have translated into a much improved understanding of the computational architecture of the basal ganglia.

And yet, beyond the immediate bounds of basal ganglia researchers, many basic questions about the basal ganglia remain challenging: How do inhibitory processes contribute to its overall functions? What is its role in aspects of cognitive function, including language, learning, memory, and decision-making? How is it involved in complex patterning, sequencing, and action selection of learned movements and thoughts? How does it mediate processes of emotion and motivation such as associative learning, stimulus reinforcement, and reward? How is its role in neuropsychiatric conditions such as depression, obsessive-compulsive disorders, and addiction, or in neurodegenerative conditions such as Parkinson's Disease and Huntington's Disease, now articulated? Such questions, appraised by a significant breadth of research on the basal ganglia over the past 20 years, provide the impetus for this volume. While grounded in a neurobiology-cognitive neuroscience framework, the volume binds an assortment of research perspectives, altogether giving an updated formulation of the basal ganglia.

It is well known, however, that even with the advances made in understanding this brain system, a unifying theory or model still proves difficult and elusive. And the lack of a unifying framework also signifies the far-from-complete state of understanding of the basal ganglia. This can also be attributed in part to differing interpretations of agreed-upon basal ganglia mechanisms (hardly surprising in brain science). This volume simply aims to synthesize some of the major lines of recent work within neuroscience that have focused on the basal ganglia. It brings together a diverse set of contributions from researchers working across all levels of the genome-to-phenome strata, from molecular systems to circuit-level phenotypes. The volume does not presume nor tacitly suggest a single unifying structure, which at the current time would be lofty and premature. To the extent that some novel and integrative models of the basal ganglia have been formulated, the volume represents them.

1.2 Anatomic Layout and Nomenclature

The basal ganglia have historically been defined as large telencephalic subcortical nuclear masses lying at the base of the forebrain. The word "ganglion" derives from the ancient Greek and Latin to describe a swelling and/or an object with a round

shape. The expression "basal ganglia" derives from the apparent shape of these brain regions at the base of the forebrain.[1] The anatomist Thomas Willis is recognized for his early identification and description, in 1664, of one the most prominent basal ganglia structures, the *striatum* (see Parent 2012 for an historical account). Extensive historical accounts are also given by other chapters in this volume. The name striatum reflects its striated appearance on gross anatomical dissections due to the presence of myelinated fibers of the internal capsule traversing it. In primates, the striatum can be subdivided into a *caudate nucleus*, a *putamen,* and a *ventral striatum*. The ventral striatum includes the *nucleus accumbens* and some more ventral regions and its existence as a functional entity was proposed in the 1970s (Heimer and Wilson 1975). In rodents, the caudate and putamen form only one structure simply known as the striatum or caudo-putamen (or caudate-putamen). The rodent striatum is often referred to as dorsal striatum to distinguish it from the ventral striatum (i.e., nucleus accumbens). Based on phylogenetic considerations, the caudate-putamen is sometimes called the neostriatum. Studies carried out in the late 1970s and early 1980s have shown that the primate or rodent striatum can be subdivided into two intermingled compartments originally defined on the basis of their histochemical properties (Graybiel and Ragsdale 1978). These compartments, which became known as the patch or striosome compartment and the matrix compartment, have a different connectivity and have recently been proposed to play a differential role in the critic/actor model of associative learning (Fujiyama et al. 2015).

The *pallidum*, also known as the *globus pallidus* (GP), is another structure of the basal ganglia. In primates, the GP is subdivided into an external segment, the globus pallidus externus or external globus pallidus (Gpe) (also named the lateral segment of the GP or simply GP in rodents), and an internal segment, the globus pallidus internus or internal globus pallidus (Gpi) (also named the medial segment of the GP) (see Figs. 1.1 and 1.2). The rodent entopeduncular nucleus (EP or EPN) is the equivalent of the primate Gpi. As described in the chapter from Groenewegen and colleagues in this volume (Chap. 2), another subdivision of the GP known as the ventral pallidum shares preferential connections with the ventral striatum. In addition to the telencephalic structures identified by early anatomists, current definitions of the basal ganglia include the *subthalamic nucleus* (STN), *the substantia nigra* (SN), and the *ventral tegmental area* (VTA). The SN can itself be subdivided into three regions: the pars compacta (SNc), the pars reticulata (SNr), and the pars lateralis (SNl). In primates, the caudate nucleus follows the C-shape aspect of the lateral ventricles. The region anterolateral to the thalamus is known as the head. The region

[1] In neuroanatomy, the term "ganglion" typically refers to an encapsulated mass or swelling of cell bodies lying outside the central nervous system. A spinal ganglion is a prime example. By this definition, the term "Basal Ganglia" describing large grey matter masses in the central nervous system (brain) is a misnomer but the term is now established by convention. Though not a matter of great debate or interest, there are differing (and difficult to verify) accounts as to how the term "ganglia" came to be applied to the grey nuclear masses comprised in large part by the caudate nucleus, putamen, and globus pallidus: One is that early anatomists mistook these masses as ganglia-like; another is that the term ganglion was gradually extended to include the grey matter masses that form the basal ganglia.

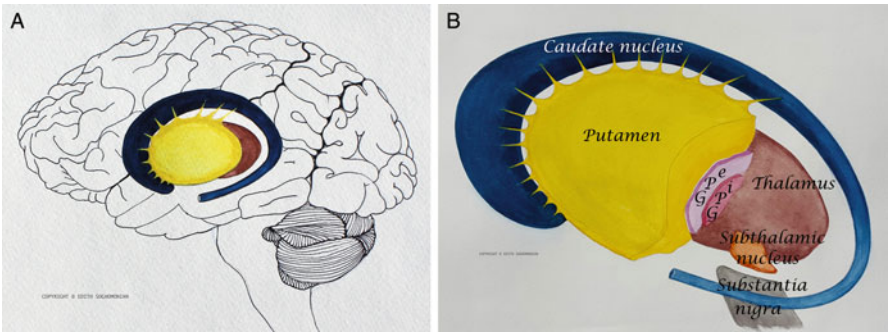

Fig. 1.1 Illustration of the general anatomic locus and orientation of major basal ganglia structures in the primate brain. (**a**) The basal ganglia are represented in superposition to show embeddedness under the cerebral cortex. (**b**) The major basal ganglia nuclei are shown in relation to the thalamus. The caudate nucleus has a characteristic C-shape that follows the C-shape of the lateral ventricles. The GPe and GPi are located between the putamen and the thalamus. The putamen has an approximate oval-shell shape when viewed laterally and sits medial to the insular cortex and lateral to the GP. The subthalamic nucleus is located in the diencephalon while the substantia nigra is located in the mesencephalon. Note that the two subdivisions of the substantia nigra are not shown. Note also the presence of thin bridges of grey matter between the head of the caudate nucleus and the putamen. These bridges are known as pontes grisei caudatolenticularis. *GPi* globus pallidus internus, *GPe* globus pallidus externus. (It is worth noting that the anatomic arrangement of the basal ganglia is difficult to appreciate through standard slice dissection or images/representations of these slices (coronal, sagittal, or transverse)—and this is likely a contributing reason that a grasp of its anatomy eludes many students. The 3D rostral-caudal extent of the structures combined with the medial-ventro-lateral "layering" order can to a limited degree be conveyed with renderings of a 3D perspective as shown in (**b**). However, a very effective way of grasping the anatomic layout of the caudate and the putamen is through the process of blunt dissection of the brain—following medial and lateral approaches, respectively. It is perhaps not a coincidence that the late neuroanatomist, Lennart Heimer, whose pioneering work on the basal ganglia is referenced throughout this volume, was a passionate advocate of the blunt dissection technique as a means to appreciate the basal ganglia and other structures)

superior-lateral to the thalamus is known as the body and the region caudo-ventral to the thalamus is known as the tail (Fig. 1.1a, b).

The striatum is known as the input structure of the basal ganglia because it receives massive inputs from sensory, associative, motor, and limbic regions of the cerebral cortex. Evidence that these inputs are topographically segregated throughout the basal ganglia has led to the concept that different parallel circuits in the basal ganglia are concerned with the processing of information from different functional cortical regions (Alexander and Crutcher 1990). The striatum directly and indirectly controls the activity of neurons in the SNr and GPi (or rodent EP). These two nuclei are known as the output regions of the basal ganglia because they project outside the basal ganglia to the thalamus and to the brainstem. The thalamic nuclei that receive inputs from the basal ganglia project to the frontal lobe to include prefrontal regions in addition to motor and premotor cortical regions (Middleton and Strick 2002). This anatomical organization suggests that the basal ganglia are able to integrate information from multiple sensorimotor, associative, and limbic cortical regions in

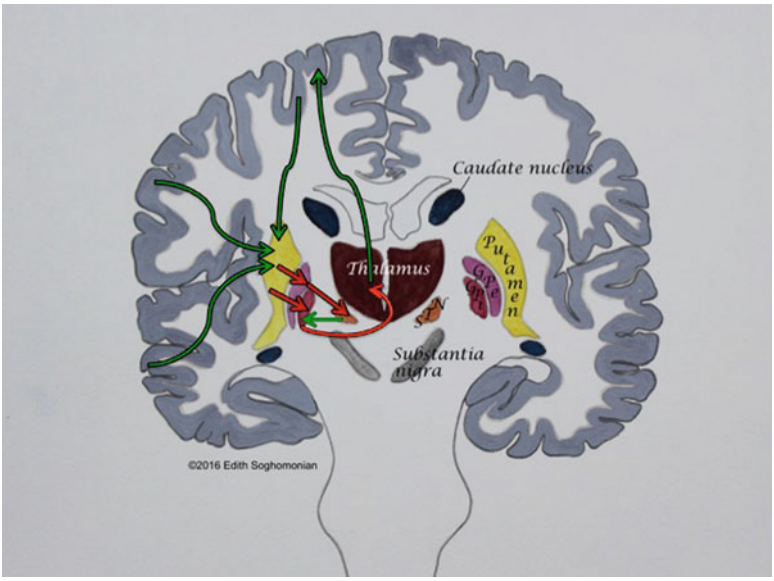

Fig. 1.2 Relative positions of major basal ganglia nuclei in the primate brain presented in a coronal view schematic (*right side*) and major connectivity between basal ganglia nuclei (*left side*). The *red arrows* indicate inhibitory projections and the *green arrows* excitatory projections. The caudate and putamen receive massive projections from all major cortical regions (for clarity, only projections to the putamen are illustrated). Neurons in the caudate and putamen send GABAergic projections to the GPe (known as indirect pathway) or send GABAergic projections to the GPi and substantia nigra, pars reticulata (SNr) (known as direct pathway). Neurons in the GPe project to the STN, which sends glutamatergic projections to the GPi and SNr (only projections to the GPi are illustrated for clarity). The GPi and SNr send GABAergic projections to the thalamus, which then sends glutamatergic projections to the frontal and prefrontal cortex. Not shown on this simplified drawing are the direct projections from the GPe to the GPi and SNr, the reciprocal projection from the STN to the GPe, or the direct projections from the frontal cortex to the STN (known as the hyperdirect pathway). *GPi* internal segment of the globus pallidus, *GPe* external segment of the globus pallidus, *STN* subthalamic nucleus

order to modulate the activity of the frontal, prefrontal, and orbitofrontal regions of the cerebral cortex as well as key brainstem structures involved in motor control. This particular anatomical organization is consistent with the notion that the basal ganglia are able to control a widespread range of motor and cognitive functions.

1.3 Structure of the Volume

The objective of this volume is, again, to present recent perspectives on the contributions of the basal ganglia to motor control and cognitive function, emotion, and motivation. It includes work on how these functions, as mediated by the basal ganglia, are affected in a range of motor, cognitive, and neuropsychiatric disorders.

These topics are diverse and cover a wide range of concepts and experimental data, and this makes for an inherent overlap of themes across the volume. For example, in addition to the first section of the volume which is centered on basal ganglia neuroanatomy, chapters throughout the volume invariably begin with a review of essential neuroanatomy or neural systems as relates to the central point of the chapter. The multiple renderings will serve the reader with understanding, reinforcing, and consolidating basal ganglia anatomy and circuitry—and understanding the anatomical organization of the basal ganglia is crucial to the understanding of their function. The diversity and overlap of themes covered in the chapters of this volume make for a number of possible ways by which the chapters can be grouped: Do they relate to the same neuroanatomic or circuit systems; or do they concern the same cognitive or motor process; or are they centered on a particular disorder, etc. After careful consideration, the chapters were clustered based on their essential topic of focus or their conceptual direction. A chapter, for example, may give considerable attention to major circuits of the basal ganglia but if the chapter's purpose was to then apply its elaborate layout to a theme of language processing, it was grouped within Part III (that is centered on Cognition, Learning, and Decision-Making). The volume has five parts—five broad thematic groupings.

Chapters in Part I focus on the anatomic and functional organization of the basal ganglia but this is also served by their discussions of the role of the basal ganglia in motor and cognitive function. In Chap. 2, Groenewegen and colleagues present a detailed description of the anatomic and functional organization of limbic-associated circuits of the basal ganglia, with a discussion of their role in motivation and reward. In Chap. 3, Soghomonian presents an overview of the experimental evidence supporting the concept of a direct and indirect pathway and discusses earlier and more recent experimental evidence suggesting that these two pathways play an opposite and/or complementary role in action selection, movement control, and learning. Smith and colleagues, in Chap. 4, present a detailed description of thalamo-striatal projections involving the centromedian and parafascicular nuclei of the thalamus, and discuss the evidence that these circuits play an important role in attention and motivation. Chapter 5, by Bullock, integrates current knowledge on the functional organization of dopaminergic circuits and provides an experimental and computational view of the role of these circuits in reward, outcome-guided learning, and action selection.

Chapters in Part II discuss traditionally less appreciated motor functions and dysfunctions of the basal ganglia in neurological disorders such as Parkinson's disease and dystonia. In Chap. 6, Kucinski and Sarter describe an experimental model designed to investigate the contribution of the cholinergic and dopaminergic systems in the execution of cognitively demanding motor tasks and gait impairments in patients with Parkinson's disease. In Chap. 7, Chen and colleagues review the evidence for functional and anatomical interactions between the basal ganglia and the cerebellum. They also discuss how the cerebellum and the basal ganglia could contribute to dystonia. Alcacer and colleagues, in Chap. 8, review current knowledge of the molecular and cellular plasticity associated with the pathogenesis of abnormal involuntary movements induced by levodopa in Parkinson's disease.

Chapters in Part III discuss the contribution of the basal ganglia to learning and cognition, including basal ganglia-mediated cognitive dysfunction in clinical disorders. In Chap. 9, Putcha and colleagues identify major cognitive deficits in Parkinson's disease and present a thorough review of the clinical and imaging literature, documenting deficits in visual perception and cognitive-action coupling. In Chap. 10, Bohsali and Crosson discuss the possible contribution of the basal ganglia to lexical-semantic processing, and review the evidence for a functional connectivity between the basal ganglia, the pre-supplementary area, and Broca's area in the prefrontal cortex. The potential role of this connectivity in the production of language is discussed. Chapter 11 provides a discussion by Diaz and colleagues on the mechanisms involved in controlled (goal-oriented) versus automatic (habit) learning and the role of the striatum in learning in the context of the "failure of acquisition" theory. In Chap. 12, Patel and colleagues present an overview of the role of the basal ganglia in associative learning and motivation with a specific focus on monkey and human studies. They discuss the alteration of these functions in a number of neurological diseases. Chapter 13 by Patton and colleagues follows, discussing how alcohol consumption remodels the dorsal striatal macro- and micro-circuitry to promote the expression of habitual action strategies.

Chapters in Part IV are focused on the role of the basal ganglia in motivation, decision-making, reinforcement learning, and addiction. In Chap. 14, Baunez reviews the major connections of the subthalamic nucleus and presents novel insights into the role of this basal ganglia nucleus in reward, addiction treatment, and neurological disease. In Chap. 15, Tinaz and Stern review the role of the basal ganglia in decision-making and discuss basal ganglia-produced impairments in decision-making in a number of neurological diseases and mood disorders. Boulet and Colleagues, in Chap. 16, describe the role of the basal ganglia in motivational deficits and apathy in Parkinson's disease. They focus their discussion on the role of the dopaminergic system in these deficits, as well as on the effects of deep brain stimulation of the subthalamic nucleus. In Chap. 17, Guercio and Pierce review the role of dopamine and glutamate in the mesocorticolimbic system as relates to the reinstatement of cocaine seeking. They discuss the underlying anatomical, neurobiological, and neurochemical bases of cocaine craving and relapse.

Chapters in Part V use a more integrative and/or computational approach to describe the general organizational principles of the basal ganglia. In Chap. 18, Devan and colleagues present an historical overview of the studies that led to the notion that different subdivisions of the striatum are associated with different learning mechanisms. They also explain how Bayesian computational approaches help understand and define the role of the basal ganglia in learning. In Chap. 19, Grossberg presents several computational models that simulate how the basal ganglia contribute to associative and reinforcement learning, and to movement gating. In Chap. 20, Yin proposes a novel perspective on the function of the basal ganglia based on the principle of hierarchical control. This model hypothesizes that the basal ganglia output is involved in the generation of transition errors to adjust reference signals of position controllers in the midbrain and brainstem.

The array of perspectives on the basal ganglia carried within this volume derives from the collective force of many subdisciplines of brain-behavioral studies—cellular neuroscience and neurobiology, cognitive and computational neuroscience, and neuropsychology, among others. The contributions synthesized and condensed under the umbrella of a single volume may help make a small consolidated step towards the understanding of the basal ganglia.

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Part I
Functional and Anatomical Organization of Basal Ganglia: Limbic and Motor Circuits

Chapter 2
Limbic-Basal Ganglia Circuits Parallel and Integrative Aspects

Henk J. Groenewegen, Pieter Voorn, and Jørgen Scheel-Krüger

2.1 Introduction: The Evolvement of the Concept of the Ventral Striatopallidal System

The basal ganglia are considered to consist of the striatum, the pallidum, the subthalamic nucleus, and the substantia nigra. Traditionally, with respect to the striatopallidal structures, this concept was restricted to the caudate nucleus and putamen as the main parts of the striatum and the internal and external segments of the globus pallidus as the constituents of the pallidum. With the pioneering work of Lennart Heimer, Walle Nauta, and colleagues in the seventies of the last century, it became increasingly accepted that the nucleus accumbens and parts of the olfactory tubercle in the basal forebrain are a rostroventral extension of the striatum (Heimer and Wilson 1975; Nauta et al. 1978). In line with this insight, it could be demonstrated that part of a region of the basal forebrain, until then indicated as the 'substantia innominata', constitutes a ventral extension of the pallidum, i.e., the ventral pallidum (Heimer and Wilson 1975; Nauta et al. 1978; Heimer et al. 1997). As a consequence of this 'expansion' of the basal ganglia concept, i.e., that they include parts that receive input from limbic structures, such as the hippocampus, amygdala, and the prefrontal cortex, the functional role of the basal ganglia 'expanded' from traditionally related to sensorimotor and behavioral functions to also include cognitive, social-emotional, motivational, and mnemonic functions in relation to behavior. Heimer and colleagues were the first to elaborate on two parallel striatopallidal

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systems, a dorsal and a ventral one, that via their distinctive relay nuclei in the thalamus have an influence on, respectively, the somatomotor and the associative, prefrontal cortical regions in the frontal lobe (Heimer and Wilson 1975). They emphasized that, whereas the dorsal and ventral striatum receive functionally different inputs, carrying either somatomotor or limbic/associative information, the basic cellular, chemoarchitectonic and connectional organization in these two parallel circuits appears to be very similar. Therefore, somatomotor and limbic cortical information, via separate dorsal and ventral striatopallidal channels, in which comparable neuronal mechanisms play a role, lead to transfer of these streams of information via the thalamus back to different somatomotor or limbic-associated parts of the frontal lobe. It was further stipulated in these early days that, at the level of the striatum, the transfer of information is modulated by dopamine from the nigrostriatal and mesolimbic systems originating in substantia nigra pars compacta and the ventral tegmental area (VTA), respectively.

Although the parallel nature of the somatomotor and limbic cortical-basal ganglia circuits was emphasized at the time, Nauta and colleagues also showed that a major output of the nucleus accumbens reaches the VTA and substantia nigra pars compacta, in which the dopaminergic neurons project back to both the ventral and dorsal striatum (Nauta et al. 1978). That led them to hypothesize that there exists a dopaminergic feed-forward circuit for the integration of the ventral and dorsal circuitries, i.e., a means to integrate limbic and motor functions. Together with the pioneering electrophysiological work of Gordon Mogenson and his colleagues (Mogenson et al. 1980) on the ventral striatum as a key structure involved in the translation of 'motivation into action', these ideas now form the cornerstones for our understanding of the role of the cortical-basal ganglia circuits in motor, cognitive, and emotional/motivational behaviors and their dysfunctioning in neurological and psychiatric disorders (e.g. Voorn et al. 2004; Humphries and Prescott 2010; Haber and Behrens 2014; Everitt and Robbins 2015; Floresco 2015).

The concept of a parallel organization of corticostriatopallidal projections in the sensorimotor and limbic realms, as put forward by Heimer and Nauta and co-workers, was further developed by Alexander, DeLong, and colleagues in their seminal review on the organization of basal ganglia-thalamocortical circuits (Alexander et al. 1986; DeLong 1990; also DeLong and Georgopoulos 1981). In primates, Alexander et al. (1986) proposed the existence of five parallel, functionally segregated basal ganglia-thalamocortical circuits: a somatomotor, an oculomotor, and three complex circuits, one of which was designated as the 'limbic circuit'. These circuits have their origin in distinct (pre)frontal cortical regions from which the corticostriatal projections originate and further include topographically organized striatopallidal/striatonigral and pallido/nigrothalamic projections to distinct medial and ventral nuclei of the thalamic complex. The different thalamic nuclei targeted by the internal globus pallidus, ventral pallidum, and substantia nigra pars reticulata project back to the (pre)frontal cortical areas of origin of the individual circuits, in this way forming closed loops (Alexander et al. 1986; Groenewegen et al. 1990). At the level of the striatum, projections from other more posterior cortical areas, i.e., from the parietal, occipital, and temporal cortices, converge with their associated and mutually interacting frontal cortical areas (Yeterian and Van Hoesen 1978; Selemon and Goldman-Rakic 1985) in

order to subserve the integration of information from these sensory association cortices with higher order cognitive areas of the prefrontal-striatal system (e.g. Cavada and Goldman-Rakic 1989; Flaherty and Graybiel 1991). Recent studies show the functional significance of such integration at the level of the caudate nucleus in value processing and decision making within local microcircuitries to be discussed later. Furthermore, the corticostriatal circuitry involving the rostral head of the caudate nucleus is important for flexible (short-term) values; the caudal tail of the caudate plays a role in stable (long-term) values and the behavioral decisions made on that basis (Kim and Hikosaka 2013, 2015).

Parts of the output of the basal ganglia-thalamocortical circuits, primarily originating in the different (pre)frontal cortical regions, are directed at motor areas in the brainstem, such as the superior colliculus, the midbrain extrapyramidal area, the pedunculopontine nucleus, and the reticular formation, as well as the spinal cord. The limbic-related parts of the cortical-basal ganglia system project, in addition, to hypothalamic and brainstem areas that are involved in various types of emotional and incentive, cue-directed motor behavior (Mogenson et al. 1980) and the regulation of eating/drinking, autonomic, and endocrine functions (Kelley 1999; Richard et al. 2013; Castro et al. 2015).

As already indicated above, within the five initially identified basal ganglia-thalamocortical circuits (Alexander et al. 1986), various functionally different subcircuits have been identified (e.g., somatomotor functions: Alexander et al. 1990; decision making: Kim and Hikosaka 2013; incentive behavior: Richard et al. 2013). Without ignoring this multiplicity of the circuits between the (pre)frontal cortex and the basal ganglia, a classification into three larger 'families' of circuits within the basal ganglia-thalamocortical system is nowadays most frequently being adopted: a collection of somatomotor circuits, a group of complex or associative circuits, and a 'family' of limbic, emotional, and motivational circuits (cf. Parent and Hazrati 1995a; Humphries and Prescott 2010). In line with a partitioning of the striatum and the pallidum into somatomotor, associative, and limbic parts, also in the subthalamic nucleus, these three functionally different regions have been identified based on their different afferent striatopallidal and frontal cortical inputs (Groenewegen and Berendse 1990; Parent and Hazrati 1995b; review: Temel et al. 2005).

Whereas Nauta and Heimer and their colleagues, based on their experimental work, concentrated primarily on the organization of corticostriatopallidal circuits in rodents, Alexander and colleagues based their ideas about the basal ganglia-thalamocortical circuits primarily on electrophysiological and neuroanatomical results in primates. This facilitated the extrapolation of the neuronal relationships between the basal ganglia and the thalamocortical system from the rodent and primate brain to the human situation. In a recent study, special attention was paid at the homologies between the cortical-basal ganglia systems in rodents and primates (Heilbronner et al. 2016). The above-mentioned early conceptual papers have inspired many researchers in the last decades to investigate in more detail the various different subdivisions of the basal ganglia not only structurally and functionally, but also with respect to their putative roles in neurological and psychiatric disorders. It has thus been hypothesized already in the seventies and eighties of the last century that specific dysfunctions exist in particular basal ganglia-thalamocortical circuits in neurological disorders, such as

Parkinson's disease and Huntington's disease (Alexander et al. 1986; Delong 1990; Albin et al. 1989), and in psychiatric disorders, such as schizophrenia, obsessive-compulsive disorders, Tourette syndrome, drug addiction, and depression (e.g., Stevens 1973; Cummings 1993; Mega and Cummings 1994; Mink 1996; Humphries and Prescott 2010; Willner et al. 2013; Tremblay et al. 2015). In the last two decades, with the great advent of modern neuroimaging techniques, the functional–anatomical relationships of the cerebral cortex, basal ganglia, and thalamus have been extensively studied in humans (e.g., Lehericy et al. 2004; Barnes et al. 2010; Jeon et al. 2014). The results of these studies confirm and extend the existence of multiple, functionally segregated, as well as interacting circuits between these structures also in the human forebrain (e.g., Postuma and Dagher 2006; Jung et al. 2014; Kotz et al. 2014; Haber and Behrens 2014). This further opens the way to explore the dysfunctional circuitry in neurological and psychiatric disorders.

In the following part of this chapter, we will review the main input–output relationships of the 'limbic', ventral striatopallidal system, primarily based on findings in rats with some reference to primates. Whereas it is already generally acknowledged that the striatum, as the input structure of the basal ganglia, is an important site for the integration of information from multiple and different sources, recent data show that there is even more overlap between corticostriatal projections than has long been assumed. This extends our understanding of the architecture of the parallel basal ganglia-thalamocortical loops in providing rich and specific possibilities for interactions between these parallel loops with functionally different roles. This may be the basis for the flexibility in behavioral and cognitive functioning in animals and man. With respect to the outputs, the ventral striatopallidal system parallels the projections of its dorsal counterpart in that there are strong projections to the mediodorsal thalamus, but it is unique in that it has also projections to the dopaminergic cell groups in the ventral mesencephalon. These projections provide the possibility for the ventral striatopallidal system to modulate the dopamine input to the dorsal striatum (Nauta et al. 1978; Haber et al. 2000; Voorn et al. 2004; Belin and Everitt 2008) (see also Fig. 2.5). Interestingly, in recent years there has been renewed interest in the projections from the habenula, part of the epithalamus, to the mesencephalon. Thus, several studies have shown that the lateral habenula has a direct and an indirect influence on the dopaminergic cells of the VTA, namely via the mesencephalic GABAergic rostromedial tegmental nucleus (RMTg; also indicated as the 'tail part' of the VTA) (e.g. Yetnikoff et al. 2015). Since the ventral pallidum, like the internal segment of the globus pallidus, consistently projects to the lateral habenula, there exists yet another pathway for the modulation of the dopaminergic systems by the limbic part of the basal ganglia.

2.2 What Is the "Limbic" Ventral Striatum?

Since the inclusion of the nucleus accumbens and parts of the olfactory tubercle as 'true' parts of the striatum was based on cytoarchitectonic criteria (Heimer and Wilson 1975), a clear distinction with the classical dorsal striatum (caudate nucleus

and putamen) cannot be based on cellular characteristics. Histochemical or immunohistochemical characteristics provide in some cases differences and in other instances great similarities between dorsal and ventral parts of the striatum. For example, the distribution of the acetylcholine metabolizing enzyme acetylcholinesterase (AChE) is quite homogeneous throughout the striatum and its distribution was considered as supporting the inclusion of the nucleus accumbens and olfactory tubercle in the family of striatal nuclei (Heimer and Wilson 1975). By contrast, the calcium-binding protein calbindin D_{28K}, present in striatal GABAergic medium-sized spiny neurons, is quite unevenly distributed over the striatum with a low density in its ventromedial part, defining the shell of the nucleus accumbens, and with higher densities in the core and in large parts of the caudate-putamen, but again with low density in its dorsolateral (somatomotor) part (Zahm and Brog 1992). Dopamine is distributed over the entire striatum, showing areas with higher or lower concentration throughout (Voorn et al. 1986, 2004). By contrast, neurotransmitters like serotonin and noradrenalin are concentrated primarily in the ventromedial parts of the striatum, noradrenalin even confined to the most ventromedial region of the nucleus accumbens, i.e., the medial shell (Delfs et al. 1998; human: Tong et al. 2005). The serotonin innervation extends into the medial and ventral parts of the caudate-putamen complex and, of quite some clinical interest, serotonin fibers in the medial shell are different in that they lack the serotonin transporter (Brown and Molliver 2000). Thus, as has been concluded previously, there appears to be no clear boundary between the dorsal and the ventral striatum on the basis of cytoarchitecture, myeloarchitecture, or chemoarchitecture (Voorn et al. 2004). However, as will be discussed in the next paragraphs in more detail, the organization of inputs and outputs presents a somewhat different distinction within the striatum as a whole, namely a dorsolateral-to-ventromedial orientation of striatal zones that are reached by afferents from different (pre)frontal cortical areas and their associated subnuclei of the intralaminar and midline thalamus as well as from distinctive amygdala and hippocampal areas. In that way, a distinction between striatal zones, respectively, innervated by (1) cortical sensorimotor fibers, (2) higher order association cortical fibers, and (3) limbic and visceral cortical and subcortical structures can be distinguished. This provides support for a dorsolateral-to-ventromedial-oriented functional organization of the striatum into three functionally different zones, which appears to be quite universal for different species, including rodent, non-human primates, and humans (Voorn et al. 2004; Haber et al. 2000; Stoessl et al. 2014) (Fig. 2.1A). Interestingly, in the human brain, the vascularization of the striatal complex follows this three-partition and its orientation (Feekes and Cassell 2006) (Fig. 2.1B). The striatal area innervated by limbic structures like the hippocampus, amygdala, and ventromedial prefrontal and anterior agranular insular cortical areas in this way includes the nucleus accumbens and striatal elements of the olfactory tubercle, as well as ventromedial parts of the caudate nucleus and ventral parts of the putamen. It is now generally accepted that this ventromedial region of the striatum is the 'limbic' striatum.[1]

[1] The term 'limbic' deserves some attention since it is being widely used in the literature, but often in different ways. We should still keep in mind the words of A. Brodal (1981, page 690), namely

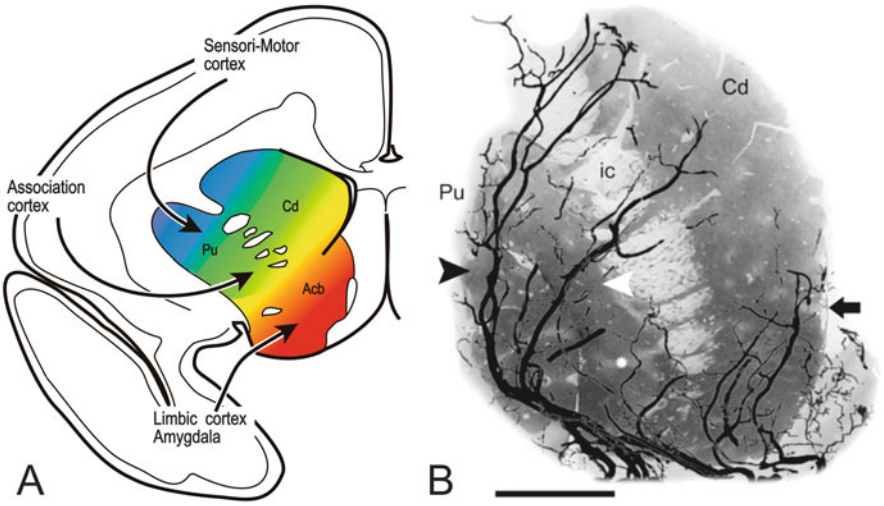

Fig. 2.1 Three-partitioning of the striatum based on cortical afferents and vascularization. (**A**) Schematic representation of the topographical organization of the projections from functionally different cortical areas to the striatum. Note that the functional subdivision of the striatum, related to the corticostriatal topography, does not follow the boundaries between caudate nucleus and putamen: there exists a dorsolateral-to-ventromedial gradient rather than a functional division between the caudate nucleus and the putamen. Boundaries between the different functional areas are not sharply defined but merely consist of transition zones. (**B**) Three vascular territories shown in calbindin-immunostained section of the human striatum largely corresponding with the functional three-partitioning shown in (**A**). The lateral lenticulostriate artery (*black arrowhead*) supplies the dorsolateral part of the striatum, the medial lenticulostriate artery (*white arrowhead*) vascularizes the intermediate striatal zone, and the recurrent artery of Heubner (*arrow*) supplies the ventromedial striatum including the nucleus accumbens. From: Feekes and Cassell (2006), figure 4; Courtesy Martin Cassell and with permission from Oxford University Press. *Acb* nucleus accumbens, *Cd* caudate nucleus, *ic* internal capsule, *Pu* putamen

It should be noted that by far the most studies on the striatum, whether anatomical, electrophysiological or behavioral, concentrate on the rostral parts of the striatal complex. However, the caudal part of the striatum also contains extensive areas, including the amygdalostriatal transition zone, which receive inputs from limbic structures, such as the hippocampus and posterior insular areas. This caudal part of

that the term looses its meaning when the structural and functional definitions do not coincide and become so diffuse that finally the entire brain can be considered to belong to the 'limbic system' (cf. also Nauta 1986; Nieuwenhuys 1996). However, whereas the term 'limbic' cannot be discarded nowadays, it remains very important to define what is exactly meant with the term and which brain areas are considered to be part of the 'limbic system'. Even though these structures may have quite diverse functions, we consider the amygdala, hippocampus and hypothalamus as the 'core structures' of the limbic system. Brain regions that are directly influenced by these core limbic structures are considered also to belong to the limbic system, i.e., in rodents the ventromedial and insular parts of the prefrontal cortex, midline thalamic nuclei and structures along the pathway of the medial forebrain bundle (preoptic, hypothalamic and medial midbrain structures). As indicated in the text, the region of the striatum innervated by 'limbic' brain structures mentioned here is considered the 'limbic striatum'. Nevertheless, the borders between 'limbic' and 'associative/cognitive' related parts of the striatum remain diffuse.

the striatum may also be considered part of the 'limbic' striatum (e.g., Groenewegen et al. 1987; Fudge et al. 2004; Heimer et al. 1999). This striatal region still is a relatively unexplored area of the basal ganglia.

The delineation of a 'limbic' striatum becomes even more complex when we take into account the compartmental nature of the striatum. Both dorsal and ventral striatum contain characteristic inhomogeneities that are primarily visible using neurochemical or immunohistochemical staining techniques. In the dorsal striatum (caudate nucleus and putamen) using such methods, patch-matrix (rats) or striosome-matrix compartments (primates, cats) can be recognized (as originally described by Graybiel and Ragsdale 1978; reviews: Graybiel 1990; Gerfen 1992; Dudman and Gerfen 2015). Within the ventral striatum, the nucleus accumbens can be subdivided into an outer shell subregion and an inner core subregion, among others on the basis of the distribution of several neuropeptides (cholecystokinin, substance P, enkephalin), opioid receptors, and calbindin D_{28K} (e.g. Záborszky et al. 1985; Voorn et al. 1989; Zahm and Brog 1992; Groenewegen et al. 1999a). Like the dorsal striatal patch and matrix compartments, the distinction of shell and core subregions of the nucleus accumbens is primarily based upon differential neurochemical and immunohistochemical characteristics and this differentiation is also supported by numerous behavioral studies (see: Dalley et al. 2004, 2011; Humphries and Prescott 2010; Floresco 2015; Haber and Behrens 2014).

The dorsal part of the core of the nucleus accumbens contains patches like the dorsally adjacent caudate-putamen complex. As will be briefly touched upon below, patch and matrix compartments in caudate-putamen as well as shell and core in the nucleus accumbens have different inputs and outputs (e.g. Graybiel 1990; Gerfen 1992; Groenewegen et al. 1999a). Based on such differential inputs, patches in the dorsal striatum may represent 'limbic' striatal islands in a striatal matrix that on the basis of its cortical inputs must be considered to belong to the associative part of the striatum (Gerfen 1992; Berendse et al. 1992; Eblen and Graybiel 1995). This unique intermingling of limbic and associative striatal elements forms the basis of its established role in the integration of emotional and higher cognitive behavioral functions (e.g. Friedman et al. 2015). In short, the latter authors showed that the limbic-innervated striosomes located in the associative part of the caudate-putamen influence decision-making for choices with cost-benefit tradeoffs that are processed in the matrix compartment in which these striosomes are embedded.

2.3 Afferent Connections of the "Limbic" Striatum

2.3.1 Hippocampal and Amygdaloid Inputs

The hippocampal formation (hippocampus proper and subiculum) and the amygdala reach primarily the ventromedial parts of the striatum, in particular the nucleus accumbens, the striatal elements of the olfactory tubercle, and the ventromedial parts of the caudate-putamen (Groenewegen et al. 1987, 1999b; Wright et al. 1996). The hippocampal afferents originate predominantly in the subiculum and to a lesser extent in the CA1 region and they are mostly restricted to the shell region of the nucleus accumbens,

although the medial and rostroventral core also receives hippocampal projections. In rats, there is a clear topographical arrangement in the hippocampal-striatal projections in that the ventral hippocampus projects primarily to the medial shell, while progressively more dorsal parts of the hippocampus[2] project to successively more rostrolateral parts of the shell and adjacent core of the nucleus accumbens (Groenewegen et al. 1987; monkey: Friedman et al. 2002) (Fig. 2.2). As will be briefly discussed below, the excitatory hippocampal inputs interact with thalamic, amygdaloid, and prefrontal cortical inputs. Convergence of these inputs onto individual medium-sized spiny neurons can either lead to an additive or a competitive effect on these neurons. In the first circumstance, the medium-sized output neurons are brought in an 'upstate' by one input and in a state of firing action potentials by the second input. In the second, i.e., the competitive circumstance, one input prevents the second from bringing the output neurons to become active. In other words, convergence of excitatory inputs may lead to either opening or closing the gate for striatal output (Calhoon and O'Donnell 2013). The character of interactions between hippocampal and amygdaloid inputs is dependent on the rostrocaudal level in the nucleus accumbens (Gill and Grace 2011).

The entorhinal cortex, which is closely associated with the hippocampal formation, projects primarily to the lateral core and lateral shell of the nucleus accumbens and more sparsely to a medial rim of the caudate-putamen, bordering the lateral ventricle. The entorhinal fibers originate both in the medial and lateral entorhinal cortex with a slight topographical arrangement, the medial entorhinal fibers terminating more rostrally than the lateral entorhinal fibers (Totterdell and Meredith 1997).

The amygdaloid inputs to the striatum, originating primarily in different subnuclei of the basal amygdaloid complex, have a more widespread distribution and these projections are likewise topographically organized (Wright et al. 1996). Caudal parts of the basal amygdaloid complex project to the medial shell and core of the nucleus accumbens, with a dominance for the caudal part of the nucleus. Intermediate and rostral parts of the basal amygdala project to, respectively, more lateral and dorsal parts of shell and core of the nucleus accumbens and the adjacent caudate-putamen complex (Wright et al. 1996). As can be appreciated from Fig. 2.2,

[2] In primates the posterior-to-anterior axis in the hippocampal formation corresponds to the dorsal-to-ventral axis in rodents.

Fig. 2.2 (continued) and amygdaloid fibers in the medial and lateral parts of the nucleus accumbens. Details of the hippocampal and amygdaloid projections can be found in Groenewegen et al. (1987) and Wright et al. (1996). The distribution of retrogradely labeled neurons in the nucleus accumbens following injections in the ventromedial and ventrolateral parts of the ventral pallidum (**C**) shows a mediolateral topographical organization. A similar conclusion can be drawn for the organization of the ventral striatal projections to the ventral mesencephalon as shown in (**D**). Combining the various patterns of afferents from the hippocampus and amygdala and efferents to the ventral pallidum and the ventral mesencephalon shows a rich spectrum of input-output channels through the ventral striatum. ac anterior commissure, AcbC core of the nucleus accumbens, AcbSh shell of the nucleus accumbens, BST bed nucleus of the stria terminalis, cBmg caudal part of the magnocellular basal amygdaloid nucleus, cBpc caudal part of the parvicellular basal amygdaloid nucleus, CP caudate-putamen, CA1 cornu Ammonis area 1, LPO lateral preoptica area, lVTA lateral part of the ventral tegmental area, mSN medial part of the substantia nigra, OT olfactory tubercle, rBmg rostral part of the magnocellular basal amygdaloid nucleus, VP ventral pallidum, *VPd* dorsal subcommissural part of VP, *VPm* medial part of VP, *VPvm* ventromedial part of VP, *VPv* ventral part of VP, *VPvl* ventrolateral part of VP, *VTA* ventral tegmental area

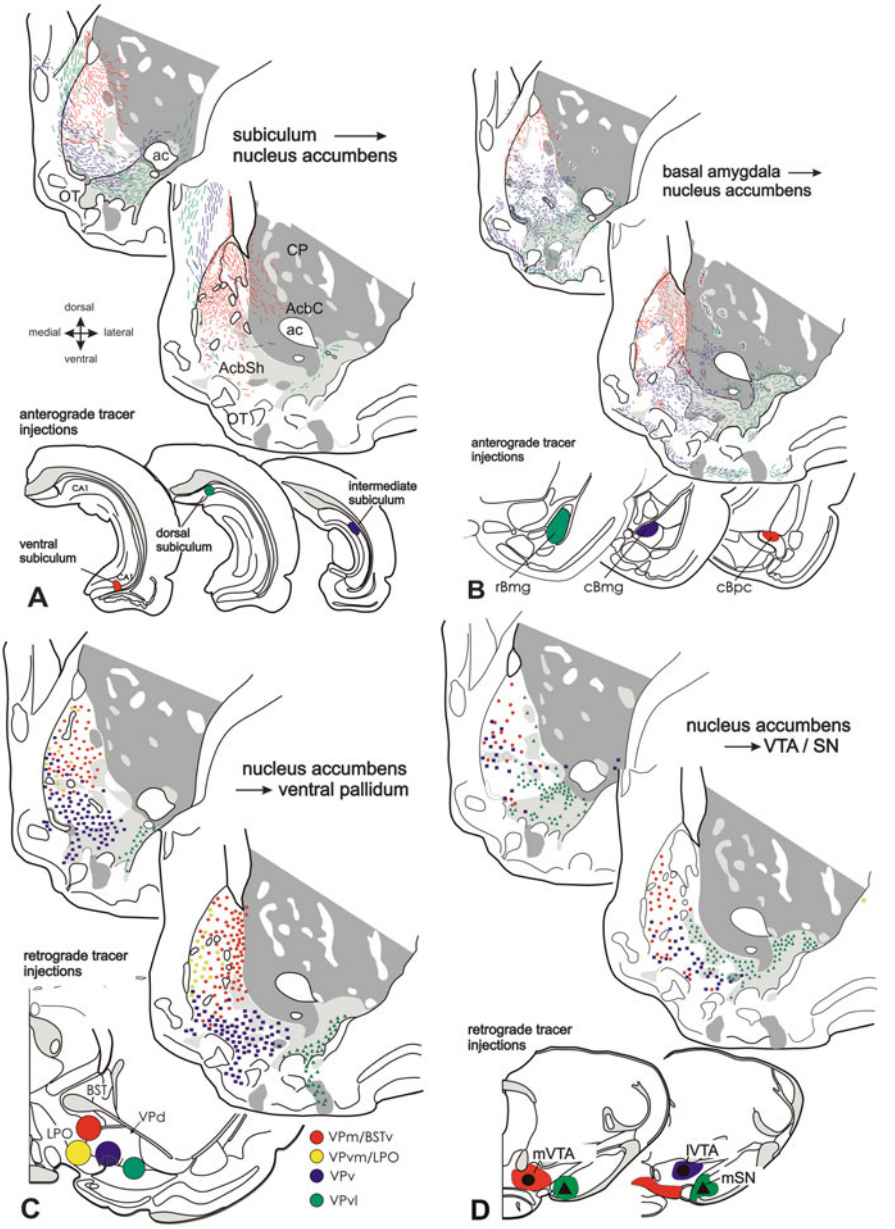

Fig. 2.2 Schematic representation of the distribution of anterograde and retrograde labeling in the nucleus accumbens and olfactory tubercle following injections in different parts of the hippocampal formation (**A**), the basal amygdaloid complex (**B**), the ventral pallidum (**C**), and the ventral mesencephalon (**D**). The drawings of the ventral striatum are based on sections immunostained for the calcium-binding protein calbindin D_{28K}, showing the shell (AcbSh) and core (AcbC) subregions, as well as the patches in the core and the ventral caudate-putamen (CP). Fibers and terminals originating from the ventral subiculum (**A**) and those from the caudal part of the parvicellular basal amygdaloid nucleus (**B**) are represented in *blue* (*primarily in the medial shell*), those from the intermediate part of the subiculum (AII-IV) and from the mid-rostrocaudal amygdala (BII-IV) are shown in *red* (*predominantly in the intermediate shell*), and the fibers and terminals from the dorsal subiculum (**A**) and the rostral part of the magnocellular basal amygdaloid nucleus (**B**) are depicted in *green* (*mostly in the lateral shell*). Note the varying degrees of overlap between hippocampal

the hippocampal and amygdaloid inputs form a complex mosaic of overlapping and interdigitating projections, in part related to cellular and immunohistochemical heterogeneities in the receiving striatal tissue (Pennartz et al. 1994; Groenewegen et al. 1999b; Voorn et al. 2004).

2.3.2 Cortical Inputs

Inputs from the prefrontal cortex are derived from all cortical subareas and display a clear topographical relationship with different parts of the striatal complex (Fig. 2.3). The most ventral areas of the medial prefrontal cortex, i.e., the medial orbital and infralimbic areas, project to the ventromedial parts of the striatal complex, including the medial shell of the nucleus accumbens, the medial parts of the olfactory tubercle, and the ventromedial part of the caudate-putamen complex at the inferior tip of the lateral ventricle. The medial orbital and infralimbic cortices form the cortical node of the endocrine parallel corticostriatal loop by way of its efferents to various areas in the lateral hypothalamus (Kelley 1999). The prelimbic cortex and the more dorsally situated ventral and dorsal anterior cingulate areas project to successively more lateral and dorsal zones of the caudate-putamen, extending into the dorsal core of the nucleus accumbens (e.g. Berendse et al. 1992; Voorn et al. 2004) (Fig. 2.3). The laterally located ventral and dorsal agranular insular areas of the prefrontal cortex project to laterally situated regions in the ventral part of the striatal complex. The ventral agranular insular area reaches the lateral part of the olfactory tubercle and the lateral shell of the nucleus accumbens; the dorsal agranular insular area entertains the more dorsally located core of the nucleus accumbens and the adjacent ventral caudate-putamen (Berendse et al. 1992) (Fig. 2.3). The orbital cortical areas located in the ventral part of the frontal lobe likewise show a medial-to-lateral topography in their projections to the striatum, and these projections extensively overlap with the projections from the medial and lateral prefrontal areas mentioned above (Schilman et al. 2008; Groenewegen and Uylings 2010) (Fig. 2.3). The most dorsolateral part of the caudate-putamen is not reached by prefrontal afferents, but is innervated by the somatosensory cortices. The functionally different striatal zones, defined on the basis of the topography of the projections from functionally different (pre)frontal cortical areas (Fig. 2.3), give rise to topographically organized striatopallidal and striatonigral projections, which via their associated thalamic nuclei lead back to functionally related parts of the (pre)frontal cortex, thus forming the well-known parallel basal ganglia-thalamocortical circuits.

Fig. 2.3 (continued) projection area is represented in **E** and **F** with a *stippled line*. The ventrolateral and lateral orbital areas both project quite strongly to the most lateral part of the shell of the nucleus accumbens. In **C** and **E**, shell and core are delineated with *stippled lines* (*black* in **C** and *white* in **E**). *ac* anterior commissure, *ACd* dorsal anterior cingulate cortex, *AId* dorsal agranular insular cortex, *AIv* ventral agranular insular cortex, *DLO* dorsolateral orbital cortex, *FR2* frontal area 2, *IL* infralimbic cortex, *LO* lateral orbital cortex, *MO* medial orbital cortex, *PFC* prefrontal cortex, *PLd* dorsal prelimbic cortex, *PLv* ventral prelimbic cortex, *VLO* ventrolateral orbital cortex, *VO* ventral orbital cortex

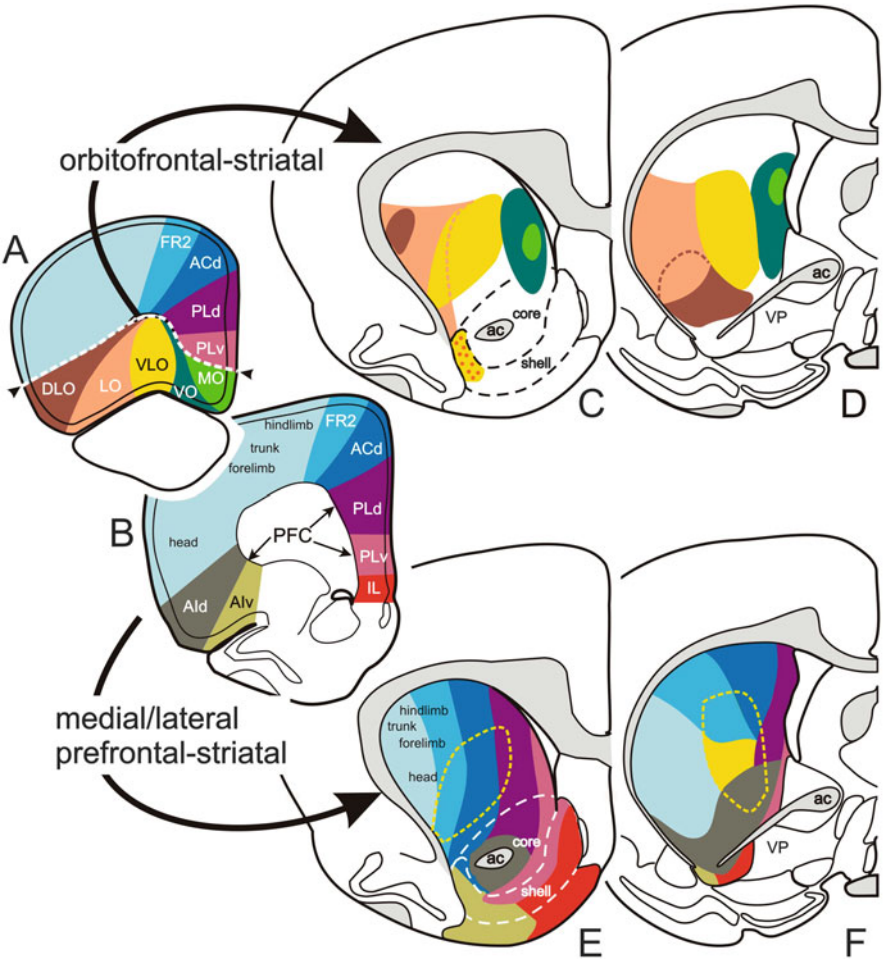

Fig. 2.3 Schematic drawing summarizing the topographical arrangement of the cortico-striatal projections originating in the orbital prefrontal cortex (**A**, **C**, **D**) and the medial and lateral prefrontal cortices (**A**, **B**, **E**, **F**). The prefrontal cortical areas and their connectionally related striatal targets are coded in the same color. Since there is a considerable overlap between the orbital projections on the one hand (**C**, **D**) and the medial and lateral prefrontal projections on the other hand (**E**, **F**), these projections are represented in two different sets of a rostral and a caudal striatal level. As shown in (**E**) and (**F**), the dorsolateral striatum receives somatotopically organized inputs from the sensorimotor cortices (*light blue*), the most ventromedial part of the striatum collects inputs from the infralimbic and ventral prelimbic areas (*red* and *purple*). Striatal areas intermediate between these extremes receive projections from the dorsal prelimbic, anterior cingulate, and Fr2 areas. The ventral agranular insular area projects to the lateral shell and adjacent olfactory tubercle, while the dorsal agranular insular area sends fibers to the core (**E**) and a broad mediolateral zone in the ventral caudate-putamen more caudally (**F**). Although the global relationships between the projection areas from different medial and lateral prefrontal cortices are maintained from rostral to caudal, the relative space occupied by the projections from various cortical areas changes from rostral to caudal (compare **E** and **F**). The orbital prefrontal projection areas in the striatum show a medial-to-lateral topographical organization (**C**, **D**). The medial and ventral orbital areas overlap considerably in the medial part of the striatum, while the lateral and dorsolateral orbital areas overlap quite extensively in the lateral part of the striatum (*stippled lines*). In an intermediate position, in the central part of the caudate-putamen, lies the projection area of the ventrolateral orbital area. To show the overlap of the ventrolateral orbital projection with the projections of the medial and lateral prefrontal areas, the ventrolateral

It must be realized that the representation of the topographical organization of the prefrontal corticostriatal projections as represented in Fig. 2.3 is a schematic one, aimed to present an 'easy' understandable overview, emphasizing the ventromedial-to-dorsolateral organizational aspect in the limbic-to-cognitive-to-motor corticostriatal afferent systems. Yet, overlap between the projections from (pre)frontal cortical and parietal, occipital, and temporal cortical areas at the level of the striatum also provides the anatomical substrate for interactions and integration of information between and within these circuits. With respect to prefrontal and orbitofrontal corticostriatal projections, it has recently been shown that there is more extensive and also specific overlap between individual prefrontal corticostriatal projections than previously assumed (Mailly et al. 2013) (Fig. 2.4 dealt with below). This is primarily based on the fact that two patterns of corticostriatal projections can be distinguished. Thus, all prefrontal cortical areas have a primary, 'focal' striatal target area in which dense projections from that particular cortical area terminate, as well as a quite extensive more 'diffuse' terminal field that is distributed along the borders of the focal terminal field in the striatum, expanding the striatal area that is reached by a particular cortical area. It is important to note that the relative extension of the dense and diffuse areas is not related to the extent of the injection sites in the cortex, but is primarily related to the identity of the injected cortical area. Such dual mode of corticostriatal innervation observed following the tracing of the projections of defined cortical regions, involving large collections of neurons in different layers, may be reminiscent of the patterns of axonal arborizations observed at a single cell level (Kincaid and Wilson 1996; Zheng and Wilson 2002). Thus, some corticostriatal neurons provide a high density of terminals in a small striatal volume, whereas others have a low background innervation. These two modes of corticostriatal innervation appear to originate from distinct cortical layers (Kincaid and Wilson 1996; Zheng and Wilson 2002; cf also Wright et al. 1999). Whether this is indeed the case for the dense and diffuse projections originating in the prefrontal cortex needs to be further established and would be of functional interest since different layers of the cortex receive functionally different inputs (Calzavara et al. 2007; Haber and Calzavara 2009; Mailly et al. 2013).

Fig. 2.4 (continued) projection areas are represented. Both the degree of overlap between the projections from different cortical areas as well as their 'private' areas can be appreciated and is quantitatively shown in (**C**). (**C**) Using the methodology described in Mailly et al. (2010), the volumes of overlap between the focal projections of the nine different cortical areas have been calculated. The pie charts give a quantitative representation of these volumes of overlap. In each case, the portions of the pie chart represent the amount of the focal projection field from a given cortical area that is overlapped by the focal projection fields from the other cortical areas. The portion of the pie chart represented with the color code of the reference area indicates the 'private' part of the focal projection field remaining *segregated* from the focal projection fields of all other areas. Notable is the lack of complete overlap for the focal projections (**B**) and the rather limited portion of the projection remaining segregated from other cortical focal projection areas (**C**). Color codes: DLO (*purple*), VLO (*green*), PL (*yellow*), MOVO (*red*), ACd (*orange*), IL (*brown*), ACv (*cyan*), AID (*magenta*), and FR2 (*blue*). *ACd* dorsal anterior cingulate cortex, *ACv* ventral anterior cingulate cortex, *AID* dorsal agranular insular cortex, *cc* corpus callosum, *DLO* dorsolateral orbital cortex, *FR2* frontal area 2, *IL* infralimbic cortex, *MOVO* medial orbital and ventral orbital cortices, *PL* prelimbic cortex, *VLO* ventrolateral orbital cortex. Adapted from figures 1 and 6 in Mailly et al. (2013)

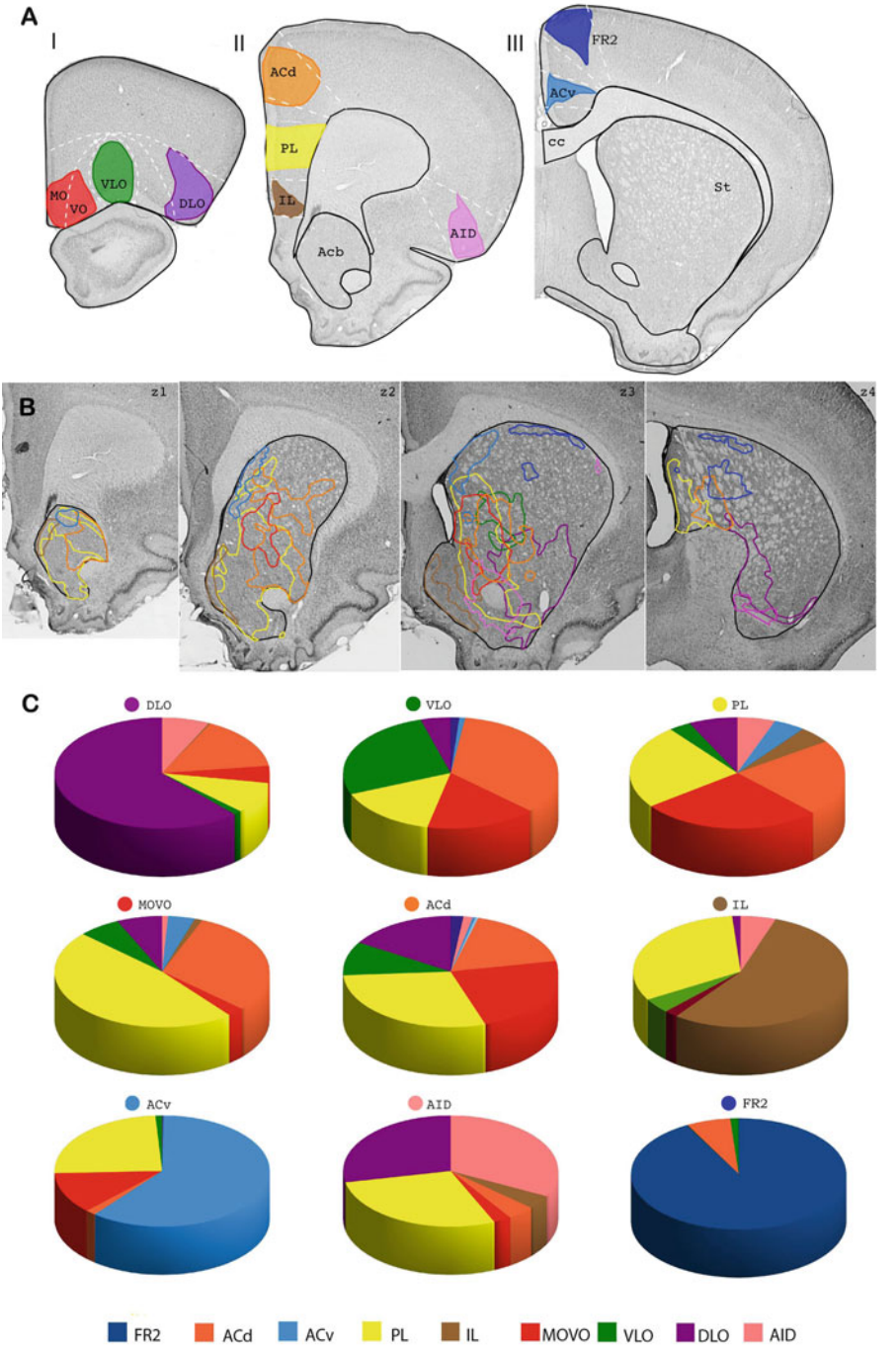

Fig. 2.4 Patterns and degree of overlap of the cortico-striatal projections from nine cytoarchitectonically different prefrontal cortical areas. (**A**) Location and extent of injection sites of anterograde tracers in the prefrontal cortex, represented in three transverse sections (arranged rostral [I] to caudal [III]) and color-coded as a reference for (**B**) and (**C**). (**B**) In four transverse Nissl-stained sections through the striatum (arranged rostral [z1] to caudal [z4]), the outer borders of the focal

The diffuse terminal fields in most cases have a particular orientation with respect to the dense terminal area and are thus not necessarily globally distributed around the primary terminal field. The focal projections of individual prefrontal cortical areas show varying degrees of overlap with each other, but all prefrontal areas have their own 'private' target area largely preserving the previously described ventromedial to dorsolateral topographical organization of prefrontal-striatal projections (Voorn et al. 2004; Groenewegen and Uylings 2010). Figure 2.4 shows that, considering the patterns and degree of overlap between the focal projections areas, the extent of the 'private' area may vary considerably. Thus, the medial and ventral orbital areas appear to have the most restricted 'private' striatal territory, since their projections show an extensive overlap with the projections from other prefrontal areas. Conversely, the FR2 area has the least overlap with other prefrontal projections and has the most extensive 'private' area (Fig. 2.4B, C). It is noteworthy that there appears to be a high degree of overlap between the projections from adjacent prefrontal areas in the rostral part of the caudate-putamen, while these projection areas gradually segregate in caudal parts of the caudate-putamen complex (Mailly et al. 2013) (Fig. 2.4B). It will be clear that the diffuse corticostriatal projections in most cases show an even more extensive overlap with the 'focal plus diffuse' projection areas of neighboring and/or interconnected cortical areas and provide in this way a further means of convergence and integration (e.g. Reep et al. 2003; Haber et al. 2007; Calzavara et al. 2007; Asher and Lodge 2012; Mailly et al. 2013). In summary, besides segregated projections consistent with parallel processing, the overlapping projection territories establish specific patterns of integration spatially organized along the dorsoventral, mediolateral, and anteroposterior striatal axes. More specifically, the extensive striatal projection fields from the prelimbic and anterior cingulate areas, which partly overlap the terminal fields from medial, orbital, and lateral prefrontal cortical areas, provide putative domains of convergence for integration between reward, cognitive, and motor processes (Mailly et al. 2013).

As indicated already above, particular layers of the prelimbic area in both rats (Gerfen 1992; Berendse et al. 1992) and primates (Eblen and Graybiel 1995) project rather selectively to the striatal patches of a rather wide area of the limbic and associative striatum (not represented in the present figures). This arrangement also provides an anatomical basis for the integration of emotional-motivational aspects into cognitive processes (Friedman et al. 2015).

2.3.3 Subcortical Inputs

Subcortical inputs to the limbic striatum are derived from various nuclei.

The *thalamic midline and intralaminar nuclei* project densely and in a topographical manner to the striatal elements of the olfactory tubercle, the nucleus accumbens, and the ventromedial part of the caudate-putamen complex (Groenewegen and Berendse 1990; Smith et al. 2004, 2009). Although also some of the specific relay nuclei of the thalamus, such as the ventral anterior and mediodorsal nuclei, send fibers to the striatum, these projections are much sparser. The midline paraventricular

nucleus targets primarily the shell of the nucleus accumbens as well as the patches in the adjacent parts of the core of the accumbens and the ventromedial part of the caudate-putamen (Berendse and Groenewegen 1990; Smith et al. 2004, 2009; Vertes et al. 2015). The intermediodorsal thalamic nucleus projects more extensively to the nucleus accumbens core and adjacent caudate-putamen. The central medial, paracentral, and central lateral nuclei in the intralaminar thalamic complex distribute to successively more dorsal and lateral parts of the caudate-putamen. The anterior part of the parafascicular nucleus projects to the ventral striatum, while its posterior part targets the caudate-putamen (Berendse and Groenewegen 1990; Smith et al. 2004, 2009). An important aspect in the organization of the thalamostriatal projections is that there appears to be a 'triadic' relationship between midline/intralaminar thalamus, (pre)frontal cortex, and striatum: an individual thalamic nucleus projects to both a prefrontal cortical area and a region in the striatum which in turn are connected by corticostriatal projections. The midline and intralaminar thalamic nuclei are in this way able to influence the transfer of information through the cortical–basal ganglia circuits both at the cortical and at the striatal level (Groenewegen and Berendse 1994; Smith et al. 2009). Interestingly, thalamic afferents of the striatum target preferentially the striatal cholinergic interneurons (Gonzales et al. 2015; Gonzales and Smith 2015; see also below).

Other subcortical inputs to the limbic striatum are derived from return projections from the *ventral pallidum* and dorsally adjacent regions of the *ventromedial globus pallidus* (in rats this nucleus is considered to be the equivalent of the external segment of the pallidum in primates). These ventral pallidal projections are roughly topographically organized, aiming at a striatal area that is somewhat wider than the area from which they receive projection. Furthermore, pallidostriatal fibers terminate on medium-sized spiny output neurons, but also, and rather specifically, on fast-spiking GABAergic, parvalbumin-expressing interneurons in the striatum (Bolam et al. 2000; Voorn 2010; see also below). The caudomedial part of the shell of the nucleus accumbens receives inputs from parts of the *extended amygdala* in the basal forebrain, including the bed nucleus of the stria terminalis. This part of the shell may be considered as a transitional zone between the striatum and the extended amygdala (Zahm 2000). Further inputs are derived from the preoptic-lateral hypothalamic region, afferents that primarily reach the shell of the nucleus accumbens (Brog et al. 1993; Zahm and Brog 1992).

Limbic striatal afferents from the brainstem are primarily derived from *monoaminergic cell groups,* of which the dopaminergic cell groups in the ventral mesencephalon have been most extensively studied. In a recent analysis of the organization of the ascending dopaminergic projections to the ventral striatum, including primarily the nucleus accumbens' core and shell and the striatal elements of the olfactory tubercle, Ikemoto (2007) concluded that the caudomedial dopaminergic nuclei in the ventral tegmental area (VTA) project to the medial shell and medial olfactory tubercle, while more rostrolateral nuclei in the VTA project to the lateral shell and olfactory tubercle, dissociating these two striatal regions from each and from the nucleus accumbens core. The latter accumbal region receives its dopaminergic input from slightly more laterally located dopaminergic neurons in the rostral VTA and adjacent substantia

nigra pars compacta (Ikemoto 2007). The dopaminergic cell groups projecting to lateral shell/olfactory tubercle and to the accumbens core show a considerable degree of overlap. The interpretation of these data, together with a host of pharmacobehavioral data, is that the striatal elements of the olfactory tubercle form a continuum with the accumbens shell and that, for both structures, a mediolateral distinction is apparent (Ikemoto 2007). Lammel et al. (2012) showed that dopaminergic neurons located in the medial VTA, projecting to the medial shell and core as well as to the medial prefrontal cortex, have fast-firing properties, while the more lateral VTA dopamine neurons, projecting to the lateral shell and dorsal striatum, show the more conventional type of lower firing rates. It should further be noted that the VTA projections to the nucleus accumbens are rather heterogeneous, including not only pure dopaminergic fibers, but also dopamine afferents with glutamate or GABA as co-transmitters, as well as pure GABAergic and glutamatergic inputs (cf. Chuhma et al. 2014). In further detail, the degree of heterogeneity of the dopamine neuron transmission is further exemplified by the fact that dopaminergic fibers to medium-sized spiny neurons in the medial shell of the nucleus accumbens use glutamate as a co-transmitter, while this is not the case in the caudate-putamen (Hnasko et al. 2010; Stuber et al. 2010). However, dopaminergic fibers in the caudate-putamen that contact medium-sized spiny neurons may use GABA as a co-transmitter (Tritsch et al. 2012). Furthermore, some of the VTA GABAergic fibers rather selectively target the cholinergic interneurons in the accumbens (Chuhma et al. 2009; Van Zessen et al. 2012; Brown et al. 2012; Taylor et al. 2014). This heterogeneity in the ascending ventral mesencephalic projections to the forebrain, including the ventral striatum, might be an important clue to a better understanding of the great variety of functions in which the ventral striatum is involved, from reward- to aversive-guided behavior (Carlzon and Thomas 2009; Lammel et al. 2014).

With respect to the *serotonergic system*, there appear to be two structurally and functionally distinct projections to the ventral striatum. Serotonergic fibers that reach the most extensive part of the ventral striatum, i.e., the accumbens' lateral shell and core and the ventromedial part of the caudate-putamen, consist of fibers with small varicosities and boutons expressing the serotonin transporter. In contrast, the caudomedial shell receives serotonergic fibers displaying larger varicosities that lack the expression of the serotonin transporter (Brown and Molliver 2000). *Noradrenergic fibers* reaching the ventral striatum almost exclusively target the caudomedial shell of the nucleus accumbens and these fibers originate from the locus coeruleus (A1 region) and, in particular, the nucleus of the solitary tract (A2 region) (Berridge et al. 1997; Delfs et al. 1998).

Thus, the medial shell of the nucleus accumbens receives the densest and most diverse monoaminergic modulatory inputs, and this region is also rich in hippocampal and amygdaloid inputs (Fig. 2.2; cf. also Kerfoot et al. 2008). More dorsally and laterally along the ventromedial-to-dorsolateral axis, serotonin and dopamine are both present in the intermediate striatal part, while the dorsolateral striatal area is primarily innervated by dopamine (Voorn et al. 2004; Ikemoto 2007).

Cholinergic fibers in the striatum have long been thought to be exclusively derived from intrinsic striatal cholinergic interneurons. Recent findings, however, demonstrate that there are also extrinsic cholinergic projections to both the dorsal

and ventral striatum, originating in the pedunculopontine and laterodorsal tegmental nuclei of the brainstem, respectively (Dautan et al. 2014). The cholinergic neurons in the laterodorsal tegmental nucleus also send collaterals to the thalamus and the dopaminergic cell groups in the ventral mesencephalon, in this way providing different ways of cholinergic modulation of ventral striatal information processing. However, the extrinsic and intrinsic striatal cholinergic systems are thought to play differential and complementary roles in the processing of reward-related information in the striatum (Dautan et al. 2014).

2.3.4 Distribution of Glutamate and GABA Transporters in the Striatum

In a recent study, Wouterlood et al. (2012) analyzed the distribution of glutamate and GABA transporters in the striatum. There appear to be gradients in the densities of the glutamate transporters VGluT1 and VGluT2, known to originate from the cerebral cortex and the thalamus, respectively, as well as the GABA transporter. These gradients could only in part be related to the known distribution of afferents with an identified expression of either VGluT1 or VGluT2. The density of VGluT1 transporters, expressed in corticostriatal fibers, increases along the ventrolateral-to-dorsomedial axis in the striatum. Thus, in striatal regions primarily innervated by insular cortical areas, the density of VGluT1 transporters is much lower than in the dorsomedial striatum, which is innervated by the anterior cingulate and dorsal prelimbic cortices (Fig. 2.3). The axis of the gradient in the density of VGluT2 transporters is perpendicular to that of the VGluT1 transporters, i.e., dense ventromedially and decreasing towards the dorsolateral striatum. VGluT2 transporters are associated with thalamic, but also with amygdaloid and hippocampal afferent fibers. Thus, the medial shell, which receives the highest density of amygdaloid and hippocampal inputs, as well as a very dense input from the thalamic paraventricular and anterior parafascicular nuclei, shows the highest density of VGluT2 transporters. In contrast, the dorsolateral striatum, receiving virtually no limbic inputs, has the lowest density of VGluT2 transporters. The functional significance of these differences in densities of glutamate transporters remains to be established.

2.4 Intrinsic Striatal Circuitry

Before discussing the efferent connections of the ventral striatum, it is of interest to discuss the role of the striatal interneurons in the translation of the cortical and subcortical inputs into the ventral striatal output. The midbrain dopamine neurons in synchrony with cortex and thalamus specifically innervate the striatal interneurons as an intermediary target before the GABAergic medium-sized spiny projection neurons are reached. Striatal interneurons belong to various subclasses of GABAergic and cholinergic cells that amount to less than 5 % of the striatal neuronal population.

2.4.1 Cholinergic Interneurons

The largest neurons in the striatum are the giant aspiny cholinergic interneurons, comprising less than 1 % of the striatal neurons in rats, and these neurons are electrophysiologically described as tonically active neurons (TANs). Their dense and widespread local axon collateral plexus is largely restricted to the striatal matrix where the axons primarily target the medium-sized spiny projection neurons. Furthermore, due to their very extensive dendritic and axonal network, each interneuron may contact and mutually interact with several hundreds of these striatal projection neurons. The cholinergic interneurons receive direct afferents from dopaminergic cells as well as glutamatergic afferents from cortical sources, a very dense innervation from intralaminar thalamic nuclei, and a GABAergic input from medium-sized spiny projection neurons (Tepper and Bolam 2004; Meredith and Wouterlood 1990; Lapper and Bolam 1992; Chuhma et al. 2014; Gonzales et al. 2013; Gonzales and Smith 2015). The activity of the striatal cholinergic interneurons is very important for the global function of the striatal systems and their specific pattern of neuronal firing activity is to a large degree dependent on the excitatory NMDA receptor-mediated glutamatergic thalamic inputs and the more sparse cortical AMPA glutamatergic input (Lapper and Bolam 1992; Ding et al. 2010). In their extensive review, Gonzales and Smith (2015) discussed current knowledge on their complicated receptor modulations of afferent and efferent connections and their important role in the dorsal and ventral striatal systems in conditional reinforcement learning, drug addiction, and in Parkinson's disease.

Cholinergic interneurons modulate via excitatory nicotinic and neuromodulatory muscarinic receptors the sub- and suprathreshold responses of medium-sized spiny output neurons (Chuhma et al. 2014; Gonzales et al. 2015). The interactions of the cholinergic axons also overlap with the extrinsic dopaminergic terminals and it has long been known that these two systems have synchronized reciprocal relationships within the striatum (Chuhma et al. 2014; Threlfell and Craig 2011). The thalamic- and cortical-induced burst firing activity of the TANs leads to a nicotinic receptor-mediated local dopamine release from the dopamine terminals, to be followed by a dopamine-mediated inhibitory control via dopamine D2 receptors localized directly on the cholinergic neurons. Additional inhibitory control of the TANs is mediated by inhibitory muscarinic receptors and the induced GABA release from medium-sized spiny neurons. Of specific interest is that the cholinergic interneurons in the nucleus accumbens are in addition controlled by a direct inhibitory input from midbrain ventral tegmental GABAergic neurons (Brown et al. 2012). The reader is referred to Chap. 5 for a more detailed discussion of the functional role of striatal cholinergic interneurons.

It has been shown that the dopamine-acetylcholine interactions occur at different levels, through pre- and postsynaptic actions. These interactions may vary in the context of the dynamic changes in firing patterns of either the dopaminergic or the cholinergic neurons (Threlfell and Craig 2011). For example, cholinergic neurons have been shown to display strong burst-pause-burst patterns of firing during contextual cue-induced

learning. Following a phase of a high intensity of bursting, the nicotinic receptors mediating the local dopamine terminal release show desensitization, to be followed by a drop in the dopamine release and a concomitant decrease of the D2 receptor-mediated inhibitory control of the TANs. After a short pause, the nicotinic receptors recover and the dopamine release may return. The local striatal dopamine release, which is crucial for habit learning, is by this mechanism of action dependent on the glutamatergic midline and intralaminar thalamic input to the cholinergic interneurons. Thus, striatal dopamine release may by this mechanism of action be indirectly controlled by sensory contextual cues from the thalamus and influenced by the cortex (Ding et al. 2010; Doig et al. 2010; Chuhma et al. 2014; Threlfell and Craig 2011; Aosaki et al. 2010).

Interestingly, some VTA dopaminergic neurons use glutamate or GABA as co-transmitters to directly and immediately influence the firing of cholinergic interneurons with a regional specificity. Thus, within the medial shell, dopamine and glutamatergic neurons drive a burst-pause firing sequence. In contrast, in the dorsal striatum, dopamine and its co-transmitter GABA induce a pause in firing in cholinergic neurons. In the core of the nucleus accumbens, there is a mixed reaction to this activity of the dopaminergic neurons (Chuhma et al. 2014). The mutual interaction between cholinergic and dopamine activity subserves by this regional differentiation a target-specific functional modulation for the dorsal and ventral striatal output channels (Threlfell and Craig 2011; Chuhma et al. 2014).

The activation of the cholinergic interneurons drives inhibitory GABAergic responses in the medium-sized spiny striatal projection neurons. In a series of elegant studies using optogenetic methods, Nelson et al. (2014) showed that activation of striatal cholinergic neurons triggers a disynaptic inhibitory synaptic response in medium-sized spiny neurons mediated in large part by the cholinergic nicotinic activation of GABA release from striatal dopamine terminals. The striatal cholinergic interneurons are thus via nicotinic acetylcholine receptors able to influence striatal neuronal output by dual control of dopamine and GABA release.

Acetylcholine neurotransmission in the nucleus accumbens contributes to contextual cue learning. In the context of drug addiction, it has been shown that acetylcholine transmission in the accumbens inhibits cue-induced heroin reinstatement (Zhou et al., 2007) and modulates cocaine self-administration (review: Gonzales and Smith 2015).

2.4.2 GABAergic Interneurons

The striatal GABA interneurons constitute only a small percentage (less than 3–4 %) of the total striatal neuronal population, but provide nevertheless very important functions in basal ganglia. There exist two major GABAergic interneuron populations, i.e., persistent low-threshold (PLT) and fast spiking (FS) interneurons, which differ substantially in their excitatory inputs and inhibitory outputs (Gittis et al. 2010). The fast spiking parvalbumin-containing GABAergic interneurons project strongly to the medium-sized spiny neurons (Taverna et al. 2007) and target hundreds of striatal

output neurons with a certain preference for neurons of the direct striatal output path (Gittis et al. 2010). Furthermore, the fast spiking interneurons also form GABAergic synapses onto other fast spiking interneurons, but not on the other subpopulations of striatal interneurons (Gittis et al. 2010). Fast spiking interneurons respond with preference to cortical stimulation via AMPA receptors in favor of the medium-sized spiny output neurons (Parthasarathy and Graybiel 1997; Ramanathan et al. 2002; Mallet et al. 2005). Interactions between GABAergic medium-sized spiny neurons are relatively sparse (e.g. Taverna et al. 2007; Turnstall et al. 2002) and the inhibitory control of the striatal output thus appears to arise from the fast spiking interneurons. The strong perisomatic GABAergic synapses of the fast spiking interneurons onto hundreds of striatal output neurons provide mechanisms for synchronized regional lateral inhibition (Bennett and Bolam 1994; Gittis et al. 2010). Through cortically induced feed-forward inhibitory mechanisms, the fast spiking GABAergic interneurons play an important role in the selection of populations of striatal output neurons, a mechanism which is supposed to be the basis for action selection and suppression of unwanted actions via the dopamine D1 and D2 output channels (direct and indirect pathway, respectively) (Parthasarathy and Graybiel 1997; Gage et al. 2010). A strong inhibitory feedback from a subpopulation of pallidal neurons rather selectively onto the proximal parts of the fast spiking parvalbumin positive interneurons may also be crucial for this mechanism (Bennett and Bolam 1994; Bolam et al. 2000; Voorn 2010). In this context, it is of interest to note that decreased numbers of striatal fast spiking interneurons are suggested to be associated with Tourette syndrome (Kalanithi et al. 2005), dystonia (Gernert et al. 2000), and have also been hypothesized to amplify imbalances in striatal output in Parkinson's disease (Mallet et al. 2006).

The persistent low-threshold GABAergic interneurons receiving NMDA and AMPA receptor glutamatergic innervation (Gittis et al. 2010) may contain various neuropeptides, such as NPY, somatostatin, and nitric oxide. Their efferent connections are relatively sparse, but they are found in close proximity to glial cells and blood vessels (Aoki and Pickel 1990) and have been suggested to be potential candidates for regulating blood flow or glial signaling in the striatum.

Like the medium-sized spiny neurons, the GABAergic interneurons receive excitatory inputs from the cerebral cortex, thalamus, amygdala and hippocampus, inhibitory inputs from the pallidum, and are modulated by the monoamines dopamine, serotonin, and noradrenaline.

2.5 Efferent Connections of the "Limbic" Striatum

2.5.1 Ventral Striatal Efferents

The efferent projections of the ventral, limbic striatum to a large degree parallel those of the dorsal striatum, i.e., they reach the ventral pallidum, ventral parts of the globus pallidus, the most medial part of the entopeduncular nucleus (which in rats is considered the homologue of the primate internal segment of the globus pallidus)

together with the medially adjacent part of the lateral hypothalamus, and the substantia nigra pars reticulata (e.g. Heimer et al. 1991). However, the limbic striatum as a whole reaches more targets in the diencephalon and brainstem than the dorsal striatum, albeit that there appear to be considerable regional differences. Thus, the projections of the striatal elements of the olfactory tubercle are rather restricted and do not reach farther than the ventral pallidum, i.e., to those parts that extend rostrally from the main body of the ventral pallidum as 'fingers' into the deep layers of the olfactory tubercle, and to the most ventral parts of the subcommissural part of the ventral pallidum. By contrast, the medial shell has the most widespread target areas (Heimer et al. 1991; Kelley 1999; Zahm 2000; Zahm et al. 2013). Thus, the medial shell projects to parts of the extended amygdala, including the bed nucleus of the stria terminalis, the ventromedial parts of the ventral pallidum, the lateral preoptic area, and the lateral hypothalamus along the course of the descending accumbal shell fibers. In the mesencephalon, fibers from the medial shell target the VTA and dorsal parts of the substantia nigra pars compacta and continue caudodorsally to reach the retrorubral field and lateral and dorsal parts of the mesencephalic tegmentum, including the lateral part of the periaqueductal grey matter, the midbrain extrapyramidal area, i.e., a region close to the pedunculopontine nucleus and most likely part of the midbrain locomotor area (Nauta et al. 1978; Rye et al. 1987; Heimer et al. 1991; Groenewegen et al. 1999a; Zahm 2000; Tripathi et al. 2010; Sherman et al. 2015). In turn, the lateral shell of the nucleus accumbens has somewhat more restricted targets that include the ventrolateral part of the ventral pallidum, the lateral hypothalamus, and the VTA. The terminals of the lateral shell are generally located more laterally in the target areas than to those of the medial shell.

Based on the pattern of its efferent projections to the bed nucleus of the stria terminalis as well as to the lateral preoptic and lateral hypothalamic areas, the caudal part of the dorsomedial shell has been considered as a striatal zone in transition with the extended amygdala (Alheid and Heimer 1988). More recently, Zahm and colleagues have argued that a more rostral part of the medial shell, i.e., the 'hedonic hotspot' of Peciña and Berridge (2005), forms a striatal zone in transition with the lateral septum (Zahm et al. 2013). These authors emphasize that transitional zones in boundary areas of the basal forebrain are important for the understanding of the complex functions of the basal forebrain.

Projections from the core of the nucleus accumbens target the dorsal subcommissural part of the ventral pallidum, the medial parts of the entopeduncular and subthalamic nuclei, and the dorsomedial part of the substantia nigra pars reticulata (Heimer et al. 1991; Tripathi et al. 2010). The ventromedial part of the caudate-putamen, located just dorsal to the core of the nucleus accumbens, projects to the dorsal globus pallidus and the entopeduncular nucleus, just dorsal and lateral to the projections of the nucleus accumbens core, respectively. Likewise, in the pars reticulata of the substantia nigra, the ventromedial caudate-putamen fibers terminate more laterally and ventrally than those from the accumbens core. In a recent single axon tracing study, Tripathi and colleagues (2010) largely confirmed this pattern of topographical projections and further showed that there is overlap between core and shell efferent terminals in several target areas, such that core fibers tend to innervate

terminal regions of the shell in the ventral pallidum and substantia nigra. Core projections to the ventral pallidum consist of both short axons terminating in this nucleus and long range axons that give off terminals in the ventral pallidum on their way to more caudal targets. Their results also confirm that intrastriatal axons connect core and shell with each other with a dominance for core projections to the shell (Van Dongen et al. 2005; Tripathi et al. 2010).

The output pathways of the striatum are generally divided into a direct pathway and an indirect pathway that both lead ultimately from the striatum to the output nuclei of the basal ganglia, i.e., the internal segment of the globus pallidus (entopeduncular nucleus in rodents) and the reticular part of the substantia nigra. The striatal neurons giving rise to the monosynaptic direct pathway express the D1 receptor and the neuropeptides substance P and dynorphin. Activation of this pathway, for example through corticostriatal inputs, disinhibits, via the entopeduncular nucleus and substantia nigra reticulata, the target nuclei of the basal ganglia such as various thalamic nuclei and the superior colliculus. The indirect striatal output pathway first leads to the external segment of the globus pallidus, subsequently to the subthalamic nucleus, which in turn projects to internal segment of the globus pallidus and the reticular substantia nigra, i.e., the basal ganglia output nuclei. The striatal neurons giving rise to this indirect pathway express the D2 receptor and the opioid peptide enkephalin. Activation of this pathway leads to a disinhibition of the subthalamic nucleus, which through its glutamatergic action leads to a higher neuronal activity of the GABAergic output nuclei (review see: Dudman and Gerfen 2015). Whereas activation of the direct pathway results in the expression of motor and cognitive programs at the level of the (pre)frontal cortex, the indirect pathway, which is through its multitude of connections with other structures (not mentioned above) also considered as the 'indirect network', has a more modulatory role in the expression of these programs, probably by inhibiting competing cognitive outcomes and motor actions (Mink 1996; Redgrave et al. 1999; Bolam et al. 2000). Finally, a 'hyperdirect' pathway exists that involves direct excitatory projections from the frontal cortex to the subthalamic nucleus (Nambu et al. 2002; Haynes and Haber 2013). The activation of this pathway will lead to a higher level of activity of the GABAergic projections from the basal ganglia output nuclei and the suppression of motor programs.

Although the ventral striatum does not significantly differ from the dorsal striatum with respect to the content of two populations of striatal output neurons, the clear segregation of direct and indirect output pathways as described above has been a matter of dispute. The ventral pallidum cannot be easily divided into an internal and an external segment, but seems to be a mixture of both. It has a direct output to the mediodorsal thalamus, but also projects to the medial part of the subthalamic nucleus and receives projections back from this nucleus (Groenewegen and Berendse 1990; Groenewegen et al. 1996). This mixed characteristic of direct and indirect pathways in the ventral striatopallidal system also follows from recent electrophysiological and optogenetic studies that show that the projections from the nucleus accumbens core to both the ventral pallidum and the ventral mesencephalon consist of D1- and D2-expressing medium-sized spiny neurons (Kupchik et al. 2015). This implies that the output of the ventral pallidum to the mediodorsal thalamus may be modulated by

both D1- and D2-dopaminergic mechanisms acting at the level of the nucleus accumbens, leading to, respectively, disinhibition and inhibition of the thalamo-prefrontal cortical circuits. This is an important conclusion with respect to the regulation of motivated behavior, certainly also in the context of addictive behavior where the D2 receptor is decreased (Pennartz et al. 2009; Stefanik et al. 2013; Kupchik et al. 2015).

The projections from the ventral striatum to the ventral mesencephalon, in particular to the dopaminergic cell groups in VTA and substantia nigra pars compacta, deserve some further elaboration. As already noted by Nauta et al. (1978), efferents from the nucleus accumbens may in the ventral mesencephalon be in a position to influence the dopaminergic projections to both the ventral and the dorsal striatum. In primates, a spiral-like organization of the striato-mesencephalic-striatal projections has been proposed. This proposal was based on the observation that ventral striatal fibers reach medially located dopaminergic cell groups that project back to the striatal area of origin and, in addition, to more laterally located dopaminergic neurons that project to a more dorsally located striatal area (Haber et al. 2000). In several sequential ventral-to-dorsal steps, limbic striatal regions may influence via the dopaminergic system the associative striatal regions and in the latter, finally, the sensorimotor parts of the striatum (Haber et al. 2000; Voorn et al. 2004). Such step-by-step organization is less likely in rats since the ventral striatal efferents reach the dorsal tier of the substantia nigra, which contains neurons that directly project to extensive parts of the caudate-putamen, including the dorsolateral sensorimotor part (Fig. 2.5) (Van Dongen et al. 2009; Wouterlood et al., unpublished). Therefore, the ventral-to-dorsal striato-nigro-striatal pathway in rats appears to be less differentiated than in primates. The functional importance of these pathways is signified by their role in drug-addictive behavior. More specifically, by employing a disconnection procedure, Belin and Everitt (2008) demonstrated that the dopamine-mediated ventral-to-dorsal pathway is essential in the development and performance of cocaine-seeking behavior.

2.5.2 Ventral Striatopallidal Projections: The Extended Circuitry

Considering the limbic striatal projections in a more comprehensive perspective, it is important to discuss also the projections of a number of ventral striatal target areas, i.e., the ventral pallidum and the dopaminergic cell groups in the VTA. As schematically indicated in Fig. 2.5, projections from the ventral pallidum reach many of the targets that are also innervated by the ventral striatum, such as the lateral hypothalamus, the medial part of the subthalamic nucleus, the VTA and pars reticulata of the substantia nigra, as well as the more caudally located tegmental areas of the mesencephalon. In general terms, this could imply that these areas are under both the inhibitory and the subsequent disinhibitory influence of the ventral striatal and ventral pallidal projections, respectively. As suggested by Tripathi and colleagues (2010, 2013), the fact that single neurons in the nucleus accumbens send collaterals to the ventral pallidum as well as to other targets or “output nuclei” like

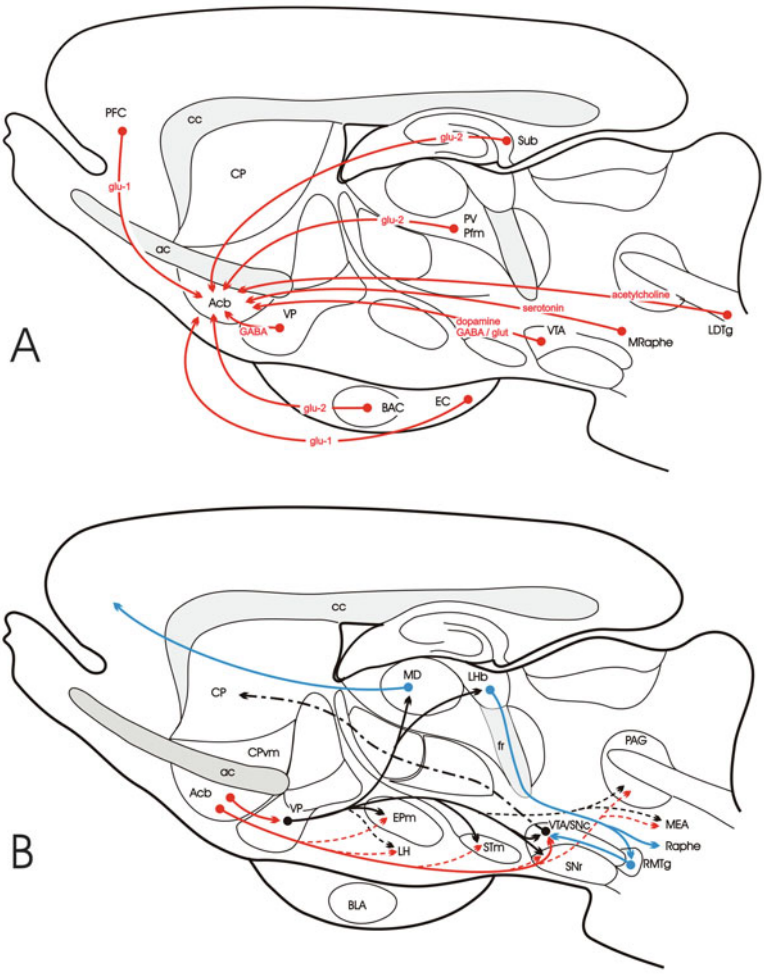

Fig. 2.5 Schematic representation of the main afferents (**A**) and efferents (**B**) of the ventral striatum. In (**A**) the neurotransmitters of the various afferents are indicated. For the glutamatergic projections, the expression of the vesicular glutamate transporter VGlut1 (glu-1) of VGlut2 (glu-2) is indicated. In (**B**) the ventral striatal projections are shown in *red*, the subsequent ventral pallidal projections in *black* (*dashed lines* for both indicate less strong projections). Furthermore, the projections from the lateral habenula to the various targets in the ventral mesencephalon are represented in *blue*, as well as those from the rostral mesencephalic tegmental nucleus to the VTA. The dopaminergic projections from the dorsal tiers of VTA/SNc to the dorsal striatum (caudate-putamen) are represented with a *dashed black arrow*. These projections represent the spiraling projections from the ventral striatum via the dopaminergic system to the dorsal striatum (Haber et al. 2000; Van Dongen et al., 2009). *ac* anterior commissure, *Acb* nucleus accumbens, *BAC* basal amygdaloid complex, *cc* corpus callosum, *CP* caudate-putamen, *CPvm* ventromedial part of CP, *EC* entorhinal cortex, *EPm* medial part of the entopeduncular nucleus, *fr* fasciculus retroflexus, *LH* lateral hypothalamus, *LHb* lateral habenula, *MD* mediodorsal thalamic nucleus, *MEA* midbrain extrapyramidal area, *MRaphe* median raphe nucleus, *PAG* periaqueductal grey matter, *PFC* prefrontal cortex, *PV* paraventricular thalamic nucleus, *VTA* ventral tegmental area, *RMTg* rostral mesencephalic tegmental nucleus, *SNc* pars compacta of the substantia nigra, *SNr* pars reticulata of the substantia nigra, *STm* medial part of the subthalamic nucleus, *Sub* subiculum, *VP* ventral pallidum, *VTA* ventral tegmental area

the lateral hypothalamus, the substantia reticulata, and the VTA, which are also targeted by ventral pallidal terminals, provides the basis for a possible mechanism of temporal inhibition through the direct collateral, and subsequent disinhibition of either individual or small sets of neurons, by the collateral to ventral pallidum and subsequent projection of pallidal axons. As these authors emphasize, this hypothetical neural scheme presupposes that the accumbal axon and the pallidal axon innervate the same individual or small set of neurons, which has still to be demonstrated. However, such ventral pallidal collateralization patterns would provide the anatomical basis at the single axon level for the multisystem integration that may take place in the basal forebrain to elicit an integrated response (Tripathi et al. 2013).

Significant projections from the ventral pallidum are directed to the mediodorsal thalamic nucleus, such that there is a clear topography in this 'limbic' pallidothalamic system. Ventromedial parts of the ventral pallidum project to the medial segment of the mediodorsal nucleus, more lateral and dorsal parts of the ventral pallidum to the lateral and paralamellar segments of the mediodorsal nucleus (Groenewegen 1988; Groenewegen et al. 1990; Zahm and Heimer 1990). The pallidal elements of the olfactory tubercle project to the central segment of the mediodorsal nucleus. Via this topographically arranged ventral pallidothalamic system, various limbic basal ganglia—thalamocortical circuits are remarkably and interestingly 'closed' with different prefrontal cortical areas that project to the limbic striatum (Voorn et al. 2004; Smith et al. 2004, 2009; however see also Joel and Weiner 1994). These projections form the basis for the 'limbic' basal ganglia-thalamocortical circuits with the prefrontal cortex (Alexander et al. 1986; Groenewegen et al. 1990).

Until quite recently, the output of the ventral pallidum to the lateral habenula has been largely neglected, as was the role and position of the lateral habenula in the circuitry of the basal ganglia more in general. The recently evoked interest in the differential projections from the lateral habenula to various nuclei in the ventral mesencephalon (e.g. Matsumoto and Hikosaka 2008; Hikosaka et al. 2014) make it of great interest to study in more detail the organization of the projections from the ventral pallidum to this structure. Previous studies have shown that the ventral pallidal terminations in the lateral habenula are relatively heavy (Groenewegen et al. 1993, 1999c; Fig. 2.6). To a large degree, the ventral pallidal fibers terminating in the habenula are collaterals of those fibers projecting also to the mediodorsal nucleus (Tripathi et al. 2013). The direct projections to the lateral habenula give the ventral striatopallidal system access, via the lateral habenular-mesencephalic projections, to the dopaminergic, serotonergic, and cholinergic cell groups in the mesencephalon, as well as to the recently described GABAergic rostromedial tegmental nucleus. The latter nucleus projects to dopaminergic neurons in the rostrally adjacent VTA (Geisler and Zahm 2005). Thus, as argued by Zahm and co-workers (Yetnikoff et al. 2015), the ventral striatopallidal system, together with a number of their target areas in the lateral preoptic and lateral hypothalamic areas, form a continuum that receives and integrates information from a wide array of prefrontal cortical areas and limbic structures such as the hippocampus and amygdala, and that reaches via the lateral habenula and via the rostromedial tegmental nucleus (RMTg) the dopaminergic and serotonergic cell groups in the midbrain. In other words, the

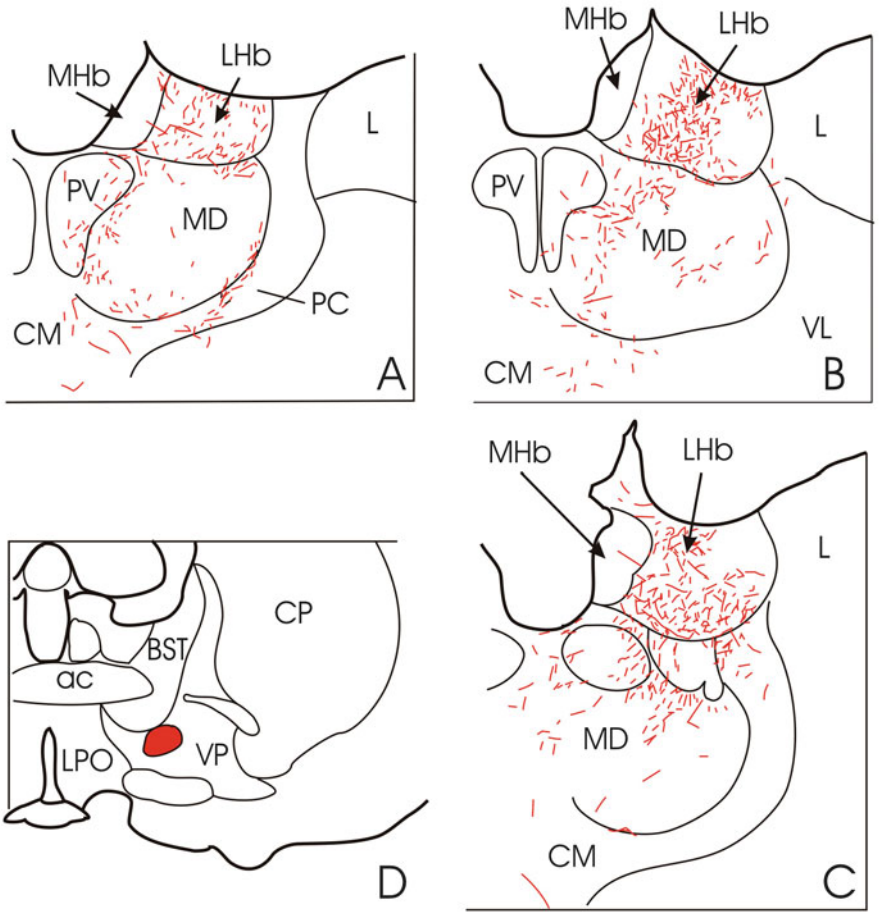

Fig. 2.6 Projections from the ventral pallidum to the lateral habenula. Chartings of anterograde labeling of fibers and terminals in the dorsomedial part of the thalamus and the habenula, represented in three levels (**A–C** rostral to caudal) following an injection of an anterograde tracer in the ventral pallidum (**D**). Note the rather dense labeling in the medial part of the lateral habenula. *ac* anterior commissure, *BST* bed nucleus of the stria terminalis, *CM* central medial thalamic nucleus, *CP* caudate putamen, *LHb* lateral habenula, *MHb* medial habenula, *L* lateral thalamic nucleus, *LPO* lateral preoptic area, *MD* mediodorsal thalamic nucleus, *PC* paracentral thalamic nucleus, *PV* paraventricular thalamic nucleus, *VL* ventrolateral thalamic nucleus, *VP* ventral pallidum

various regions in the forebrain that are influenced by limbic and autonomic inputs, i.e., the ventral striatopallidal system, the extended amygdala, and the septal-preoptic system, collectively influence directly as well as indirectly via the lateral habenula the dopaminergic and serotonergic cell groups that have, in turn, such a great impact on the limbic and behavioral structures in the forebrain.

In the direct and indirect influence of the basal forebrain structures on the dopaminergic and serotonergic cell groups, the rostromedial tegmental nucleus (RMTg) plays a key role. This GABAergic cell group in the caudal part of the VTA receives

a strong input from the lateral segment of the lateral habenula and projects strongly to dopaminergic cells in the rostral VTA and the serotonergic neurons in the raphe nuclei (Yetnikoff et al. 2014). While the VTA dopaminergic cell groups, i.e., the mesolimbic dopamine system, have long been considered to be an essential part of the reward system of the brain, the loop through the lateral habenula and the rostromedial tegmental nucleus is considered to be part of systems related to aversive behaviors in which the activity of dopaminergic neurons also appears to play a role. In particular, the lateral habenula has been shown to be an essential nodal point for the expression of negative motivational value (Matsumoto and Hikosaka 2008; Barrot et al. 2012; Stopper and Floresco 2014; Hikosaka et al. 2014). The glutamatergic projections from the lateral habenula are considered to activate the GABAergic neurons in the rostromedial tegmental nucleus, which in turn inhibit the dopaminergic neurons in the rostral VTA. Through this mechanism, negative reward or the omission of a predicted reward is able to influence the dopaminergic system projecting to the cortico-subcortical circuits to express motor, cognitive, and behavioral output. Furthermore, recent tract tracing studies show that there is a rather precise topographical organization in the afferent and efferent connections of the dopaminergic cell groups, representing a much higher degree of differentiation than has long been assumed (Geisler and Zahm 2005; Ikemoto 2007; Ikemoto et al. 2015; Yetnikoff et al. 2014). In line with this, both reward- and aversion-affiliated midbrain dopamine neurons have been demonstrated to exist (Lammel et al. 2012, 2014). These novel insights in the organization of the inputs and outputs of both the dopaminergic and the serotonergic systems are highly relevant for the understanding of normal reward- and aversive-related behaviors as well as their impaired expression in drug addiction, depression, obsessive-compulsive disorders, and possible other psychiatric disorders.

With respect to the ventral striatopallidal system, it will be of interest to investigate in more detail the organization of the projections to the medial and lateral segments of the lateral habenula. These two habenular segments differentially project to the ventral mesencephalon, i.e., the medial part of the lateral habenula projects directly to the dopaminergic neurons in the rostral VTA, while its lateral part has an indirect influence on the dopaminergic cells via the rostromedial tegmental nucleus (Gonçalves et al. 2012). In view of the highly compartmentalized nature of the ventral striatopallidal system, it would be of interest to investigate whether particular limbic corticostriatal channels have a specific influence on either of the two segments of the lateral habenula.

2.6 Concluding Remarks and Future Perspectives

The partitioning of cortical-basal ganglia connections into limbic, cognitive, and motor circuits and their mutual interactions remains an important concept in understanding the role of these cortical and subcortical structures in behavioral functions and their dysfunctions in neurological and psychiatric disorders. However, the

above-described rich connectional interactions between functional domains within the parallel and interacting corticostriatal systems, as well the recently recognized differentiation within the ascending dopaminergic system, provide an increased insight in ways of integration between the limbic, cognitive, and motor domains. The rather recent description of the pathways from the basal forebrain, including those from the ventral striatopallidal system, via the lateral habenula to the ventral tegmental GABAergic and dopaminergic cell groups, as well as to the serotonergic raphe nuclei, provides an important clue for the understanding of the dopaminergic system in both reward- and aversive-related behavior. In addition, the relatively unexplored projection from lateral habenula to the cholinergic laterodorsal tegmental nucleus deserves further study since the cholinergic neurons in this region provide widespread projections to the forebrain, including the basal nucleus of Meynert, the ventral striatum, and the prefrontal cortex (Satoh and Fibiger 1986; Tripathi et al. 2013). What needs further analysis is how these diverse streams of information are organized in the forebrain before they reach either of the two subsets of dopaminergic neurons. Which subregions of prefrontal and insular cortical areas provide the content via corticostriatal pathways that finally lead to rather opposing behavioral outputs? Which interactions take place at the level of the ventral striatum to select for a particular output? And how are the output pathways via the pallidal and nigral structures ultimately organized? These are some of the questions that still need to be answered.

With the advent of very sophisticated technical approaches such as optogenetics combined with behavioral approaches, such questions may be answered in the near future. Likewise, functional brain imaging (fMRI) and diffusion-tensor imaging tract-tracing (DTI) may also provide answers to these questions in the human brain, both with respect to normal functioning, as well as in the context of some neurological and psychiatric diseases.

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Chapter 3
Anatomy and Function of the Direct and Indirect Striatal Pathways

Jean-Jacques Soghomonian

3.1 Introduction

Several subtypes of striatal neurons were described during the 1970s and 1980s using the Golgi labeling method or electron microscopy (e.g., Kemp and Powell 1971; Fox et al. 1971; Danner and Pfister 1979; Dimova et al. 1980; Preston et al. 1980; Wilson and Groves 1980; Bishop et al. 1982; Bolam et al. 1981b; Chang and Kitai 1982; Chang et al. 1982; Tanaka 1980; DiFiglia et al. 1976; Graveland and DiFiglia 1985; Graveland et al. 1985). In a series of detailed studies carried out in the monkey, DiFiglia and co-workers identified up to six types of neurons in the striatum: type I and type II spiny neurons, type I, type II, and type III aspiny neurons, and a very small cell apparently devoid of an axon that could be a glial cell (DiFiglia et al. 1976, 1979). Type I spiny neurons were relatively small in size (20–14 μm) and exhibited four to seven dendrites forming a spherical field around the cell body. The dendrites were described as smooth near the cell body, but they became heavily covered with dendritic spines more distally. The type I neuron has been also identified as the medium-sized spiny neuron (MSN or MSPN) or medium spiny I neuron in the cat and rodent (Kemp and Powell 1971; Dimova et al. 1980; Chang et al. 1982; Bishop et al. 1982). Type I neurons were considered to account for as much as 95–96 % of all striatal neurons (Kemp and Powell 1971). The monkey type II spiny neuron has a spindle-shaped cell body, thicker dendrites, less spines, and a more extensive dendritic field than type I and represents less than 1 % of all striatal neurons. This neuronal type has also been described in cats and rodents (Kemp and Powell 1971; Dimova et al. 1980; Chang et al. 1982; Bishop et al. 1982). The function of the type II spiny neuron is still not clear, but one study found a similar neuron containing neuropeptide Y (Kubota et al. 1991). Aspiny striatal neurons

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are considered to be local interneurons (Kawaguchi et al. 1997). This chapter will focus on the phenotype and function of projection medium spiny neurons (MSN) that constitute the majority of striatal neurons.

3.2 Phenotypic Diversity of Medium Spiny Striatal Neurons

Earlier immunohistochemical studies have established that MSN contain the GABA-synthetizing enzyme glutamic acid decarboxylase (Gad) and are releasing GABA as their primary neurotransmitter (Ribak et al. 1979; Vincent et al. 1982; Nagai et al. 1983; Ottersen and Storm-Mathisen 1984; Bolam et al. 1985; Smith et al. 1987). The presence of the mRNA encoding for Gad in most striatal neurons was confirmed later on using in situ hybridization histochemistry (Chesselet et al. 1987). Although all MSN are defined as GABAergic, they can be subdivided based on their connectivity and phenotype. This chapter will review the evidence supporting the notion that striatal MSN can be subdivided into two large populations based on connectivity, morphology, chemical phenotype, and physiology. These two subtypes contribute to the so-called direct and indirect pathway of the basal ganglia and their properties play a central role in current models of basal ganglia organization (Albin et al. 1989; Crossman 1987; DeLong 1983, 1990). The chapter will also review the experimental evidence that these two pathways play distinct roles in the control of motor and cognitive functions.

3.2.1 Co-expression of Peptides

Immunohistochemical studies carried out in the 1980s and 1990s have thoroughly documented that MSN co-express GABA with one or more than one of the three peptides met-enkephalin, substance P, and dynorphin. Immunohistochemical studies combined with tract-tracing methods found that substance P and dynorphin are co-expressed in specific populations of striatal projection neurons, whereas enkephalin is present in other populations of striatal projection neurons (Anderson and Reiner 1990). Such an organization was documented in different species including pigeons, turtles, and rats (Anderson and Reiner 1990). Co-expression of substance P and dynorphin immunoreactivities was found in both the striosome and matrix striatal compartments (Besson et al. 1990). However, the percentage of substance P- and dynorphin co-localization was slightly higher in striosomes than in the matrix. Conversely, about two-thirds of all neurons were identified as enkephalin-positive in both matrix and striosomes (Besson et al. 1990). In another study comparing cats and rats, Penny and colleagues found that neurons immunoreactive for dynorphin made up about half of the neurons in rat striatum and a little less than half in the cat. Labeling for enkephalin was found in a little less than half of the neurons in the rat and about half of the neurons in the cat (Penny et al. 1986). Substance

P-immunoreactive neurons made up to 38 % of MSN in the rat and 39 % in the cat (Penny et al. 1986). An analysis using in situ hybridization histochemistry reported that the dynorphin mRNA was distributed in about half of patch and half of matrix neurons, while the enkephalin and the substance P mRNA were expressed in a little more than half of patch and about half of matrix neurons (Gerfen and Young 1988). Altogether, these immunohistochemical and in situ hybridization findings indicate that MSN can be subdivided into two major and numerically comparable populations, one that co-expresses substance P and dynorphin and one that co-expresses enkephalin. As discussed in the following paragraphs, there is evidence that a subpopulation of MSN co-expresses the three peptides, but the prevalence of these MSN remains controversial.

An earlier immunohistochemical study by Besson and colleagues (Besson et al. 1990) found that a majority of MSN expressing substance P/dynorphin also expressed enkephalin. In a more recent combined immunohistochemical and retrograde transport study in the monkey, about half of striatal neurons were found to co-express dynorphin and enkephalin (Nadjar et al. 2006). In a combined patch-clamp and PCR study, it was confirmed that some MSN co-express detectable levels of substance P and enkephalin mRNAs, but the frequency of these neurons could not be assessed (Surmeier et al. 1996). On the other hand, a more recent RT-PCR study by Wang and colleagues found that in 4-week-old rats, 11 % of MSN contained both substance P and enkephalin, while in 4-month-old rats, co-localization was only 3 % (Wang et al. 2006). In another study, the same group found that 32.3 % of MSN that contain both substance P and enkephalin are localized in the striosomal compartment (Wang et al. 2007). An immunohistochemical study in the rat nucleus accumbens found than less than 30 % of neurons co-express enkephalin and substance P, whereas more than 69 % co-express substance P and dynorphin (Furuta et al. 2002). Altogether, these findings support the likelihood that some MSN neurons co-express the three peptides, but the extent of co-localization varies between studies. Such differences could be partly explained by methodological (i.e., immunohistochemical versus gene expression studies) or species differences. As discussed above, it is also possible that the reported variability is due to developmental factors and/or differences between striatal compartments (Wang et al. 2006, 2007; Furuta et al. 2002).

3.2.2 Medium Spiny Neurons Connectivity

Early tract-tracing studies determined that the striatum contains projection neurons sending axons to the ipsilateral GP and/or to the SNr (Szabo 1967; 1970). Later on, it was reported that most striatal neurons are projection neurons (Bolam et al. 1981a, b; Graybiel and Ragsdale 1979) and combined Golgi and retrograde labeling methods identified them as MSN (Somogyi and Smith 1979). Retrograde axonal transport studies in primates further indicated that striatal projection neurons could be subdivided on the basis of their projections to the Gpe or to the Gpi and SNr (Parent

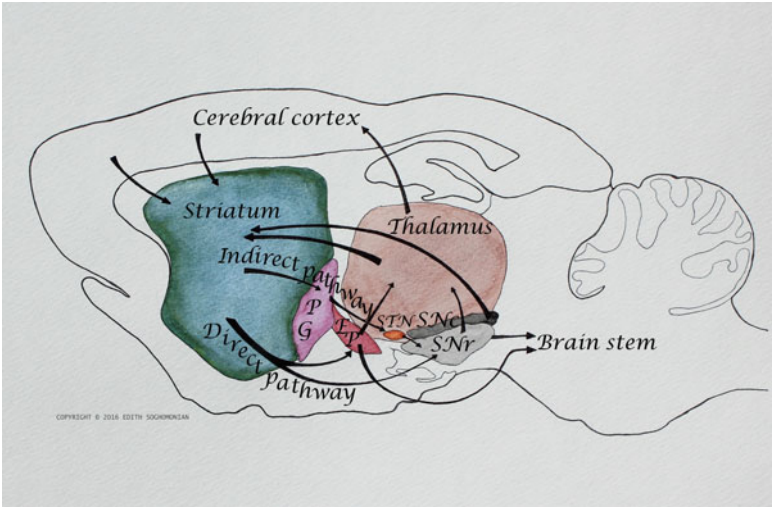

Fig. 3.1 Illustrates the major connections between basal ganglia structures and the organization of the direct and indirect pathway in a sagittal view of the rat brain. As discussed in this chapter, the subdivision into a direct and indirect pathway is a simplification since indirect pathway MSN can send axon collaterals to the SNr/EP, while direct pathway MSN can send axon collaterals to the GP. *GP* globus pallidus, *EP* entopeduncular nucleus, *STN* subthalamic nucleus, *SNc* substantia nigra pars compacta, *SNr* substantia nigra, pars reticulata

et al. 1984a, b) and at least three types of neurons were distinguished based on the fact that they projected either to the Gpe alone, to the SNr alone, or to both structures (Feger and Crossman 1984). Single cell-tracing methods provided further insights into the connectivity of striatal neurons and confirmed that MSN projected to more than one structure (Chan et al. 1981; Wilson and Phelan 1982; Parent et al. 1995a, b; Wu et al. 2000). In the primate, at least three types of striatal neurons were identified based on their target region (Parent et al. 1984a,1995a, b). One type projected to the GPe alone, a second type projected to the GPe and GPi, and a third type projected to the GPi, GPe, and SNr (Parent et al. 1995a, b). In the rat striatum, neurons were similarly subdivided into three types. Type I neurons projected to the GP only, type IIa neurons projected primarily to the SNr and EP, but also sent a small projection to the GP and type IIb neurons projected to the GP and SNr but not to the EP (Kawaguchi et al. 1990). The proportion of striatal neurons projecting to these different structures was not documented in this later study. A retrograde labeling study found that about one third of MSN that project to the GP have axon collaterals to the SNr (Castle et al. 2005).

In summary, tract-tracing combined with single-cell labeling studies have revealed that some MSN preferentially project to the GP (primate Gpe), while others preferentially project to the EP (or the primate Gpi) and to the SNr. In the literature, MSN that project to the GP (or primate GPe) are known as striatopallidal or indirect pathway neurons, while MSN that project to the SNr and/or EP (primate Gpi) are known as striatonigral or direct pathway neurons (Fig. 3.1). However, it is

apparent that this subdivision is a simplification and that some MSN do not fit this strict classification. Using viral gene transfer strategies in transgenic mice, it has been shown that the density of axon collaterals in the GP made by MSN that primarily project to the SNr (direct pathway) increases when the excitability of striatopallidal neurons is increased (Cazorla et al. 2014 and 2015). This indicates that the specificity of axonal projections from MSN can be modulated and further calls into questions the notion that striatal projections can be rigidly subdivided into a direct and indirect pathway.

As discussed in previous paragraphs, MSN can express various combinations of peptides (Besson et al. 1990; Surmeier et al. 1996; Reiner et al. 1999; Nadjar et al. 2006; Wang et al. 2006, 2007). In the rat, it was reported that striatal neurons labeled after an injection of retrograde tracer in the SNr were labeled with dynorphin and substance P, but only 1 % co-expressed enkephalin immunoreactivity (Lee et al. 1997). In contrast, neurons labeled after an injection into the GP were labeled with enkephalin, but only 17 % and 10 % were, respectively, labeled for dynorphin and substance P (Lee et al. 1997). An in situ hybridization study in the rat has shown that the majority of neurons expressing enkephalin project to the GP while a few project to the SNr, whereas neurons expressing dynorphin and substance P project mainly to the SNr but a few also project to the GP (Gerfen and Young 1988). In the monkey, 70 % and 50 % for neurons labeled after an injection of retrograde tracer, respectively, into the GPe or into the GPi co-expressed the three peptides (Nadjar et al. 2006). It is unclear if the discrepancy in co-expression between rodent and primate studies is due to species and/or methodological differences. In any case, current evidence suggests that MSN that co-express the three peptides may be those that do not fit the strict definition of direct and indirect pathway neuron.

3.2.3 Segregated Expression of Dopamine Receptors

Early neurochemical studies have shown that the dopamine D1 and D2 receptors are the two major subtypes of dopamine receptors expressed in the striatum and that they exert opposite effects on the activation of adenylyl cyclase, with D1 receptors being stimulatory and D2 receptors inhibitory (Kebabian and Calne 1979; Stoof and Kabadian 1981, 1984). Molecular cloning studies have determined that the family of dopamine D1 receptors includes the Drd1a and Drd5 receptors and that the family of dopamine D2 receptors includes the Drd2, Drd3, and Drd4 receptors (review in Beaulieu and Gainetdinov 2011). Although all dopamine receptors are expressed in the striatum (Surmeier et al. 1996), the Drd1a and the Drd2 receptors are the most abundant. The following paragraphs discuss the notion that the expression of the Drd1a and Drd2 receptors also contributes to define two different populations of MSN. This is an important notion since most studies carried out in genetically engineered mice or using viral delivery methods are based on it.

In a combined immunohistochemical and electron microscope study in the rat striatum, no co-localization of the D1 and D2 receptor was seen (Hersch et al.

1995). On the other hand, a study found that all striatal neurons co-expressed the D1 and D2 receptor (Aizman et al. 2000). However, between these two extreme outcomes, most other studies support the idea that only a subset of MSN co-expresses the D1 and D2 receptor (e.g. Meador-Woodruff et al. 1991; Weiner et al. 1991; Lester et al. 1993; Larson and Ariano 1994; Deng et al. 2006). The possibility that only some MSN co-express the Drd1a and Drd2 receptors was confirmed using PCR combined with path-clamp (Surmeier et al. 1996). The development of the Bacterial Artificial Chromosome (BAC) technology and genetically engineered mice has confirmed, at least in rodents, the limited co-expression of dopamine D1 and D2 receptors (e.g. Valjent et al. 2009). In mice expressing the marker tdTomato under the control of the Drd1a promotor and green fluorescent protein under the control of the Drd2 promotor, at embryonic day 18 only about 10 % of MSN were double-labeled. This proportion decreased at post-natal day 1 and 14 (Thibault et al. 2013). Similar evidence for limited co-expression was found in the neonatal mouse (Biezonski et al. 2015).

There is evidence that the segregation or co-expression of dopamine Drd1a and Drd2 receptors may correlate with the pattern of expression of specific peptides. Using a combination of patch-clamp and single-cell qPCR analysis, it was found that MSN having detectable levels of enkephalin, but not substance P mRNA, expressed high levels of the Drd2 receptor mRNA, while MSN with detectable levels of substance P but not enkephalin mRNA expressed high levels of the Drd1a receptor mRNA (Surmeier et al. 1996). The mRNAs for other dopamine receptor subtypes were rarely detected in MSN expressing enkephalin, but some co-expressed the D1b receptor (Surmeier et al. 1996). Conversely, the Drd3 receptor mRNA was detected in one-half of MSN expressing substance P, but other dopamine receptors were rarely detected (Surmeier et al. 1996). Finally, most MSN that co-expressed detectable levels of substance P and enkephalin mRNAs also co-expressed the Drd1a and Drd2 mRNAs (Surmeier et al. 1996).

Current evidence supports the notion that the segregation of MSN based on the expression of specific dopamine receptors and/or peptides correlates with a pattern of projection. This possibility is supported by several immunohistochemical and gene expression studies that have shown that Drd1a receptors are expressed in MSNs that primarily project to the SNr and/or the EP (or primate Gpi), while Drd2 receptors are expressed in MSNs that primarily project to the GP (or primate Gpe) (Aubert et al. 2000; Beckstead et al. 1988; Gerfen et al. 1990; Harrison et al. 1990; Le Moine et al. 1991; Harrison et al. 1992; Herve et al. 1993; Le Moine and Bloch 1995; Yung et al. 1995). Several studies in genetically engineered mice have confirmed that fluorescence induced by the activity of the Drdr1a receptor promotor in the striatum is high in the SNr, while fluorescence induced by the activity of the Drd2 receptor in the striatum is high in the GP (Gong et al. 2003; Lobo et al. 2006; Gertler et al. 2008; Bertran-Gonzalez et al. 2008; Shuen et al. 2008; Matamales et al. 2009). However, a combined confocal and retrograde labeling study in the rat found that although a large majority of neurons projecting to the SNr and EP also expressed the D1 receptor, 23 % of neurons projecting to the GP also expressed the D1 receptor (Deng et al. 2006). Conversely, although the vast majority of MSN projecting to the GP were labeled for the D2 receptor, 40 % of MSN projecting to

the SNr and EP were also labeled for the D2 receptor (Deng et al. 2006). Another study confirmed that although MSN neurons projecting to the SNr mainly express the Drd1a receptor, some also expressed the Drd2 receptor (Matamales et al. 2009). In another study, however, MSN labeled with a retrograde marker injected in the SNr did not express the D2 receptor (Gertler et al. 2008). A combined retrograde and immunohistochemical study in the monkey from Nadjar and colleagues has shown that MSN projecting to the Gpi or to the Gpe are immunolabeled for both dynorphin and enkephalin and for both the D1 or D2 receptor (Nadjar et al. 2006).

In conclusion, most experimental studies support the notion that MSN can be subdivided based on their expression of the Drd1a and Drd2 receptors, of the peptides enkephalin, substance P, and dynorphin, and on their area of projection. One consensus that emerges is that most MSN that project to the SNr and the GPi (or rodent EP) also express substance P and dynorphin and the Drd1a receptor, while most MSN that project to the GPe (or rodent GP) also express enkephalin and the Drd2 receptor. Gene expression studies support this dichotomy since drugs acting on D1 receptors or on D2 receptors differentially modulate gene expression of peptides preferentially expressed by direct or indirect pathway neurons (e.g. Bertran-Gonzalez et al. 2008; Gerfen et al. 1990; Cenci et al. 1992; Cole et al. 1992; Dragunow et al. 1990; Laprade and Soghomonian 1995; Robertson et al. 1992). However, based on the data discussed above, it is also clear that some MSN can co-express both the Drd1 and Drd2 receptors and can co-express the peptides enkephalin and substance P/dynorphin. The possibility that those MSN that co-express all markers are those that project to the SNr, EP (or Gpi), and GP (or Gpe) is supported by some studies. Interestingly, it has been recently shown that the activation of Drd2-expressing MSN in genetically modified mice increases the density of axon collaterals from direct pathway neurons to the GP (Cazorla et al. 2014). These striatonigral axon collaterals are functional and able to inhibit the firing rate of GP neurons (Cazorla et al. 2014). In contrast, the density of axon collaterals from striatonigral neurons to the GP did not change when the excitability of Drd1-expressing striatonigral neurons was modulated (Cazorla et al. 2014). This pioneering study indicates that the connectivity of MSN is not static, but can be modulated in different physiological conditions and it further emphasizes the notion that the subdivision of MSN into a direct and indirect pathway is a simplification. The possibility that MSN that do not fit the strict classification of direct and indirect pathway neuron play a distinct role in the physiology of the basal ganglia remains to be determined. With this caveat in mind, the following paragraphs will present and discuss evidence that the so-called direct and indirect MSN have different physiological properties and functional roles.

3.2.4 Membrane Properties of Direct and Indirect Pathway Neurons

The heterogeneous connectivity and chemical phenotype of striatal projection neurons are paralleled by heterogeneous electrophysiological and morphological properties. The organization of MSN into Drd1a and Drd2-expressing subsets may be

determined in part by cortical inputs because striatal neurons expressing the Drd1 receptor receive a majority of inputs from cortical neurons whose projections are restricted to the telencephalon, whereas striatal neurons expressing the Drd2 receptor receive more input from cortical neurons that contribute to the pyramidal tract (Lei et al. 2004). Using RT-PCR and confocal microscopy in slice preparations from mutant mice expressing eGFP under the activity of the dopamine Drd1 or Drd2 receptor, it was reported that Drd1-expressing striatal neurons are less excitable than Drd2-expressing neurons (Gertler et al. 2008). In addition, Drd1-expressing neurons have more primary dendrites than Drd2-expressing neurons (Gertler et al. 2008). Such a difference in excitability was also documented in another study showing that the threshold for firing action potentials is lower in Drd2-expressing than in Drd1-expressing MSN (Cepeda et al. 2008). Whole-cell and outside-out patch recordings in slices from bacterial artificial chromosome (BAC) transgenic mice were used to examine the role of $GABA_A$ receptor-mediated currents in dopamine receptor Drd1- and Drd2-expressing neurons (Ade et al. 2008). Although inhibitory synaptic currents were similar between the two neuronal populations, D2-expressing neurons had greater $GABA_A$ receptor-mediated tonic currents. Low GABA concentrations produced larger whole-cell responses and longer GABA channel openings in Drd2- than in Drd1-expressing neurons (Ade et al. 2008). It has been reported that the loss of dopamine innervation to the striatum differentially affects the excitability of Drd1- and Drd2-expressing neurons (Fieblinger et al. 2014). In parkinsonian mice, intrinsic excitability of Drd2-expressing neurons was depressed. High-dose L-DOPA treatment normalized intrinsic excitability. In contrast, the intrinsic excitability of Drd1-expressing neurons was significantly elevated and high-dose L-DOPA partially normalized this effect (Fieblinger et al. 2014). Altogether, these studies reinforce the notion that the different connectivity and chemical phenotype of Drd1 and Drd2-expressing striatal neurons is paralleled by different functional properties. The factors contributing to these differences remain unclear, but could involve cortical inputs because an electron microscopy study has shown that cortical synapses are smaller on Drd1- than on Drd2-expressing neurons (Lei et al. 2004).

3.3 Functions of the Direct and Indirect Pathway

3.3.1 Movement Control

The classical functional models of the basal ganglia are based on the notion that activation of the striatal direct pathway facilitates movement, while activation of the indirect pathway inhibits movement (Alexander et al. 1986; Alexander and Crutcher 1990; DeLong 1990). These models are supported by anatomical and physiological data and propose that paucity or loss of movement in Parkinson's disease results from an increased activation of indirect pathway neurons and a decreased activation of direct pathway neurons (Albin et al. 1989). This dual effect would result in an

increased basal ganglia output and an increased inhibition of thalamo-cortical projections to the frontal and prefrontal cortex ultimately leading to a lesser activation of cortical motor and premotor regions. Gene expression studies are consistent with an opposite role of the direct and indirect pathway on movement because in experimental models of Parkinson's disease, enkephalin gene expression in the indirect pathway is increased and preprodynorphin and preprotachykinin expression is decreased in the direct pathway (Reviewed in Soghomonian and Chesselet 2000). These changes in peptide gene expression have been considered to parallel changes in neuronal activity. A complementary role of the direct and indirect pathway in movement control was proposed in another model in which the direct pathway would contribute to the selection of motor programs, while the indirect pathway would inhibit competing motor programs (Mink 1996). The idea that the direct and indirect pathways have opposite and/or complementary roles on movement has been tested in transgenic mice models and using viral targeting methods. For instance, optogenics has been used in mice expressing channelrhodopsin-2 under the activity of the dopamine Drd1a or Drd2 receptors with the objective of independently manipulating direct or indirect pathway MSN. Using this approach, it was found that the bilateral excitation of striatal neurons expressing the dopamine Drd2 gene elicited a Parkinsonian state in mice, characterized by increased freezing, bradykinesia, and decreased locomotor initiation (Kravitz et al. 2010). In contrast, activation of striatal neurons expressing the Drd1a gene reduced freezing episodes and increased locomotion (Kravitz et al. 2010). In addition, activation of Drd1a-expressing neurons completely rescued freezing, bradykinesia, and deficits in locomotor initiation observed in a 6-hydroxydopamine-lesioned mouse model of Parkinson's disease (Kravitz et al. 2010). Conversely, other evidence has shown that the experimental ablation or disruption of the indirect pathway increases motor activity (Durieux et al. 2009; Bateup et al. 2010). Although the studies described above are consistent with the hypothesis that the direct and indirect pathways play an opposite role in the activation of movement, they do not clarify their respective role in various aspects of movement performance such as movement selection, initiation, termination, or in instrumental learning. The following paragraphs review and discuss studies that have attempted to address these questions.

Using a Cre-dependent viral expression of the genetically encoded calcium indicator GCaMP3 in Drd1a receptor- or A2a receptor-expressing (respectively direct and indirect pathway neurons) neurons in the striatum, Cui and co-workers were able to study the pattern of activation of direct and indirect pathway neurons during the execution of movement in mice performing an operant task (Cui et al. 2013). They found that both pathways were co-activated during the initiation of movement and that their concurrent activation preceded the initiation of contraversive movements and predicted the occurrence of movement (Cui et al. 2013). These findings suggest that the initiation and execution of normal movements requires a co-activation of direct and indirect striatal circuits. The finding of a co-activation of direct and indirect pathway MSN is consistent with the model proposing that these pathways could contribute to concomitantly activate selected movements and inhibit competing movements. In a study combining optogenetic identification of direct

and indirect pathway MSN with electrophysiological recordings in mice that were trained to learn a rapid motor sequence, Jin and colleagues (Jin et al. 2014) found that similar percentages of direct and indirect pathway MSN responded during the start or the end of the sequence. However, while direct pathway neurons responded similarly at the start and end of the sequence, indirect pathway neurons preferentially responded at the start of the sequence (Jin et al. 2014). Jin and colleagues interpreted this result as evidence that the direct pathway plays a preferential role in the initiation of movement, while the indirect pathway plays a preferential role in the inhibition of competing motor programs (Jin et al. 2014). The finding that the majority of changes in MSN activity occurred at the start and end of a motor sequence rather than during the sequence itself was interpreted as evidence that the basal ganglia control sequences of movements (chunking), rather than individual movements (Jin et al. 2014). In another study, genetically engineered mice were trained to execute two distinct and sequential responses to get a reward in an operant chamber (Rothwell et al. 2015). Using selective manipulations of direct and indirect pathway neurons, the study reported that serial order learning strengthened cortical synapses on direct pathway neurons (Rothwell et al. 2015).

The dual role of the direct and indirect pathways on movement is paralleled by a dual effect on neurons in the output regions of the basal ganglia. Indeed, the effectiveness of optogenetic stimulation of the direct pathway in producing movement significantly correlated with the extent of inhibition of a subpopulation of SNr neurons (Freeze et al. 2013). In contrast, motor suppression induced by activation of the indirect pathway seemed to be most strongly influenced by the population of excited SNr neurons (Freeze et al. 2013). Freeze and colleagues argued that the striatal direct and indirect pathways represent an inhibitory gate that can respectively open or close motor output from the basal ganglia (Freeze et al. 2013). This interpretation is consistent with other experimental evidence that signals through the striatopallidal indirect pathway inhibit movements through a phasic excitation of the SNr (Sano et al. 2013). In their study, Jin and colleagues found that the activity in the SNr correlated with that of direct pathway neurons, while activity in the GP correlated with that of indirect pathway neurons (Jin et al. 2014).

Most studies reviewed above are consistent with the hypothesis that activation of direct pathway neurons facilitates movement, while activation of indirect pathway neurons inhibits movement. A more complex theoretical model has been proposed in which activation of indirect pathway MSN would contribute to both the selection and concurrent inhibition of competing movements (Keeler et al. 2014). The model, which is based on evidence that dopamine D1 and D2 receptors have different biochemical properties and that their pharmacological manipulation differentially alter different phases of movement in an operant task, proposes that the direct and the indirect pathway are, respectively, involved in the preparation and the selection of movement (Keeler et al. 2014). In this model, the activation of a small subset of indirect pathway MSN would contribute to select movement and concurrently would exert a lateral inhibition on neighboring indirect pathway MSN to inhibit competing movements. In this model, the paucity of movement observed in Parkinson's disease could be explained by an abnormal activation of large popula-

tions of indirect pathway MSN so that the mechanisms leading to movement selection via lateral inhibition would be disrupted (Keeler et al. 2014). The possibility that the indirect pathway is involved in movement selection appears consistent with experimental evidence that its selective elimination impairs the accuracy of response selection in the execution of an auditory discrimination task without influencing the response time (Nishizawa et al. 2012). Conversely, selective elimination of the striatonigral pathway lengthens the response time, but does not affect the accuracy of a response selection in a two-choice reaction time task dependent on a visual stimulus (Fukabor et al. 2012). In conclusion, the exact role of the direct and indirect pathway in the control of movement remains hypothetical and future studies using more refined methods should help settle the uncertainty about the role of these pathways in movement initiation and movement selection.

3.3.2 Associative Learning, Social Behavior, and Decision Making

The basal ganglia and the striatum play an important role in learning and executing a motor performance in response to a specific sensory or environmental context (Seger and Spiering 2011). In particular, the striatum is involved in action-outcome learning and in habit learning. In action-outcome learning, the performance of a specific behavior depends on a mental representation of the outcome. In habit learning, the performance depends on a particular context. Habits are less sensitive to reward devaluation, indicating a competition between action-outcome learning and habits. The ventromedial striatum may be preferentially involved in action-outcome learning, while the dorsolateral striatum may be preferentially involved in habit learning (Balleine et al. 2007). The reader is referred to Chaps. 5, 11, 12, 18, and 19 for more detailed discussions on the role of the striatum in learning. The objective in the following paragraphs will be to discuss the respective contribution of the striatal direct and indirect pathways to learning and learning-dependent behaviors such as social behavior and decision-making.

A number of studies have used genetically engineered mice to selectively manipulate the direct or indirect pathways and assess the impact on operant learning. These studies suggest a differential role of the direct and indirect pathways in different aspects of associative and reward-based learning. In particular, these studies support the notion that the direct pathway is involved in reward-based learning, whereas the indirect pathway may be involved in avoidance behavior. For instance, in a place preference paradigm in an operant box, optogenic stimulation of Drd1a-expressing neurons induced a persistent reinforcement, whereas stimulation of Drd2-expressing neurons induced a transient punishment (Kravitz et al. 2012). Using another genetic approach to selectively inactivate with tetanus-toxin striatal neurons expressing substance P or enkephalin (direct and indirect neurons, respectively), Hikida and colleagues found that loss of the direct but not the indirect pathway impaired reward-based learning (Hikida et al. 2016). In contrast, the avoidance

aversive behavior in a dark chamber associated with an electric shock was impaired after loss of the indirect but not the direct pathway, leading the authors to conclude that the indirect pathway is critical for evoking aversive behavior (Hikida et al. 2010, 2016). Using a similar experimental approach, it was shown that Drd1a receptors in the direct pathway are critical for the acquisition, but not for the expression of appetitive reward learning (Hikida et al. 2013). In contrast, activation of Drd2 receptors in indirect pathway neurons was critical for both the acquisition and expression of aversive behavior (Hikida et al. 2013). When the transmission of either direct or indirect pathway MSN was unilaterally blocked using tetanus toxin, infusion of protein kinase A inhibitors in the accumbens core abolished passive avoidance to an electric shock when the indirect pathway was blocked (Yamaguchi et al. 2015). In addition, protein kinase A activity was increased in indirect pathway and decreased in direct pathway neurons in both aversive memory formation and retrieval (Yamaguchi et al. 2015), indicating that the second messengers systems associated with dopamine receptors are involved in these effects. In another series of experiments, mice were trained to lick a spout in response to a whisker deflection (Sippy et al. 2015). Striatal projection neurons in the dorsolateral striatum showed a strong task-related modulation and increased their activity in successful trials (Sippy et al. 2015). However, direct but not indirect pathway neurons exhibited a prominent early sensory response and optogenetic stimulation of direct pathway neurons substituted for whisker stimulation in trained mice (Sippy et al. 2015). These data support the hypothesis that direct pathway neurons are permissive for the initiation of learned reward-based action (Sippy et al. 2015). Francis and colleagues documented a dual effect of the direct and indirect pathways in mood and motivated behavior. Specifically, the activity of Drd1a-expressing neurons was decreased, while the activity of Drd2-expressing neurons was increased in mice displaying depression-like behaviors after chronic social defeat stress (Francis et al. 2015). Stimulation of Drd1a-expressing neurons increased behavioral resilience to depression, while inhibition induced depressive-like behavior after chronic social defeat stress. In contrast, the repeated activation of indirect pathway neurons in stress naïve mice induced social avoidance following a subthreshold exposure to a social defeat stress (Francis et al. 2015). Another study has shown that stimulation of Drd2-expressing neurons of the nucleus accumbens converts risk-preferring rats to risk-averse rats (Zalocusky et al. 2016). This finding is consistent with a general role of the indirect pathway in avoidance behavior.

Other studies indicate that in addition to be involved in avoidance behavior, the indirect pathway may play an important role in mediating cognitive flexibility by preventing the execution of actions that used to be rewarded but that are not anymore. Using the transmission-blocking tetanus toxin approach in the mouse, it was documented that the direct pathway in the nucleus accumbens is required for learning the association between a visually cued task and a reward (Yawata et al. 2012). In contrast, inactivation of the indirect pathway did not impair learning acquisition, but it increased perseverative behavior in response to a strategy switch in which the reward was placed in another location (Yawata et al. 2012). In this study, the administration of the D2 receptor agonist quinpirole tended to increase perse-

verative errors, particularly during the switching task, thus confirming that a decreased inhibitory action of D2 receptors on indirect pathway neurons is necessary for learning a new strategy (Yawata et al. 2012; Nakanishi et al. 2014). These data are consistent with the model of "Go" and "No Go" in which the Go signal is provided by activation of the direct pathway and the "No Go" signal by activation of the indirect pathway (Frank et al. 2004; Frank 2011). In such a case, a decreased activation of indirect pathway neurons could lead to perseveration and enhance the expression of habits. This is otherwise supported by evidence that post-synaptic plasticity of Drd2-expressing striatopallidal neurons in the dorsolateral striatum correlates with habit learning (Shan et al. 2015). In addition, habitual behavior in mice was correlated with a strengthening of direct and indirect pathway neurons in the dorsolateral striatum (O'Hare et al. 2016), but neurons in the direct pathway had a tendency to fire before the indirect pathway and habit suppression correlated with a weakened direct pathway output while habit expression correlated with indirect pathway event amplitude (O'Hare et al. 2016).

3.3.3 Addiction and Obesity

It is well-established that the striatum and dopamine are involved in reward-mediated behaviors and in addiction (Schultz 2011 and 2013; Hyman et al. 2006). On the other hand, food intake is regulated via several mechanisms, among which the reward system plays an important role. Obesity can be the result of excessive food consumption and may involve mechanisms similar to those involved in drug abuse (Kenny et al. 2013). The following paragraphs discuss evidence that the direct and indirect pathway play a dual role in addiction and in obesity.

Earlier studies have documented that pharmacological antagonists of D1 receptors block conditioned place preference for cocaine (Hiroi and White 1991; Baker et al. 1998). Using a fluorescent calcium indicator as a marker of neuronal activity, it was found that cocaine intake shifts the balance between the direct and indirect pathway towards the direct pathway (Luo et al. 2011) and loss of the direct pathway reduces locomotor activity and attenuates locomotor sensitization to repeated cocaine (Hikida et al. 2016). Similarly, decreased excitability of the direct pathway impairs persistence of amphetamine-induced behavioral sensitization (Ferguson et al. 2011). In the conditioned place preference paradigm, blockade of the direct but not indirect pathway reduces cocaine-induced place preference (Hikida et al. 2016). Optical activation of nucleus accumbens Drd1a- but not Drd2-expressing MSN enhanced morphine-conditioned place preference (Koo et al. 2014). In another study, it was found that activation of dopamine D1 receptors on the direct pathway is important for inducing cocaine-dependent sensitization and cocaine-induced addictive behavior (Hikida et al. 2013). Lobo and colleagues subsequently reported that a targeted deletion of Tropomyosin-related kinase B (TrkB), the receptor for the brain-derived neurotropic factor (BDNF), in direct pathway MSN diminished the rewarding properties of cocaine (Lobo et al. 2006). Loss of the dopamine-receptor

activated second messenger DARPP-32, in direct but not in indirect pathway MSN, prevented the stimulatory action of the psychomimetic phencyclidine on motor activity (Bonito-Oliva et al. 2016). Altogether, these findings are consistent with the notion that the activation of the direct pathway plays a key role in several addictive effects induced by psychostimulants. In contrast, activation of the indirect pathway seems to play an opposite role on several psychostimulant-induced behaviors. For instance, there is evidence that increasing the activity of the indirect pathway promotes resilience to compulsive cocaine seeking (Bock et al. 2013). Lobo and colleagues reported that the targeted deletion of the neurotrophic receptor TrkB in Drd2-expressing MSNs enhanced cocaine reward (Lobo et al. 2006). Moreover, TrkB deletion in Drd2-expressing MSN increased the excitability of indirect pathway neurons and optogenetic stimulation of these neurons decreased cocaine reward-seeking behavior (Lobo et al. 2006). Loss of the indirect pathway also leads to a delayed cocaine sensitization, although sensitization eventually re-emerges (Hikida et al. 2013). A decreased excitability of the indirect pathway facilitates behavioral sensitization (Ferguson et al. 2011). An increased synaptic strength of glutamatergic synapses on Drd2-expressing indirect pathway neurons in the nucleus accumbens was documented in mice with a history of intravenous cocaine self-administration (Bock et al. 2013). This synaptic strengthening was inversely correlated with the emergence of compulsive-like cocaine responding (Bock et al. 2013). Altogether, these data suggest that activation of the indirect pathway may oppose the addictive properties of drugs of abuse.

Adenosine A2a receptors are densely expressed in striatopallidal neurons (Svenningsson et al. 1997; Schiffmann et al. 2007). Pharmacological agonists that modulate adenosine A2a receptors and increase striatopallidal transmission reduced consumption of both highly palatable and standard chow in rats (Micioni Di Bonaventura et al. 2012) and reduced lever-pressing for food rewards (Jones-Cage et al. 2012). Conversely, pharmacological blockade of A2a receptors increased palatable food consumption when administered alone and enhanced palatable food intake triggered by intra-accumbens administration of an μ-opioid receptor agonist (DAMGO) (Pritchett et al. 2010). These findings are reminiscent of the inhibitory effects of indirect pathway stimulation on drug reward described in the previous paragraphs and suggest that Drd2-expressing indirect pathway neurons may regulate food intake in much the same way that they regulate drug rewards. A link between compulsive eating and indirect pathway neurons is supported by some studies. In particular, viral knockdown of Drd2 receptors in the striatum accelerates the development of compulsive food-seeking behavior in rats (Johnson and Kenny 2010), suggesting that the indirect pathway may control compulsive food-seeking.

3.4 Conclusions

The existence of a direct and indirect striatal pathway is supported by considerable experimental evidence, but there is also evidence that this segregation is not absolute. In addition, recent evidence indicates that both the density of MSN axonal

projections to a specific target and the expression of phenotypic markers in MSN can change during the development of the brain and/or in response to physiological challenges. Studies in genetically engineered mice have documented that the manipulation of neurons that preferentially express phenotypic markers of direct or indirect pathway neurons (i.e., dopamine Drd1a versus Drd2 receptors or enkephalin versus substance P and dynorphin) has a different impact on behavior. It should be emphasized, however, that most mice studies manipulate subsets of MSN based on their expression of specific dopamine receptors rather than on their specific area of projection. Thus, the function of MSN that do not fit the strict definition of direct or indirect pathway neuron (i.e. neurons that project to all output regions of the basal ganglia) remains unclear.

Another major outcome of recent experimental studies in mice has been to support the notion that the direct and indirect pathways play an opposite and/or complementary role in the organization of movement, in associative and in reward-based learning. In particular, current evidence supports the notion that the direct pathway is involved in the facilitation of movement and reward-associated actions, while the indirect pathway is involved in the inhibition of competing motor actions and/or the inhibition of unrewarded actions. It is important to emphasize that most studies leading to these conclusions involved experimental conditions in which the activity of large numbers of MSN was homogeneously manipulated, a situation that most likely does not occur in physiological conditions. In fact, the temporal and spatial pattern of activation or deactivation of direct and indirect pathway neurons during the preparation, initiation, execution, and termination of actions is complex. This suggests that different subsets of direct and indirect MSN code for different variables associated with an action. In order to provide a better insight into the functions of MSN, future studies should aim at activating and/or deactivating more discrete subsets of direct or indirect pathway neurons and multi-synaptic neuronal circuits associated with different subsets of direct and/or indirect pathway neurons.

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Chapter 4
The Thalamostriatal System and Cognition

Yoland Smith, Rosa Villalba, and Adriana Galvan

4.1 Introduction

A contribution of the basal ganglia in cognition is well established. The connections between the caudate nucleus, the prefrontal cortex, and other associative cortices are key elements of the basal ganglia-thalamocortical loops that regulate cognitive behaviors (Alexander et al. 1986, 1990) Neurodegenerative disorders that affect the caudate nucleus and associative territories of other basal ganglia nuclei often lead to cognitive deficits (Grahn et al. 2008, 2009; Haber and Brucker 2009; O'Callaghan et al. 2014; Robbins and Cools 2014). The reader is referred to Chap. 5, 9, 11–16, 18, and 19 in this volume for further discussions on the role of the striatum and its basal ganglia targets in associative learning and cognition. In this chapter, we will discuss evidence that functional connections between the caudal intralaminar nuclei of the thalamus and the striatum also contribute to cognitive processes related to learning and attention.

Despite the fact that strong anatomical connections from the thalamus to the striatum were first described as early as the 1940s (Vogt and Vogt 1941a, b; Cowan and Powell 1956; Powell and Cowan 1954, 1956) and that the evolution of the thalamostriatal system predates that of the corticostriatal projections (Butler 1994; Reiner et al. 2010; Stephenson-Jones et al. 2011), much remains to be known about the role of the thalamostriatal system in mammals. However, the last two decades have witnessed significant advances in our understanding of various aspects of the anatomy and physiology of this system, and highlighted the potential role of the centromedian (CM) and parafascicular (Pf) nuclei, the main sources of thalamic inputs to the striatum, in cognition (Kinomura et al. 1996; Bradfield et al. 2013a, b; Brown et al. 2010; Kato et al. 2011; Matsumoto et al. 2001; Minamimoto and

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Kimura 2002; Kimura et al. 2004; Smith et al. 2004, 2009, 2011, 2014; Galvan et al. 2016). Furthermore, evidence that the CM/Pf complex is severely degenerated in Parkinson's disease (PD) and Huntington's chorea (HD), combined with the fact that lesion or deep brain stimulation of this nuclear group alleviates some of the motor and non-motor symptoms of Tourette's syndrome and PD has reinvigorated interest in developing a deeper understanding of the CM/Pf complex and its functional relationships with the striatum.

4.2 Anatomy of the CM/PF-Striatal System

The CM/Pf in primates is the main, but not exclusive, source of thalamic inputs to the striatum (Smith and Parent 1986; Groenewegen and Berendse 1994; Smith et al. 2004, 2009, 2011, 2014). In rodents, the nuclear complex is much smaller, being made up exclusively of a single cell group called the Pf (Groenewegen and Berendse 1994; Smith et al. 2004). As shown in Fig. 4.1, the thalamostriatal projection system in primates invades the entire striatum and is functionally organized; the caudal and dorsolateral tiers of Pf are connected with associative striatal regions (i.e., caudate nucleus and pre-commissural putamen), while the CM provides inputs to the sensorimotor striatum (i.e., post-commissural putamen). In rodents, the medial Pf provides the bulk of inputs to the associative striatum, while the lateral Pf is preferentially connected with the sensorimotor part of the caudate putamen complex (Groenewegen and Berendse 1994). Both the CM and Pf projections avoid the striosomes (or patches) to terminate exclusively in the matrix compartment of the striatum (Herkenham and Pert 1981; Raju et al. 2006). The whole CM/Pf complex provides inputs to the striatum although the lateral part of the CM appears to be preferentially connected with the primary motor cortex in primates (Fig. 4.1).

Through prominent GABAergic projections from the basal ganglia output nuclei (i.e., internal globus pallidus and substantia nigra pars reticulata), the CM/Pf complex is part of functionally segregated subcortical loops that involve different parts of the CM/Pf and the basal ganglia nuclei (Sidibe et al. 1997, 2002; Smith et al. 2004, 2009, 2014; Galvan et al. 2011, 2016). In addition to basal ganglia inputs, the CM/Pf complex receives afferents from motor, premotor, and somatosensory cortices, while cortical inputs to Pf originate preferentially from the frontal and supplementary eye fields, and associative areas of the parietal cortex (Sidibe et al. 2002; Galvan and Smith 2011; Galvan et al. 2016; Smith et al. 2014). The CM/Pf also receives inputs from subcortical sources, including the pedunculopontine tegmental nucleus, the superior colliculus, the cerebellum, the raphe nuclei, the locus coeruleus, the parabrachial nuclei and the mesencephalic, pontine and medullary reticular formation (Edwards and de Olmos 1976; Comans and Snow 1981; Steriade and Glenn 1982; Chevalier and Deniau 1984; Hallanger et al. 1987; Cornwall and Phillipson 1988; Vertes and Martin 1988; Pare et al. 1988; Parent et al. 1988; Lavoie and Parent 1991; Royce et al. 1991; Grunwerg and Krauthamer 1992; Newman and Ginsberg 1994; Ichinohe and Shoumura 1998; Krout et al. 2001; Vertes et al. 2010; Barroso-Chinea et al. 2011, ; Iwai et al. 2015).

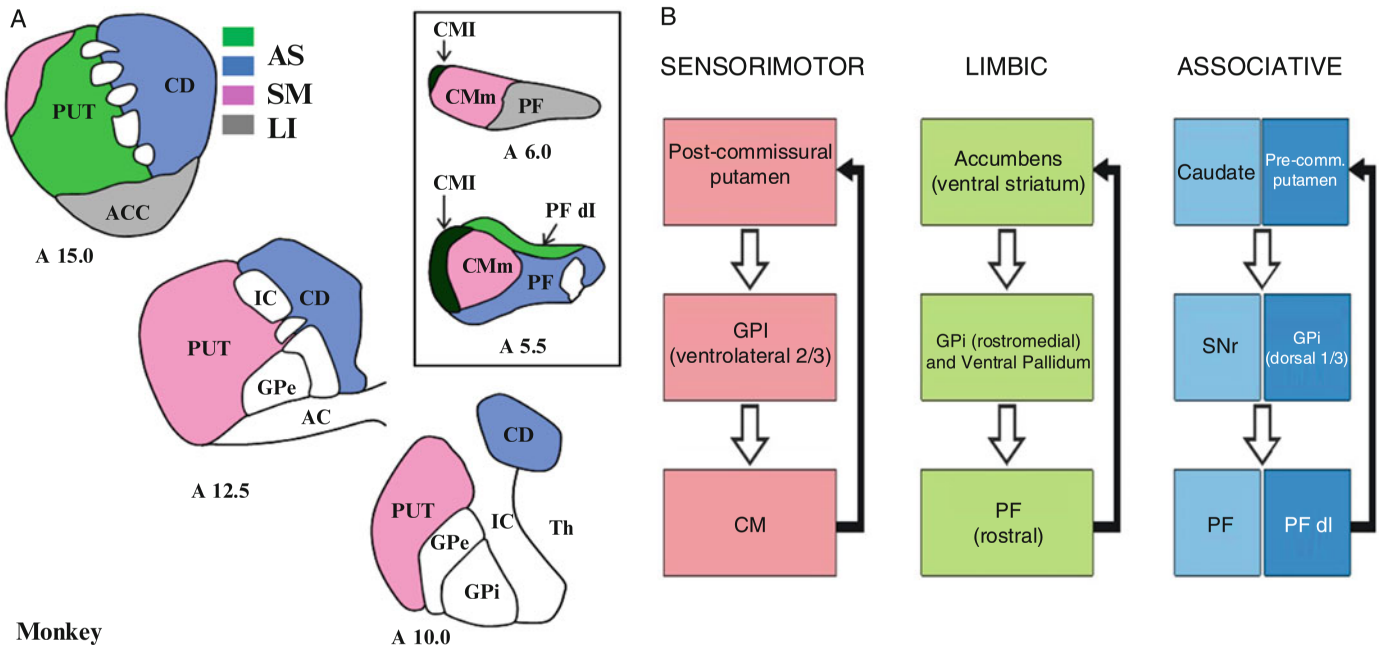
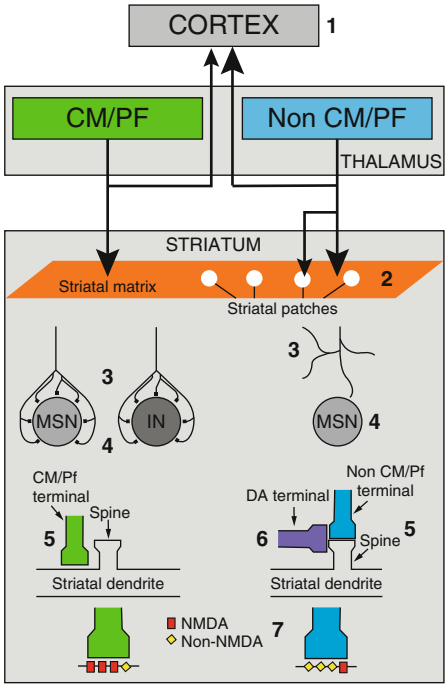


Fig. 4.1 (**a**) Color-coded thalamostriatal connections between different sectors of the CM/Pf complex and different functional regions of the striatum in monkeys. The antero-posterior stereotaxic coordinates that correspond approximately to the levels of the schematics depicted are indicated in the *lower left corner* of each drawing. (**b**) Functionally segregated basal ganglia-thalamostriatal loops that flow through different regions of the basal ganglia and CM/Pf complex in primates. *AC* anterior commissure, *ACC* nucleus accumbens, *AS* associative territory, *CD* caudate nucleus, *CMl* centromedian nucleus-lateral part, *CMm* centromedian nucleus-medial part, *GPe* globus pallidus, external segment, *GPi* globus pallidus, internal segment, *IC* internal capsule, *LI* limbic territory, *PF* parafascicular nucleus, *PFdl* parafascicular nucleus-dorsolateral part, *PUT* putamen, *SM* sensorimotor territory, *SNr* substantia nigra pars reticulata, *Th* thalamus

It is noteworthy that the CM/Pf is not the sole source of thalamic inputs to the striatum, other thalamic nuclei, including the midline, the rostral intralaminar, the ventral motor nuclear group, the mediodorsal and the pulvinar also provide specific and topographically organized striatal projections that invade the sensorimotor, associative, and limbic striatal territories (Parent et al. 1983; Beckstead 1984; Smith and Parent 1986; Tanaka et al. 1986; Berendse and Groenewegen 1990; Nakano et al. 1990; Ragsdale and Graybiel 1991; Groenewegen and Berendse 1994; Deschenes et al. 1995; Gimenez-Amaya et al. 1995; de las Heras et al. 1998, 1999; Mengual et al. 1999; Haber and McFarland 2001; Ichinohe et al. 2001; McFarland and Haber 2001; Erro et al. 2002; Van der Werf et al. 2002; Wall et al. 2013; Alloway et al. 2014).

4.3 The Dual CM/Pf-Versus Non-CM/Pf-Striatal Systems

In recent years, it has become clear that the thalamostriatal systems could be divided into two subsystems based on the origin and pattern of synaptic connection of the thalamic terminals with striatal neurons (Galvan et al. 2011, 2016; Smith et al. 2014). The CM/Pf projections target dendritic shafts (~70 %) and spines (~30 %) of striatal medium spiny projection neurons (MSNs) and interneurons (mostly cholinergic interneurons) (Sidibe and Smith 1999; Nanda et al. 2009; Smith et al. 2004, 2011, 2014), while inputs from other thalamic nuclei target almost exclusively dendritic spines (Galvan and Smith 2011; Raju et al. 2006, 2008; Smith et al. 2004, 2009), a pattern strikingly similar to that of the corticostriatal afferents. Another distinguishing feature between the synaptic connectivity of these two thalamostriatal systems relates to the structural relationships of the thalamic terminals with dopaminergic afferents. While non-CM/Pf thalamic terminals are commonly found in close proximity to dopaminergic boutons, such relationships between CM/Pf and dopaminergic terminals are rarely seen (Smith et al. 1994; Raju et al. 2006; Moss and Bolam 2008) suggesting that the regulation of CM/Pf inputs by dopamine is likely to be mediated through non-synaptic volume transmission of the dopaminergic system (Rice 2000; Moss and Bolam 2008). Additional anatomical differences between these two subsystems have been recognized and discussed in detail in some of our previous reviews (Galvan et al. 2011, 2016; Smith et al. 2014). For instance, thalamic inputs from CM/Pf are focal and converge upon restricted striatal regions, while axonal projections from other thalamic nuclei are more diffuse and scattered across widespread striatal subsectors (Deschenes et al. 1995; Sidibe and Smith 1996; Ichinohe et al. 2001; Parent and Parent 2005). Optogenetic activation of terminals from CM/Pf or non-CM/Pf nuclei differ in their recruitment of post-synaptic glutamate receptors; the physiological effects of synapses formed by CM/Pf terminals are mediated by both NMDA and AMPA glutamate receptors, while those from non-CM/Pf terminals rely exclusively on AMPA receptors (Ellender et al. 2013; Smith et al. 2014; Galvan et al. 2016) (Fig. 4.2).



1 Degree of cortical innervation
- CM/PF: Projects preferentially to the striatum, with collaterals to cortex.
- Non CM/PF: Project preferentially to the cortex, with collaterals to the striatum.

2 Matrix/Patch preference
- CM/PF: Innervates preferentially matrix.
- Non CM/PF: Shows no clear preference for matrix or patches.

3 Pattern of innervation
- CM/PF: Focal, convergent sites of termination in the striatum.
- Non CM/PF: Diffuse pattern of termination in the striatum.

4 Cellular targets
- CM/PF: Contacts MSNs and interneurons (IN).
- Non CM/PF: Contacts mostly MSNs.

5 Synaptic connectivity
- CM/PF: Forms mostly axo–dendritic synapses.
- Non CM/PF: Forms almost exclusively axo–spinous synapses.

6 Relationship with DA terminals
- CM/PF: No spatial relationships with dopaminergic (DA) terminals.
- Non CM/PF: Converge with DA terminals onto common dendritic spines.

7 Ratio of NMDA/Non-NMDA receptors
- CM/PF: Higher proportion of NMDA receptors
- Non CM/PF: Higher proportion of non–NMDA receptors

8 Susceptibility to degeneration
- CM/PF: Partial neuronal loss in Parkinson's Disease
- Non CM/PF: Not affected in Parkinson's Disease

Fig. 4.2 Summary of the different anatomical and neurochemical features that distinguish the lamostriatal systems that originate from CM/Pf versus non-CM/Pf thalamic nuclei. The description of the comparative features between the two systems numbered in the drawing is given on the right. *DA* dopamine, *IN* striatal interneuron, *MSN* medium spiny projection neuron, *NMDA* NMDA glutamate receptor

4.4 The CM/Pf-Striatal System Regulates Activity of Striatal Cholinergic Interneurons

Reward-associated events evoke pause responses in striatal tonically active neurons (TANs) (the likely electrophysiologic correlate of cholinergic interneurons) (Goldberg and Reynolds 2011). These responses are regulated in part by the CM/Pf-striatal system (Goldberg and Reynolds 2011) because they are almost completely abolished by chemical inactivation of the CM/Pf complex in monkeys (Matsumoto et al. 2001) (Fig. 4.3). These observations are consistent with the fact that cholinergic interneurons receive massive synaptic inputs from CM/Pf and that CM stimulation strongly affects TAN activity (Sidibe and Smith 1999; Nanda et al. 2009; Brown et al. 2010; Bradfield et al. 2013a, b). Several mechanisms have been proposed to explain how activation of the glutamatergic CM/Pf-striatal projection evokes pause responses in TANs (Ding et al. 2010; Smith et al. 2011; Fisher and Reynolds 2014; Goldberg and Reynolds 2011). Altogether, these observations lead to the proposal that the CM/Pf-striatal system may contribute to attention shifting,

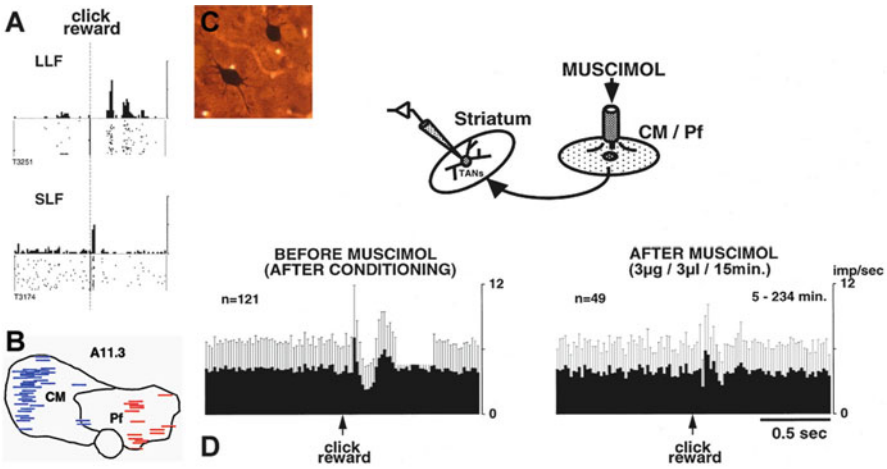


Fig. 4.3 Summary of electrophysiological data showing sensory responses of two types of CM/PF neurons (**a**) and striatal Tonically Active Neurons (TANs) (**d**) in rhesus monkeys. (**a**) Spike rasters and accompanying histograms showing representative activity of a CM neuron with long-latency facilitation (LLF) and a PF neuron with short-latency facilitation (SLF) after presentation of the sensory stimulus. (**b**) Approximate location of recorded LLF (*blue bars*) and SLF (*red bars*) neurons in the monkey CM/PF complex. (**c**) ChAt-positive striatal cholinergic interneurons in the monkey putamen. (**d**) Effects of muscimol-induced inactivation of neuronal activity in CM and PF on the firing of TANs recorded concurrently during performance of a stimulus-with-reward task. The experimental setup is shown at the *top*. The histograms illustrate the population response of TANs to the sensory stimulus associated with reward prior to muscimol injection into the CM/PF complex. *Numbers* indicate total number of neurons recorded. Modified with permission from Matsumoto et al. 2001

behavior switching, action selection, and reinforcement processes, in part through regulating the activity of striatal cholinergic interneurons and projection neurons (Matsumoto et al. 2001; Minamimoto and Kimura 2002; Minamimoto et al. 2005; Brown et al. 2010; Smith et al. 2011; Bradfield et al. 2013b; Fisher and Reynolds 2014).

4.5 Differential Role of CM and Pf Neurons in Cognition

Imaging studies have demonstrated selective increases in regional cerebral blood flow (rCBF) in the reticular formation and CM/Pf of humans as they transition from a relaxed awake state to participation in an attention-demanding reaction-time task (Kinomura et al. 1996). More recent observations in primates showed that CM and Pf neurons respond to behaviorally salient attention-related visual, auditory, and somatosensory stimuli (Matsumoto et al. 2001; Minamimoto and Kimura 2002; Kimura et al. 2004; Minamimoto et al. 2005, 2014). In these studies, the response latencies in Pf were much shorter than those in CM (Matsumoto et al. 2001;

Minamimoto and Kimura 2002; Minamimoto et al. 2005). Compatible with the view that responses of CM/Pf neurons to external events were related to attention in rewarded tasks, these responses were initially independent of the presence or absence of reward, but faded quickly upon repeated stimulus presentation, if stimuli were not followed by reward (Matsumoto et al. 2001; Minamimoto et al. 2002; Kimura et al. 2004). Kimura and colleagues found that acute pharmacologic Pf inactivation in monkeys disrupts attention processes more efficiently than CM inactivation, suggesting a differential role of the Pf-caudate nucleus versus CM-putamen projection in regulating attention-related cognitive processes in primates (Minamimoto and Kimura 2002; Minamimoto et al. 2014) (Fig. 4.3).

Further evidence along those lines comes from other observations suggesting that CM neurons are involved in a mechanism complementary to decision and action bias, and that the thalamostriatal projection from CM is involved in stimulus-driven attentional and motivational control of action and learning (Minamimoto et al. 2005, 2009, 2014). It has been suggested that the CM-striatal system signals the discrepancy between internal pre-action bias and external demand. Through this process, the CM-striatal projection likely mediates the switch from the motivationally guided pre-action bias to a counteracting bias more suitable to the demand (Minamimoto et al. 2005, 2009, 2014).

Additional evidence for a "cognitive" role of the projections from the caudal intralaminar complex to the striatum comes from studies in mice in which selective immunotoxin lesions of the Pf-striatal projection (corresponding to the CM/Pf projection in primates), impair performance in a visual discrimination learning task (Kato et al. 2011). In this study, selective elimination of the Pf-striatal pathway before the acquisition of discrimination impaired the response accuracy and delayed the motor response in the acquisition of the task (Kato et al. 2011). On the other hand, if the projection was lesioned after the acquisition, the response accuracy was disturbed without any apparent change in the response time (Kato et al. 2011). It is noteworthy that neither pre- nor post-learning acquisition lesion of the Pf-striatal projection influenced spontaneous locomotion and motor skill learning (Kato et al. 2011). Because the CM and Pf are not clearly delineated in rodents, this study could not assess the relative impact of either nucleus on cognitive task performance.

Another strong evidence that selective ablation of the thalamostriatal system impairs cognition comes from Bradfield et al. (2013a) who showed that cytotoxic lesion of Pf neurons that project selectively to the posterior dorsomedial striatum (i.e., associative region of the rodent striatum) altered the firing rate and intrinsic activity of striatal cholinergic interneurons and produced significant deficit in goal-directed learning after changes in action-outcome contingency. In light of their findings the authors suggested that the plasticity between new and existing learning had been impaired by the thalamostriatal system lesion, which altered the flexibility in encoding action-outcome associations in response to a changing environment (Bradfield et al. 2013a, b).

In addition to these animal studies, case reports of patients with discrete infarct lesion of the CM/Pf complex who display various forms of attentional deficits, provide further evidence for a role of the CM/PF complex in cognition (Mennemeier et al.

1997; Liebermann et al. 2013). Some of these individuals were found to display a distinct dysexecutive syndrome characterized by deficits in shifting between cognitive sets, leaving other executive and memory functions much less affected (Liebermann et al. 2013). In light of these observations, we and others have suggested that the thalamostriatal system from CM/Pf is involved in regulating behavioral switching (or flexibility), reinforcement, and action selection (Kimura et al. 2004; Brown et al. 2010; Smith et al. 2011; Bradfield et al. 2013a, b; Fisher and Reynolds 2014; Minamimoto et al. 2014). Thus, the CM/Pf-striatal system appears to play an important role in detecting changes in incoming information important to shift goal-directed actions, which complements active cognitive processes in learning and filtering incoming information mediated by corticostriatal systems from associative cortices.

A key issue that remains to be addressed, however, is the relative contribution of the Pf-caudate versus CM-putamen projection in mediating these cognitive processes. Through series of behavioral, imaging and recording studies in rodents and primates, it is well established that the sensorimotor putamen plays a key role in habit learning (Jog et al. 1999; Yin and Knowlton 2006; Balleine et al. 2009; Balleine and O'Doherty 2010; Redgrave et al. 2010; Howe et al. 2011), while the anterior putamen and the caudate nucleus are involved in goal-directed learning [see Redgrave et al. 2010 for review]. In light of the recording data from Kimura and colleagues and the Pf lesion studies in rodents discussed above, it is clear that both the CM and Pf projections to the striatum contribute to the cognitive role of the thalamostriatal system in attentional set-shifting and behavioral switching, but the relative importance of each network in various aspects of cognition remains poorly understood. The impact of selective lesion of the CM-putamen or the Pf-caudate projection on cognition should be achieved to further address these points.

4.6 CM/Pf Cell Loss in Neurodegenerative Diseases: Potential Impact upon Early Cognitive Impairments

Postmortem studies have revealed 30–40 % CM/Pf neuronal loss in parkinsonian patients, even at an early stage of the disease (Xuereb et al. 1991; Heinsen et al. 1996; Henderson et al. 2000a, b, 2005; Brooks and Halliday 2009; Halliday 2009) (Fig. 4.4a). Significant CM/Pf neuronal loss has also been found in progressive supranuclear palsy and Huntington's disease (HD) (Heinsen et al. 1996; Henderson et al. 2000a, b). In animal models, CM/Pf cell loss can be induced in monkeys chronically treated with low doses of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Fig. 4.4b, c) or in rodents that receive intrastriatal injections of MPP+. Data from other rodent models of PD are controversial, some authors having reported neuronal loss, while others did not, in 6-OHDA-treated rats and mice (see Villalba et al. 2015, for review). In chronically MPTP-treated monkeys, the CM/Pf cell loss is seen even in motor-asymptomatic animals with minimal nigrostriatal dopaminergic denervation (Villalba et al. 2014). Loss of thalamostriatal terminals has been reported in a

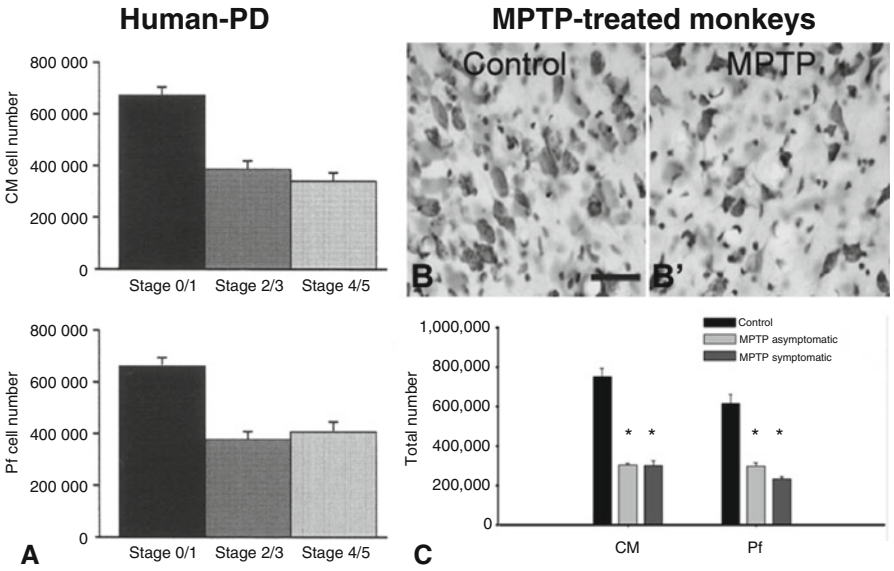


Fig. 4.4 Loss of CM/Pf neurons in Parkinson's disease patients and in chronically MPTP-treated monkeys. (**a**) Data from Henderson et al. (2000a, b) showing the significant decrease in the total number of neurons in the CM and PF of PD patients. Note that the extent of cell loss is as pronounced in patients with mild (Stage 2/3 Hoehn and Yahr scale) or severe (Stage 4/5 Hoehn and Yahr scale) parkinsonian motor symptoms, suggesting that CM/Pf neuronal degeneration is an early pathological phenomenon in PD (Modified with permission from Henderson et al. 2000a, b). (**b**, **b′**) Nissl-stained neurons in the CM of a control (**b**) and an MPTP-treated parkinsonian monkey (**b′**). Note the significant decreased density of neuronal cell body profile in the CM of the parkinsonian animal. (**c**) Stereological total cell number assessment in the CM and Pf of two groups of MPTP-treated monkeys. The *light gray bars* depict total cell number in the CM/Pf of motor-asymptomatic monkeys with partial (~40 % striatal dopamine denervation) depletion of the nigrostriatal dopaminergic system, while the darker bars illustrate total cell number in motor-symptomatic animals with severe $n \sim 80$ % striatal dopamine denervation) striatal dopamine denervation. Note that the extent of neuronal loss is the same in both groups of MPTP-treated monkeys, which support the human data shown in A. Scale bars: 50 μm. Modified with permission from Villalba et al. 2014

mouse model of Huntington's disease (Deng et al. 2014). The mechanisms of specific thalamic cell death in any of these conditions remain unknown. Loss of CM/Pf neurons in MPTP-treated monkeys results in a significant decrease in the density of vGluT2-positive (i.e., thalamostriatal) terminals in the associative and sensorimotor striatal territories (Villalba et al. 2015). It remains unclear if this thalamic denervation affects preferentially specific striatal projection neurons and interneurons. Although the functional consequences of this thalamic degeneration in PD remain to be established, it is likely to contribute to early cognitive deficits in attentional set-shifting and cognitive flexibility commonly seen in these patients (Brown and Marsden 1990; Dimberger and Jahanshahi 2013; Gerrits et al. 2015).

4.7 The CM/PF as a Target for Neurosurgical Interventions in Brain Disorders

The CM/Pf complex and the surrounding region of the caudal thalamus have been surgically targeted to alleviate symptoms of various brain disorders including chronic pain, seizures, impairments of consciousness, or movement disorders. For the purpose of this chapter, the following discussion will be mainly focused on the impact of CM/Pf surgeries on cognitive functions in patients with Tourette's syndrome, PD, or impaired consciousness.

Attempts at treating patients with Tourette's syndrome using ablation of intralaminar and medial thalamic nuclei date back from the 1960s (Hassler and Dieckmann 1970, 1973; de Divitiis et al. 1977; Hassler 1982). Although the effects were variable, some patients displayed significant reductions in tic frequency and compulsions. Since then, some TS patients underwent CM/Pf deep brain stimulation (DBS), which often reduced the frequency and severity of motor tics (Visser-Vandewalle et al. 2003, 2004, 2006; Temel and Visser-Vandewalle 2004; Houeto et al. 2005; Ackermans et al. 2006, 2008, 2010, 2011; Bajwa et al. 2007; Maciunas et al. 2007; Servello et al. 2008, 2010; Shields et al. 2008; Porta et al. 2009; Hariz and Robertson, 2010; Ackermans et al. 2011; Sassi et al. 2011; Maling et al. 2012; Savica et al. 2012; Visser-Vandewalle and Kuhn 2013), and had a major impact upon the psychiatric components of the disease, including obsessive-compulsive behaviors and anxiety (Houeto et al. 2005; Mink 2006; Visser-Vandewalle et al. 2006; Neuner et al. 2009; Krack et al. 2010; Sassi et al. 2011). These multimodal effects of CM/Pf surgical procedures are consistent with the fact that the CM/Pf complex is part of motor, associative, and limbic basal ganglia circuits (Fig. 4.1) (Kim et al. 2013). The use of CM/Pf DBS in PD patients remains experimental because only a few patients underwent such procedure. Overall, the effects have been variable, though positive effects on L-DOPA-induced dyskinesia, freezing of gait and tremor have been reported (Caparros-Lefebvre et al. 1999; Mazzone et al. 2006; Peppe et al. 2008; Stefani et al. 2009).

DBS in the central thalamus has been shown to improve behavioral responsiveness and general alertness following severe brain injury in humans (Schiff et al. 2007; Schiff 2008, 2009, 2013). This procedure restores consciousness in some comatose patients or patients in a vegetative state by changing the arousal state. Although the exact surgical target for these procedures extends beyond the confines of the CM/Pf, the convergent evidence that the CM/Pf complex is highly sensitive to arousal (see above) strongly suggests a possible involvement of the CM/Pf-striatal system in these effects.

4.8 Concluding Remarks

The increased knowledge of the CM/Pf complex in recent years has opened up tremendous opportunities for a better understanding of the role this nuclear complex and its connections with the striatum may play in cognition. Evidence for a potential role

of the CM/Pf-striatal system in attention, set-shifting, and cognitive flexibility is highly significant because these functions are impaired in neurodegenerative diseases that affect the basal ganglia, particularly PD and HD. The fact that CM/Pf neurons undergo massive degeneration in these diseases further supports this possibility. Future studies aimed at dissecting out the respective role of the CM-putamen versus Pf-caudate nucleus in cognition, and the involvement of these networks in cognitive impairments associated with PD are warranted. On a therapeutic perspective, additional knowledge about the cellular and molecular properties of CM/Pf neurons that make them particularly sensitive to neurodegeneration must be gained, so that potential protective or neurorestorative therapies can be considered.

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Chapter 5
Dopamine and Its Actions in the Basal Ganglia System

Daniel Bullock

5.1 Introduction: Consensus Summary of Dopamine's Actions in the Circuitry of the Basal Ganglia

There have been many recent excellent reviews of selected aspects of the dopamine (DA) system, including the range of stimuli and internal signals to which DA neurons respond (e.g., Bromberg-Martin et al. 2010; Schultz 2013), how DA release depends jointly on DA neuron firing and myriad factors present at release sites in the basal ganglia (BG) (e.g., Rice et al. 2011), the systematic effects of DA in the striatum (e.g., Gerfen and Surmeier 2011), and the role dopamine plays in various neurological disorders (e.g., Linnet 2014; Lloyd et al. 2014; Covey et al. 2014; Belujon and Grace 2015; Nutt et al. 2015) beyond its critical role in Parkinson's disease and schizophrenia (e.g., Iversen and Iversen 2007). This chapter will reprise many of the key findings needed to understand the consensus that is emerging about the neural systems—especially the BG system—within which DA plays its most critical role.

Like noradrenaline (NA), dopamine (DA) is an aminergic neurotransmitter, and Dahlström and Fuxe (1964) identified and designated 14 clusters of aminergic neurons: A1–A7 designate NA clusters, and A8–A14 designate DA clusters, most in the midbrain (see also Björklund and Dunnett 2007). In each cluster, DA cells are mixed with other cell types, but in all of these clusters, the aminergic neurons represent a large proportion of cells, and they typically project aminergic axons far beyond the nuclei in which their somas reside. Other brain structures also contain intermixed

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DA neurons—a good example is the retina—but these neurons are not a large proportion of the total, and function as interneurons, with no projections beyond the area. Recently, Fuxe and colleagues (2010) reviewed the huge literature that has developed since the A8–A14 clusters were mapped. They reprised impressive evidence that (1) a highly similar mapping applies across a wide range of mammalian species and (2) DA often works via volume transmission, which utilizes diffusion well beyond release sites (Rice and Cragg 2008; but see Ishikawa et al. 2013), hence does not require that the DA release sites be immediately adjacent to the receptors at which DA acts. Of course, all systemically delivered neuroactive drugs also work via volume transmission, after crossing the blood–brain barrier. Consistent with this mode of operation, single DA neurons exhibit remarkably widespread branching, with multiple axonal bushes, in target areas such as the striatum (e.g., Matsuda et al 2009). Thus, DA is typically regarded as a nonspecific, "broadcast" signal, highly distinct from the specific, topographically organized projections found in other neural systems, e.g., at successive stages of processing within a sensory modality, or in the motor output pathways.

Although DA signals play diverse roles in the neural symphony, one prototypical and vital role is as a primary mediator of the ancient learning process by which animals explore novel environments and thereby learn both to choose actions that are expected to lead to more rewarding outcomes, and to suppress actions expected to lead to less rewarding or aversive outcomes. Dopamine strongly affects such learning via its systematic effects on LTD and LTP of glutamatergic synapses between afferents to striatum and the medium spiny neurons (MSPNs) that project from striatum to other BG nuclei. However, DA also has strong effects on performance, including both motor and cognitive performance. Its influence on performance is powerfully attested by the tight link between striatal DA loss and Parkinsonian akinesia, but it is also revealed in much subtler ways, such as a higher velocity of eye movements to rewarded than to equidistant but non-rewarded targets (Hong and Hikosaka 2011), and altered reaction time distributions following sleep deprivation, which have been reproduced in a computational model that includes dopamine–adenosine interactions in striatum (Bullock and St. Hilaire 2014).

Action selection based on expected outcomes is enabled by mammalian forebrain circuits, among which the striatum and other constituents of the BG (see Fig. 5.1) have a preeminent status (Swanson 2005; Gurney et al. 2015). Although DA innervation is densest in striatum, it also reaches many other parts of the brain, especially parts of the BG, thalamus, and cerebral cortex. Moreover, the innervation of cerebral cortex is significantly more elaborated in primates than in rodents (Smith et al. 2014). Because operation of the BG is so critically dependent on dense innervation from DA neurons of cluster A10 (much of which falls in the VTA), A9 (mostly in the SNc), and A8 (mostly in the retrorubral area = RRA), these pools are regarded as an integral part of the BG system in this chapter. Thus, the BG system spans cells found in both the subcortical forebrain and the midbrain.

DA acts differentially in striatum by facilitating a "direct", action-promoting pathway, and by simultaneously dis-facilitating an "indirect", action-opposing path-

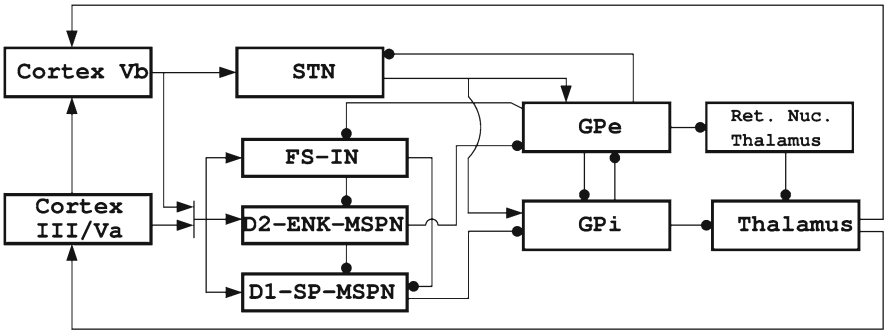

Fig. 5.1 Basic connectivity of the basal ganglia. Arrowheads indicate glutamatergic links; all others are GABAergic, but MSPNs co-release ENK or SP. *STN* subthalamic nucleus, *FSIN* Fast-spiking interneuron, *MSPN* medium spiny projection neuron, *D2* dopamine D2 receptor, *ENK* enkephalin, *D1* dopamine D1 receptor, *SP* substance P, *GPe* globus pallidus externus, *GPi* globus pallidus internus, *Ret. Nuc.* thalamus reticular nucleus of the thalamus, Vb, III, and Va are layers of cerebral cortex. Adapted from Bullock et al. (2009)

way (see Fig. 5.1). The same DA signal can have such opponent effects because DA-recipient cells express either D1-type DA receptors (namely D_1 or D_5 receptors), which facilitate neural activation, or D2-type receptors (namely D_2, D_3, or D_4 receptors), which dis-facilitate neural activation. The striatal cells of origin of the direct (GO) and indirect (NO-GO) pathways are variously called medium spiny neurons (MSNs or MSPNs), or Medium densely Spiny Projection Neurons (MdSNs). The D1-M4-SP-DYN-GABA-MSPNs of the direct pathway express both dopamine D1 receptors (D1Rs) and muscarinic m4 receptors (M4Rs), and co-release GABA, substance P (SP), and dynorphin (DYN). The D2-M1-ENK-GABA-MSPNs of the indirect, "NOGO" or "STOP," pathway express dopamine D2 receptors (D2Rs) and muscarinic m1 receptors (M1Rs), and co-release GABA and enkephalin (ENK).

As one might expect, the simple D1-MSPN vs. D2-MSPN scheme for striatum, proposed in seminal works such as Gerfen et al. (1990), does not capture the *entire* story of MSPN types and their projections to targets outside striatum (e.g., Surmeier et al. 1996; Sonomura et al. 2007). Nevertheless, it remains a valid and key starting point for understanding the system's fundamental organization (Gerfen and Surmeier 2011). The differential action of DA on these two opponent pathways, which is well established for the striatum in primates and rodents and schematized in Fig. 5.2, appears to be *extremely* ancient in the animal kingdom. Such opponent pathways are ubiquitous across the vertebrates (Reiner 2009), including even jawless fish (Grillner and Robertson 2015), and recent reports have argued for a systematic homology between the core vertebrate and arthropod neural circuits for DA-guided behavior control (Strausfeld and Hirth 2013) and reinforcement learning (Waddell 2013).

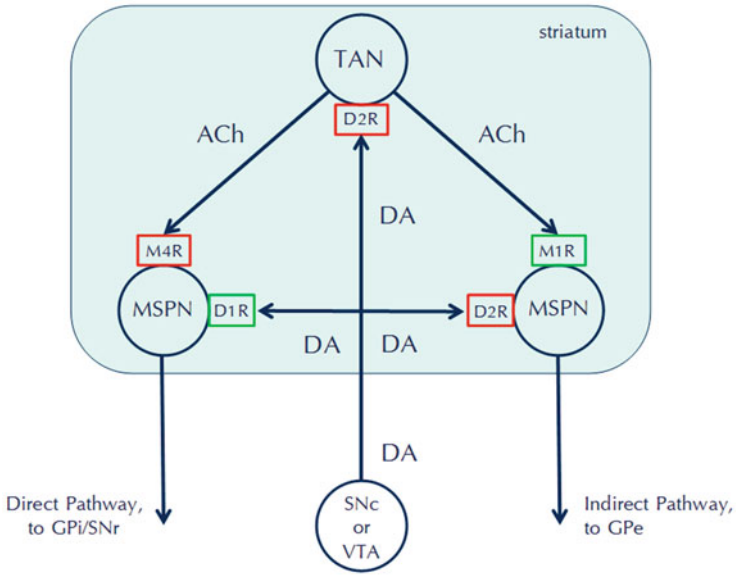

Fig. 5.2 How tonically active neurons (TAN) mediate part of the DAergic regulation of medium spiny neurons (MSPN) in striatum. Acetylcholine (ACh) released by a TAN inhibits MSPN expressing the dopamine D1 receptor (D1R) via the muscarinic 4 receptor (M4R) and stimulates MSPN expressing the dopamine D2 receptor (D2R) via the muscarinic 1 receptor (M1R). Dopamine (DA) released by the substantia nigra pars compacta (SNc) or the ventral tegmental area (VTA) stimulates MSPN expressing the D1R receptor and inhibits MSPN expressing the D2R receptor. Dopamine also inhibits TAN via the dopamine D2 receptor. *GPe* globus pallidus externus, *GPi* globus pallidus internus, *SNr* substantia nigra, pars reticulata

5.2 The Dopamine-Acetylcholine Cascade in Striatum

It can be expected that such an ancient neural feature as learned behavior guided by rewards and punishments would be robustly supported by multiple, partly redundant, mechanisms in modern brains. Indeed, Fig. 5.2 (adapted from Tan and Bullock 2008a) highlights the fact that in mammals, there is a well-established dopamine-acetylcholine cascade within the striatum. In addition to its direct action on MSPNs, DA acts via D2Rs to inhibit large ACh-releasing striatal interneurons, which are alternately called TANs (tonically active neurons) or ChINs (cholinergic interneurons). A close study of Fig. 5.2 reveals that the actions of DA and ACh are synergistic. A DA burst will induce TAN pausing, and both the DA increment and the ACh decrement favor the direct pathway's D1-MSPNs over the indirect pathway's D2-MSPNs; conversely, a DA dip will disinhibit TANs, and both the DA decrement and the ACh increment favor the indirect over the direct pathway MSPNs. These opposing synergistic actions are possible because both DA neurons and TANs are tonically active ("pacemaker") neurons that can exhibit antiphase bursts and pauses

(Morris et al. 2004), and because DA has opposite actions via D1Rs and D2Rs, whereas ACh has a reversed set of opposite actions via M1Rs and M4Rs (Kaneko et al. 2000; Hoebel et al. 2007). A human watchmaker of the old school would admire the beauty of this machine.

The robustness-promoting redundancy probably has several further components. For example, the DAergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) is complemented by a GABAergic projection, and Cohen et al. (2012) presented data indicating that all VTA GABA neurons (presumably including those projecting to NAcc) showed sustained increases in activity during an interval between onset of a reward-predicting odor-cue and actual reward delivery. Since the VTA GABAergic projection to NAcc synapses preferentially on TANs (Brown et al. 2013), this projection's effect in striatum is synergistic with the effect of the DAergic projection: it promotes the direct pathway while opposing the indirect pathway.

The Fig. 5.2 circuit helps to explain a wide range of effects. For example, both DA agonists and acetylcholine (Ach) antagonists can help normalize function in a striatum suffering from DA depletion, e.g., in the striatum of patients with Parkinson's Disease (PD). Early findings of a critical role for striatal DA loss in PD (Hornykiewcz 1973) have been abundantly supported (e.g., Iversen and Iversen 2007), and it has been verified that some human DA cell populations that project to striatum, such as those in the ventral tier of the substantia, pars compacta (SNc), are usually lost much earlier in the disease process than other DA cell populations, such as those in the VTA (Damier et al. 1999) or (in the primate MPTP model of PD) in the periaqueductal gray (PAG) (Shaw et al. 2010). The DA-ACh cascade in Fig. 5.2 has also been strongly implicated in dystonia. Recent research (e.g., Sciamanna, et al. 2014; Jaunarajs et al. 2015) indicates that DYT1-type dystonia depends on a genetic mutation that flips the sign of action of DA in the striatal DA-ACh cascade: the mutation makes D2R activation excitatory to striatal TANs, not inhibitory. This affects not just performance but also learning, because some DA- and D2R-dependent learning effects, once attributed solely to direct DA action on D2-MSPNs, are mediated by D2Rs on TANs (Wang et al. 2006). The reader is referred to Chap. 7 in this volume for further discussion on the possible role of the basal ganglia in dystonia.

However, the Fig. 5.2 circuit is not the whole story, even for striatum, and DA loss in other parts of BG also contributes to motor disorders (Rommelfanger and Wichmann 2010). More broadly, there are clinically important differences between primates and rodents in DAergic innervation beyond the BG (Smith et al. 2014). Notably, there is much greater DAergic innervation of motor cortex from SNc in primates than in rodents (Berger et al. 1991; Williams and Goldman-Rakic 1998). In consequence, DA loss in humans may have dramatic motor effects beyond the striatum and other BG nuclei. A further caveat is that DA cell loss is often accompanied by cell loss in other monoaminergic nuclei of the midbrain/brainstem (Surmeier and Sulzer 2013), and some animal models involve a PD-like syndrome with cell loss *restricted* to such nuclei, e.g., the locus coeruleus (Delaville et al. 2011). More generally, many effects of DA loss on motor and cognitive performance can be partly mimicked by loss of other neuromodulators.

5.3 Multiple Components Found in Dopamine Neuron Signals

DA neurons operate in several modes. They are spontaneously active pacemakers, and the associated tonic release of DA is vital for normal performance of actions mediated by BG circuits. Rapid progress in understanding the learning effects of DA was catalyzed by the discovery that the DA signal in SNc/VTA also has distinct phasic components, which are responsive to learning. In addition to the tonic component associated with pacemaker firing, Schultz and colleagues (e.g., Schultz 1998) observed *burst and dip components* that reflect positive and negative reward prediction errors (R-PEs). Fiorillo et al. (2003) later discovered an *uncertainty component* (of the DA signal in SNc and VTA) that is maximal when the odds of a favorable vs. unfavorable outcome are even ($p = 0.5$ for either). The same component is often called a risk signal.

5.3.1 Dopamine as an Internal Reinforcement Signal

A consensus has emerged that the phasic components of the DA signal—bursts and dips—have all the characteristics of an internal reinforcement signal, i.e., an internal signal that always shows appropriate properties when events that constitute positive or negative reinforcers occur. Event types that constitute positive or negative reinforcers have been established in behavioral studies of reinforcement learning in both classical (Pavlovian) and operant conditioning paradigms. Rewards that are not completely predictable in timing and magnitude elicit a DA burst response in SNc and VTA (Schultz 1998, 2013; Bermudez and Schultz 2014), whereas onset of an aversive input elicits a DA pause response (Tan et al. 2012; Mileykovskiy and Morales 2011; Fiorillo 2013; Fiorillo et al. 2013). Also, the offset of an aversive stimulus—a strong negative reinforcer of learned avoidance responses—induces rebound DA release (Budygin et al. 2012; Navratilova et al. 2012; Fiorillo et al. 2013). It has been shown that bored animals will work to earn presentations of novel, non-aversive stimuli (they are positive reinforcers), and such stimuli elicit DA bursts (e.g., Bromberg-Martin et al. 2010) until their novelty wears off (Lloyd et al. 2014). Similarly, both the burst responses of DA neurons and the reinforcing power of a primary reward wane with satiation for that reward (Cone et al. 2014; Ostlund et al. 2011).

Moreover, it has been shown, mostly through classical conditioning paradigms, that when a cue-A reliably predicts a following reward, cue-A by itself can serve as a (conditioned) reinforcer. Such reward-predicting cues also elicit DA bursts. After such training with a cue-A, the introduction of a redundant cue-B, coincident with cue-A, does not lead to any new learning about cue-B, a phenomenon known as blocking. Notably, cue-B does not become a conditioned reinforcer. This suggests that after cue-A is established as a reliable predictor of reward, and cue-B coincident with cue-A is followed by that reward, that reward is no longer a reinforcer in

the context of cue-A. Indeed, once cue-A is established as a reliable predictor of reward, the reward itself no longer elicits a DA burst (Schultz 1998, 2013). This effect is graded: to the extent that cue-A is less than perfectly reliable as a predictor—because the exact timing, magnitude, or probability of reward is not certain, a second cue-B can be learned. Correspondingly, such uncertainty leads to less than complete suppression of the DA cells' burst responses to reward, and the residual burst response to reward appears to depend more on probability than reward size (cf. Tan et al. 2008). Finally, if a conditioned reinforcer cue-A is ever not followed by the expected reward, it begins to extinguish as a conditioned reinforcer. This suggests the existence of an internal signal of opposite sign, and indeed, every such presentation of cue-A followed by omission of the expected reward induces a DA dip (Schultz 1998, 2013). From such correspondences, and the mediation of positive reinforcement learning by D1 and D2 receptors (e.g., Steinberg et al. 2014), it appears that the phasic components of the DA signal observed in SNc and VTA, and in striatal zones that receive the signal in the form of increments or decrements of DA release, are suitable to guide reinforcement learning of the type seen in behavioral studies with many species of animals.

Associative learning has been shown to depend on more than the dopaminergic reward prediction error signal. Notably, it also depends on an arousal or attentional signal that is high when surprising outcomes occur (cf. Song and Fellous 2014). Recently, evidence has begun to accumulate that these arousal signals are present in the basolateral amygdala (BLA), which projects strongly to the ventral striatum. Moreover, the BLA arousal signal itself depends on DAergic R-PE signals sent to BLA (Esber et al. 2012). Thus, DAergic R-PE signals can effect striatum via the direct projections from VTA/SNc as well as indirectly via the BLA.

5.3.2 Reward Prediction Errors, Punishment Prediction Errors, or Both?

Because of the burst and dip components of DA neurons, the hypothesis was advanced that the phasic components of the DA signal constitute a reward prediction error signal: a burst occurs whenever an outcome is better than expected, and a dip whenever an outcome is worse than expected. As already noted, an unexpected aversive event causes a dip in DA neuron firing. Suppose that a cue-C is followed reliably by an aversive event. Will that cue-C come to elicit a DA firing dip, and will the aversive event itself no longer cause a DA dip on trials when cue-C is presented as predictor of the aversive event? If the answer to these questions was to be yes, for at least some DA neurons that also show R-PE signals to rewarding cues and events, then it could be claimed that such DA cells signal a full range of value prediction errors, whether the events involved are aversive or rewarding. This question is still unsettled. Fiorillo (2013) showed that many DA neurons in dorsal SNc do not code prediction errors for aversive stimuli. Though they do show dips in response to aversive stimuli, they do not stop responding to cue-signaled aversive stimuli once

the animal has learned the predictive status of the cue. From these studies, Fiorillo concluded that the prediction error processing systems for reward must be separate from that for aversive/punishing events: there are two dimensions, rather than a single dimension with both negative and positive regions. Below, this "separate dimensions" conclusion is endorsed, but with the caveat that separable DA cell clusters probably mediate the separate A-PE (aversive prediction error) signaling. Indeed, Fiorillo's exclusion of DA cells from the latter system has been challenged (Morrens 2014) on grounds that Fiorillo (2013) recorded very few cells in VTA, which in some other studies (e.g., Matsumoto and Hikosaka 2009; Matsumoto and Takada 2013) has been shown to have a higher percentage of DA neurons that respond to both rewards and aversive events.

Although both Fiorillo (2013) and Morrens (2014) state that no one has identified A-PE cells, striatal A-PE signals have been reported (e.g., Delgado et al. 2008), and others report that A-PE cells, as such, have been identified, but remain understudied relative to DA neurons in VTA and SNc. Johansen et al. (2010) and McNally et al. (2011) summarized rodent data indicating that an A-PE is computed in the vlPAG (ventrolateral periaqueductal grey). In this system, the learned, cue-dependent expectation of an aversive outcome appears to be mediated in part by release of an endogenous opioid, which is capable of canceling the effect on vlPAG neurons of an ascending pain signal (Cole and McNally 2007; Krasne et al. 2011). Roy et al. (2014) reported analyses of human functional magnetic resonance imaging (fMRI) data that supported the hypothesis regarding PAG (fMRI resolution was insufficient to isolate vlPAG), while also ruling out several other candidate areas, such as the ventral striatum, as sites that compute A-PEs.

Whereas in the fear conditioning model of Krasne et al. (2011), which is based mostly on rodent data, the source of learned expectations sent to PAG is the CeA (central nucleus of the amygdala), the human fMRI study of Roy et al. (2014) implicated the putamen and vmPFC. However, there may be no cross-species discrepancy because the CeA, a key part of the EA (extended amygdala; Zahm et al. 2011), borders the putamen, and like putamen, can be classified as a striatal territory (Swanson 2000), in which the dominant type of cells are MSPNs that receive a convergence of glutamatergic inputs (from cortex and pyramid-rich amygdalar nuclei, notably BLA) and ascending DAergic inputs from the midbrain. Indeed, the lateral CeA, lCeA, which is a key site of fear conditioning and is medial to and continuous with the putamen, contains GABAergic and somatostatin-positive long-range projection neurons that directly inhibit PAG neurons (Penzo et al. 2014; Penzo et al. 2015). Finally, although McHugh et al. (2014) report blood oxygenation-dependent (BOLD) and local field potential (LFP) responses (but not single unit responses) in basolateral amygdala (BLA) that reflect A-PEs, this is consistent with the proposal that the primary A-PE computation occurs in PAG. The multiple pathways by which PAG output affects BLA, another major site of fear learning, remain to be established, but one via mid and intralaminar thalamus is a good candidate, because it has been implicated in mediation of the PE-dependent blocking effect in fear conditioning (Sengupta and McNally 2014).

One caveat noted by McNally et al. (2011) is that whereas the A-PE cells of vlPAG exhibit robust positive prediction errors, they have not been shown to exhibit responses (e.g., pauses) that are indicative of negative prediction errors. However, Berg et al. (2014) have recently reported that neurons in the adjacent dorsal raphe nucleus (DRN) do exhibit robust responses to negative A-PEs. They further showed that lesions of DRN did not impair fear acquisition on deterministic schedules, but did impair learning during fear extinction and during adaptation to Pavlovian fear conditioning that used probabilistic CS-US contingencies. This selectivity is just what is expected if DRN mediates negative but not positive A-PE signals. Furthermore, the DRN innervates both BLA and CeA sectors of the amygdala.

Such data immediately raise the question of whether DA neurons are critically involved in the PAG/DRN system for computing A-PEs and projecting PE signals to learning sites in the EA. In fact, there is a continuous vein of DA neurons within the vlPAG and adjacent retrorubral area that is known as dcA10 (Hasue and Shammah-Lagnado 2002; Yetnikoff, et al. 2014), i.e., the dorso-caudal compartment of A10 (whereas the main compartment of the DA neuron population known as A10 is in the VTA). Three classes of DA cells are known to exist in vlPAG, and its DA cells have been implicated as mediators of PAG's role in opioid reward and reduction of nociception (Flores et al. 2006; Dougalis et al. 2012; see also Messanvi et al. 2013, which has implicated an additional DAergic projection from A13 in opioid effects). Moreover, Hasue and Shammah-Lagnado (2002) reported that nearly half of the tyrosine hydroxylase-labeled fibers in CeA originated in the vlPAG. Such tyrosine hydroxylase fibers are usually indicative of neurons that release DA, and Poulin et al. (2014) reported that their DA neuron subtype DA^{2D} was localized in PAG and DRN and projected to two territories, the striatum-like lateral central amygdala (lCeA) and the pallidum-like oval portion of the bed nucleus of the stria terminalis (oBST), but not to other striatal or pallidal territories. Because of this specificity of projection, DAergic A-PEs could have appropriately different effects than DAergic R-PEs arising in SNc or the main part of VTA. Although definitive research appears to be lacking, an otherwise puzzling observation consistent with this possibility is the finding (Flores et al. 2006) that D2R blockade in vPAG (and adjacent DAergic RLi) dose-dependently opposed the rewarding effects of opioids. If this effect were assumed to be mediated by D2Rs acting as inhibitory autoreceptors on DA cells that signal *R-PEs*, it is very puzzling. If instead these DA cells signal *A-PEs*, the result is as expected: D2R blockade would lead to greater DA release in lCeA that would oppose opioid reward by promoting learned aversion. Such direct competition between the processing of rewarding and aversive stimuli has been demonstrated in recent studies (Choi et al. 2014; Namburi et al. 2015). If verified, the hypothesis of A-PE-mediating DA cells, in vPAG/DRN, that project uniquely to both lCeA and oBST is of great interest. Both areas are strongly implicated in conditioned fear and anxiety (Day et al. 2005, 2008; Haubensak et al. 2010; Fox et al. 2015).

Although direct activation of *identified* DA cells in vlPAG by aversive cue onsets has not yet been reported, there have been such reports for some other A10 subpopulations, e.g., a subset of VTA dopamine neurons (Gore et al. 2014; Brischoux

et al. 2009) that are important for normal fear conditioning (Zweifel et al. 2011). Relatedly, increments of DA release to aversive cue onsets have been observed in the shell of NAcc (Badrinarayan et al. 2012). Finally, Poulin et al. (2014) noted that their Vip-expressing DA^{2D} pool in PAG/DRN did not project to cortex, and Flores et al. (2006) noted three total (non-NE) TH-labeled neuron types in the vPAG/DRN. One that is DAergic has projections to PFC and has been implicated in ascending arousal and control of waking (Lu et al. 2006). It has also been suggested (Misu et al. 1996) that some of the TH-labeled neurons of dcA10 are DOPAergic but not DAergic; they release DA's endogenous precursor, L-DOPA, instead of DA. This is of interest because L-DOPA as such has been shown to act as a transmitter (Misu et al 2002; Porras et al. 2014). In striatum, it can act via D2 receptors on TANs (see Fig. 5.2) to reduce ACh release.

Figure 5.3 summarizes the emerging picture regarding prediction error (PE) computations involving DA neurons in SNc and VTA (left column), and vlPAG (middle column), corresponding respectively to the Poulin et al. (2014) types DA^{1A} (ventral tier SNc), DA^{1B} (dorsal tier SNc), DA^{2A} and DA^{2B} (in VTA), and DA^{2D} (in PAG/DRN). The rightmost column in Fig. 5.3 makes the point that PE computation is not exclusive to DA neurons. As exemplified here, it is also performed by non-DAergic neurons in the olivary nuclei, another ancient subcortical region. In all, the three columns in the Fig. 5.3 cover four sites for computing PEs in "Pavlovian" (CS-US) learning paradigms. In each case, a neural stage compares a learned centrifugal inhibitory expectation with an unlearned centripetal excitation to compute a PE that serves as a "teaching signal." The comparisons respectively involve: convergence of CS-induced inhibitory dorsal or ventral striatal output and rewarding-US-induced excitatory inputs to DAergic R-PE cells of the SNc/VTA; convergence of inhibitory CeA output and excitatory (nociceptive) US inputs to proposed DAergic A-PE cells of the vlPAG; and convergence of inhibitory deep-cerebellar (DNC) output and excitatory US input to glutamatergic PE neurons of the olivary nuclei, which are the source of the climbing fiber signals that gate learning in the cerebellar cortex (Medina et al. 2002). There is growing evidence that similar "neural comparators" enable PE computations in cerebral cortex (Berteau et al. 2013).

Further evidence that the two DAergic circuits in Fig. 5.3 mediate reward vs. aversion learning comes from studies showing that the NAcc-VTA system and the CeA-PAG system have opponent properties (Namburi et al. 2015; Nasser and McNally 2013). Nevertheless, it is vital to remember that the amygdala system, as a whole, mediates the assignment of salience to a full range of motivationally relevant cues, not only those that predict punishment. Notably, much research (e.g., Esber et al. 2015) has implicated a projection from CeA via SNc to the dorsolateral striatum (DLS) both in reward-guided learning of conditioned orienting responses and in the enhanced attention accorded to surprising omissions of expected stimuli. Altered DA release in DLS by fibers from SNc is a common factor in these learning and performance effects.

In summary, for many years mammalian research implicated DA in R-PE computations and appetitive learning. Recent data suggest an equally pivotal role for DA

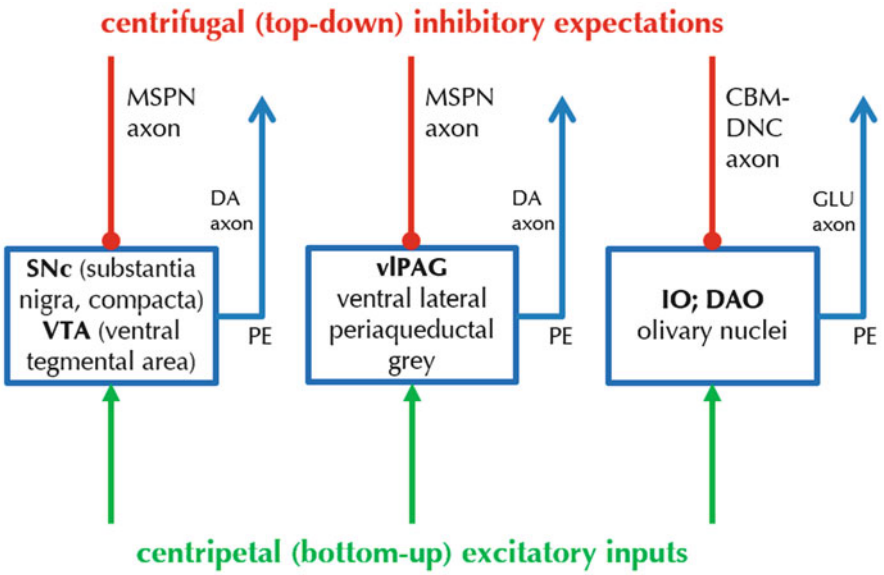

Fig. 5.3 Comparisons of inhibitory expectation signals with excitatory stimulus-induced signals are mediated by dopamine neurons of VTA or SNc (*left*), dopamine neurons of the ventral lateral periaqueductal grey (*middle*; vlPAG), and by glutamate-releasing neurons of the olivary nuclei (*right*; IO and DAO). *MSPN* medium spiny neuron, *DA* dopamine, *GLU* glutamate, *DNC* deep cerebellar nucleus, *CBM* cerebellum, *PE* prediction error

in A-PE computations and aversion learning. For arthropods (e.g., drosophila), research proceeded in the opposite order. Early studies implicated DA in aversion learning, but recent research shows an equally vital role in appetitive learning (Waddell 2013).

5.3.3 Dopamine Cell Firing Rate Is Only One Factor Controlling Dopamine Release Amounts

Charting the relationship between the behavior of DA neurons and actual release of DA from fiber terminals in striatum or other brain areas has proven to be surprisingly complex. This is because several distinct factors act on DA fiber terminals to modulate or gate release (Zhang and Sulzer 2012; Cachope and Cheer 2014). For example, Howland et al. (2002) and Jones et al. (2010) have reported evidence that activation of glutamatergic fibers projecting from BLA to NAcc caused release of DA in NAcc, even when the VTA was inactivated with lidocaine. In contrast, Taepavarapruk et al. (2008) reported that activation of glutamatergic fibers from hippocampus to NAcc enhanced DA release in NAcc only if the VTA was

coincidently activated. Threlfell and colleagues (2011, 2012) have reported that ACh release from TANs strongly affects striatal DA release, and does so differently in ventral vs. dorsal striatum. Brimblecombe and Cragg (2015) presented evidence from mice that striatal DA release is partly controlled by striatal SP, in a way that varies across three chemically defined striatal compartments (Graybiel and Ragsdale 1978; Faull et al. 1989). Notably, SP promoted DA release in striosome centers, opposed DA release in striosome-matrix border zones, and had no effect on DA release in the striatal matrix. This suggests that SP-sensitive neurokinin receptors are expressed in DA neurons projecting to striosomes, but not in those projecting to matrix. This aligns well with the finding (Gerfen et al. 1987) that the midbrain DA neurons projecting to striosomes (aka striatal patches) are segregated from those projecting to the matrix. In particular, a large proportion of striosome-projecting DA neurons were found in the ventral tier of the SN, which is also the locus of the DA neurons that are most vulnerable in human PD (Damier et al. 1999). Finally, it should be noted that once released, then, depending on site-specific factors such as local diffusion rates and dopamine transporter (DAT) levels, DA acts for shorter or longer intervals, and at sites nearer or more distal to terminal release sites. Across the ventromedial to dorsolateral axis of the striatum, there is sufficient covariation of terminal density (hence number of release sites) and DAT expression to imply significantly different signal dynamics, and, presumably, related effects on synaptic learning processes that are gated by DA (Wickens et al. 2007; Patrick et al. 2014).

5.3.4 Does the Magnitude of Dopamine Release Indicate the Subjective Utility of an Option?

After training with reward-predicting cues (Fiorillo et al. 2003; Tobler et al. 2005), the magnitude of DA single neuron and DA population burst responses to cues scales with the expected value, i.e., the product of reward size and the conditional probability of reward given the cue, p(rewardlcue). Such results suggest, but do not entail, that DA might serve as the "common currency" used to weight options prior to decision-making. However, there appear to be limitations of ventral striatal DA release as a predictor of action selection when response costs are significant (e.g., Hollon et al. 2014). Moreover, there is abundant evidence that there are both DAergic and non-DAergic evaluation systems in the brain (e.g., Dranias et al. 2008; Brooks et al. 2010).

A well-known result from the operant conditioning literature is that an animal will switch its preference from an option A, which gives a larger reward that is earned by more responses, to an option B, which gives a smaller reward for fewer responses, if the difference in the response costs is large enough. In short, action preference depends on a cost–benefit analysis, not solely on the expected benefit. Evidence suggests that DA release is important to motivate choices that entail

response costs (Salamone et al. 2003; Mott et al. 2009; Ostlund et al 2012). But does the amount of DA released itself reflect expected response costs? This answer is a qualified "yes" for NAcc: DA release is less when a cue predicts a reward with a high response cost relative to a cue that predicts the same reward with a smaller response cost (Day et al. 2010). However, when actual preference (choice between alternatives) is used to create a common value scale for response costs and reward magnitudes, it can be shown that DA release is less sensitive to response cost changes than to equivalent (for purposes of decision/preferences) reward magnitude changes (e.g., Gan et al. 2010). This result implies that DA release cannot be used to predict behavioral decisions once response cost is increased to a point at which an animal will switch from a higher-reward, higher-cost option to a lower-reward, lower-cost option. This implication was tested in Hollon et al. (2014), who showed in rats that cue-evoked DA release in the NAcc core sensitively reflects the reward expected, given a cue signaling a response option, but less sensitively reflects the response costs entailed by the same option. They further showed that measurements of the relative sizes of cue-induced DA releases in NAcc core to a cue-A and a cue-B cannot be used to predict an actor's behavioral preference between the options signaled by cues A and B if the response costs associated with the larger reward option were high enough that the animal preferred the option with smaller reward but little response cost.

Thus, available data indicate that DA release in the NAcc core, as such, is not a "common currency" that reflects the net "expected subjective utility" of an option, once all factors (costs and benefits) have been considered. How generalizable is this result? One caveat is that the NAcc is better associated with Pavlovian conditioning and activation of innate behaviors than with non-innate behaviors acquired by operant conditioning (Gruber and McDonald 2012), although NAcc is important for invigorating learned behaviors. It remains possible that DA release in some striatal zone better associated with learned strategies and behaviors, e.g., dorsomedial (DMS) or dorsolateral (DLS) striatum, will be shown to reflect an integration of benefits with costs that gives appropriate weighting to costs, and so predicts actual decisions. Finally, this unsettled issue of a DA signal that reflects costs and benefits must be separated from the issue of whether striatal activations, e.g., of MSPNs, prior to decision reflect expected benefits and costs. There is some evidence that they do (Day et al. 2011), although the relative sensitivity to both factors needs further examination.

5.3.5 Dopaminergic Control of Synaptic Plasticity

In the BG, DA signals act to modulate experience-induced changes in the strength of thalamo-striatal and cortico-striatal synapses. This is true for synapses onto both major types of striatal projection neurons: D1-M4-SP-DYN-GABA-MSPNs (direct pathway neurons) and D2-M1-ENK-GABA-MSPNs (indirect pathway neurons).

Several studies have shown that some learning can occur without DA signal changes. However, many more have shown that DA level shifts can oppositely change the relative dominance of long-term potentiation (LTP) vs. long-term depression (LTD) in the indirect vs. direct pathways, while also acting as a modulator of learning rates. A series of computational models (e.g., Reynolds and Wickens 2002; Brown et al. 2004; Frank 2005; Gurney et al. 2015) have aligned behind the complex hypothesis that: (1) high DA, resulting from a burst release, promotes both LTP of task-activated cortico-striatal synapses onto direct path MSPNs and LTD of task-activated cortico-striatal synapses onto indirect pathway MSPNs and (2) low DA, resulting from a dip below baseline DA levels, of the type induced by nonappearance of an expected reward, promotes both LTD of task-activated cortico-striatal synapses onto direct path MSPNs and LTP of task-activated cortico-striatal synapses onto indirect pathway MSPNs. Such learning effects of DA fully complement the performance effects of DA described earlier. These hypotheses, together with their implications for reward-guided acquisition and extinction of behavior, were shown to be reconcilable with some key in vitro studies of striatal plasticity (e.g., Shen et al. 2008) in the systematic modeling study of Gurney et al. (2015).

5.3.6 Dynamics of DA Signaling Across Ventromedial to Dorsolateral Striatum in Habit Formation

Extensive research shows that the pathways that mediate habitual performance can differ markedly from the pathways that mediate performance at initial acquisition, and until a habit is formed. One generalization is that features of the reinforcement schedule, in particular the contingencies between response and reward delivery, have a strong effect on which part of the forebrain, and notably, the striatum, will come to mediate performance (Yin et al. 2005, 2006; Gruber and McDonald 2012). In many cases, behavioral control is first mediated by ventral striatum (VS), then by dorsomedial striatum (DMS) and finally, if the schedule is habit-forming, by dorsolateral striatum (DLS). Correspondingly, DA can modulate learning about three fundamental aspects of reinforcement contingencies (Colwill and Rescorla 1986; Dickinson et al. 1995): stimulus–outcome associations (in the VS, notably NAcc), response–outcome associations (in the DMS), and stimulus–response associations (in the DLS). The reader is referred to Chaps. 2, 11–13, and 18 in this volume for further discussions on the role of the dorsolateral and dorsomedial striatum.

In this context, a key question is whether there are learning-correlated shifts in DA delivery to striatal parts that correspond to transfer of control among those parts. There is growing evidence that there is a correspondence between DA delivery shifts and behavior control shifts. For example, Ito et al. (2002) found that elevated DA release in dorsal striatum accompanies presentation of a cocaine-predicting CS if it is produced contingent on a response but not if it's presented non-contingently. At the same stage of learning, the same response-contingent presentation of a

cocaine-predicting CS does not produce elevated DA release in the shell or core of the NAcc. However, noncontingent presentation of a cocaine-predicting CS does produce DA release in the core, but not the shell, of NAcc. More recently, researchers have used fast-scan voltammetry (FSCV) to assess phasic DA release in VS vs. DMS and DLS as training progresses, again with cocaine as reward. Willuhn et al. (2012) showed that during training, the response-contingent DA release in DLS waxed as the release in VS (NAcc core) waned. Similarly, but using response-contingent cued delivery of alcohol as a reward, Shnitko and Robinson (2015) reported phasic DA release to the cue in both VS and DLS, but not DMS. The "not DMS" was not surprising, because the study used a VI-30s reinforcement schedule, which reduces the response–outcome contingency, and does not promote behavior control by the DMS. No computational model has simulated even this range of striatal-subarea-specific DA releases, let alone the many others now known. Nevertheless, most should be explicable with four principles compatible with models that have had significant success with subsets of the data: (1) inhibition/cancellation of DA burst responses to predictable rewards (or reward-predicting cues) depends on predictions mediated by parts of the striatum (Fig. 5.3); (2) no part of the striatum projects to all the DA neurons that send DAergic afferents back to striatum; (3) the predictions mediated by a given part of the striatum can only be as good as the information it receives, and has had a chance to learn to use, as a basis for predictions; and (4) different parts of striatum differ fundamentally in the kind of information they receive and use for prediction.

Any learning-gating signal that has the form of a PE signal vanishes under normal conditions once it is perfectly predictable by a learner with a given predictive competence. If, due to an imposition of "abnormal conditions," the signal that normally requires a PE occurs without it, then one can expect a learning-induced disorder in the system. Most addictive drugs qualify as impositions of abnormal conditions in this sense, because they interfere with the normal dependence of DA elevations on PEs. For example, cocaine blocks the action of DATs, and opioids disinhibit DA neurons in VTA. The consequences are often explicable as an abnormal accentuation of the normal progression toward habitual control by DLS (e.g., Everitt and Robbins 2016).

5.3.7 Formal Models for Learned Control of DA Release, and Learning Effects of DA Release

The basic correspondences between signals inferred to exist from behavioral studies of reinforcement learning and DA signals have been simulated with computational models that range from abstract models to models based on identified excitatory and inhibitory afferents to the DA neuron pools. Tan and Bullock (2008a, b) extended the computational model of Brown et al. (1999) to include not only the DAergic bursts and dips indicative of R-PE computations but also DAergic uncertainty

responses. Figure 5.4 depicts the structure of the model, which serves here to highlight two hypotheses regarding computational and clinically important roles of two underemphasized features of the BG circuit. The first feature is the differential expression of MORs (mu opioid receptors) on direct pathway (D1R expressing) MSPNs that lie in striatal patches—striosomes—and project fibers that synapse on DA neurons in the VTA and SN (Fujiyama et al. 2011; Watabe-Uchida et al. 2012). Both Brown et al. (1999) and Tan and Bullock (2008a, b) hypothesized that the projection from striosomes to VTA/SNc carried the descending inhibitory expectation needed to compute R-PEs (Fig. 5.3). One observation consistent with this idea is that opioid activation of MORs, which inhibits such MSPNs, is itself reinforcing. This follows, because inhibiting MSPNs that inhibit DA neurons has a disinhibitory effect on DA release. Cui et al. (2014) have presented impressive evidence that activation of MORs on striosomal MSPNs was indeed sufficient to cause elevated DA release in striatum, and to generate the opioid reinforcement effect in two standard paradigms: conditioned place preference (a Pavlovian learning test) and fixed-ratio responding for opioid self-administration (an operant learning test). In the transgenic mice created for the test, MORs were expressed only on striosomal D1R-expressing neurons. These MORs were found both on the neurons' somas in striatum and on their axon terminals in VTA/SNc. Equally important, MORs were absent elsewhere; notably, they were not present on inhibitory neurons in the VTA. Because such neurons normally express MORs, they may also mediate part of the opioid reinforcement effect (Bourdy and Barrot 2012). Indeed, Cui et al. (2014) also showed that the opioid reinforcement effect was not quite as strong as in wild-type controls. Notably, the transgenic mice showed more sensitivity to response cost than controls. They terminated work at an earlier point when subjected to a progressive ratio schedule, in which the cost increases until the animal no longer finds the reward (in this case opioid) worth the effort. In addition, knockouts in mice of neurokinin 1 receptors, which are highly expressed on DA neurons that project to striosomes, prevent addiction to opioids (Murtra et al. 2000). Overall, such results are consistent with the hypothesis that learned inhibitory expectations signaled by striosomal MSPNs are important for R-PE computations by DA neurons.

A second feature highlighted by the model of Tan and Bullock (2008a, b), shown in Fig. 5.4, is that all direct pathway MSPNs, including those that preferentially target SNr/GPi, co-release substance P and GABA. Their simulations showed that such co-release makes it possible for DA neurons to exhibit uncertainty (aka risk) responses. These take the form of a slow upward ramp of DA neuron spiking rate between the onset of a cue that predicts reward with an intermediate probability (e.g., 25–75 % of trials) and the occurrence or nonoccurrence of actual reward. In the model, SP released by direct pathway MSPNs excites DA neurons, but this is partly or wholly counteracted by co-release of GABA, which acts both to inhibit DA neurons and SP release, the latter via presynaptic $GABA_B$ receptors. The net effect is a signal of the form alpha*$p(1-p)$, where alpha is a scaling constant and p denotes the conditional probability of reward given the cue, i.e., p(reward|cue). This signal is an inverted-U function of probability with a peak value when $p=0.5$. The local receptor responses to SP and GABA are consistent with the model's

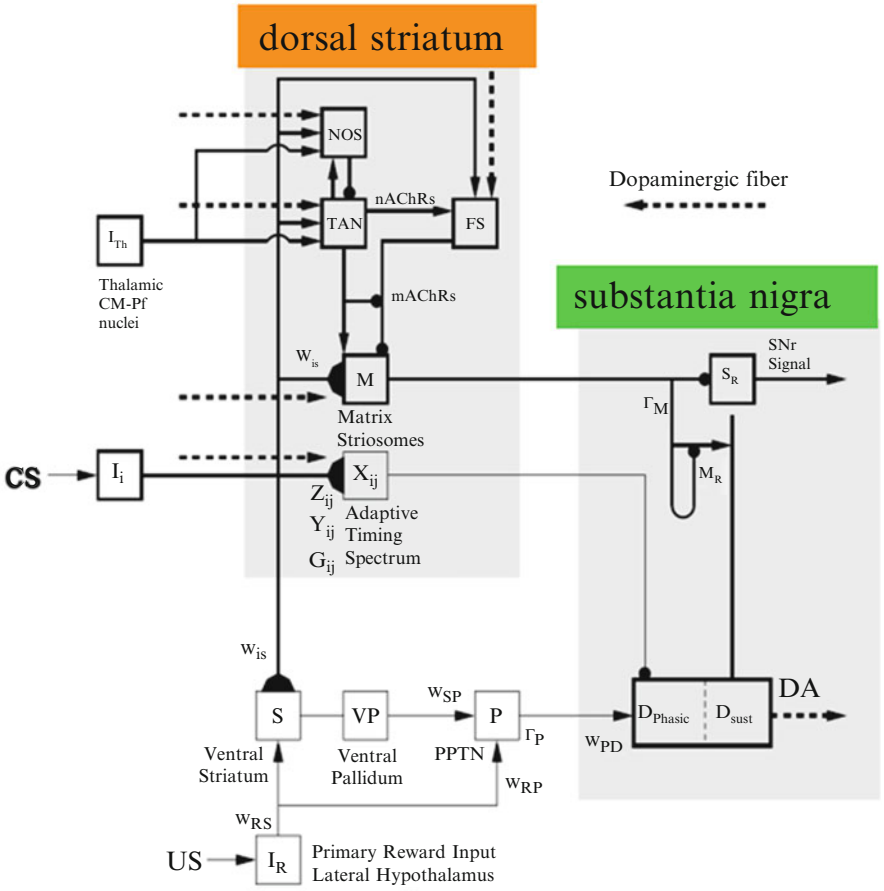

Fig. 5.4 Model implicating the dorsal striatum and substantia nigra in adaptation of dopamine signaling during learning on probabilistic schedules of reinforcement. *NOS* nitric oxide releasing interneuron, *TAN* tonically active neuron, *FS* fast-spiking striatal interneuron, I_{Th} outputs from the centro-median (CM) and parafascicular (Pf) complex of the thalamus, *DA* dopamine, *SNr* substantia nigra, pars reticulata, *nAChRs* nicotinic acetylcholine receptors, *mAChRs* muscarinic acetylcholine receptors, *CS* conditional stimulus, *US* unconditional stimulus, *PPTN* pedunculo-pontine nucleus. Adapted from Tan and Bullock (2008a, b)

assumptions. However, these factors might be occluded by some other factors present in vivo, but not modeled. It will be interesting to see the results of a direct test, in part because this is one of very few models that highlight a computation role for co-release. Finally, although this shows a possible subcortical, and presumably ancient, basis for computing uncertainty, risk-related responses have been observed in several parts of the brain beyond the striatum and VTA/SNc (Schultz et al. 2008; Monosov and Hikosaka 2013).

5.3.8 The Role of Dopamine in Electrical Coupling and Synchronous Oscillations

Dopamine, which modulates the strength of electrical coupling via gap junctions in the retina, also modulates such coupling between at least two classes of striatal neurons. Notably, DA increases coupling between D2-MSPNs but decreases coupling between fast-spiking interneurons (FSINs). These may be important effects because high coupling promotes synchronization among the neurons so coupled. If the neurons involved have a complement of intrinsic currents and a network embedding that allows periodic, i.e., oscillatory, burst firing, then such synchronization leads to amplification of LFP power at the frequency of the oscillation. For example, PD is characterized by elevated synchronous oscillations in the beta frequency band, and loss of DA plays a key role in the genesis of this PD symptom (which correlates with PD bradykinesia, as distinct from PD tremor, which is lower frequency and usually has a later onset in disease progression). Consistent with the scheme in Fig. 5.2, DA loss leads to elevated ACh in striatum, and such elevation can be mimicked by administration of the cholinergic agonist, carbachol, which acts via muscarinic acetylcholine receptors (mAChRs) to promote beta rhythm genesis (McCarthy et al. 2011).

In the computational model presented by McCarthy et al. (2011), the causal sequence is as follows. M-current (so called because it is modulated by muscarinic ACh receptors) normally reduces cell excitability, so its reduction is excitatory. Reduced DA leads to increased ACh. Increased ACh acts via M1-type mAChRs to reduce the M-current from 1.3 to 1.2 mS/cm^2. (Note from Fig. 5.2 that M1-type AChRs are differentially associated with D2-MSPNs, which are more excitable when DA is low.) The reduced M-current makes MSPNs more excitable and more likely to exhibit rebound spiking following $GABA_A$-receptor-mediated MSPN–MSPN interactions. Vital to the computational model is that the M-current is a slow, voltage-dependent current that persists during inter-spike intervals and has lower values for more hyperpolarized voltages (hence can be reduced by $GABA_A$-receptor effects). In the model, the MSPNs oscillate asynchronously at 8 Hz without synaptic $GABA_A$-receptor interactions; adding the latter leads to more hyperpolarization; this reduces the M-current, and increases excitability; this allows a higher firing frequency, in the beta range, up to 22 Hz in the model (at which value the background excitation of the MSPNs, and their $GABA_A$ feedback interactions, is at the model's max); the synaptic interaction also promotes synchronization of the beta frequency spiking across the population.

Although the model is enlightening, it does not integrate the full range of effects of DA loss that probably contribute to elevated beta genesis in PD. For example, the model depends on a synaptic excitatory background, presumably from cortex. Yet it neglects the fact that the cortical input to MSPNs is filtered by the FSINs, which, as

noted above, would become more strongly coupled by gap junctions upon loss of DA. This would increase their tendency to fire synchronously. Moreover, most studies show that the feed-forward inhibition of MSPNs from FSINs is more potent than the feedback inhibition of MSPNs by other MSPNs, and this needs to be included in striatal beta models, because cortex also participates in the beta rhythm. Indeed, data and modeling by Gittis et al. (2011) indicate that FSINs also play a prominent role in elevated synchrony in an animal PD model (see also Damodaran et al. 2014). Among other effects, they showed that connectivity between FSINs and D2-MSPNs became much stronger upon DA depletion. Finally, it should be added that in frontal cortex, DA acts via D2Rs on the class of pyramidal neurons that project differentially to D2-MSPNs (e.g., Shepherd 2013; Reiner et al. 2010), and these cells, which also project to the subthalamic nucleus (STN) (see Fig. 5.1), are hypoactive and hyper-synchronous in rodent PD models (Orieux et al. 2002). Thus, although DA-loss/elevated-ACh in striatum may be a trigger, a full understand of elevated beta genesis in PD will require computational models that simulate the entire BG-thalamo-cortical loop.

5.4 Conclusions: Dopamine's Broad Implications

Because the DA system is a highly conserved system at the heart of outcome-guided learning and action selection, its understanding will have extremely broad ramifications. In particular, DA has insinuated itself into all of behavior, from eye movements to locomotion to language. Figure 5.5 illustrates a recent model (Civier et al. 2013) of stuttering that highlights the pathways (from deep layer V of frontal cortex to D2-MSPNs in striatum) just mentioned as involved in PD beta genesis, although in this case the problem is modeled as arising from excess DA, which can lead to abnormal syllable prolongation (one aspect of stuttering) by over-inhibiting D2-MSPNs, thus reducing activation of the indirect pathway, which mediates syllable termination. As the DA system is further understood, many more integrative models of this type will be proposed, tested, and corrected. That will create an environment in which increasingly intelligent and efficient choices can be made regarding how to best integrate experiential, pharmaceutical, and other therapies to improve clinical outcomes.

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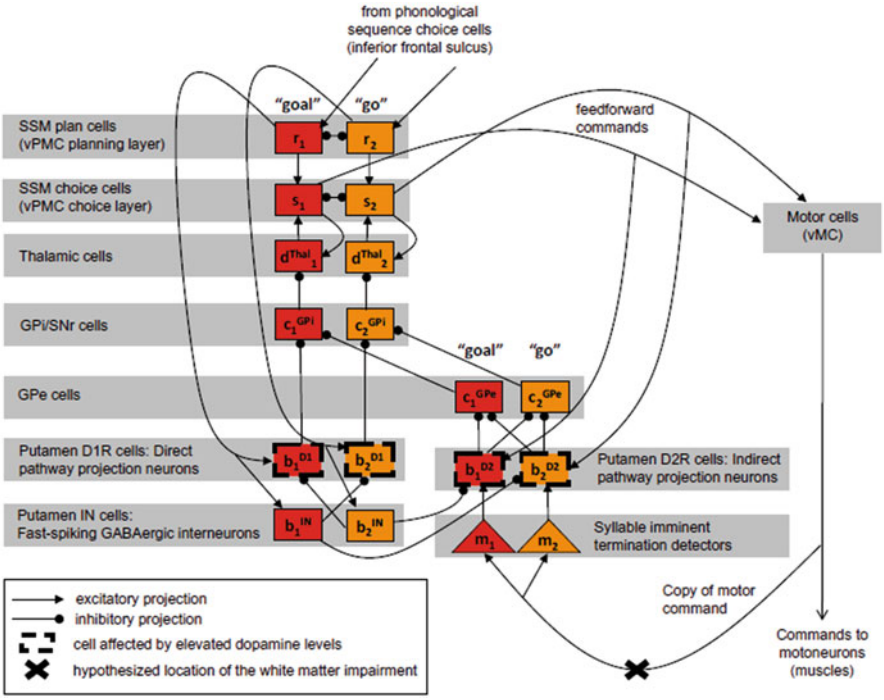

Fig. 5.5 Idealized circuitry of a loop involving the basal ganglia (BG) and ventral premotor cortex (vPMC). Cells are represented by colored boxes, and inside each box is the speech production model's variable name for the cell's activation level. The model treats the cortico–striatal–pallidal–thalamic projections as a set of competitive channels. Two of these are included in the diagram and coded by different colors: one channel is for a well-learned syllable "goal" (*red boxes*; variables with subscript 1) and the other channel is for a well-learned syllable "go" (*orange boxes*; variables with subscript 2). Within each channel are two medium spiny neurons (MSPNs: a putamen D1-MSPN, shown projecting to GPi/SNr (globus pallidus internus/substantia nigra, pars reticulata), and a putamen D2-MSPN, shown projecting to GPe (globus pallidus externus). These are marked in the legend as the key cells affected by elevated dopamine in some persons who stutter. Also shown for each channel are: one striatal GABAergic interneuron cell (putamen IN cell), a fast-spiking GABAergic interneuron (FSIN) mediating feed-forward inhibition, and one internal pallidum cell (GPi/SNr), one external pallidum cell (GPe), and one thalamic cell. The cortical columns are shown as well, each represented by one SSM ("speech sound map") cell at a vPMC planning layer, and one SSM cell at a deeper vPMC choice layer (Modeled projections from the vPMC planning layer to the thalamus are omitted for simplicity). The deep layer motor cells of the vMC (ventral motor cortex), as well as their afferents (from the vPMC choice layer) and efferents (to the brainstem), are shown on the right. The cortico-striatal white matter fibers, that arise from the vMC's efferents, feed into a stage (not modeled as a single cell, but algorithmically, so depicted as a *triangle*) that detects imminent syllable completion. This stage outputs a transient syllable-completion signal to the putamen D2-MSPNs cells. In this model, the latter must be recruited to terminate syllable production. Elevated DA makes such recruitment less reliable and slow, and this generates one component of stuttering. Adapted from Civier et al. (2013)

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Part II
Motor Function, Dystonia and Dyskinesia

Chapter 6
Cortico-Striatal, Cognitive-Motor Interactions Underlying Complex Movement Control Deficits

Aaron Kucinski and Martin Sarter

6.1 Introduction

We often take for granted the ability to navigate through the environment, perform complex movements, and engage in multiple tasks simultaneously, for example, quickly maneuvering around obstacles on a busy city sidewalk, or walking down a flight of stairs while carrying out a conversation. Such tasks require highly evolved neuronal circuits and rapid communication between diverse brain regions, particularly those involved in focusing and shifting attention, devising and executing complex motor sequences, adjusting ongoing motion, error correction, and strategically sorting motor behavior into habitual (automated) and more flexible (goal-oriented) components (Balleine et al. 2009; Balleine and O'Doherty 2010; Redgrave et al. 2010). The basal ganglia are a series of subcortical nuclei that function in the initiation and fine-tuning of motor actions. Within the basal ganglia, input from lower brain regions and the cortex converge on the striatum, allowing for the superimposition of cognitive control strategies over basic motor sequencing programs, with the ultimate goal to perform efficient goal-directed movements (Alexander et al. 1990; Redgrave et al. 2010; Samejima and Doya 2007).

The striatum is comprised of predominately GABAergic medium spiny neurons that propagate motor commands through the "direct" and "indirect" motor pathways of the basal ganglia (Albin et al. 1989). Classically, the striatum has been divided into functional territories based on afferent and efferent connectivity and functions. The dorsal striatum, innervated by substantia nigra pars compact (SNc) terminals, is divided into a dorsolateral section that forms connections with sensory and motor cortices and a dorsomedial section with connections to frontal and parietal association cortices (Lynd-Balta and Haber 1994). The ventral striatum (nucleus accumbens) receives innervation from the ventral tegmental area (VTA) and

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predominately forms connections with limbic structures in the cortex as well as the amygdala and hippocampus (Zaborszky et al. 1985). Despite these divisions, the striatum is largely a physiologically homogenous structure, and recent classifications have distinguished subregions based on how they encode various aspects of goal-directed behaviors such as learning and valuing associations, selecting actions, and motivating motor behavior (Schultz 2000; Voorn et al. 2004).

Underlying complex motor and goal-directed behavior are networks of parallel and topographically organized cortico-BG-cortical loops, which provide intricate connectivity between the cortex, striatum, and thalamus (Alexander et al. 1990; Haber et al. 2000; Logan et al. 2014). There is extensive overlap between these parallel circuits, as diffuse projection fields/terminals in the striatum allow for cross-communication between networks (Mailly et al. 2013). Recently, a system of hierarchical control of motor action has been described that accounts for the parallel organization of these circuits (Dezfouli and Balleine 2012; Haruno and Kawato 2006). Briefly, following detection of relevant cues, an associative (cognitive) loop, including connections between the prefrontal cortex and dorsomedial striatum, evaluates actions based on comparisons between the predicted values of outcomes towards specific goals and then converts small goals into detailed motor plans (Haruno and Kawato 2006; Ostlund et al. 2009). These intrinsically guided "goal-directed" operations are flexible but slow and carry comparatively high computational costs (Redgrave et al. 2010).

After determining a goal, lower level processes break down movement requirements into simpler and more manageable actions (Ostlund et al. 2009). These actions are habitual and occur automatically following learning, are extrinsically guided, and allow for focus on other behaviors such as assessment of external cues or secondary tasks (Yin et al. 2004). Connections between the dorsolateral striatum and the motor cortex (motor loop) mediate fast and inflexible habitual movement (Yin et al. 2004). Habitual movement does not require feedback once started; however, movement can be interrupted if attention is turned to competing actions (Matsumoto et al. 1999). The performance of complex movement relies not only on the efficiency of each of these pathways, but on the ability to rapidly switch between them in order to achieve goal-directed objectives (Hikosaka and Isoda 2010). For example, while driving a car on a long stretch of highway your sensory-motor functions are under habitual control; however, if a potential danger on the road catches your attention, an immediate switch to goal-directed control is required to perform actions needed to avoid a collision (Monsell 2003).

Although complex movement is guided by many cognitive operations, attention is particularly vital, as focus must be maintained on obstacles in the environment (external cues) as well as on body posture, step placement, gait, balance, and internal cues in order to guide movement (Bohnen et al. 2011; Yogev-Seligmann et al. 2008). The following chapter will address a cortical-striatal circuitry model and in-depth analysis of one particular cognitive-motor symptom, falls, to elucidate mechanisms that underlie attentional control of movement. The propensity to fall is a debilitating symptom in the elderly and individuals with Parkinson's Disease (PD) (Balash et al. 2005; Wood et al. 2002). Using a rodent model with attentional impairments as well as partial loss of dopamine terminals in the dorsal striatum, we determined that falls

in a novel beam apparatus arose primarily due to an "unmasking" of cholinergic-driven attentional control over impaired motor sequencing and low movement vigor from striatal dopamine loss (Kucinski et al. 2013). In addition, extensive striatal dopamine loss caused falls associated with frequent freezing episodes.

6.2 Cortico-Striatal, Cognitive-Motor Deficits in Parkinson's Disease

Motor output of the basal ganglia is predominately driven by the neurotransmitter dopamine, as D1 and D2 receptors on striatal GABAergic medium spiny neurons govern input selection from cortical and subcortical brain structures and relay motor commands through the "direct" and "indirect" pathways of the basal ganglia (Albin et al. 1989). Monosynaptic projections to the globus pallidus interior (GPi) and substantia nigra reticulata (SNr) ("direct pathway") and polysynaptic connections via the external globus pallidus exterior (GPe) and subthalamic nucleus (STN) ("indirect pathway") maintain thalamic and brainstem structures under tonic inhibitory control (Albin et al. 1989; Chevalier and Deniau 1990). This inhibition is released by signals from stratio-nigral-pallidal projections, thus allowing movement to proceed. Dopamine activates excitatory D1 and inhibitory D2 receptors located on medium spiny neurons that give rise to the direct and indirect pathways, respectively (Gerfen et al. 1990).

Loss of dopamine terminals in the dorsal striatum has detrimental effects on basal ganglia function, most notably, the severe movement deficits observed in PD such as hypokinesia and dyskinesia (Morris et al. 1994). In PD, there is a progressive degeneration of striatal-projecting substantia nigra pars compacta (SNc) dopamine neurons, causing reduced activation of excitatory "direct" and inhibitory "indirect" pathway projections and reduced thalamic output to the cortex and brainstem motor centers (DeLong 1990). Reduced inhibition of D2 receptors on projections to the GPe disinhibits the STN, causing an overdrive of inhibitory GPi and SNr output to the thalamus, while decreased D1 receptor activation reduces inhibitory signaling to the GPi and SNr, which also inhibits thalamic output (DeLong 1990).

Levodopa is used with moderate success to improve basic motor functions in PD patients; however, a cluster of related motor symptoms do not improve with levodopa therapy, including postural instability, motor control deficits, and a propensity for falls (McNeely et al. 2012; Sethi 2008).

In addition to loss of dopamine neurons, degeneration of cholinergic neurons in the basal forebrain (BF) and loss of cortical acetylcholine (ACh) occur in about 50 % of PD patients (Bohnen and Albin 2009; Nakano and Hirano 1984; Shimada et al. 2009). Degeneration of cortical cholinergic innervations in PD patients is more extensive than in the brains of older adults and reaches and possibly exceeds BF cholinergic cell loss in Alzheimer's disease (Bohnen et al. 2003). PD patients typically suffer from a range of cognitive impairments, including reduced attention, impaired episodic memory, visuospatial dysfunction, and deficits in task-set switching and executive planning (Cameron et al. 2010; Dirnberger and Jahanshahi 2013;

Dubois and Pillon 1997). Although dementia may eventually develop with PD in 20–40 % of cases (Bosboom et al. 2004), most often a characteristic course of cognitive changes, not primarily classified as dementia, accompanies the disease.

These cognitive impairments in the elderly and PD patients, specifically, a lowered capacity to sustain and divide attention, are associated with the propensity to fall (Allcock et al. 2009; Hausdorff et al. 2006; Holtzer et al. 2007; LaPointe et al. 2010; Nagamatsu et al. 2013). About two-thirds of PD patients experience falls at least once per year (Balash et al. 2005; Wood et al. 2002), requiring long-term hospitalization and rehabilitation (Dellinger and Stevens 2006; Grimbergen et al. 2004). Evidence from PD fallers indicates that cholinergic deficits, in the cortex primarily but also the brainstem pedunculopontine nucleus (PPN), correlated more strongly with falls than loss of nigrostriatal dopamine (Bohnen et al. 2009). Levels of cortical and thalamic acetylcholinesterase (AChE), which likely reflect the reduced density of cholinergic synapses, differentiated PD fallers from non-fallers (Bohnen and Albin 2011). Furthermore, the extent of caudate nucleus dopaminergic and cortical cholinergic denervation independently correlated with cognitive dysfunction and the interaction of both system losses caused further cognitive decline (Bohnen et al. 2015).

Cholinergic inputs from the basal forebrain are necessary for a wide range of behavioral processes, including attentional performance required for the detection and use of instructive cues to guide decisions about ongoing behavior (McGaughy et al. 1996; Muir et al. 1992; Turchi and Sarter 1997). Lesion studies have confirmed that loss of cholinergic function disrupts sustained, selective, and divided attention performance (Bucci et al. 1998; Dalley et al. 2004; McGaughy et al. 1996). Underlying cholinergic-driven attentional operations are brief cholinergic release events (“transients”) necessary for monitoring and acting on cues as well as a slower neuromodulatory component that influences the cortical target circuitry that contributes to the generation of the transients (Guillem et al. 2011; Parikh et al. 2008, 2010). Levels of slower cholinergic neuromodulation are associated with goal-directed or top-down control of attention. For example, higher levels of cholinergic neuromodulatory activity are seen in response to presenting a distractor (St Peters et al. 2011). Conversely, animals that exhibit dampened neuromodulatory cholinergic activity as a trait show relatively poor and highly fluctuating levels of attentional performance (Paolone et al. 2013). Thus, removal of the cortical cholinergic input system attenuates both cue-driven (or bottom-up) and goal-driven (or top-down) aspects of attentional performance.

6.3 Modeling Falls and Cognitive-Motor Deficits with Dual Cholinergic and Dopaminergic System Losses

Given that cortical cholinergic and attentional deficits are predictors of falls in PD patients, we hypothesized that losses of cortical ACh combined with partial loss of striatal dopamine, particularly in the associative (dorsomedial) striatum, would detriment the ability to perform complex movements and increase fall propensity in rodents. To assess falls, a novel beam traversal apparatus was developed for rats, the Michigan Complex Motor Control Task (MCMCT) (Kucinski et al. 2013). This system was designed to tax the ability to rapidly correct movement errors while traversing

dynamic surfaces (rotating square rods; ten rotations per minute). Traversing rotating rods requires persistent attentional control of gait, limb coordination, and carefully timed and placed steps. To maintain cognitive challenge, rats were tested on a battery of progressively demanding traversal conditions that included reversing and alternating the direction of rotation of the rods, placing the rods at inclines up to 35°, and incorporating passive and active distractors along the rods. Following baseline training, rats were administered bilateral infusions of cholinergic-specific neurotoxin 192-IGg saporin into the nucleus basalis of Meynert (nbM) of the BF, which reliably eliminates 50–90 % of cholinergic cell bodies in this region (Kucinski et al. 2013; Kucinski and Sarter 2015). Dopamine terminals in the dorsomedial "associative" striatum were bilaterally lesioned with 6-hydroxydopamine (6-OHDA). Rats received both types of lesions or lesions to either system alone. In addition to assessment of complex movement and falls on the MCMCT, rats were tested on a sustained attention task.

The results indicated that falls from the rotating rods were moderately but significantly increased in rats with cholinergic BF lesions; however, falls were robustly increased in rats with both cholinergic and striatal dopamine lesions (Duals, "DL"). Falls in DL rats were consistently high across the rotating rod conditions; however, impaired traversal performance in rats with BF lesions was revealed only in particularly complex trials (when the direction of the rotating rod was reversed from the familiar direction). Striatal dopamine loss alone did not impair MCMCT performance, suggesting that compensatory attentional mechanisms contributed to the prevention of falls in these animals.

We closely examined gait and posture characteristics of DL rats to determine possible risk factors for falls from the rotating rods. DL rats exhibited a number of gait and posture abnormalities, such as slower traversal speed, less distance covered with each step, slower stride cycle, an abnormal "slouched posture," and lack of corrective movements following slips, such as active tail motion to regain balance. These risk factors for falls are analogous to those observed in human PD fallers such as slow gait speed, insufficient recovery movements following slips, abnormal traversing posture, and reduced step frequency (Grimbergen et al. 2004). Such deficits may reflect impairments in the planning and sequencing of movements and, more generally, low "motor motivation" caused primarily by the impact of striatal dopamine loss (Mazzoni et al. 2007).

Performance on the attentional task was similarly impaired in rats with BF lesions and rats in DL rats, indicating that cholinergic loss alone impaired attentional performance and that striatal dopamine loss did not exacerbate such impairment (Kucinski et al. 2013). Similar to MCMCT performance, rats with only striatal dopamine losses had no deficits on the attention task, and actually performed better than sham rats on one task condition. In DL rats, poor attentional performance correlated with fall rates on the MCMCT. Quantitative histological analyses indicated that in DL rats, but not in rats with dopaminergic deafferentation alone, larger and more precisely placed dorsomedial striatal dopamine loss predicted higher fall rates. Collectively, we interpreted these findings as indicating that, in the presence of attentional control deficits, impairments in the striatal control of complex movements, gait, and balance resulting from loss of dopamine are "unmasked," causing gait and posture disturbances and falls.

From these findings we can describe a cognitive-motor circuitry model that accounts for falls arising from loss of cortical acetylcholine and striatal dopamine (see Fig. 6.1). When navigating complex surfaces such as stairs, or making sudden

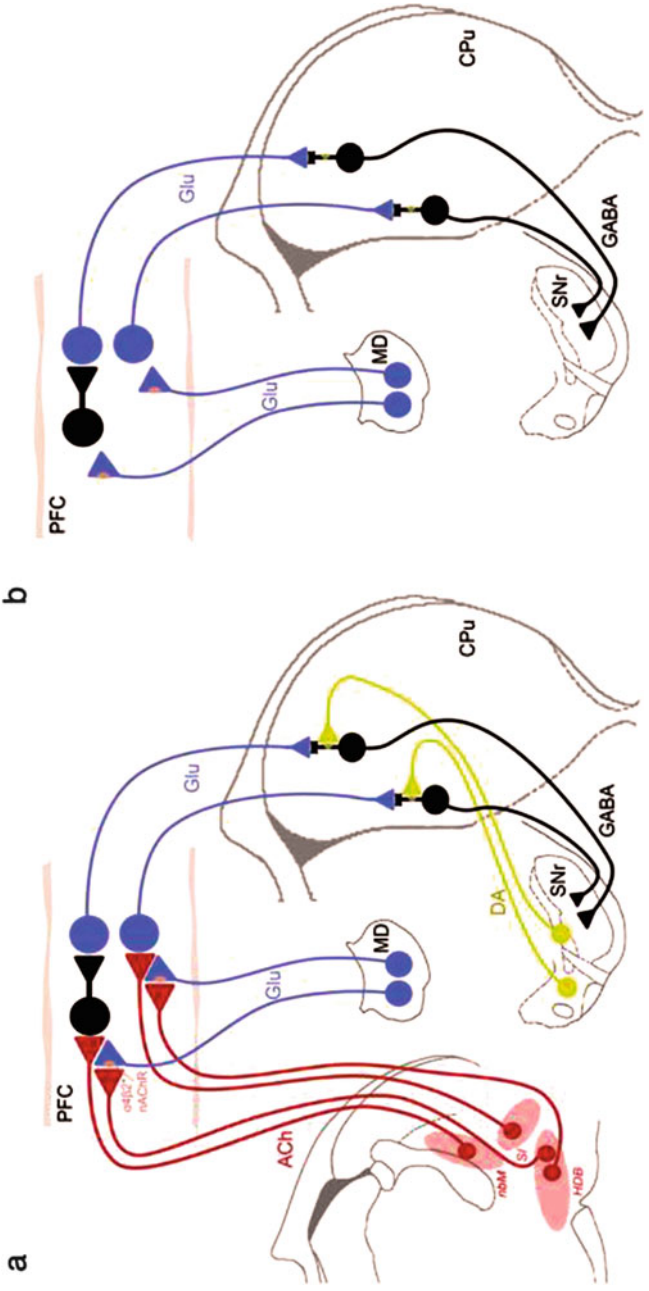
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Fig. 6.1 Schematic illustration of the neurocircuitry underlying attentional–motor interactions in the intact brain (**a**), and following the dual loss of basal forebrain cholinergic neurons and striatal dopamine (**b**) that is hypothesized to be essential for falls. The figure is not designed to provide a comprehensive illustration of the known circuitry, including the synaptic organization within individual regions. Rather, it represents the major anatomical–functional interactions deduced from research in PD fallers and, to a lesser degree, older adults prone to falls, and in an animal model of PD falling (Kucinski et al. 2013). In the intact brain (**a**), cholinergic projections to the cortex arise from the nucleus basalis of Meynert (nbM), the substantia innominata (SI), and the horizontal nucleus of the diagonal band (HDB) of the basal forebrain. The precise origin of cholinergic projections in these regions depends on the cortical target region but all subregions contribute to cortical innervation (Luiten et al. 1987; Zaborszky et al. 2015). In prefrontal cortex (PFC), cholinergic neurons contact GABAergic inhibitory interneurons and pyramidal cells and, as illustrated, both innervation patterns may contribute to cortico-striatal output. In the cortex, two types of cholinergic activity likely originate from separate neurons in the basal forebrain. First, as detailed in the main text, for certain cues to be detected, the cues need to evoke a brief cholinergic release event or "transient" (Howe et al. 2013). Furthermore, cue-evoked glutamate release from mediodorsal thalamic (MD) input is necessary but not sufficient to evoke such a cholinergic transient (Parikh et al. 2007, 2010). The exact mechanisms linking this glutamatergic–cholinergic transient interaction are unknown and the figure indicates a parsimonious direct contact at cholinergic terminals. Cholinergic transients are thought to be the primary source for cholinergic stimulation of prefrontal output. The second, neuromodulatory component of cholinergic activity influences glutamatergic–cholinergic transients via stimulation of α4β2* nAChR expressed by glutamatergic terminals (Lambe et al. 2003) (Note that other thalamic inputs to cortical neurons are not shown). Cortical projections to medium spiny neurons (MSNs) in the striatum preferentially make contact at the head of spines that are also contacted, as illustrated, by dopaminergic afferents (DA) from the midbrain (CPu, caudate-putamen). In the rat model, converging dopamine loss and the functional impact of cholinergic deafferentation of prefrontal cortex for cortico-striatal function was found to be essential for generating high rates of falls. This finding primarily implicates dopamine D1 receptor-expressing MSNs of the direct projection pathway to the midbrain (SNr, substantia nigra, pars reticulata). As illustrated in (**b**), falling in older adults and, more severely, PD, is a result of striatal dopamine loss and cortical cholinergic deafferentation, yielding striatal circuitry that lacks information about the efficacy of gait, posture, and movement and that is impaired in selecting and sequencing motor actions, resulting in slow and reluctant movements or fails to initiate movement altogether

turns, or in rats traversing rotating rods, attention to cues related to dynamic surfaces and distractions as well as body posture, balance, gait control, and step placement are critical in guiding ongoing movement. With disruption of cortico-striatal systems, particularly within the "associative" cortical-BG loop, there may be failure to detect and process cues and rapidly integrate relevant information into ongoing motor actions. In attentionally demanding situations, cholinergic transients report the presence of cues to the striatum and thus, following cholinergic loss, the striatum may be largely deprived of information that normally reports the presence of cues, including those normally detected and employed to support complex movement, such as limb placement onto a dynamic surface or slips that would normally trigger corrective action.

Direct pathway projecting medium spiny neurons of the striatum that innervate primarily the SNr and the GPi are contacted by prefrontal cortex efferents (Wall et al. 2013) and are also modulated by ascending midbrain dopamine neurons via D1 receptors on dendritic spines (Pickel et al. 1981). Dopamine thus selects certain cortico-striatal input over others and, therefore, dopaminergic deafferentation may disrupt selection or filtering of cortical inputs (Bamford et al. 2004; Devan et al. 1999; Guthrie et al. 2013; Kim et al. 2013; Strafella et al. 2005). Therefore, loss of dopamine and cortical cholinergic input may additively impair striatal function. In the context of ongoing complex movements, impaired cortico-striatal input selection may therefore slow and even stop complex movement sequences (Kim et al. 2013; e.g., Bhutani et al. 2013; Yin 2014), yielding the sensorimotor risk factors for falls.

In older adults and PD patients, it is hypothesized that a major cause of falls is the consumption of limited attentional resources by a secondary task, and thus withdrawal of such resources from supervising gait, balance, and complex movement (Amboni et al. 2013; Plotnik et al. 2011; Tombu and Jolicoeur 2003; Yogev-Seligmann et al. 2013). In the presence of cholinergic cell loss and reduced attentional resources, additional taxation nearly abolishes the attentional monitoring of motor action. As a result, gait freezes, postural imbalance, error-prone movements, and eventually falls are more likely to occur (Uemura et al. 2012). With an intact cholinergic system, performance errors activate the neuromodulatory component of cortical cholinergic activity to enhance the detection of cues and errors to stabilize and recover performance (St Peters et al. 2011).

6.4 Falls Resulting from Extensive Striatal Dopamine Loss

The majority of common movements, such as walking, are largely automatic, controlled by habitual motor pathways (Redgrave et al. 2010). Automation of learned movement allows for focus on other cognitive operations and provides additional attentional resources for recovery from unexpected movement errors, distractions, and multitasking (Hikosaka and Isoda 2010). With aging and with loss of striatal dopamine in PD, walking speed is reduced and there is less vigorous toe push-off,

more step timing variability, smaller steps, decreased arm swing, forward bended posture, and frontal plane instability (Bridenbaugh and Kressig 2011; Kurz et al. 2013; Marchese et al. 2003; Mazzoni et al. 2007; Winter et al. 1990). Dopamine loss is known to slow responding and decrease accuracy in tasks involving habitual/automatic responding or tasks requiring shifts between behavioral contingencies (Baunez and Robbins 1999; Darvas and Palmiter 2009; Domenger and Schwarting 2008; Hauber and Schmidt 1994; Lex and Hauber 2010; Rogers et al. 2001). Thus, in addition to falls that originate from the combined attentional-motoric deficits described above, falls may result from relatively severe impairments in normally habitual motor functions caused by striatal dopamine loss, especially when traversing dynamic surfaces (Cole et al. 2011; Wood et al. 2002; Woollacott and Shumway-Cook 2002).

To assess the impact of large dopamine losses on fall propensity, more extensive 6-OHDA lesions that extended into the dorsolateral and dorsomedial striatum were administered to rats. As in the previous experiment, rats performed traversals with a progressively demanding battery of MCMCT conditions, including inclines and reversing the direction of the rotating rod. These large dopamine lesions increased falls and slowed traversal speed (Kucinski et al. 2015). Falls were characterized by frequent freezing episodes, defined as stoppages of forward traversal movement for more than 1 s. Freezing episodes occurred both spontaneously (with no obvious trigger) or following stepping errors. Despite these impairments, falls were less frequent than falls in DL rats tested previously. In addition, large dopamine losses did not impair the ability to perform increasingly complex movements, such as traversing the rotating rod when the direction of rotation was reversed, as was the case in DL rats or rats with only BF cholinergic lesions. However, falls that were triggered by a doorframe distractor, a distractor designed to model doorframe-evoked freezing of gait episodes in PD patients (Cowie et al. 2012), were preceded by longer periods of immobility and occurred earlier in the run compared to DL rats. Thus, we hypothesized that falls in these two lesion models stemmed from different cognitive-behavioral mechanisms—large dopamine lesions of the dorsal striatum caused falling due to propensity of freezing forward movement, while dorsomedial lesions combined with cortical cholinergic loss models falls resulting from impairments in attentional-motor interactions and complex movement control.

Freezing of gait (FOG), a sudden disturbance of gait, in which patients often feel stuck with their feet being "glued to the floor," occurs in 30–60 % of the PD patients. FOG is common in challenging situations with increased "mental stress" (Giladi and Hausdorff 2006) and can often be overcome by applying external tricks such as visual or auditory cues (Nieuwboer et al. 1997). Freezing episodes can be triggered by disruptions in gait rhythm control and symmetry, postural control, and step scaling as well as attentional shifts (Cowie et al. 2012; Plotnik et al. 2012). It was hypothesized that subcortical regions may fail to "update" motor sets during ongoing task performance during freezing episodes (Chee et al. 2009), thus shifting habitual-driven movement to goal-directed movement. Such a shift would necessitate an over-reliance on cortical networks to complete tasks normally handled by automatic networks and reduce efficiency and delay movement responses (Hallett

2008; Shine et al. 2011; Spildooren et al. 2010). PD patients exhibit greater activity in cortical, including prefrontal, regions while performing automatic movements, suggesting recruitment of complex cognitive networks even for relatively undemanding gait and posture control (Wu and Hallett 2005). With an increased reliance on cognitive resources to carry out habitual actions, falls may occur primarily due to the inability to perform intricate, attention-demanding actions when needed. In these situations, compensatory mechanisms to limit the degree of gait disruption and limb incoordination or to disengage from the freezing response may be insufficient and/or deployed too late to prevent falls (Fasano et al. 2012).

6.5 Preventing Falls

Severe motor deficits in PD patients such as loss of motor vigor and gait impairments are benefited with levodopa treatment; however, levodopa does not generally improve and can worsen cognitive symptoms (Cools et al. 2001, 2007; Schneider et al. 2013). Importantly, falls and related complex motor impairments tend to be unresponsive to levodopa (Koller et al. 1989; McNeely and Earhart 2013; Michalowska et al. 2005; Sethi 2008) and often additional motor impairments such as dyskinesia can occur with levodopa treatment (Huot et al. 2013; Iravani et al. 2012). However, despite its shortcomings, levodopa is essential for enhancing basic motor functions in PD. Given that falls in PD and our rodent model ("DLs") are associated with reduced cholinergic-attentional control of movement, specifically, reduced detection and reporting of external and interoperceptive cues related to ongoing motion, co-administration of compounds that enhance cortical cholinergic activity and improve attention may reduce fall propensity in levodopa-treated patients.

The postsynaptic targets of cortically projecting BF neurons include nicotinic acetylcholine receptors (nAChRs) on the terminals of thalamic glutamatergic projections. The neuromodulatory effects of ACh influence the generation of cholinergic transients via this target (Aracri et al. 2013; Guillem et al. 2011; Howe et al. 2010; Parikh et al. 2008, 2010). Our previous studies indicated nAChR agonist α4β2* reliably enhanced attentional performance in non-lesioned rats (Howe et al. 2010). Also, stimulation of α4β2* nAChRs in the cortex mimics and amplifies the cholinergic neuromodulatory effects on cortical cue detection circuitry and thus enhances top-down control of attention (Howe et al. 2010; Parikh et al. 2010). As predicted by the beneficial effects on attention in animals, α4β2* nAChR agonists improve symptoms of adult ADHD (Apostol et al. 2012; Bain et al. 2013). Cholinergic agents that do not specifically target nAChRs, such as acetylcholinesterase inhibitors (McCall et al. 2013; Possin et al. 2013) or muscarinic (m) AChR agonists (Hasselmo and Sarter 2011), have thus far yielded inconclusive effects on falls and PD-related attentional deficits.

Recent evidence has supported the hypothesis that stimulation of α4β2* nAChRs in combination with levodopa can benefit cognitive symptoms (Decamp and

Schneider 2009; Schneider et al. 1999, 2003) as well as motor symptoms that are not addressed by levodopa, such as dyskinesias (Huang et al. 2011; Quik et al. 2008). In our DL rat model (Kucinski et al. 2013), co-administration of the α4β2* nAChR agonist ABT-089 (Arneric et al. 2007) with levodopa and benserazide reduced falls from the rotating rods on the MCMCT by approximately 50 %. Also, nonspecific nAChR agonist varenicline and other nAChR agonists, such as agonists of the α6β2* subtype, have been effective at reducing levodopa-induced dyskinisia in non-human primates (Zhang et al. 2013) and in a rat lesion model (Huang et al. 2011). Thus, nAChRs appear to be a viable therapeutic target for improving cholinergic-mediated attentional deficits as well as falls in PD.

6.6 Conclusions and Future Directions

Complex movement relies on networks of cortical-BG-cortical loops that integrate sensorimotor and cognitive operations to achieve goal-directed objectives (Alexander et al. 1990; Haber et al. 2000). The basal ganglia and its connections with the cortex compartmentalize motor control into habitual and goal-directed components, mediated by distinct but overlapping pathways (Balleine and O'Doherty 2010; Redgrave et al. 2010). This parallel organization is essential for performing complex motor operations such as responding to cues, action selection, and motor feedback (Balleine et al. 2009).

Attention is a particularly important cognitive operation that is essential for guiding complex movement. Detection and reporting of external and interoceptive cues to the striatum is an example of cognitive-motor communication that underlies complex and flexible goal-directed behaviors (Amboni et al. 2013; Yogev-Seligmann et al. 2008). Our lesion studies have demonstrated that loss of cholinergic-driven attentional control over damaged striatal circuitry reveals robust impairments in complex movements, particularly increased falls (Kucinski et al. 2013). This finding is corroborated by observations in PD patients with attentional impairments and cortical cholinergic losses that are prone to falls (Allcock et al. 2009; LaPointe et al. 2010; Nagamatsu et al. 2013). In addition, large dopamine lesions resulted in FOG-associated falls (Kucinski et al. 2015) which may involve the loss of motor automation and the shifting of cognitive resources to attend to basic motor operations, thus taxing the ability to perform essential cognitive functions such as detecting cues, processing distractors, and rapidly correcting movement errors (Fasano et al. 2012; Hallett 2008). These models of complex movement deficits and falls, together with evidence from PD fallers, help to elucidate mechanisms that underscore cognitive-motor interactions in mediating movement and behavior.

In future work, we will continue to explore brain–behavior relationships associated with cognitive control of movement and fall behavior. First, given that cholinergic-attentional processes guide complex motor control, we expect higher levels of neuromodulatory ACh activity in the prefrontal cortex during attentionally demanding MCMCT conditions, specifically during traversals of rotating rods, rela-

tive to nondemanding trials with a wider and stationary plank surface. Brain analytes from the cortex will be collected by in vivo microdialysis using a modified MCMCT apparatus with dialysis lines attached to an overhead sliding rig that moves along with the animals as they traverse the plank and rods. Following each traversal, rats receive water rewards in boxed chambers on both ends of the beam, which are surrounded by motorized retractable walls that are brought down to signify the start of the next traversal, thus minimizing experimenter interference during the task. ACh and other brain neurotransmitters in the prefrontal cortex will be assessed using HPLC-mass spectrometry. Furthermore, given our hypothesis that cholinergic-attentional control compensates for striatal-mediated motor deficits following partial loss of striatal dopamine, we expect cholinergic release on the rotating rod to be further amplified in rats with striatal dopamine lesions, consistent with an increased reliance on cognitive control over habitual movement.

In addition, brief cholinergic release events ("transients") may be assessed using enzyme-sensitive microelectrodes/amperometry (Howe et al. 2010; Parikh et al. 2008, 2010) during MCMCT traversals. Cholinergic transients in the medial prefrontal cortex are required for detection and selection of appropriate cues, as well as the sequencing and execution of cue-associated responses (Parikh et al. 2008). We expect that cholinergic transients, measured on the timescale of seconds, are required to perform attention-demanding movements such as postural and balance adjustments during recovery from slips or movements needed to maintain balance on the rotating rods or while processing distractors. Also, recent advances in wireless optogenetic technology (Kim et al. 2013; McCall et al. 2013; Stark et al. 2012) may allow for the activation of cholinergic-attentional circuitry during performance of MCMCT traversals. We have previously determined that BF cholinergic stimulation enhances the detection of signals in an attention task and, conversely, evokes "false alarms" in non-signal trials (reporting the presence of signals when they were not presented) (submitted for publication). A major goal will be to stimulate cortical cholinergic circuits in rats with extensive loss of striatal dopamine in order to enhance cholinergic-attentional supervision over movement during beam traversals and thus prevent falls.

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Chapter 7
Interactions Between the Basal Ganglia and the Cerebellum and Role in Neurological Disorders

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7.1 The Cerebellum

Many functions have been attributed to the cerebellum—especially in more recent years—but the most consistently and historically agreed upon function of the cerebellum is that it coordinates movements (Fine et al. 2002; Ito 1984; Medina 2011; Rolando 1828). The cerebellum can be grossly subdivided into three divisions. The most medial is the vermis. The lateral regions are known as the lateral hemispheres, and the region between the hemispheres and the vermis is the paravermis. The cerebellum also has some somatotopy, similar to that of other brain regions (Ghez and Thach 2000; Ito 1984; Manni and Petrosini 2004).

The circuitry of cerebellar pathways is illustrated in Fig. 7.1. The primary input to the cerebellum is the mossy fibers. This system originates from the brain stem and spinal cord and relays information from throughout the brain to the cerebellar cortex (Eccles et al. 1966b). Mossy fibers form excitatory synapses on an extensive array of granule cells, the most abundant cell type in the brain. Granule cell axons extend and bifurcate in the cerebellar cortex, forming the parallel fibers, and *en passant* synapses formed by these axons make excitatory connections with a set of interneurons in the cerebellar cortex (Palay and Chan-Palay 1974; y Cajal 1889). The parallel fibers themselves are the primary input to the computational unit of the cerebellum: the Purkinje cell (Ito 1984).

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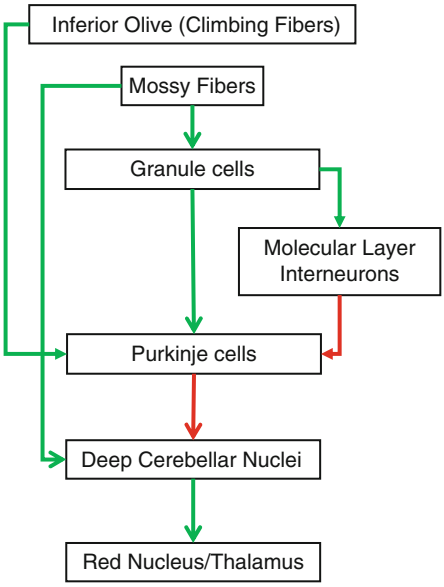

Fig. 7.1 Simplified diagram of the classic cerebellar microcircuit. *Green arrows* denote excitatory connections and *red arrows* denote inhibitory connections

The Purkinje cell integrates over 150,000 excitatory parallel fiber inputs (Palay and Chan-Palay 1974). Purkinje cells also receive robust excitatory innervation from the climbing fibers (y Cajal 1888), which originate outside the cerebellum in the inferior olive (Szentagothai and Rajkovits 1959). Climbing fiber input is known to alter Purkinje cell activity by way of the complex spike—a large excitatory event that excites and then transiently pauses Purkinje cell activity (Eccles et al. 1966a). GABAergic pauses in Purkinje cell activity are primarily caused by input from local interneurons which comprise a dense network for lateral inhibition (Dizon and Khodakhah 2011; Szentagothai 1983).

Purkinje cells have a tonic, GABAergic output that converges on the deep cerebellar nuclei, the principal output of the cerebellum. The deep cerebellar nuclei also receive some excitatory inputs from mossy fiber collaterals (the same fibers that eventually synapse on granule cells) (Ito et al. 1970; Jansen and Brodal 1940). The deep nuclei are heterogeneous, comprising multiple cell types, though their efferents terminating in the midbrain are largely excitatory (Batini et al. 1992). There are three anatomical groups of deep cerebellar nuclei. From most medial to most lateral they are the fastigial, interposed, and dentate (or lateral) deep nuclei. Deep cerebellar nuclei primarily receive input from Purkinje cells in the same lobule. Thus, the Purkinje cells of the vermis primarily project to the fastigial, the paravermis to the interposed, and the lateral hemispheres to the dentate nucleus (Jansen and Brodal 1940). The inputs to each of these subregions suggest differences in function—the vermis and paravermis primarily receive sensory input from the cortex and spinocerebellar tracts and the lateral hemispheres receive inputs and output to the motor and prefrontal cortices. These anatomical divisions also suggest that the lateral hemispheres (and thus the dentate nucleus) might compute more cognitive processes, as well as motor information (Ghez and Thach 2000; Ito 1984).

As discussed above, the most common function assigned to the cerebellum is the coordination of movements. Much of this understanding stems from conditions where the cerebellum has been damaged. Historically, lesions of the cerebellum have been associated with ataxia—the lack of muscle coordination. Luigi Rolando made the first clear perturbations to the cerebellum although he concluded that the cerebellum controlled limb muscles (Rolando 1828). Marie-Jean-Pierre Flourens followed later, concluding that the cerebellum played a role in motor coordination, since animals with cerebellar damage tended to have clumsy or awkward movements (Flourens 1824). This role in motor coordination was more clearly tested by John Dalton, who removed the cerebellum from pigeons. He then observed motor behaviors remarkably similar to the effects of alcohol intoxication. Even more remarkably, these pigeons recovered most of their abilities two and a half weeks after the ablation (Dalton 1861; Fine et al. 2002), owing perhaps to some compensatory mechanism.

Activity in the cerebellum very clearly correlates with motor behavior. This has been demonstrated with both eye and limb movements in both Purkinje and deep nuclei cells (Ito 1984; Lisberger and Fuchs 1978; Thach 1968, 1970, 1975). The kinematics of these limb movements reliably correlates with arm and wrist movements (Thach 1968). Importantly, this information about these movements is reliably transmitted from the cerebellum to the thalamic nuclei (Uno et al. 1970). Moreover, directly controlling Purkinje cell activity results in similar movement kinematics (Heiney et al. 2014) suggesting that the cerebellum may play a causal role in motor behaviors as well.

7.2 The Basal Ganglia

The reader is referred to Chaps. 1–5 and 14 in this volume for further descriptions of the anatomy and circuitry of the basal ganglia. The basal ganglia comprise the striatum, the substantia nigra pars reticulata and compacta, the globus pallidus externa and interna, and the subthalamic nucleus. In primates, the lateral and medial aspects of the striatum are divided into the putamen and caudate, respectively (Fig. 7.2).

Models of basal ganglia function and physiology are pervasive in the literature and are being updated continuously. The most influential is no doubt the one proposed by Albin, Young, and Penney. This work was largely substantiated by physiology done by Mahlon Delong, who did the initial descriptions of physiology across the basal ganglia and elaborated on the model (Alexander et al. 1986; DeLong 1971, 1972, 1973, 1983). In this model, the GABAergic projection neurons of the striatum (medium spiny neurons or MSNs) project differentially depending on the expression of the dopamine receptor. These neurons receive dopamine input from the substantia nigra, pars compacta, and are primarily driven by cortical activity. MSNs expressing the D1 receptor are part of the "direct pathway," and MSNs expressing the D2 receptor are part of the "indirect pathway." For clarity, it needs to be stated

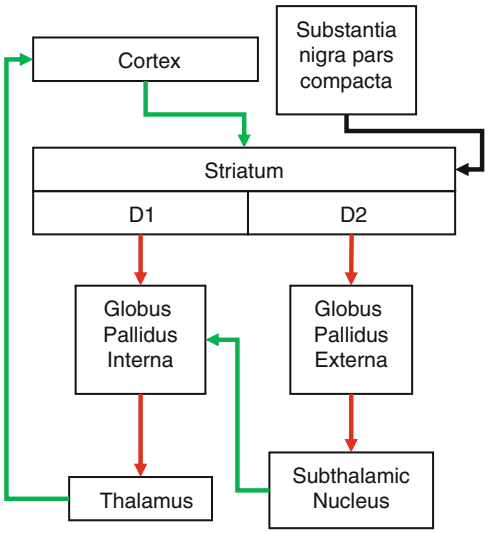

Fig. 7.2 Simplified classical diagram of the direct/indirect pathways in the basal ganglia. *Green arrows* denote excitatory connections, *red* indicate inhibitory connections, and the *black arrow* indicates dopaminergic projections. D1 and D2 indicate specific striatal cell types expressing D1 and D2 receptors

that the molecular markers (D1/D2) for the direct/indirect pathways were not clear in Albin and colleagues' original conception of the model and were demonstrated later (Gerfen et al. 1990; Gerfen and Young 1988; Kawaguchi et al. 1990). Direct pathway MSNs project to the globus pallidus interna or substantia nigra, pars reticulata. Both the globus pallidus and substantia nigra reticulata send inhibitory projections to the thalamus. In the other pathway, D2 MSNs first send projections to the globus pallidus externa. This nucleus subsequently inhibits the subthalamic nucleus, which in turn sends excitatory projections to the globus pallidus interna and substantia nigra reticulata. Again, both of these nuclei send inhibitory projections to the thalamus. Taken together, activity in the direct pathway MSNs facilitates thalamic activity while activity in the indirect pathway inhibits thalamic activity. By extension, increases in thalamic activity increase an animal's propensity to move through the thalamus' extensive connections with the cortex. Thus, the direct pathway facilitates movement and the indirect pathway inhibits it. It is thought that the basal ganglia select different assemblies of neurons, facilitating or inhibiting different motor patterns via these pathways, thereby influencing the animal's behavior (Albin et al. 1989; Mink 1996).

While this model is useful in thinking of how the basal ganglia work, and fairly predictive when considering basal ganglia disorders, it has been complicated by newer anatomical studies. Although a complete review of this is outside the scope of this chapter, it is important to at least recognize these points. For example, there is a very robust cortical input to the subthalamic nuclei, circumventing the striatum (Nambu et al. 2002). There are also strong projections from the globus pallidus back to the interneurons of the striatum (Bevan et al. 1998) and some excitatory projections from the substantia nigra to the reticular portions of the thalamus (Antal et al. 2014).

For brevity, additional discussion will be limited to the input to the basal ganglia—the striatum. The striatum can be divided into the dorsolateral aspect, mediolateral aspect, and the ventral aspect, otherwise known as the nucleus accumbens. In general, the more lateral regions are more motor related and the more medial are more associative. The accumbens has the distinction of receiving significant dopaminergic inputs from the ventral tegmental area and is associated with more reward-related behaviors (Heimer and Wilson 1975; Voorn et al. 2004).

7.3 Cerebellar-Basal Ganglia Interactions: Historical Perspective

Since the cerebellum and basal ganglia are critically important for motor control, many have postulated that they might cooperate to generate motor-related signals, and many have searched for the substrates of this cooperation.

One of the proposed functions of the basal ganglia is to disinhibit the thalamus to allow for movement (by decreasing activity from the globus pallidus interna or substantia nigra reticulate Albin et al. 1989). In following with this idea, some believed that the basal ganglia could regulate cerebellar outputs by controlling cerebellar projections in the thalamus. This idea required three components. First, the globus pallidus and substantia nigra must have inhibitory outputs in the thalamus. This was demonstrated to be the case. Stimulating either nucleus resulted in monosynaptic inhibitory postsynaptic potentials in the ventral motor nuclei (Ueki et al. 1977; Uno and Yoshida 1975). Second, the cerebellar projection to the thalamus must be sensitive to changes in thalamic activity. In fact, the cerebellar input to the thalamus was demonstrated to be heavily modulated by different anesthestics (MacLeod and James 1984). The depth of anesthesia reliably controlled the mode of activation of thalamic neurons—under deeper conditions, thalamic neurons entered a hyperpolarized, burst firing mode. When the cerebellum was stimulated, thalamic spiking responses were significantly delayed and more variable. Thus, it was conceivable that an inhibitory input might hyperpolarize the thalamus such that cerebellar inputs would be "gated" by the thalamus (MacLeod and James 1984). Taken together, cerebellar activity reliably changed thalamic activity, and could in turn be modulated by changes in thalamic mode, fulfilling this second criterion. The third condition was that the terminal fields of the cerebellum and the basal ganglia must overlap in a common thalamic territory. This proved to be much more difficult to demonstrate. Functionally, there was some evidence that this was the case. GABA (to decrease activity) or bicuculline (to increase activity) was microinjected into the substantia nigra while thalamic responses to cerebellar stimulation were monitored. In these conditions, GABA in the substantia nigra increased the probability of a cerebellar response at the thalamus, and bicuculline decreased it (Chevalier and Deniau 1982). Other groups used a different approach. To find thalamic neurons responsive to both cerebellar and basal ganglia stimulation, they delivered stimuli to

the globus pallidus and dentate nucleus of the cerebellum. In doing so, they found a minimal number of neurons responding to both cerebellar and basal ganglia stimulation (Uno and Yoshida 1975; Yamamoto et al. 1984).

To test the hypothesis directly, an anterograde anatomical tracing study was conducted. Tracers were injected into the dentate nucleus of the cerebellum, the globus pallidus, and substantia nigra, and the terminal fields in the thalamus were investigated. The findings partly contradicted the author's earlier stances because they observed that the terminal fields were only minimally convergent (Deniau et al. 1992). The notion that the cerebellum and basal ganglia have separate terminal fields in the thalamus has largely been maintained since this earlier study. Communication and convergence between the two structures was reported, but it was limited primarily to the cerebral cortex (Rouiller et al. 1994).

The simplest method by which the cerebellum and basal ganglia could communicate is directly. This is to say that one region sends outputs directly to the other. To test this possibility, the cerebellum was stimulated and different parts of the basal ganglia were recorded in a number of preparations. Responses were in fact observed in the striatum although they occurred at fairly long latencies with variable reliability (50–350 ms delays). Interestingly, these responses were blocked when the thalamus was ablated (Ratcheson and Li 1969; Voskanian and Fanardzhian 1983). Responses were also observed in the globus pallidus although these were only observed in a small fraction (5 %) of recorded neurons (Li and Parker 1969). Taken together, these responses indicated that while there may be a functional connection between the cerebellum and the basal ganglia, the impact of cerebellar inputs to the basal ganglia is small and at best, variable.

While these data have suggested that the cerebellum might not have a significant input to the basal ganglia, there has been some evidence that the cerebellum might play a modulatory role in basal ganglia physiology through an action on the dopaminergic system. Stimulating the cerebellum increases dopamine release in the striatum in cats (Nieoullon et al. 1978; Nieoullon and Dusticier 1980). How exactly the cerebellum affects the substantia nigra activity is not completely clear although recent anatomical data suggests that there are direct inputs from the cerebellum to both the substantia nigra and ventral tegmental area (Watabe-Uchida et al. 2012).

The idea that the cerebellum and the basal ganglia cooperate to generate motor-related signals has persisted through the years (Doya 1999, 2000). In contrast to previous studies, two groups were able to elicit responses in the caudate nucleus/striatum following cerebellar stimulation although the pathway by which these responses were elicited remained ambiguous (Bareš et al. 2015; Moroz and Bureš 1984). Two anatomical tracing studies in particular gave direct communication between the structures a plausible substrate. A disynaptic connection from the dentate nucleus of the cerebellum to the striatum through the intralaminar nuclei was uncovered in rats (Ichinohe et al. 2000) and monkeys (Hoshi et al. 2005). Importantly, lesioning the same intralaminar nuclei could also cause deficits in motor behavior (Jeljeli et al. 2000).

Functional confirmation of this anatomical connection from the cerebellum to the basal ganglia was demonstrated in a series of electrophysiological recordings done in awake, freely moving mice. Action potentials in the striatum could be elicited on average 9 ms after exciting the cerebellum. The thalamus was both necessary and sufficient for these impulses to alter striatal activity. The rapid timing and subcortical involvement of this response suggested a separate avenue for cerebellar, motor-related information to reach the striatum. Along with these rapid changes in striatal activity, the cerebellar input also had the ability to influence corticostriatal plasticity. High-frequency stimulation of the cortex, which is known to induce a depression of the corticostriatal response, could be changed to potentiation if the cerebellum was simultaneously stimulated at high frequency (Chen et al. 2014). Thus, simultaneous cerebellar and cortical activity could differentially change corticostriatal activity. The function of cerebellar inputs to the basal ganglia might then be twofold: to dynamically "inform" the basal ganglia of information relating to motor coordination and to bias ongoing cortico-basal ganglia activity through plasticity (Chen et al. 2014).

7.4 Basal Ganglia to Cerebellar Communication

Reciprocal communication between brain structures has been proposed as a general feature of neural circuits, in particular those involved in motor systems (Kelly and Strick 2003; Middleton and Strick 2000). Thus, if there are robust inputs from the cerebellum to the basal ganglia one might expect the reverse to be true.

Remarkably, early work has already demonstrated some of the functional properties of basal ganglia to cerebellar communication. The earliest report involved stimulation of the caudate nucleus (part of the striatum) while recording in the cerebellar cortex. Coxe and Snider reported two waves of evoked local field potentials with 5 and 12–15 ms latencies (Coxe and Snider 1956). Elaborating on this, Fox and Williams found that they could block the longer latency response by lesioning the inferior olive, the source of climbing fiber inputs to the cerebellar cortex. The short latency response was attributed to inputs via the mossy fibers. Although the magnitude of these responses varied, they were observed across the majority of the cerebellar cortex. Furthermore, Fox and Williams found that the latero-ventral portion of the caudate most readily elicited responses in the cerebellum (Fox and Williams 1968).

In 1977, single neuron responses were recorded in chronically implanted cats following caudate stimulation (Hablitz and Wray 1977). Even more detailed analyses of these single neuron responses were conducted a year later by Bratus and Moroz. They initially replicated the caudate to cerebellar responses observed by these previous groups, but followed with experiments stimulating the globus pallidus and substantia nigra, both of which are downstream of the caudate nucleus in the basal ganglia circuitry. Stimulating either of these nuclei reliably elicited responses throughout the cerebellum, albeit slightly faster than the responses elicited by stimulation of the caudate nucleus. Overall, their stimulations resulted in more than 70 % of

cerebellar neurons responding in numerous ways: complex potentials corresponding to climbing fiber inputs, phasic increases/decreases in firing, or even prolonged tonic changes in firing. These observations led them to propose robust connectivity between the caudate and the cerebellar cortex, likely being mediated by either or both downstream basal ganglia nuclei, the substantia nigra and globus pallidus (Bratus and Moroz 1978). A later study found that responses were even more readily elicited in the cerebellar vermis by stimulating the putamen (the counterpart of the caudate inside the striatum) (Manetto and Lidsky 1988).

Cerebellar responses to caudate stimulation were further replicated in freely moving rats in an attempt to gain some understanding as the type of information this pathway might convey. Caudate-cerebellar responses were used to interfere with cerebellar activity during a reaching task. Importantly, they observed that about 25 % of cerebellar neurons reacted to both reach related activity and caudate stimulation. This suggested that caudate input to the cerebellum might play a role in motor behaviors. Triggering caudate stimulation to the reaching movement was also sufficient to disrupt the motor behavior, but the animal quickly adapted to the perturbation (Moroz and Bures 1982).

None of these reports were able to demonstrate an anatomical pathway linking the basal ganglia to the cerebellum. Seminal work by Bostan and colleagues uncovered a disynaptic pathway linking the subthalamic nuclei to the cerebellar cortex. Although not tested explicitly, the pontine nuclei are proposed as the intermediary in this connection (Bostan et al. 2010, 2013; Bostan and Strick 2010).

It is as of yet unknown whether the responses elicited by caudate, pallidal, nigral, or putamen stimulation in earlier studies were dependent on the subthalamic-cerebellum projection. Few studies have examined this pathway although one electrophysiological study has proposed a pathway similar to the one demonstrated by Bostan and colleagues (Perciavalle et al. 1987). Two groups have explicitly examined this pathway in the context of high-frequency stimulation of the subthalamic nucleus for the alleviation of Parkinson's disease. In a recent set of electrophysiological experiments done in the rat 6-OHDA model of Parkinson's disease, Sutton et al. delivered high-frequency stimuli to the subthalamic nucleus while recording from the pedunculopontine tegmental nucleus. They observed suppression of activity in the pedunculopontine tegmental nucleus for the whole duration of their stimulation. They followed these experiments with recordings in the Purkinje cells of the cerebellar cortex and deep cerebellar nuclei. In Purkinje cells, they observed a brief decrease in activity for the duration of the train of stimuli to the subthalamic nucleus. Deep nuclei cells responded with a brief increase in activity (Sutton et al. 2014). Similarly, another group examined cFos (an immediate-early gene reflecting levels of neural activity) upregulation in the cerebellum following high-frequency stimulation of the subthalamic nucleus. They observed increased cFos in all three deep cerebellar nuclei (Moers-Hornikx et al. 2011). These experiments are consistent with the existence of a functional connectivity between the subthalamic nucleus and the cerebellum though the detailed anatomical analysis of the pathway remains to be done.

7.5 Pathological Consequences of Aberrant Interaction Between the Cerebellum and Basal Ganglia

Because the basal ganglia and the cerebellum play a key role in motor behavior, it is expected that dysfunction of either of these structures will result in motor disorders. Indeed, several pathological studies in humans and animal models have linked pathology of the basal ganglia to Parkinson's disease (Jankovic 2008), dystonia (Stacy 2007), Huntington's disease (Vonsattel et al. 2011), and Tourette's syndrome (Cohen and Leckman 1992). Likewise, pathology of the cerebellum has been directly associated with ataxia, tremor, and nystagmus among others (Fine et al. 2002; Nashold and Slaughter 1969). It has been dogmatically thought that dysfunction of one of these structures could only manifest in pathologies specific to that structure. However, the use of novel tools in basic research such as optogenetics, tracers with fluorescent tags, and unharmed viruses such as rabies and herpes virus to study second-and third-order synapses have challenged old paradigms in which a single structure is responsible for a motor disorder. Recent findings using these techniques suggest that multiple motor disorders are the consequence of a pathological network as opposed to a single dysfunctional brain region (Calderon et al. 2011; Neychev et al. 2008, 2011).

An example of this novel view is dystonia. Dystonia, according to recent consensus (Albanese et al. 2013), is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Despite its heterogeneous clinical expressions, this is a disease historically attributed to basal ganglia dysfunction as evidenced by autopsy findings and numerous functional imaging studies (Krystkowiak et al. 1998; Stacy 2007). Furthermore, neurosurgical interventions like lesioning or electrical stimulation of the basal ganglia can improve dystonic symptoms (Larson 2014; Vidailhet et al. 2005). Finally, pharmacological or anatomical manipulations of the basal ganglia are common strategies for creating animal models of dystonia (Liu et al. 2013; Palfi et al. 1996). Since evidence for basal ganglia dysfunction leading to dystonia was robust, imaging studies showing cerebellar abnormalities were often interpreted as secondary to the causal pathology in the basal ganglia (Sadnicka et al. 2012). These interpretations seemed consistent with earlier histological studies that did not provide support for the existence of reciprocal connections between the cerebellum and the basal ganglia (Rouiller 1994; Deniau 1992).

Strong evidence from animal models has begun to revolutionize the view that the basal ganglia is the only locus for dystonia. Animal models for spinocerebellar ataxia type II, Rapid Onset Dystonia Parkinsonism (DYT12), early onset dystonia (DYT1), and cerebellar ataxia-cayman type have shown that abnormal activity in the cerebellum is sufficient to cause dystonia (Fremont et al. 2014; LeDoux and Lorden 1998; Neychev et al. 2008; Pizoli et al. 2002). Importantly, several patients with dystonia have shown abnormalities in eye-blink conditioning and saccadic adaptation (Sadnicka et al. 2012; van Gaalen et al. 2011), dysfunctions that are traditionally associated with the cerebellum but not the basal ganglia. Moreover, autopsy and

clinical imaging studies have shown the presence of focal cerebellar lesions in patients with dystonia (Sadnicka et al. 2012; Turgut et al. 1995; Zadro et al. 2008). Surgical studies have shown a direct role of the cerebellum in dystonia since interventions in the deep cerebellar nuclei (dentatectomy in particular) ameliorate dystonia (Heimburger 1967; Zervas et al. 1967). Thus, the role of the cerebellum in dystonia has been well documented.

Clear evidence that dystonia arises from a network disorder involving the basal ganglia and the cerebellum is supported mainly through animal models (Brown and Lorden 1989; Fremont et al. 2014; Neychev et al. 2008; Pizoli et al. 2002). Here, we discuss data obtained from animal models of Rapid Onset Dystonia Parkinsonism (RDP) (Calderon et al. 2011; Fremont et al. 2015). The mechanisms underlying this disease provide an example as to how abnormal cerebellar activity can influence the basal ganglia via the disynaptic pathway through the thalamus.

7.5.1 Rapid Onset Dystonia Parkinsonism (DYT12)

Rapid onset dystonia parkinsonism (RDP) was identified as a distinctive syndrome in 1992. Dr. William Dobyns named the disorder RDP because of its rapid onset and evolution of symptoms, the combination of dystonic and parkinsonian symptoms, and its minimal response to L-Dopa (Dobyns et al. 1993). Since then, genetic studies of the disease have shown that at least eleven mutations (de Carvalho Aguiar et al. 2004; Heinzen et al. 2014) in the ATP1A3 gene, located on chromosome 19, produce loss of function of the α3 isoform of the Na^+/K^+-ATPase pump (sodium pump). This is a protein that participates in the control of ionic gradients across the cell membrane and has been extensively studied (Skou 1957).

A pharmacological model for RDP was developed to acutely mimick the loss-of-function mutations by using low concentrations of ouabain, an exquisitely selective inhibitor of the sodium pump (Allen et al. 1970). Unexpectedly, instead of observing dystonia when ouabain was perfused into the basal ganglia, this animal model showed parkinsonian symptoms including rigidity, akinesia, and tremor (Calderon et al. 2011). In contrast, infusion of ouabain into the cerebellum was necessary and sufficient to induce dystonia (Calderon et al. 2011; Fremont et al. 2014). Likewise, a more recent genetic model designed to knockdown the α3 sodium pump using RNA interference (*sh*RNA) reproduced these pharmacological findings, confirming that disruption of only the α3 isoform is sufficient to induce dystonia (Fremont et al. 2015).

Both pharmacologic and genetic (*sh*RNA) models have shown that dystonia is associated with erratic firing of cerebellar neurons (Fremont et al. 2014, 2015). In vivo recordings from Purkinje and deep cerebellar nuclei cells (DCN) have shown that there is high-frequency bursting activity during dystonic episodes. As Purkinje cell activity is highly sensitive to partially blocking sodium pumps (Fremont et al. 2014), it was suggested that the erratic firing of DCN is the result of Purkinje cell activity driving these cells.

Given that the cerebellum has this robust functional input to the basal ganglia, and accumulating evidence has associated basal ganglia dysfunction with dystonia, a logical hypothesis was that aberrant cerebellar activity might cause dystonia by imposing this aberrant activity on the basal ganglia. An initial approach (Calderon et al. 2011) showed that lesioning the centrolateral thalamus prevented cerebellar induction of dystonia, suggesting that cerebellar-induced dystonia is the consequence of a dynamic interaction between the cerebellum and basal ganglia. Importantly, striatal neurons exhibited significantly aberrant, and oftentimes bursting activity, during episodes of cerebellar-induced dystonia (Chen et al. 2014). This type of irregular activity has been observed in patients with dystonia (Starr et al. 2004). An elegant set of experiments has also showed that optogenetic silencing of intralaminar thalamic neurons lessened dystonia within seconds after thalamic silencing (Chen et al. 2014). Together, these data demonstrate that aberrant activity from the cerebellum can adversely impact striatal activity to cause dystonia.

7.5.2 Aberrant Cerebellar Activity May Prompt Dystonia in Other Pathologies

Here, we have discussed RDP at length, a condition where aberrant interaction between the cerebellum and basal ganglia has been studied in detail. However, there are many different types of monogenic dystonia (Lohmann and Klein 2013), in which human carriers of genetic mutations associated with dystonia exhibit abnormalities in both the basal ganglia and the cerebellum, and communication between these structures may participate in the pathophysiology of the disease. Examples are:

7.5.2.1 Myoclonus Dystonia (DYT11)

This is an inherited dystonia caused by mutations in the *SGCE* gene that expresses the protein ε-sarcoglycan. fMRI studies of these patients show cerebellar hyperactivation suggesting that the cortico-ponto-cerebello-thalamo-cortical system is affected (van der Salm et al. 2013).

7.5.2.2 Early Onset Primary Dystonia (DYT1)

This is another inherited dystonia caused by mutations in the *TOR1A* gene that expresses the protein Torsin A. This protein is widely expressed in the basal ganglia and the cerebellum, especially in spines and dendrites of Purkinje cells (Puglisi et al. 2013). Several studies using positron emission tomography (PET) have shown patterns of increased metabolic activity in the midbrain, cerebellum, and thalamus during sustained dystonia and in carriers of the DYT1 mutation, but not in normal

controls (Eidelberg et al. 1998; Ulug et al. 2011). In transgenic mice that express the human mutant of Torsin A (hmT1), there is increased glucose utilization in cerebellum and substantia nigra, pars compacta, and reduced activity in caudal-caudate putamen suggesting an abnormal cerebellar–basal ganglia interaction as an important component of the etiology of the disease (Zhao et al. 2011).

7.5.2.3 Whispering Dysphonia (DYT4)

This is a monogenic dystonia that is caused by mutations in the *TUBB4A* gene—a gene that expresses dimeric proteins that constitute neuronal microtubules. It is suggested that these mutations may produce aberrant connections due to axon guidance defects and dysfunction in synaptic and/or axonal transport of proteins. Structural magnetic resonance images of the brain from these patients seem normal, suggesting a specifically functional disruption (Lohmann et al. 2013). Interestingly, hypomyelinization with atrophy of the basal ganglia and the cerebellum (H-ABC) is a disease within the DYT4 familiy characterized by mutations in the same *TUBB4A* gene, but often produces more extreme symptoms (Ferreira et al. 2014; Lohmann et al. 2013). It is suggested that aberrant communication between the cerebellum-basal ganglia may play a significant role in these pathologies. Detailed functional studies in patients with DYT4 and H-ABC are required to determine the role of aberrant communication between cerebellum-basal ganglia in these patients.

Blepharospasm is a focal dystonia in which aberrant cerebello-basal ganglia communication may play a critical role in its pathology. Apart from the multiple disturbances of the basal ganglia associated with blepharospasm such as striatal gliosis and putamen degeneration (Larumbe et al. 1993) functional studies in patients with blepharospasm have recently shown that the cerebellum is an essential contributor to the disease (Yang et al. 2014). Further functional studies are required to better understand how functional defects in this network result in the pathology and degeneration observed in the basal ganglia.

7.5.2.4 Syndromes Associated with Mutations in the α3 sodium pump

Motor control structures, such as the basal ganglia, cerebellum, thalamus and cortex seem to be particularly sensitive to mutations in the α3 isoform of the sodium pump: (1) the majority of pathological conditions associated with these mutations are associated with motor disorders in humans and animal models (Calderon et al. 2011; de Carvalho Aguiar et al. 2004; Fremont et al. 2015). (2) The sodium pump is an important regulator of brain excitability. It contributes to the after-hyperpolarization of the cell (Gulledge et al. 2013). (3) Sodium pump controls intrinsic activity of particular neuronal cell types, and dysfunctional sodium pumps may convert tonic intrinsic firing to erratic firing (Fremont et al. 2014).

Mutations in the α3 sodium pump have been found in RDP (described before), alternating hemiplegia of childhood (AHC) and cerebellar ataxia, areflexia, pes

cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome (Sweney et al. 2015). Specific dysfunction of one or more of these motor control structures may be sufficient to recapitulate the resulting symptomatology. However, given the importance of communication between these structures, as exemplified by RDP, altered communication between the cerebellum, basal ganglia and other areas cannot be discounted. Further mechanistic studies of these syndromes are necessary to understand their pathophysiology.

7.5.3 Parkinson's Disease

A hallmark of this disease is the loss of dopaminergic neurons of the substantia nigra pars compacta, resulting in the manifestation of tremor, rigidity, bradykinesia, and akinesia. However, more recent data suggests that cerebellar interactions with the basal ganglia may contribute to the symptoms of Parkinson's disease (Martinu and Monchi 2013; Wichmann et al. 2011; Wu and Hallett 2013). Several studies indicate that cerebellar activity is also abnormal in Parkinson's disease (Ghaemi et al. 2002; Rascol et al. 1997). In parkinsonian patients (Lenz et al. 1988) and in nonhuman primate models of the disease (Guehl et al. 2003), oscillatory activity similar to tremor frequencies has been recorded in thalamic areas that receive cerebellar, but not basal ganglia inputs. Furthermore, several studies have suggested that targeting the cerebellar recipient zone in the thalamus is effective for treating parkinsonian tremor (Narabayashi et al. 1987). Thus, it is plausible that abnormal activity in cerebellar circuits may produce parkinsonian tremor. Additionally, deep brain stimulation of the subthalamic nucleus reduces motor symptoms in Parkinson's disease while normalizing cerebellar activity and function (Hilker et al. 2004). Therefore, these findings suggest that altered interactions between the basal ganglia and cerebellum may contribute to symptoms of Parkinson's disease.

7.5.4 Psychiatric Disorders

Disorders like DYT11, DYT12 and Parkinson's disease where the cerebellum-basal ganglia network is altered often include significant psychiatric symptoms like anxiety, fear and depression along with their apparent motor dysfunctions (Brashear et al. 2007, 2012; Peall et al. 2011). While a discrete pathway to generate these psychiatric dysfunctions has yet to be described, it is possible that cerebellar interactions with the basal ganglia might play a role. Indeed, the role of cerebellar–basal ganglia interactions in psychiatric dysfunctions seems to be an open and promising area for future studies.

Conclusion

The basal ganglia and the cerebellum are two major subcortical brain regions involved in motor control but evidence for an interaction between these regions has remained scant until recently. Multiple lines of evidence described in this chapter provide strong support for functionally relevant interactions between the cerebellum and the basal ganglia network in normal and in pathological conditions. Future studies should aim at determining the mechanisms and functional consequences of these interactions. This could lead to the development of novel therapeutic tools to treat pathologies in which aberrant interaction between these structures plays a prominent role.

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Chapter 8
Signaling Mechanisms in L-DOPA-Induced Dyskinesia

Cristina Alcacer, Veronica Francardo, and M. Angela Cenci

8.1 Introduction

Parkinson's disease (PD) is characterized by typical movement disorders, in particular, loss of spontaneous movements (akinesia) and slowness of movement (bradykinesia). These motor symptoms are due to the degeneration of nigrostriatal dopamine (DA) neurons and the ensuing loss of DA in the striatum. The DA precursor L-3,4 dihydroxyphenylalanine (L-DOPA) remains the most effective treatment for PD. However, after an initial period of full efficacy, this treatment is complicated by L-DOPA-induced dyskinesia (LID), abnormal involuntary movements (AIMs) having both hyperkinetic and dystonic components. LID has been estimated to affect approximately 80 % of PD patients within 10 years (Rascol 2000; Rascol et al. 2015; Van Gerpen et al. 2006). A better understanding of the neuronal mechanisms underlying the development of LID is essential to identify effective therapeutic strategies (Cenci and Lindgren 2007; Jenner 2008).

Among all the basal ganglia nuclei, the striatum is attributed a pivotal role in generating parkinsonian and dyskinetic motor features, as indicated by the marked effects of striatum-targeted interventions (Bateup et al. 2010; Fasano et al. 2010; Santini et al. 2007). At least 90 % of all striatal neurons are the GABAergic spiny projection neurons (SPNs). There are however two distinct categories of SPNs, those projecting to the substantia nigra reticulata and the internal globus pallidus, so-called "direct pathway" spiny projection neurons (dSPNs) (Gong et al. 2003; Kawaguchi et al. 1990) and those projecting to the external globus pallidus, the

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"indirect pathway" spiny projection neurons (iSPN) (Fink et al. 1992; Gerfen et al. 1990). Interestingly, the expression of DA receptors is segregated between SPNs, dSPNs express D1 receptor (D1R) (Gerfen et al. 1990), and iSPNs express D2 receptor (D2R) as well as the adenosine A2a receptor (Fink et al. 1992; Gerfen et al. 1990). The striatum also contains interneurons (5–10 % in rodents Gerfen and Surmeier 2011). While the role of striatal GABAergic interneurons in LID is currently unknown, the function of cholinergic interneurons has started to be explored. Thus, recent studies in rodent PD models have shown that long-term treatment with L-DOPA raises the excitability of cholinergic interneurons, and that this phenomenon is causally linked with the development of dyskinesia (Ding et al. 2011; Won et al. 2014).

During the past 10 years, an intense basic research has focused on molecular pathways mediating LID. D1R-mediated signaling in the striatum has been strongly implicated in LID (Darmopil et al. 2009; Westin et al. 2007). Indeed, ablation of D1 but not D2Rs was able to prevent the development of LID in the mouse (Darmopil et al. 2009). Moreover, D1R agonists are more efficient than D2R agonists in inducing dyskinesia in animal models of PD (Calon et al. 1999; Carta et al. 2008; Rascol et al. 2001). After L-DOPA administration, signaling pathways downstream of the D1R are strongly activated in the striatum of parkinsonian rodents (Alcacer et al. 2012; Lebel et al. 2010; Santini et al. 2007) and nonhuman primates (Santini et al. 2010). It is now well established that this enhanced D1R-dependent signaling is a key step in the induction of LID.

8.2 Dopamine D1 Receptor Supersensitivity

Two distinct classes of DA receptors were described in the late 1970s, one population named D1 able to activate adenylyl cyclase (AC) and the other one called D2, inhibiting AC activity (Kebabian et al. 1977; Kebabian and Greengard 1971). The classification of DA receptors in two main classes, termed D1 and D2, is still valid today. D1-like receptors (D1Rs) include the D1 and D5 subtypes. The D1R is most abundantly expressed in the central nervous system and in particular in the striatum, mainly in striatonigral spiny projection neurons (or dSPNs). D1Rs are positively coupled to AC through Gαs/Gαolf proteins, which promote AC activity and cAMP synthesis. D2-like receptor (D2R) population includes D2, D3, and D4 subtypes that are coupled to Gαi/o proteins, which inhibit AC and thereby reduce intracellular levels of cAMP (Herve et al. 1993; Missale et al. 1998; Stoof and Kebabian 1981; Zhuang et al. 2000). The D2Rs are abundantly expressed in the striatum where they are mostly expressed in striatopallidal SPNs (or iSPN). D2Rs are also expressed in cholinergic interneurons (Le Moine et al. 1990) and presynaptically in the terminals of dopaminergic neurons of the substantia nigra pars compacta (Levey et al. 1993).

In the parkinsonian condition, loss of DA in the striatum enhances the sensitivity of DA receptors as reflected by an increase in DA-sensitive AC activity (Krueger et al. 1976; Mishra et al. 1974; Von Voigtlander et al. 1973). This observation was reported in the 6-OHDA-lesioned rat model of PD (Herve et al. 1993) as well as in the putamen of parkinsonian patients (Pifl et al. 1992; Tong et al. 2004).

Striatal DA D1R supersensitivity has long been hypothesized as a crucial determinant to the development of LID (Gerfen 2003; Klawans et al. 1977; Rouillard et al. 1987). Recent studies have indeed linked LID to the supersensitivity of D1R and the consequent enhancement of D1-mediated signaling, in both animal models and PD patients (Alcacer et al. 2012; Aubert et al. 2005; Corvol et al. 2004; Lebel et al. 2010; Rangel-Barajas et al. 2011; Santini et al. 2007, 2009b, 2010; Westin et al. 2007).

An increase in the number of D1Rs is however not the cause of D1R supersensitivity after DA depletion. Contrary to D2R, no significant changes, and even a decrease in D1R density, have been detected after DA denervation by in vitro binding assays and in situ hybridization studies in rodents (Gerfen et al. 1990; Herve et al. 1992; Savasta et al. 1988) and by positron emission tomography studies in human (Hurley et al. 2001; Shinotoh et al. 1993; Turjanski et al. 1997).

At the signal-transduction level, two main hypotheses could explain D1R supersensitivity in the parkinsonian condition, functional–structural changes of the D1R protein that would increase its G protein-coupling efficiency (Aubert et al. 2005; Cai et al. 2002; Geurts et al. 1999), or an upregulation of Gαolf, the G protein that couples D1R to AC in the striatum (Alcacer et al. 2012; Corvol et al. 2004; Herve et al. 1993; Marcotte et al. 1994; Penit-Soria et al. 1997; Rangel-Barajas et al. 2011) (Fig. 8.1). Other hypotheses are however being explored, as the possible formation of new macromolecular signaling complexes.

8.2.1 Increased Coupling of D1R to G Protein and Enhanced Adenylyl Cyclase Activity in LID

As mentioned above, striatal D1R supersensitivity underlies the sensitized acute responses to L-DOPA in direct pathway SPNs (Fig. 8.1). After chronic L-DOPA treatment, D1R supersensitivity persists and no differences in D1R binding are observed between dyskinetic and non-dyskinetic patients (Turjanski et al. 1997), and MPTP-lesioned monkeys (Aubert et al. 2005). However, a significant increase of D1R agonist-stimulated [35S]GTPγS binding was observed in MPTP-treated monkeys and persisted after L-DOPA treatment only in animals developing dyskinesias (Aubert et al. 2005). The authors suggested that LID is linked to an increased G protein-coupling efficiency at the level of D1Rs.

Parallel studies in hemiparkinsonian rats support this hypothesis. By stimulating D1R, L-DOPA activates AC through Gαolf coupling, thus increasing cAMP production. Rangel and collaborators showed an increase in the expression and activity of

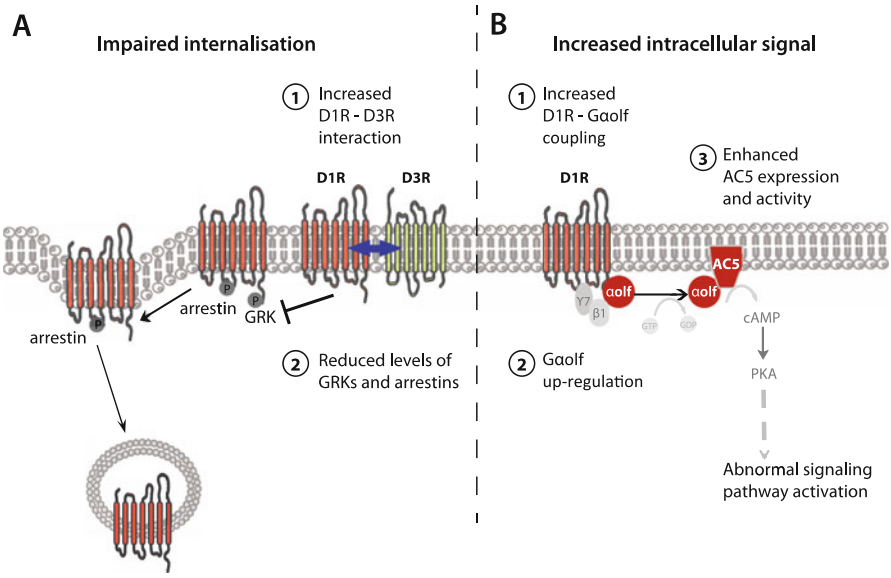

Fig. 8.1 Mechanisms underlying dopamine D1R supersensitivity. Impaired D1R internalization and increased intracellular signaling can account for D1R supersensitivity. (**a**) D1R internalization and trafficking is altered in PD and LID, shown by (1) the maintenance of D1R at the membrane due to its active anchoring to the membrane through a mechanism of interaction with D3R and (2) the abnormal reduction on the protein levels of two key proteins necessary for G protein-coupled receptors internalization, GRK6 and arrestin2. (**b**) At the signal-transduction level, different hypotheses could explain D1R supersensitivity in the parkinsonian and dyskinetic condition: (1) functional–structural changes of the D1R protein that would increase its G protein-coupling efficiency; (2) an upregulation of Gαolf, the G protein that couples D1R to adenylyl-cylase (AC) in the striatum paralleled by (3) an enhanced AC5 expression and activity; all these phenomena leading to an abnormal intracellular signaling activation

AC5 and 6 in the striatum of severe as compared to mildly dyskinetic rats (Rangel-Barajas et al. 2011). Moreover, AC5/6 increase was accompanied by a significant augmentation in cAMP production and a parallel increase in GABA release, upon D1R and forskolin stimulation, in the SNr of severely dyskinetic animals. A more recent study provides direct evidence of the involvement of AC5 in LID. In particular, AC5 knockout mice exhibit an attenuated development of LID and a reduced activation of cAMP production by L-DOPA in the striatum (Park et al. 2014).

An upregulation of Gαolf in DA-denervated striatal neurons may also contribute to this phenomenon. Studies performed both in 6-OHDA-lesioned rodents and on postmortem striatal tissue from PD patients have revealed increased levels of Gαolf (Alcacer et al. 2012; Corvol et al. 2004; Herve et al. 1993; Rangel-Barajas et al. 2011). Interestingly, in a cohort of ten parkinsonian patients receiving a prolonged L-DOPA treatment, the patients displaying the most severe LID were those with the highest striatal levels of Gαolf (Corvol et al. 2004). Accordingly, in a mouse model

of PD and LID, elevated levels of Gαolf in the striatum have been associated with LID (Alcacer et al. 2012). In the latter study, Gαolf was not only upregulated after DA denervation but its increase was correlated to the severity of dyskinesia induced by a subsequent course of L-DOPA treatment. However, mice with a genetically reduced expression of Gαolf exhibited a similar development and end-severity of LID as wild-type controls (Alcacer et al. 2012). These data indicate that the upregulation of Gαolf levels in the striatum caused by DA denervation is not a critical factor in the pathogenesis of LID.

8.2.2 Altered Trafficking of D1 Receptors

D1R internalization and trafficking is an important component in the regulation of D1R signaling, because it determines the amount of receptor proteins available to bind a ligand. Several studies have investigated the relationship between cellular D1R trafficking and dyskinesia in animal models of LID (cf. Fig. 8.1). To date, the results appear different depending on the animal models used. The subcellular localization of D1Rs has been explored in MPTP-treated monkeys receiving chronic L-DOPA treatment (Guigoni et al. 2007)). Compared to normal control animals, dyskinetic monkeys displayed an increase in the expression of D1R at the plasma membrane as well as in the cytoplasm. The authors proposed that chronic L-DOPA induces an impairment of the D1R desensitization machinery. They reported that D1R levels were not decreased at the plasma membrane in dyskinetic monkeys despite the intense stimulation of D1R resulting from chronic L-DOPA treatment, which is expected to promote D1R internalization. Consistent with the hypothesis of impairment in D1R internalization in dyskinesia, the protein levels of GRK6 and arrestin2, two key proteins necessary for G protein-coupled receptors (GPCR) internalization, were reduced in the striatum of MPTP-treated monkeys receiving chronic L-DOPA treatment (Bezard et al. 2005). Further studies have reported the importance of the homologous desensitization machinery in the expression of LID (Ahmed et al. 2010; Ahmed et al. 2008). A reduction in the concentration of GRKs was observed in dyskinetic rats and lentiviral-mediated overexpression of GRK6 in the striatum of rodent and primate models of PD markedly attenuated LID (Ahmed et al. 2010).

More direct proof of impairment of D1R internalization processes was reported in rodent models of LID. Berthet and coauthors found an increased D1R expression at the plasma membrane in dyskinetic versus non-dyskinetic rats (Berthet et al. 2009). However, in this case, the defect was not caused by the inability of D1R to be internalized since a D1R agonist was capable to induce its internalization. The maintenance of D1R at the membrane was rather attributed to its active anchoring to the membrane, possibly through a mechanism of interaction with D3R (Berthet et al. 2009) (reviewed below).

8.2.3 Formation of Novel Signaling Complexes

Like all GPCR, DA receptors are part of heteromeric complexes, composed of other receptors and ancillary proteins. Increasing evidence indicates that the molecular composition of these signaling complexes is modulated under both physiological and pathological conditions (Fiorentini et al. 2013b).

Within the field of LID, particular attention has been focused on the formation of heteromers between D1R and D3R. Although the expression of D3R is very low in the dorsal striatum under normal conditions, an upregulation of D3R mRNA has been detected in rodent and monkey models of LID (Bezard et al. 2003; Bordet et al. 1997, 2000). D1R and D3R can directly interact through an intramembrane cross-talk (Fiorentini et al. 2008; Marcellino et al. 2008). Interestingly, cotreatment with L-DOPA and a D3R antagonist, at a regimen that attenuates LID severity (Bezard et al. 2003; Visanji et al. 2009), restores the normal levels of D1R at the plasma membrane in dyskinetic animals (Berthet et al. 2009). Therefore, it has been proposed that the anchoring of D1R at the membrane in dyskinetic animals is caused by the formation of D1R–D3R heteromers, ensuing a concomitant stimulation of both D1R and D3R by L-DOPA (Berthet et al. 2009). Some authors have proposed that the supersensitivity of D1R signaling in PD and LID models is caused, at least in part, by the formation of D1–D3R heterodimers (Farre et al. 2014). Accordingly, a recent study has found a relationship between the appearance of D1–D3R complexes and the development of LID in 6-OHDA-lesioned rats (Farre et al. 2014) (cf. Fig. 8.1).

Other studies have examined signaling complexes formed by D1R and *N*-methyl-D-aspartate (NMDA) glutamate receptors in striatal neurons. D1 and NMDA receptors were found to colocalize in the striatal postsynaptic density protein fraction, and the abundance of D1R–NMDAR complexes was found to be reduced following DA denervation, and returned to normal levels following chronic treatment with L-DOPA in rats that did not develop dyskinesia. However, when chronic L-DOPA treatment produced dyskinesia, the postsynaptic abundance of D1R–NMDAR complexes was downregulated again (Fiorentini et al. 2006). Since the total striatal levels of these complexes did not change, these data suggested that the decrease of D1R–NMDAR species in the postsynaptic density reflected an altered receptor trafficking. A relocalization of D1R–NMDAR to extrasynaptic membrane compartments is bound to lead to the formation of novel signaling platforms. This phenomenon may have profound implications not only to understanding the signaling abnormalities associated with LID but also to devising new selective ligands that may target abnormal D1R-heteromeric conformations without altering the activity of native D1Rs.

Ongoing research is pursuing signaling complexes that may mediate an activation of noncanonical signaling pathways downstream of the D1R. An interesting study has reported that the D1R interacts with the tyrosine phosphatase Shp-2, which normally regulates the activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) by tyrosine kinase receptors (Fiorentini et al. 2011). This study

showed that D1R stimulation results in Shp-2 tyrosine phosphorylation and activation in primary striatal neuronal cultures and that D1R/Shp-2 interaction is required for D1R agonist to activate ERK1/2. Fiorentini and coworkers have found that a similar signaling mechanism occurs in the DA-denervated striatum and may play a role in the development of LID.

8.3 Intracellular Signaling Pathways

8.3.1 Canonical cAMP-Related Pathways

Because of D1R supersensitivity, increasing attention has been devoted to the participation of the canonical cAMP-mediated signaling in the molecular changes produced by L-DOPA and potentially linked to the development and manifestation of dyskinesia (Alcacer et al. 2012; Feyder et al. 2011; Lebel et al. 2010; Santini et al. 2007, 2010, 2012).

Stimulation of supersensitive D1Rs by L-DOPA triggers a large increase in cAMP levels and an ensuing large activation of PKA. The PKA-dependent signaling pathway has strongly been involved in the development of LID in both 6-OHDA-lesioned rodents (Lebel et al. 2010; Santini et al. 2007) and in MPTP-treated nonhuman primates (Santini et al. 2010). A first evidence of direct PKA involvement in the adverse effects of L-DOPA in a rat model of PD was provided by Oh and collaborators (Oh et al. 1997). In this study, the authors showed that blocking PKA activation by intrastriatal injection of its inhibitor, a phosphodiesterase-resistant analogue of cAMP (Rp-cAMPS), attenuated the heightened intensity of the rotational responses induced by chronic L-DOPA. However, this study did not use behavioral measures of dyskinesia.

The role of PKA in a rat model of LID was first demonstrated by Lebel et al. (2010). In this study, Rp-cAMPS was continuously infused into the striatum during a chronic course of L-DOPA treatment. Molecular and behavioral responses were analyzed. The levels of phospho-Thr34-DARPP32 (dopamine- and cAMP-regulated phosphoprotein, 32 kDa), a direct target of PKA (see below), were significantly decreased after Rp-cAMPS inhibition of PKA. Dyskinetic behavior was scored during the 21-day treatment. A partial but significant decrease in dyskinesia severity was found in animals treated with the PKA inhibitor.

As mentioned above, among the multiple PKA substrates, DARPP-32, a protein highly expressed in SPNs, plays a crucial role in the regulation of intracellular signaling downstream of the D1R (Greengard et al. 1999) (cf. Fig. 8.2). Stimulation of D1R is accompanied by the phosphorylation of DARPP-32 at the PKA site, threonine 34 (Thr-34), which converts it into a potent inhibitor of protein phosphatase 1 (PP-1) (Desdouits et al. 1995; Hemmings et al. 1984). Inhibition of PP-1 suppresses the dephosphorylation of numerous downstream targets of PKA, thus amplifying the effect of PKA activation thereby amplifying behavioral responses produced by

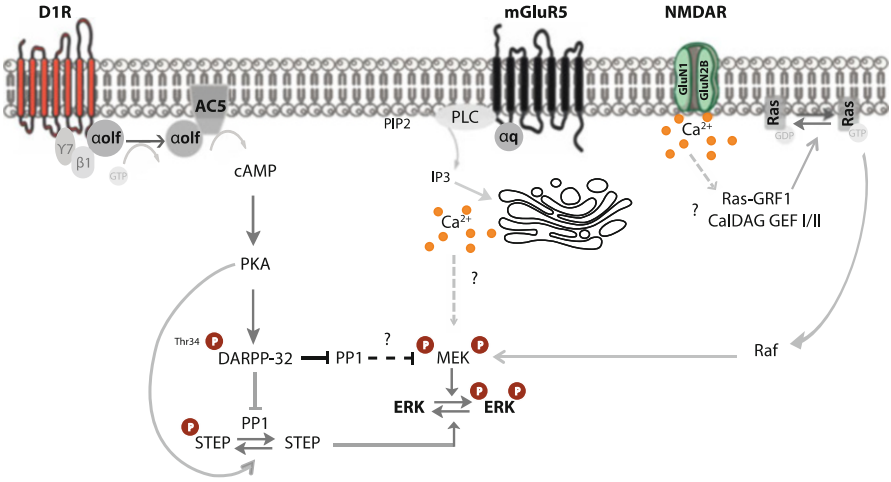

Fig. 8.2 Canonical and noncanonical pathways involved in the activation of ERK signaling in DA-denervated striatal neurons. D1-dependent extracellular signal-regulated kinase (ERK1/2) activation in the DA-denervated striatum depends on a complex interaction between PKA- and Ca^{2+}-dependent signaling pathways. D1R stimulation potentiates ERK 1/2 activation through PKA phosphorylation of DARPP-32, which stimulates ERK activity by suppressing the activity of STEP, through PP1 inhibition. D1-dependent ERK1/2 activation in the DA-denervated striatum is also critically modulated by striatal Gq-coupled receptor mGluR5-signaling. mGluR5 activation triggers IP3 formation, through PLC activation. IP3 stimulates store-dependent Ca^{2+} release from the endoplasmic reticulum therefore increasing the phosphorylation of the MEK/ERK pathway. Activation of ERK is also carried out in part by the Ca^{2+}-activated guanine nucleotide exchange factor Ras-GRF1 and CalDAG-GEFI and CalDAG-GEFII, two striatal-enriched Ras-ERK regulators. The Ras, Raf, MEK1/2 pathway activates ERK1/2 which in turn will activate specific cytoplasmic and nuclear substrates

activation of cAMP signaling (Borgkvist et al. 2007; Fienberg et al. 1998; Greengard 2001). Several lines of evidence indicate that PKA-mediated phosphorylation of DARPP-32 is implicated in dyskinesia. By using a rat model of PD and LID, the group of Picconi provided the first evidence of an association between dyskinesia and increased phosphorylation of DARPP-32 at Thr-34 residue (Picconi et al. 2003). Further studies from Santini and collaborators confirmed these results in a mouse model of LID (Santini et al. 2007). Acute administration of L-DOPA induced an abnormally large increase in the levels of Thr-34-phosphorylated DARPP-32 (pThr34-DARPP32) in the DA-denervated striatum. When mice were chronically treated with L-DOPA the levels of pThr34-DARPP-32 remained elevated only in highly dyskinetic mice. Accordingly, a positive correlation between LID severity and the levels of pThr34-DARPP-32 was established (Santini et al. 2007). These findings have been replicated in the primate model of LID (Santini et al. 2010), where striatal levels of pThr34-DARPP-32 were persistently upregulated in dyskinetic monkeys compared to non-dyskinetic ones. Furthermore, DARPP-32 knockout mice were found to exhibit a partial but significant reduction in dyskinesia severity during chronic L-DOPA treatment (Santini et al. 2007).

A more recent study has explored the differential contributions of the direct and indirect pathway on different striatal-dependent motor behaviors by using conditional DARPP-32 knockout mice (Bateup et al. 2010). Two mouse lines were generated, one in which DARPP-32 is deleted in the dSPNs (*D32f/fD1RCre+*) and the other in which DARPP-32 gene is disrupted in iSPNs (*D32f/fD2RCre+*). The two mouse lines sustained unilateral 6-OHDA lesions. Among the different behaviors analyzed, the authors examined the behavioral contribution of DARPP-32 in the two types of SPNs to LID generation. A striking difference was found between the two mouse lines in response to chronic L-DOPA treatment when lesioned with 6-OHDA. A robust reduction in total dyskinesia scores was observed in D32f/fD1R-Cre+ as compared to their control littermates D32f/fD1RCre−. In contrast, no difference in dyskinesia severity was found between D32f/fD2RCre+ and their control littermates, both groups developing similar AIMs scores. These findings provided direct behavioral evidence that selective loss of DARPP-32 in dSPNs, but not in iSPNs, can inhibit the development of LID in mice (Bateup et al. 2010).

8.3.2 Non-canonical Pathways

There is large evidence that supersensitive D1Rs activate signaling cascades additional to the canonical Gαolf-PKA-cAMP pathway (cf. Fig. 8.2 for a summary of canonical and non-canonical signaling pathways reviewed in this article). Of great importance to LID is the ability of D1R agonists or L-DOPA to induce a large activation of ERK1/2 signaling in DA-denervated striatal neurons. ERK1/2 belong to the mitogen-activated kinase (MAPK) family and are activated via phosphorylation on critical tyrosine and threonine residues by the upstream kinase MEK1/2. This pathway was originally identified as the pivotal mediator of trophic factor-induced cell division and cell plasticity (Kyosseva 2004). In a very important study, Gerfen and collaborators showed that treatment of 6-OHDA-lesioned rats with D1R agonists caused a large activation of ERK1/2 in the DA-denervated striatum (Gerfen et al. 2002). This seminal report also demonstrated that the striatal immunoreactivity for phosphorylated ERK1/2 (pERK) was almost entirely restricted to enkephalin-negative cells, i.e., dSPNs. Hence, these initial observations led to the hypothesis that the denervation-induced supersensitivity of D1Rs leads to the activation of non-canonical signaling responses involving ERK1/2 in dSPNs. It should be noted, however, that psychostimulants like cocaine, which greatly increase extracellular DA levels, can also induce ERK1/2 activation in dSPNs, as originally shown by Caboche and collaborators (Valjent et al. 2000). By favoring the activity of the dSPNs, which promotes action selection (Albin et al. 1989; DeLong 1990), this cellular response may mediate the motor activation elicited by both psychostimulants in the normal brain and dopaminergic agonists (including L-DOPA) in the DA-depleted brain. However, the increase in pERK levels induced by psychostimulants is of smaller magnitude and shorter duration than that elicited by D1R agonists or L-DOPA in the DA-depleted striatum.

The first reports clearly implicating an abnormal ERK activation in LID came in 2006 and 2007. Pavon et al. reported that pERK levels were significantly increased in the denervated mouse striatum already by a single administration of L-DOPA, and further enhanced with a chronic treatment over 25 days (Pavon et al. 2006). Importantly, pERK enhancement in the chronic L-DOPA condition was also associated with a significant upregulation of the immediate early gene FosB/ΔFosB, an established molecular marker of dyskinesia (Engeln et al. 2014). A positive linear correlation between striatal levels of pERK and the abnormal involuntary movements (AIMs) induced by L-DOPA was then provided by Westin et al. in a rat model of PD and LID (Westin et al. 2007). The latter study showed that both acute and chronic L-DOPA administration rapidly induced the phosphorylation of ERK and its nuclear target mitogen- and stress-activated kinase 1 (MSK1) in the DA-denervated striatum. Strong cellular immunoreactivity for pERK was detected in both the medial and the lateral striatum in a time interval ranging between 20 and 120 min after a single dose of L-DOPA, a time window which parallels the time course of the development of AIMs. This study also reported that bromocriptine, an antiparkinsonian drug with low dyskinesiogenic potential, did not induce any significant increase in either pERK or pMSK1 immunoreactivity, further strengthening the link between a large activation of ERK and the development of involuntary movements. Further to these results, the study reported that the striatal activation of ERK signaling by L-DOPA was dependent on the D1 class of DA receptors. Indeed, the D1R antagonist, SCH23390, completely suppressed pERK and pMSK1 induction, as well as FosB/ΔFosB upregulation, in animals treated with L-DOPA. On the contrary, cotreatment with raclopride, a D2R antagonist, had no effect on the L-DOPA-induced response. The direct link between LID, D1R, and ERK activity was later substantiated by the Moratalla group, by showing that genetic ablation of D1 but not D2 receptors suppresses AIMs in the mouse and concomitantly prevents ERK phosphorylation, phospho-acetylation of histone H3 (pAcH3) (a direct substrate of MSK1), and FosB/ΔFosB accumulation (Darmopil et al. 2009). Finally, upregulation of pERK, pMSK1, and pAcH3 levels specifically in the dSPNs was later corroborated using the BAC *Drd1a*- and *Drd2*-EGFP transgenic mice (Santini et al. 2009a).

These observations did attribute a pivotal role of ERK signaling in LID. However, they did not demonstrate that a reduction of the activity of this signal transduction pathway could ameliorate the dyskinetic symptoms. To date, different laboratories have tested the effect of inhibiting MAPK signaling on the generation of LID using various animal models and various techniques (Fasano et al. 2010; Lindgren et al. 2009; Santini et al. 2007; Schuster et al. 2008). The initial evidence was provided in 2007 by the Fisone's group, in mice (Santini et al. 2007). In this paper it was shown that pERK increase well correlated with AIMs severity, and with an enhancement of the PKA-dependent phosphorylation of the glutamate receptor GluA1 (pSer845) and pThr34-DARPP32. Previous work had proposed that in striatal cells, active pThr34-DARPP32 could stimulate ERK activity by suppressing the activity of the striatal-enriched protein tyrosine phosphatase (STEP), a direct substrate of PP-1 (Valjent et al. 2005) (cf. Fig. 8.2). Hence, in the DARPP-32 knockout animals, not

only AIMs were significantly attenuated but also pERK and pGluA1 were reduced. Finally, systemic administration of SL327, a specific inhibitor of the MEK1/2 kinases upstream of ERK1/2, robustly attenuated LID in mice (Santini et al. 2007).

These findings not only demonstrated that aberrant ERK signaling is causally linked to LID, but also pointed to this pathway as a possible therapeutic target. However, blocking this pathway may dysregulate a wide range of important functions, including memory formation, synaptic plasticity, and cell survival (Hetman and Gozdz 2004). To overcome this concern, Fasano and collaborators proposed to reduce rather than block ERK signaling by intervening on its upstream modulators. Thus, Fasano et al. examined the importance of the guanine nucleotide exchange factor Ras-GRF1 in LID models using both mice with a genetic deletion of this factor and viral vector approaches (Fasano et al. 2010) (cf. Fig. 8.2). 6-OHDA-lesioned mice with a genetic deletion of Ras-GRF1 were partially but not completely protected from developing dyskinetic behaviors on L-DOPA, and exhibited a partial reduction of pERK and FosB/ΔFosB levels in the DA-denervated striatum. To block Ras-GRF1 in dyskinetic monkeys, the authors delivered lentiviral vectors coding for dominant negative variants of Ras-GRF1 and ERK constructs to the putamen. This treatment significantly reverted LID without attenuating the antidyskinetic action of L-DOPA. These data suggest that intrastriatal inhibition of Ras-GRF1 can alleviate LID by reducing an overactive ERK1/2 signaling, without blocking this pathway completely.

The fact that Ras-GRF1 inhibition does not completely suppress dyskinesia and ERK1/2 activation (Fasano et al. 2010) may indicate that other guanine nucleotide exchange factors may be implicated in the striatal activation of ERK1/2. Graybiel and colleagues have identified two valid candidates, CalDAG-GEFI and CalDAG-GEFII (Diacylglycerol-regulated guanine nucleotide exchange factor I and II), two striatal-enriched Ras-ERK regulators, whose levels are altered upon DA depletion and L-DOPA treatment (Crittenden et al. 2009) (cf. Fig. 8.2). L-DOPA treatment produces down-regulation of CalDAG-GEFI and upregulation of CalDAG-GEFII mRNAs and proteins, and these changes are correlated with the severity of the dyskinesia.

Finally, Fiorentini et al. have shown that an aberrant increase in the phosphorylation of Shp-2 by D1R stimulation represents an additional interesting therapeutic target to counteract overactive ERK1/2 signaling in LID (Fiorentini et al. 2013a). Additionally, it may be possible to prevent the overactivation of ERK1/2 by targeting signaling components traditionally associated with Gq-coupled receptors. Thus, in the DA-denervated striatum ex vivo, Fieblinger et al. (2014b) recently demonstrated that the D1R-dependent induction of ERK1/2 signaling can be inhibited by antagonizing any of these proteins: the Gq-coupled receptor mGluR5, phospholipase C (PLC), protein kinase C (PKC), Src family kinases, or calcium mobilization from internal stores (Fieblinger et al. 2014b).

Several studies have proposed that a large upregulation of ERK/12 signaling during chronic L-DOPA treatment will induce compensatory mechanisms (i.e., an upregulation of phosphatases, cf. Heiman et al. 2014) that will eventually dampen this response. Thus, in a non-human primate model of LID, levels of phosphoryla-

tion of both ERK1/2 and ribosomal protein S6 (pS235/236, an indirect cytoplasmic target of ERK1/2) were conspicuous upon acute L-DOPA administration but declined significantly after 3 months of treatment (Santini et al. 2010). A decline during chronic treatment was not observed for either pThr34-DARPP-32 or Ser845-phosphorylated GluA1, suggesting that while ERK signaling may be more implicated in the priming for LID, cAMP signaling may be still relevant for its expression in the long term. However, this idea has been contradicted by other studies. First, a study using both 6-OHDA-lesioned mice and the Pitx3ak/ak mouse model of PD showed that L-DOPA-induced striatal ERK1/2 activation does not subside during long-term treatment, but rather shifts from being predominantly localized to SPNs to occurring in cholinergic interneurons (Ding et al. 2011). Second, as mentioned above, lentiviral-mediated inactivation of striatal Ras-ERK signaling was found to significantly improve LID in already dyskinetic monkeys, which had been treated with L-DOPA for several months prior to the vector delivery (Fasano et al. 2010). Finally, in heterozygous mice for Gαolf, L-DOPA-induced cAMP-dependent signaling was attenuated while ERK1/2 activity and AIMs remained high, suggesting that the role of ERK1/2 is preponderant over that of canonical Gαolf-mediated signaling in inducing dyskinesias (Alcacer et al. 2012).

8.3.3 Nuclear Signaling Events

It is well recognized that the Ras-ERK cascade transmits signals from the cytoplasm to the nucleus. One of the main downstream nuclear effectors implicated in ERK-dependent transcriptional regulation is the kinase MSK1. After translocation into the nucleus, ERK1/2 can phosphorylate MSK1 that, in turn, phosphorylates histone H3 on its Ser10 residue. The phosphorylation of histone H3 produces chromatin decompaction, which facilitates the binding of the transcriptional machinery and gene transcription. Recent evidence indicates that MSK1 could be involved in LID. Thus, MSK1 knockout mice develop less severe dyskinesia in response to chronic administration of L-DOPA (Feyder et al. 2014). In this study, inactivation of MSK1 affected exclusively the axial dyskinesia, suggesting that specific components of LID can be controlled by targeting specific signaling pathways downstream of ERK1/2 signaling (Feyder et al. 2014). By contrast, another recent study indicates that MSK1 is not necessary for the development of LID (Alcacer et al. 2014). Using the same transgenic mouse line, the authors showed that the lack of MSK1 in 6-OHDA-lesioned mice attenuates some previously described L-DOPA effects, including Gαolf upregulation, histone H3 phosphorylation, and ΔFosB accumulation (see below). The degree of attenuation was however not sufficient to significantly alter the development of dyskinetic behaviors. Interestingly, the absence of MSK1 had no effect on L-DOPA-induced ERK activation, suggesting an involvement of additional ERK-dependent signaling mechanisms that are independent of its nuclear signaling through MSK1. Indeed, ERK modulates several cytosolic targets, including ion channels and protein translation pathways (see below).

Among the best-studied nuclear signaling events associated with LID is the upregulation of transcription factor ΔFosB. Striatal levels of ΔFosB immunoreactivity are correlated with the severity of LID in rodents (Andersson et al. 1999; Bastide et al. 2014; Feyder et al. 2014; Pavon et al. 2006), and striatal infusion of an antisense oligonucleotide targeting FosB/ΔFosB mRNA attenuates the development of AIMs during chronic L-DOPA treatment (Andersson et al. 1999). In rodent models of LID, ΔFosB induction is restricted to SPNs of the direct pathway (Andersson et al. 1999; Darmopil et al. 2009; Feyder et al. 2014), where activation of ERK is also occurring (Darmopil et al. 2009; Santini et al. 2009a). Indeed, activation of ERK is upstream of the induction of ΔFosB (Fasano et al. 2010; Feyder et al. 2014).

In order to regulate the transcription of its target genes, ΔFosB must form heterodimers with a member of the Jun transcription factor family, JunD. In the striatum of dyskinetic rats, the dimers ΔFosB and JunD were found to be the main contributors to DNA-protein complexes containing CREB responsive elements (CRE) or AP-1 (activator protein 1) enhancers. These enhancers promote the transcription of several genes. Of relevance to LID is the upregulation of prodynorphin transcription mediated by these enhancer elements (Andersson et al. 2001). Indeed, the opioid precursor gene prodynorphin was the first striatal gene found to provide a molecular marker of LID, as its expression levels are closely and positively correlated with L-DOPA-induced AIMs scores (Cenci et al. 1998). This observation has been further confirmed in 6-OHDA-lesioned mice (Lundblad et al. 2004) as well as in a non-human primate model of LID (Aubert et al. 2005) and in parkinsonian patients (Henry et al. 2003). The importance of ΔFosB/JunD heterodimers to the development of LID was proven by Berton and collaborators (Berton et al. 2009). In this study, the authors showed that overexpressing a truncated variant of JunD (ΔJunD), which acts as a dominant negative inhibitor of ΔFosB, dramatically reduced the severity of LID in the monkey (Berton et al. 2009). Using a selective inactivation procedure, a recent study using both rats and macaques proved that the activity of striatal neurons expressing ΔFosB is causal to LID (Engeln et al. 2014). On the contrary, viral vector-induced overexpression of ΔFosB exacerbates LID in 6-OHDA-lesioned rats (Cao et al. 2010). Accordingly, a recent study in the mouse has shown that overexpression of ΔFosB specifically in dSPNs exacerbates LID. In contrast, functional inactivation of ΔFosB in the same neuronal population improves LID (Farre et al. 2014).

A recent study has revealed the involvement of the calcium-binding protein downstream regulatory element antagonistic modulator (DREAM) in the regulation of ΔFosB (Ruiz-DeDiego et al. 2015). DREAM binds to regulatory element sites called DRE in the DNA and represses transcription of target genes such as c-fos, fosB, fos-related antigen-2 (fra-2), and prodynorphin. By using a dominant-active DREAM transgenic mice and DREAM knockout mice, the authors showed that DREAM attenuates the development of LID and diminishes L-DOPA-induced expression of ΔFosB, phosphoacetylated histone H3, and dynorphin-B in the DA-denervated striatum.

8.3.4 Protein Translation Pathways

ERK1/2 is involved in the modulation of protein translation. This occurs basically through the control of the mammalian target of rapamycin (mTOR) cascade. mTOR is the essential component of mTORC1 complex, which can be activated by ERK and promotes initiation of mRNA translation and protein synthesis. mTORC1 is inhibited by rapamycin and rapamycin derivatives (or "rapalogs"). Similarly to ERK, mTORC1 is hyperactivated specifically in dSPNs in 6-OHDA-lesioned mice challenged with L-DOPA. The levels of phosphorylation of several markers downstream of mTORC1 are significantly correlated with the severity of AIMs (Santini et al. 2009b). The involvement of mTORC1 in dyskinesia was first demonstrated by showing that, in the 6-OHDA mouse model, this condition was strongly attenuated by systemic administration of rapamycin (Santini et al. 2009b). More recently, these results were validated in the rat LID model, using the rapalog, temsirolimus (CCI-779) (Decressac and Bjorklund 2013). These findings support the idea that excessive de novo protein translation can be implicated in LID pathophysiology. In line with these findings, an upstream component of the mTOR pathway, Rhes, has proven to be involved in the development of LID, further expanding the list of potential therapeutic targets (Subramaniam et al. 2012).

In the recent years, the idea of combination therapy has emerged as an interesting concept in optimizing novel therapeutic approaches, with clinical trials targeting both Ras-ERK and mTOR cascades already ongoing in oncology (Chappell et al. 2011). The data available on non-canonical intracellular signaling pathways certainly suggest that a similar path could also be taken to treat dyskinesia.

8.4 Striatal Synaptic Plasticity

The first evidence that LID is associated with abnormal plasticity of corticostriatal synapses was provided by Picconi and collaborators in a study performed in 6-OHDA-lesioned rats (Picconi et al. 2003). Rats were treated chronically with a regimen of L-DOPA with which some animals did not develop dyskinetic behaviors, whereas others did. Thereafter, the inducibility and reversal of long-term potentiation (LTP) were compared in brain slices from dyskinetic or non-dyskinetic rats. First, high frequency stimulation of cortical afferents was applied to induce LTP at corticostriatal synapses. This process occurred normally in dyskinetic rats. Thereafter, a low frequency stimulation protocol was applied to reverse LTP. Strikingly, dyskinetic rats lacked the capacity for LTP reversal (depotentiation) (Picconi et al. 2003). Depotentiation has been proposed to be crucial for the elimination of incorrect or unessential motor information (Fino et al. 2005). The inability for LTP reversal was attributed to an overactive signaling downstream of D1R, ensuing Thr34-hyperphosphorylation of DARPP-32, hence a persistent inhibition of intracellular phosphatases (Picconi et al. 2003). In addition to a deficit in LTP reversal, dyskinetic

rats lack the ability to form long-term depression (LTD), and this deficit can be rescued by treatment with phosphodiesterase inhibitors increasing striatal levels of cyclic guanosine monophosphate (Picconi et al. 2011).

The group of Fasano and Brambilla are exploring the involvement of Ras-GRF1 and ERK1/2 in the deficits of striatal synaptic plasticity associated with LID in rodent models (Cerovic et al. 2014). In a recent study, this group showed that Ras-ERK pathway was not only essential for LTP induction, but also for its reversal (depotentiation) in wild-type mice (Cerovic et al. 2014). Ablation of Ras-GRF1 caused a specific loss of LTP in the SPNs of the direct pathway without affecting LTP in the indirect pathway, suggesting that Ras-GRF1 controls LTP induced by high frequency stimulation only in dSPNs. Further studies are needed to clarify the exact role of ERK in this maladaptive synaptic plasticity associated to LID.

8.5 Changes in the Phosphorylation and Trafficking of Glutamate Receptors

There is a large body of evidence indicating that a dysfunction of glutamatergic pathways plays a key pathophysiological role in both PD and LID (Ahmed et al. 2011; Calabresi et al. 2007; Chase and Oh 2000; Hallett et al. 2005; Johnson et al. 2009; Mellone and Gardoni 2013; Sgambato-Faure and Cenci 2012). Here we will focus on recent studies that have revealed an altered phosphorylation and/or subcellular distribution of ionotropic glutamate receptors in LID models.

High levels of tyrosine-1472 phosphorylation of the NMDA receptor subunit GluN2B have been detected in the striatum in various animal models of LID (reviewed in Sgambato-Faure and Cenci 2012). Furthermore, radioligand studies performed in both non-human primate models of LID and dyskinetic patients have shown increased binding densities at GluN2B-containing NMDARs in the putamen (Calon et al. 2002).

The groups of Di Luca and Calabresi have emphasized the importance of an altered trafficking of GluN2B subunit between synaptic and extrasynaptic membrane (Gardoni et al. 2006). Studies in 6-OHDA rats have shown an association between LID and redistribution of GluN2B-NMDARs at the extrasynaptic membrane in striatal neurons (Fiorentini et al. 2006; Gardoni et al. 2006, 2012). In line with this idea, intrastriatal infusion of a peptide that disrupted the anchoring of GluN2B-NMDAR subunit to the postsynaptic density conferred LID susceptibility to previously non-dyskinetic rats (Gardoni et al. 2006). Redistribution of NMDAR subunits between synaptic and extrasynaptic compartments has also been reported in a nonhuman primate model of LID (Hallett et al. 2005). However, in this study, dyskinesiogenic L-DOPA treatment was found to normalize the synaptic levels of GluN2B and GluN1, while considerably increasing the abundance of GluN2A in postsynaptic membrane fractions (Hallett et al. 2005). This and other studies have suggested that a relative enhancement in the synaptic abundance of GluN2A plays an important pathophysiological role, and that blocking GluN2A subunit synaptic

localization may represent a mechanistic target for therapy (Gardoni et al. 2012). Altered trafficking mechanisms may also affect GluN1. As previously mentioned, LID has been associated with a loss of synaptic D1/GluN1-GluN2B-containing receptor complexes (Fiorentini et al. 2006).

A recent study has suggested an association between extrasynaptic localization of NMDAR and a loss of dendritic spines in SPN. Indeed, conditions associated with reduced spine density in either direct pathway or indirect pathway SPNs also involved an increased expression of extrasynaptic NMDARs in the affected cell population (Fieblinger et al. 2014a).

In addition to NMDA receptors, AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors or AMPARs) show changes in phosphorylation, trafficking, activity, and protein interactions in animal models of LID. Postmortem investigations have revealed elevated radioligand-binding activity to AMPARs in the putamen of parkinsonian patients with motor complications compared to patients exhibiting a good motor response to L-DOPA (Calon et al. 2002). In addition to overall changes in ligand-binding activity, the state of phosphorylation and intracellular trafficking of the AMPA receptor subunit, GluA1 is altered in LID. GluA1 is phosphorylated by PKA at Ser845. The levels of phosphorylation of this specific subunit are strongly increased in the striatum in dyskinetic mice (Santini et al. 2007) and monkeys (Santini et al. 2010). Phosphorylation of GluA1 on this specific residue raises the open channel probability (Banke et al. 2000) and surface expression of AMPA receptors (Mangiavacchi and Wolf 2004). Similar to NMDARs, an altered trafficking of AMPARs in striatal neurons has been implicated in LID by a recent study performed in MPTP-lesioned monkeys (Silverdale et al. 2010). Chronically L-DOPA-treated dyskinetic monkeys showed a marked enrichment of the GluA2/3 subunit in a postsynaptic membrane fraction relative to a cytoplasmic vesicular fraction, as well as some trend towards increased membrane expression of GluA1 too (Silverdale et al. 2010). The increased relative abundance of GluA2/3 in the postsynaptic membrane was suggested to render striatal neurons more sensitive to glutamate (Silverdale et al. 2010). A recent study emphasizes the involvement of AMPAR in LID (Charbonnier-Beaupel et al. 2015). Transcriptomic analysis revealed a significant upregulation of *nptx2* gene in dyskinetic mice. *Nptx2* is induced by neuronal activation and encodes neuronal pentraxin II (or neuronal activity-regulated pentraxin, Narp). Narp is a secreted protein that binds to the extracellular surface of AMPARs and regulates their synaptic clustering. The authors of this study concluded that Narp upregulation after L-DOPA treatment might promote abnormal plasticity of corticostriatal synapses through postsynaptic AMPAR clustering (Charbonnier-Beaupel et al. 2015; Kobylecki et al. 2010). Altogether, these data point to a critical role for an altered AMPAR function in the striatal adaptations that are associated with LID.

Additional aspects related to the involvement of AMPAR in LID are a possible upregulation of calcium-permeable AMPAR (Kobylecki et al. 2010) as well as an increased striatal expression of a specific splicing variant of the GluA2 subunit ("GluA2-flip"). An increased Gu2A-flip mRNA expression is likely to lead to enhanced AMPAR transmission in the lateral striatum due to a slower desensitization and larger amplitude in synaptic currents (Kobylecki et al. 2013).

8.6 Profiles of Genes and Protein Expression

8.6.1 Changes in Expression and Regulation of Transcription Factors and Immediate Early Genes

Among the large number of genes that are regulated by DA in the striatum, some are rapidly induced and others have slower induction kinetics. The genes that are rapidly and transiently induced are the so-called immediate early genes (IEGs). The transcription of these particular genes is induced within minutes and does not require protein synthesis. IEGs usually, but not always, encode transcription factors including c-Fos, FosB, JunB, c-Jun, Fra-1, Fra-2, and Egr-1 (also called zif268, krox24, NGF1-A) (Graybiel 1990; Hope et al. 1992; Moratalla et al. 1992; Robertson and Robertson 1989). The IEG encoding the transcription factor FosB has received particular attention in the context of PD and LID. Indeed, a splice isoform of fosB mRNA codes for the very stable transcription factor, ΔFosB, which accumulates in the dorsolateral striatum during chronic dyskinesiogenic treatment with L-DOPA (Andersson et al. 1999; Bastide et al. 2014; Berton et al. 2009; Cenci and Konradi 2010; Cenci et al. 1998; Feyder et al. 2011, 2014; Fisone and Bezard 2011; McClung et al. 2004) (cf. paragraph 8.3.3).

Among other genes, the IEGs z*if268* and *arc* are upregulated in hemiparkinsonian rats chronically treated with L-DOPA (Bastide et al. 2014; Carta et al. 2005; Charbonnier-Beaupel et al. 2015; Feyder et al. 2011; Heiman et al. 2014; Sgambato-Faure et al. 2005). In particular, it has been shown that acute L-DOPA treatment increases the levels of *Zif268* mRNA in both striatonigral and striatopallidal SPNs in the DA-denervated striatum (Bastide et al. 2014; Carta et al. 2005; Feyder et al. 2011). Interestingly, treatment with L-DOPA normalizes *Zif268* mRNA in striatopallidal but not striatonigral SPNs (Carta et al. 2005). Similarly, the expression of *arc* mRNA, an IEG implicated in cytoskeletal rearrangement and synaptic plasticity (Li et al. 2005), increases after chronic L-DOPA treatment in dynorphin-positive striatonigral SPNs (Bastide et al. 2014; Sgambato-Faure et al. 2005). Moreover, the sustained upregulation of *Arc* mRNA is restricted to the same striatal regions that exhibit ΔFosB-like immunoreactivity.

8.6.2 Gene Expression Profiles Associated with LID

Several studies have explored the striatal gene expression profiles associated with LID. These studies were performed using a microarray transcriptomic approach in the rat (El Atifi-Borel et al. 2009; Konradi et al. 2004; Lortet et al. 2013) or in the mouse (Charbonnier-Beaupel et al. 2015; Heiman et al. 2014). Konradi and collaborators examined the pattern of striatal messenger RNA expression of over 8000 genes in a rat model of PD and LID (Konradi et al. 2004). The authors approached this issue by comparing 6-OHDA-lesioned rats chronically treated with saline or

L-DOPA, and subdivided the L-DOPA-treated animals into dyskinetic and non-dyskinetic cases. The striatum of dyskinetic rats showed a profile of increased transcriptional activity of GABAergic neurons, accompanied by changes in a gene network involved in calcium-dependent signaling, with a particular upregulation of genes involved in calcium homeostasis. A dysregulation of genes involved in structural and synaptic plasticity was also observed. Finally, the pattern of gene expression in dyskinetic rats pointed to an imbalance between high metabolic demand and a reduced capacity for energy production in the striatum.

El Atifi-Borel and collaborators compared the effects of acute versus long-term L-DOPA treatment on the profiles of striatal gene expression in the DA-depleted striatum, examining nearly 5000 genes (El Atifi-Borel et al. 2009). Acute and chronic treatments regulated a common set of 16 genes mainly implicated in signal transduction, transcription, translation, homeostasis processes and synaptic transmission. The transcriptomic response was enhanced by chronic L-DOPA treatment. The main differences between the two treatments pertained to genes involved in protein synthesis, metabolism, cell proliferation, neurite outgrowth, and synaptogenesis. Long-term L-DOPA administration was thus proposed to be associated with structural cellular alterations in the striatum. Similar conclusions emerged from a transcriptional profiling study comparing the effects of dyskinesiogenic treatment with L-DOPA with those of subthalamic nucleus stimulation, an intervention that alleviates parkinsonian motor deficits without inducing dyskinesia (Lortet et al. 2013). Gene categories induced only by L-DOPA treatment included genes potentially involved in neurovascular remodeling (such as extracellular matrix–cell surface interactions) and immunity-related genes.

A recent study used a refined mRNA translational profiling approach called translating ribosome affinity purification (TRAP) to identify cell-type-specific gene expression changes in dSPNs and iSPNs as induced by DA depletion and pharmacological DA replacement in 6-OHDA-lesioned mice (Heiman et al. 2014). DA depletion followed by chronic low- or high-dose L-DOPA treatment was associated with massive changes in mRNA translation in dSPNs, compared with relatively modest changes in iSPNs. Importantly, many of the gene expression changes observed in dSPNs correlated with the severity of AIMs, strongly suggesting that dSPNs are involved in the genesis of LID. The large gene profiling obtained in this study confirmed that CREB, AP-1, and ERK signaling are major drivers of the transcriptional response to chronic dyskinesiogenic treatment with L-DOPA in dSPNs. Interestingly, several homeostatic changes induced by the treatment were observed in dSPNs, such as the upregulation of MAPK-signaling phosphatases to counteract the abnormal high activity of the MAPK cascade in LID. However, these homeostatic mechanisms failed to dampen the upregulation of an AP-1-regulated gene network (including transcription factors of the *Jun* and *Fos family*). The profound molecular adaptations of dSPNs and the limited response of iSPN during dyskinesiogenic treatment with L-DOPA support the use of dopaminergic agents with preferential D2-like receptor activity as a first-line therapy to prevent dyskinesia in PD.

The molecular signature induced by L-DOPA in the DA-depleted striatum was uncovered further by a recent important study performed in 6-OHDA-lesioned mice

(Charbonnier-Beaupel et al. 2015). The study focused, in particular, on ERK-dependent gene expression changes induced by the first administration of L-DOPA and associated with the early development of AIMs in hemiparkinsonian mice. A time-course analysis (0–6 h after treatment with L-DOPA) identified an acute signature of 709 genes, among which genes involved in protein phosphatase activity were overrepresented, suggesting that a negative feedback on ERK1/2 activation is recruited by L-DOPA itself. L-DOPA-dependent deregulation of 28 genes was blocked by pretreatment with an inhibitor of ERK1/2 activation, SL327, and 26 genes were found differentially expressed between highly and mildly dyskinetic animals following treatment with L-DOPA. The intersection list revealed five genes: *FosB*, *Th*, *Nptx2*, *Nedd4l*, and *Ccrn4l*. As mentioned before, *Nptx2* encodes neuronal pentraxin II, Narp, involved in the clustering of glutamate AMPARs. The increase in *Nptx2* expression after L-DOPA and its blockade by SL327 was confirmed by quantitative RT-PCR. Using an escalating L-DOPA dose protocol, LID severity was decreased in Narp knockout mice or after overexpression of a dominant negative form of Narp in the striatum. In conclusion, the authors of this study identified a molecular signature induced by L-DOPA in the DA-denervated striatum, dependent on ERK1/2 and associated with LID. Of particular interest was the result that Narp may be considered as a new therapeutic target in the early phases of LID development. These findings further corroborate the suggestion that changes in the composition of glutamate receptors at corticostriatal and/or thalamostriatal synapses is an important element of the maladaptive plasticity that leads to LID.

8.7 Non-neuronal Mechanisms

There is increasing evidence that L-DOPA treatment affects not only neurons but also microvessels (Hirano et al. 2008; Munoz et al. 2014; Ohlin et al. 2011, 2012) and glial cells (Bortolanza et al. 2015; Inyushin et al. 2012; Ohlin et al. 2011) within cortico-basal ganglia regions. Ohlin et al. reported that 6-OHDA-lesioned rats chronically treated with L-DOPA presented an increased expression of vascular endothelial growth factor (VEGF) in the basal ganglia astrocytes and astrocytic processes in the proximity of blood vessels (Ohlin et al. 2012). Increased microvascular density, microvascular expression of nestin (marker of immature endothelium), and upregulation of VEGF mRNA were also found in postmortem basal ganglia human tissue from PD patients with history of dyskinesia (Ohlin et al. 2012).

Another recent study reported an upregulation of VEGF protein and VEGF mRNA, accompanied by increased levels of the proinflammatory cytokine IL-1β, specifically in the striatum and substantia nigra of dyskinetic rats, effects that were prevented by an antagonist of the renin-angiotensin system (involved in the inflammatory response and VEGF synthesis) (Munoz et al. 2014). Moreover, the development of LID in the rat was described to be associated with the activation of an inflammatory cascade involving nitric oxide (NO), resulting in striatal and

pallidal astrocytosis and microglial activation (Bortolanza et al. 2015). An inhibitor of the NO synthase (NOS) was able to both prevent the activation of the glial cells that trigger the inflammatory response and also to prevent the development of LID.

All these findings strongly suggest an implication of the microvascular compartment and neuroinflammation in the development of LID.

8.7.1 Gliovascular Mechanisms

The passage of L-DOPA from blood to brain occurs via the L-type amino acid transporter system present in endothelial cells of the blood–brain barrier (Matsuo et al. 2000; Wade and Katzman 1975), and therefore depends on variables such as: (1) capillary permeability, (2) capillary surface area, (3) regional blood flow (Renkin 1985), and (4) the possibility of an active drug metabolism at the capillary level. These variables might have an important role in the development of LID. Indeed, several studies described large increase in the extracellular levels of L-DOPA in the brain of dyskinetic animals following peripheral drug administration (Buck et al. 2010; Carta et al. 2006; Porras et al. 2014). Since there are no indications that the uptake of L-DOPA by brain cells is impaired in dyskinesia, it is reasonable to suppose that the increased extracellular levels of L-DOPA depend on its increased entry.

L-DOPA uptake, conversion, and metabolism in the brain are regulated by non-neuronal elements, such as endothelial cells, pericytes, and perivascular astrocytes (Bertler et al. 1966; Inyushin et al. 2012). These cells are also key regulators of capillary permeability and regional cerebral blood flow (rCBF) (Attwell et al. 2010), in a way to match the metabolic activity of neurons (process called "neurovascular coupling"). It has been described both in a rat model of LID and patients affected by dyskinesia that when L-DOPA is administered causes a disruption of the neurovascular coupling, increasing the rCBF without elevating glucose metabolism in several basal ganglia regions (Hirano et al. 2008; Ohlin et al. 2012). Interestingly, the regions with large increase in rCBF exhibit endothelial proliferation, angiogenic activity, and increased microvascular density both in a rat model of PD and in post-mortem basal ganglia tissue from dyskinetic PD patients (Ohlin et al. 2012). This phenomenon may contribute to the presynaptic mechanisms of LID, resulting in higher extracellular levels of L-DOPA in dyskinetic subjects (Hirano et al. 2008; Ohlin et al. 2012). The mechanisms at the base of the large increases in rCBF "on" L-DOPA and the angiogenic response to the chronic treatment have not yet been clarified. However, it has been hypothesized that gliovascular cells in the affected brain regions might be involved in the neurovascular effects of L-DOPA pharmacotherapy (Ohlin et al. 2011).

8.7.2 Changes in BBB Permeability

It has been suggested that the neurodegenerative process in PD is accompanied by an impairment of the blood–brain barrier (BBB) (Bartels et al. 2008; Pisani et al. 2012), a selective diffusion barrier formed by brain endothelial cells connected by tight junctions. In PD patients with severe PD, the BBB impairment causes a reduced functionality in separating the circulating blood from the brain extracellular fluid. The consequence is, for example, an increased ratio of albumin concentrations in cerebrospinal fluid (CSF) versus plasma in PD patients with advanced disease compared to age-matched controls (Pisani et al. 2012).

This BBB dysfunction may result from a number of different mechanisms, such as: (1) the formation of new leaky vessels (Wang et al. 2005), (2) functional abnormalities in astrocytes, that maintain the tight junctions in the BBB (Ballabh et al. 2004), (3) proinflammatory cytokines (see Carvey et al. 2005), (4) lifetime exposure to dopaminergic agents that has been shown to correlate with the albumin ratio values in a group of patients with severe PD (Pisani et al. 2012).

BBB dysfunction is not a widespread phenomenon in the PD brain, but studies in both parkinsonian animals and human PD have detected BBB leakage in striatal and midbrain areas showing endothelial proliferation and other markers of active angiogenesis (Barcia et al. 2005; Carvey et al. 2005; Desai Bradaric et al. 2012; Faucheux et al. 1999; Ohlin et al. 2011, 2012; Westin et al. 2006).

BBB dysfunction is further aggravated by L-DOPA-induced dyskinesia. Indeed, rodent studies describe the presence of endothelial proliferation; increased BBB permeability; and upregulation of VEGF in the dorsolateral striatum, substantia nigra reticulata, and GPi of dyskinetic rats (Lindgren et al. 2009; Munoz et al. 2014; Ohlin et al. 2011; Westin et al. 2006). The mechanisms inducing these phenomena seem to involve the activation of ERK 1/2 via the stimulation of D1 receptors by L-DOPA. Indeed, Lindgren and coworkers show that treatment with the MEK-inhibitor SL327 is able to reduce both LID and angiogenic markers in a rat model of LID (Lindgren et al. 2009; Westin et al. 2007). Moreover, treatments antagonizing VEGF can inhibit the angiogenic activity and BBB dysfunction induced by L-DOPA in the basal ganglia (Ohlin et al. 2011), preventing at the same time the gradual increase in dyskinesia severity during a chronic course of L-DOPA administration (Munoz et al. 2014; Ohlin et al. 2011).

It has been proposed that the angiogenic activity induced by chronic L-DOPA treatment may contribute to the aggravation of LID by increasing BBB permeability and therefore the entry of L-DOPA in the motor part of the striatum and the basal ganglia output nuclei (Westin et al. 2006). A larger L-DOPA entry and a consequent higher rCBF might enhance tight junction opening between endothelial cells, particularly at the level of angiogenic or damaged microvessels (Sandoval and Witt 2008). Indeed, in support of this hypothesis, leakage of an intravenous tracer molecule having a molecular weight similar to L-DOPA has been shown in striatal and nigral regions of dyskinetic rats (Ohlin et al. 2012).

All these findings suggest that gliovascular mechanisms are strongly implicated in development of LID and protective therapies targeting the vasoactive response to L-DOPA may stabilize the microvasculature and prevent the worsening of dyskinesia over time.

8.8 Summary and Conclusions

The studies reviewed in this chapter point to the supersensitivity of D1Rs as a crucial event in LID. This supersensitivity is sustained by several features, such as an increased coupling efficiency of D1R to Gαolf, an abnormal recruitment of D1Rs at the cell surface, a relocalization of D1R associated with the formation of novel signaling complexes, and a cross-talk between canonical cAMP-related signaling pathways and noncanonical ones, ERK1/2 in particular. Supersensitive D1R appears to be the culprit in many of the peculiar molecular and functional properties attributed to the dyskinetic striatum, ranging from changes in gene transcription and protein translation to abnormal activity-dependent plasticity of corticostriatal synapses. However, several key questions remain to be elucidated. In particular, there is very little information regarding functional responses mediated by the D2 receptors and iSPN, and very little is known regarding the role of striatal interneurons in LID. Moreover, it will be important to study signaling abnormalities of important neuronal populations outside of the striatum, for example in the motor cortex, which shows abnormal plastic changes in LID (Halje et al. 2012).

Finally, the findings of abnormal neurovascular coupling and gliovascular plasticity in LID models suggest that neurotransmitter receptors expressed in non-neuronal cells are heavily implicated in the complications of L-DOPA pharmacotherapy in PD. This topic is both unexplored and very timely. Indeed, in a variety of neuropsychiatric conditions, studies are uncovering non-neuron-autonomous disease pathways and orchestrated actions of gliovascular cells, immune cells, and neurons in the response to treatment interventions (Kousik et al. 2012; Ostergaard et al. 2013; Xanthos and Sandkuhler 2014).

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Part III
Perception, Learning and Cognition

Chapter 9
Cognitive and Perceptual Impairments in Parkinson's Disease Arising from Dysfunction of the Cortex and Basal Ganglia

Deepti Putcha, Abhishek Jaywant, and Alice Cronin-Golomb

9.1 Introduction

Parkinson's disease (PD) traditionally has been considered a motor disorder, being characterized by the cardinal motor symptoms of tremor, rigidity, slowness of movement, and impairments of posture, gait, and balance. Clinical and research emphasis on the substantia nigra and dopamine has resulted in a decades-long focus on this neurotransmitter in regard to PD etiology and treatment (Goetz 2011). In recent years, there has been growing recognition that the non-motor symptoms of the disease are important contributors to quality of life that are not relieved by dopaminergic treatment (Cronin-Golomb 2013). Understanding their etiology and course may lead to the development of interventions to ease the burden experienced by those with PD.

Current research on the non-motor symptoms of PD is focused on cognition and perception and on the diagnosis and treatment of cognitive decline (Litvan et al. 2011, 2012). This focus has derived in part from the work of Braak and colleagues on the neuropathological staging of PD through examination of synucleinopathy (density of Lewy bodies and Lewy neurites) (Braak et al. 2006). This program of research established that lower-brainstem areas (important to arousal and hence to attention) are affected early, before the first motor signs of PD (Chaudhuri et al. 2011; Gaenslen et al. 2011; Gaig and Tolosa 2009; Jacob et al. 2010; Postuma et al. 2012). In later stages, the pathology extends to cortex—first to prefrontal and high-order sensory association areas (stage 5), subsequently to premotor and secondary

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sensory association areas, and finally potentially to primary cortex (stage 6) (Braak et al. 2004). The presence of Lewy bodies and cortical loss is associated with impairments in cognition.

The basal ganglia are important to cognitive as well as motor activity. Imaging studies have found that the putamen and caudate are associated with an action's motor and cognitive components, respectively (Monchi et al. 2001). The caudate head may operate in executive processing (Seger and Cincotta 2005, 2006), sharing connectivity with the dorsolateral prefrontal cortex (PFC) (Selemon and Goldman-Rakic 1985). Executive functioning tasks that involve set-shifting, planning, problem-solving, monitoring, and sequencing elicit both lateral PFC and striatal activity (Monchi et al. 2001; Provost et al. 2010; Tinaz et al. 2008). Of relevance to visuospatial cognition and attention, functional connectivity and diffusion tensor imaging analysis have demonstrated that posterior parietal cortex, especially the angular gyrus region within the inferior parietal lobe, shares strong connections with the caudate (Uddin et al. 2010), and decreased cortical thickness has been reported in PD in the right inferior parietal lobule (Pagonabarraga et al. 2013) and parieto-occipital sulcus (Tinaz et al. 2011), among other areas. Sustained attention and inhibitory control are associated with a bilateral, though slightly right-lateralized, network of regions in the PFC (Aron et al. 2004; Esterman et al. 2013), particularly the inferior frontal gyrus/opercular cortex and its connections to the anterior cingulate cortex, and dorsolateral PFC. An fMRI study of PD by Tinaz and colleagues (2008) found abnormal activation in distinct PFC areas and left caudate, indicating compromise of frontal-basal ganglia circuits. Observations of reduced subcortical volume (Ibarretxe-Bilbao et al. 2009), reduced integrity of white matter tracts (Cochrane and Ebmeier 2013), and functional hypometabolism (Hosokai et al. 2009) suggest that these frontal-basal ganglia regions are compromised in PD.

The mechanisms of PD-related motor and non-motor deficits implicate basal ganglia pathology and the resulting dysfunction of basal ganglia-thalamo-cortical dopaminergic circuitry (Barnes et al. 2010; Kwak et al. 2010), but there is as yet no clear understanding of the pathophysiology underlying these various symptoms. Studies demonstrating functional changes in the basal ganglia and cerebral cortex suggest that PD is a complex network disorder in which abnormal basal ganglia activity has profound effects on the excitability of, and synchrony between, multiple cortical regions involved in perception, motor planning and execution, and cognitive function (Galvan and Wichmann 2008; Hammond et al. 2007). Brain activity dynamically changes independently of whether or not the brain is engaging in a particular cognitive task. Indeed, it has long been proposed that spontaneous activity during rest contributes significantly to the variability observed in stimulus responses (Arieli et al. 1996; Fox et al. 2007). The brain's natural resting state was initially considered to be a passive condition serving as a baseline against which other cognitive processes could be compared. This view of rest as a passive state has been replaced with the current idea that the brain's resting state is a

dynamic state of maintenance activity (Papo 2013). A default mode network comprising the medial prefrontal lobes, posterior cingulate cortices, precuneus, inferior parietal, and lateral temporal cortices displays increased activity at rest and decreased activity during cognitively demanding tasks (Raichle et al. 2001). The organization of spontaneous resting activity in the brain is thought to reflect a history of past task-induced activations and serves to modulate future network responses (Ohl et al. 2001; Yao et al. 2007). Resting state activity is predictive of performance on a range of cognitive tasks in healthy young adults as well as in individuals with damage to basal ganglia structures, as in PD (Kounios et al. 2008; Lebedev et al. 2014).

9.2 Cortico-Striatal Connectivity and Cognition

Intrinsic functional connectivity research in PD has focused on cortical networks including the default mode network, the dorsal attention network, and the cognitive control network. Functionally, the default mode network is proposed to subserve internally directed cognition and self-monitoring (Andrews-Hanna 2012). The dorsal attention network, including the frontal eye fields and bilateral intraparietal sulci, supports external attentional control (Szczepanski et al. 2013). The cognitive control network, also referred to as the central executive network, includes regions of posterior parietal cortex and dorsolateral PFC and responds strongly to externally oriented higher-order cognition (i.e., goal-directed executive processes) through its interactions with the default mode and dorsal attention networks (Dosenbach 2006).

The pathophysiology of cognitive impairment in PD reflects a disruption of neuronal circuits between the striatum and cortical areas in the prefrontal and parietal lobes (Carbon and Marie 2003). Functional connectivity magnetic resonance imaging (fcMRI) techniques have been used to study intrinsic connectivity patterns between the basal ganglia and the cortex in non-demented PD patients and age-matched control participants. fcMRI studies have tracked reorganization of neural networks (Pawela et al. 2010), while electrophysiological examinations of effective connectivity have gone further and distinguished between pathogenic and compensatory processes among synchronous activity in rat models of PD (Moran et al. 2011). Studies of resting state functional connectivity in humans with PD using seed regions in the basal ganglia have found some evidence of compensatory remapping (Helmich et al. 2010), and others have simply shown diminished functional coherence within networks identified in healthy control participants (Kwak et al. 2010).

In PD, decreased connectivity has been reported within the default mode network, the degree to which correlated with severity of cognitive symptoms, though not with disease duration, motor impairment, or levodopa therapy (Tessitore et al. 2012).

An fMRI study by Tinaz and colleagues (2008) found reduced resting activation in areas of the default mode network, in PD relative to a control group, suggesting that regions in frontal–basal ganglia circuits are dysfunctional even at rest in mild PD. With respect to the cognitive control network, another study demonstrated that freezing of gait is particularly associated with reduced connectivity between the basal ganglia and cognitive control network (Shine et al. 2013). This group also reported that visual misperceptions in PD are related to reduced activation of regions of the dorsal attentional network (Shine et al. 2014).

DiMartino and colleagues (2008) mapped out cortico-striatal functional connectivity in healthy young adults using resting state fcMRI analysis to examine connectivity from six striatal seed regions (ventral inferior striatum, ventral superior striatum, dorsal caudate, dorsal caudal putamen, dorsal rostral putamen, and ventral rostral putamen). The investigators found that the superior ventral striatum was functionally connected with the superior and lateral orbitofrontal cortex, regions implicated in executive function and motor planning. By contrast, the inferior ventral striatum showed correlated activity with the medial orbitofrontal cortex, parahippocampal gyrus, and posterior cingulate cortex, regions implicated in emotional processing. The dorsal caudate was implicated in cognitive control, correlating with activity bilaterally in the dorsolateral prefrontal cortex, while putamen seed regions predicted activity in the primary and secondary cortical motor areas. These findings revealed subtler distinctions in cortical connectivity among striatal subregions than had previously been reported and provided evidence for distinct functional networks mapping onto specific cognitive, affective, and motor domains.

The intrinsic connectivity of these cortico-striatal networks becomes dysfunctional in PD compared to younger adults and healthy individuals age-matched to PD. One study compared intrinsic fluctuations between these groups focusing on three cortico-striatal loops involving the posterior putamen, the anterior putamen, and the caudate nucleus (Helmich et al. 2010). Differences in connectivity profiles between PD and an age-matched control group were observed specific to putamen seed regions, as in PD the posterior putamen exhibited decreased coupling with the inferior parietal cortex, while the anterior putamen demonstrated increased coupling with the same region. The authors proposed that focal dopamine depletion in the posterior putamen results in a functional disconnection with the cortex, whereas the relatively spared anterior putamen demonstrates functional compensation via hyperconnectivity with the cortex. This study provides some evidence for a possible compensatory phenomenon as a maladaptive consequence of striatal dopamine depletion in PD.

Large-scale functional network analysis exploring brain function across healthy adults and brain-disordered individuals has led to a conceptual framework referred to as the triple network model of pathology. This model highlights three distributed neural networks that are disrupted across many neuropsychiatric and neurological disorders (Menon 2011): the default mode network (DMN), the salience network (SN), and the central executive network (CEN) (Greicius et al. 2003; Menon and Uddin 2010). These three networks are considered core neurocognitive networks because they play critical roles across a wide range of cognitive tasks (Menon 2011;

Seeley et al. 2007). The CEN (including dorsolateral PFC and lateral posterior parietal cortex) refers to largely the same regions referred to in previous literature as the Cognitive Control Network, while the salience network (including anterior insula and dorsal anterior cingulate cortex) is now recognized as functional and structurally distinct from the dorsal attention network under which it had previously been conceptualized. Typically, the salience network and CEN increase activation during cognitive tasks in response to external stimuli (Dosenbach et al. 2006), whereas DMN activity is suppressed (Greicius et al. 2003; Raichle et al. 2001). The triple network model posits that during cognitively demanding tasks, allocation of attentional resources to external stimuli activates the CEN, and suppression of more internal, self-referential processes deactivates the DMN (Menon 2011), resulting in anti-correlated activity between the CEN and DMN (Fox et al. 2005). The salience network is responsible for detecting and filtering the relevant information for maintaining goal-directed behavior (Menon 2011; Seeley et al. 2007). Critically, the salience network activates the central executive network and deactivates the default mode network during cognitive tasks as well as during the resting state (Menon 2011; Seeley et al. 2007; Sridharan et al. 2008), thereby shifting attention between external and internal processes.

As the striatum is a primary target of PD pathology and becomes more dysfunctional as the disease progresses (Ravina et al. 2012), it is important to understand the structural and functional connections the striatum has with regions of the neocortex. Through reciprocal connections, striatal neurons are thought to coordinate activity in many cortical regions (Macdonald and Monchi 2011). In particular, striatal neurons are highly interconnected with neurons in the insular cortex (Chikama et al. 1997; Fudge et al. 2005), an important node of the salience network. Dopamine depletion occurs in parallel in the striatum and the insula (Christopher et al. 2014; Monchi et al. 2007; Shine et al. 2013). It has been hypothesized that the loss of dopamine receptor type 2 (D2) signaling in the insula disrupts the modulation of salience network activity, impairing its function in activating and deactivating other core neurocognitive networks (Menon and Uddin 2010). Altered cortico-striatal-thalamocortical neurocircuitry resulting from dysfunctional striatal dopaminergic function leads to aberrant assignment of salience (Kish et al. 1988; Monchi et al. 2007; Shine et al. 2013) and has important implications for understanding cognitive dysfunction. As striatal dysfunction is characteristic of PD and worsens with disease severity, functional coupling between the striatum and the salience network is likely to be disrupted as a function of disease progression.

In addition to disruption of the salience network, decreased functional connectivity within the DMN has been observed in PD during the resting state (Tessitore et al. 2012) and during cognitively demanding tasks (van Eimeren et al. 2009). The striatum is also connected with cortical areas that comprise the CEN through reciprocal circuitry with the dorsolateral prefrontal cortex and posterior parietal cortex (Alexander and Crutcher 1990; Kish et al. 1988; Leh et al. 2008), which display abnormal activations in PD during cognitively demanding tasks (Carbon et al. 2010; Eidelberg 2009; Lewis et al. 2003b; Schendan et al. 2013; Tinaz et al. 2008). These findings suggest that PD-related striatal disruptions are associated with dysfunctional

connectivity within the DMN and CEN. Recent work from our group suggests reduced functional coupling between the CEN and SN (SN=Salience Network) and paradoxically increased coupling between the DMN and CEN, in non- demented PD compared to age-matched control participants (Putcha et al. 2015). Further emphasizing the importance of connectivity between the salience network and DMN, better performance across domains of executive functions, verbal memory, and psychomotor speed was found to be associated with anti-correlated functional connectivity between the salience network and DMN in healthy aging and Parkinson's disease (Putcha et al. 2016).

9.3 Cognition in Parkinson's Disease

The cognitive deficits in PD are heterogeneous. Impairments arising from frontal or fronto-striatal dysfunction manifesting as executive dysfunction (Dirnberger and Jahanshahi 2013; Foltynie et al. 2004; Siepel et al. 2014), reduced working memory (Lewis et al. 2003a), impaired attention and planning (Dujardin et al. 1999; Williams-Gray et al. 2007), and decreased speed of information processing (Uc et al. 2005) have historically received the most attention (Baddeley and Della Sala 1996), partly because it appears that more individuals with PD exhibit frontal-type than posterior-type cognitive deficits (Miller et al. 2013). Long-term memory (visual and verbal) is nonetheless also affected in some with PD, implicating the temporal lobes (Amick et al. 2006a; Ibarretxe-Bilbao et al. 2011). A relatively recent emphasis is on visuospatial cognition in PD with corresponding focus on parietal and occipital regions as well as their connections to other brain areas (Amick et al. 2006b; Cronin-Golomb 2010; Poletti et al. 2012; Schendan et al. 2009; Stepkina et al. 2010). The pathophysiological mechanisms underlying cognitive dysfunction in non-demented PD are not well-understood (Barone et al. 2011), but there is evidence that it may be independent of the prominent motor symptoms that are a cardinal feature of the disease (Cooper et al. 1991). PD is typically characterized by the loss of dopaminergic neurons in nigrostriatal pathways and decreasing dopamine levels in the striatum (Kish et al. 1988). These local disruptions in dopamine function negatively impact the functioning of the striato-thalamo-frontal loops, indicating that distributed neural networks beyond the striatum into the neocortex are affected by disease progression (Monchi et al. 2007; Moustafa and Poletti 2013).

In the remainder of this chapter, we focus on visuospatial cognition and perception, for two reasons. First, most of the work in this area is recent relative to consideration of frontally based impairments in PD, including understanding of the contribution of perceptual compromise on cognitive abilities. Second, because the lateralization of cognitive function is more obvious in the visuospatial domain than in many others, focus in this area allows us to introduce the important concept of subtypes of PD. PD is a heterogeneous disorder with a range of clinical presentations, including the side of initial onset, as PD motor onset is almost always unilateral.

Onset on the left side of the body (LPD) reflects predominant right-hemisphere dysfunction, and on the right side (RPD) reflects predominant left-hemisphere dysfunction (Cronin-Golomb 2010; Djaldetti et al. 2006; Gomez-Esteban et al. 2010; Uitti et al. 2005). There is evidence for more dopamine depletion as well as reduction in dopamine uptake in the hemisphere contralateral to the side of onset (Kim et al. 1999; Marek et al. 1996), with DA asymmetry seen in never-medicated patients as well as those with more advanced disease (Antonini et al. 1995; Laulumaa et al. 1993; Leenders et al. 1990). Of importance in the study of PD in general, considerable asymmetry is maintained long after the disease progresses from unilateral to bilateral; those with moderate to severe bilateral motor disability still show asymmetry in the putamen and caudate and less dopamine (DA) activity contralateral to the initial side of motor onset (Antonini et al. 1995; Booij et al. 1997), and the continuance of asymmetry has been reported even at autopsy, with 25 % fewer neurons in the substantia nigra contralateral to the side of the initial motor onset than in the ipsilateral substantia nigra (Kempster et al. 1989). As predicted by understanding the basic laterality of function, those with LPD often experience cognitive impairments mediated by the right hemisphere, such as in global visuospatial perception, mild unilateral neglect of left hemispace, and problems in nonverbal memory (Amick et al. 2006a; c; Ebersbach et al. 1996; Foster et al. 2008; Lee et al. 2001; Schendan et al. 2009). By contrast, those with RPD more often have difficulty on tasks mediated by the left hemisphere, such as verbal memory (Amick et al. 2006a). As an example, we examined hierarchical pattern perception with the hypothesis that LPD would show impaired global processing, which is dependent on the integrity of the right posterior temporal-parietal junction, whereas RPD would be impaired at local-level processing because of its dependence on the left posterior temporal–parietal junction. LPD demonstrated abnormal global level processing, and RPD showed abnormal local level processing mainly when attention was biased toward the local level (Schendan et al. 2009) (Fig. 9.1).

We do not restrict our consideration of PD subgroups to side of onset, but also describe studies examining cognitive performance in subtypes according to initial motor symptom, meaning the primary motor symptom present at disease onset (Selikhova et al. 2009) or predominance of current motor symptoms (Alves et al. 2006). Relative to PD that begins with tremor, those with the non-tremor-dominant type (NTD: rigidity, akinesia, and disordered gait, posture, and balance) show greater Lewy body pathology, cognitive and functional impairment, and risk for dementia and have more perceptual difficulties (Alves et al. 2006; Lewis et al. 2005; Seichepine et al. 2011; Selikhova et al. 2009; Taylor et al. 2008). A number of studies have found a positive correlation between extent of non-tremor symptoms (bradykinesia and rigidity) and cognitive impairment, including dementia (Iwasaki et al. 1989; Marttila and Rinne 1976; Reid et al. 1989) and impact on activities of daily living and quality of life (Appleman et al. 2011; Seichepine et al. 2011). Non-tremor symptoms may be associated with more rapid disease progression (Gasparoli et al. 2002), and specifically those with postural instability/gait dysfunction (PIGD) perform more poorly than tremor-dominant PD on visuospatial tasks such as judgment of line orientation and visuoconstruction of intersecting pentagons (Sollinger et al. 2010).

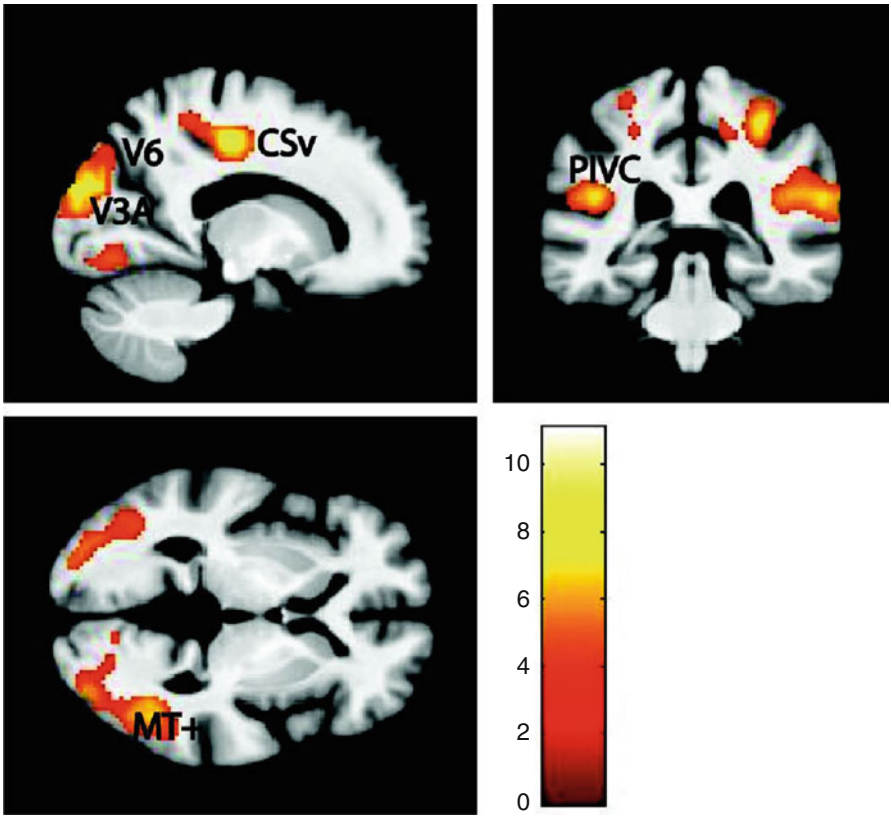

Fig. 9.1 Optic flow network-group activation results. Whole group activation (control participants and PD together) in the optic flow network in response to a flow motion > random motion contrast. Optic flow network includes visual motion areas V6, V3A, and MT+, as well as visuo-vestibular areas parieto-insular vestibular cortex (PIVC) and cingulate sulcus visual area (CSv). The image shows significant activations at $p < 0.001$ cluster corrected with a 46 voxel extent threshold to $p < 0.01$ at MNI *xyz* [−17 −34 0]. Scale bar represents the *t* statistic. (From Putcha et al. 2014; *Frontiers in Integrative Neuroscience, 8 (57)*

Poor spatial vision, depth perception, peripheral vision, and visual processing speed in PD compared to control participants are more problematic to the non-tremor subtype in mild to moderate stages of PD (Seichepine et al. 2011), as is clock-drawing in regard to spatial arrangement of features (Seichepine et al. 2015).

We have known for over two decades that those with non-tremor dominant symptoms have more neural damage that those who are tremor-dominant (Paulus and Jellinger 1991). Emerging evidence focusing on more detailed pathological differences suggests substantially different neuropathological profiles in these groups. An FP-CIT (a isotopic ligand of dopamine reuptake sites) single photon emission computed tomography (SPECT) binding study revealed reduced dopaminergic projections to the dorsal putamen in non-tremor dominant patients and to the lateral

putamen and caudate nucleus in tremor-dominant patients (Eggers et al. 2011), implying differences in the progression of pathology. Some neuropsychological and animal studies have also suggested that non-tremor predominant symptoms are associated with the basal ganglia and cortico-striatal circuit dysfunction, whereas tremor may be associated with cerebellar, thalamic, and subthalamic nucleus abnormalities (Lewis et al. 2011; Mure et al. 2011; Weinberger et al. 2009).

With respect to neuroanatomical integrity, there are few and conflicting results focusing on non-demented PD patients as a whole, likely due to the cognitive variation of the subtypes of patients studied and the analysis methods used (Ibarretxe-Bilbao et al. 2009). Decreased cortical thickness in PD relative to a control group has been reported in the left superior frontal gyrus, left lateral occipital cortex, bilateral middle temporal gyrus, right isthmus of the cingulate cortex, right inferior parietal lobule (Pagonabarraga et al. 2013), ventrolateral prefrontal cortex, parieto-occipital sulcus (Tinaz et al. 2011), and left lateral orbitofrontal cortex (Ibarretxe-Bilbao et al. 2009). There is also some evidence of subcortical atrophy in the left hippocampus (Bruck et al. 2004). There is not yet a consensus on how focal cortical thinning and subcortical atrophy relate to motor symptom type-dominance in mild to moderate stages of PD, and it is not known how cognitive dysfunction maps onto specific patterns of structural changes in the brain.

9.4 Visual Perception in Parkinson's Disease

As described above, it is now well-known that even at early stages of the disease, PD leads to changes in multiple non-motor functions, including cognition and sensory function (Chaudhuri and Schapira 2009; Cronin-Golomb 2010). Because normal cognition depends upon the integrity of the sensory and perceptual systems, it is important to consider to what extent the sensory–perceptual domains are impacted by PD. Many studies demonstrate changes in visual perception in this disorder. For example, contrast sensitivity is reduced (Amick et al. 2003; Kupersmith et al. 1982; Pieri et al. 2000) for both temporally and spatially modulated sinusoidal gratings (Price et al. 1992). Some studies have indicated diminished contrast sensitivity across a range of spatial frequencies (Price et al. 1992), whereas others have demonstrated a loss of contrast sensitivity specifically at middle and high spatial frequencies (Bodis-Wollner et al. 1987; Mestre et al. 1990). Dysfunction in the visual system in PD is not limited to contrast sensitivity, but encompasses a wide range of perceptual abilities, including decreased color perception and discrimination, altered visual motion and optic flow perception, increased visual dependence, double vision, and visual misperceptions, illusions, and hallucinations (Armstrong 2008; Bodis-Wollner 2003; Davidsdottir et al. 2005, 2008; Putcha et al. 2014; Uc et al. 2005). Recent findings from our group also demonstrate that PD impairs the ability to perceive human motion (biological motion; Jaywant, Shiffrar et al. 2016; Jaywant, Wasserman et al. 2016c). Eye movement abnormalities in some individuals include hypometric saccades that undershoot targets, reduced saccade speed,

difficulty planning saccades, and slowed smooth pursuit movements, with the main difficulty being with antisaccades (shifting the eyes in the direction opposite the cue) rather than with prosaccades (reflexive shift in the direction of the cue) (Chan et al. 2005; White et al. 1983).

Such changes in visual perception have significant functional consequences for individuals living with PD. For example, reduced contrast sensitivity is associated with poorer spatial orientation, visuoconstructional ability, visuospatial learning and memory, and visual hallucinations (Davidsdottir et al. 2005; Uc et al. 2005). Saccadic abnormalities may prevent normal foveation and hence lead to problems in visuospatial attention (Bodis-Wollner et al. 2013). Visual hallucinations and feelings of presence and passage are, in and of themselves, distressing to individuals with PD and are also strongly associated with cognitive decline and dementia (Archibald et al. 2011). Additional functional consequences of impaired visual perception in PD include bumping into objects and doorways, difficulty reading, difficulty estimating spatial relations, navigational veering, and an impaired ability to carry out visually based activities of daily living (Davidsdottir et al. 2005, 2008; Seichepine et al. 2011; Young et al. 2010).

There has been extensive debate in the literature regarding the neural mechanisms of altered visual perception in PD, with evidence implicating changes in the retina, cerebral cortex, and subcortical regions of the brain. The presumed role of the retina follows from the observation of dopaminergic amacrine cells in the inner plexiform layer of the retina in healthy adults (Balasubramanian and Gan 2014). Amacrine cells are thought to coordinate bipolar cell to ganglion cell neurotransmission and parkinsonian alterations in their functioning cause an "inappropriately dark-adapted state, resulting in larger retinal ganglion cell receptive fields and affecting contrast sensitivity, color perception, and visual acuity" (Archibald et al. 2009). Evidence for the contribution of the retina to visual dysfunction in PD comes from studies demonstrating increased latencies of visual-evoked potentials to spatial-frequency-modulated gratings (Archibald et al. 2009; Kupersmith et al. 1982) as well as electrophysiological changes in the retina measured by electroretinograms (Gottlob et al. 1987). Furthermore, contrast sensitivity is enhanced at peak (middle) spatial frequencies in the "ON" vs. "OFF" medication state (Bodis-Wollner et al. 1987) and after levodopa administration (Bulens et al. 2004), suggesting that changes in dopamine may directly affect contrast sensitivity.

Despite the possible involvement of the retina and dopaminergic retinal pathways in visual dysfunction in PD, an explanation based solely on the retina is insufficient to explain PD-related impairments. For example, Trick et al. (1994) demonstrated that adults with PD have a deficit in discriminating the orientation of high spatial frequency gratings, which suggests a cortical mechanism because orientation is known to be processed in visual cortex. Individuals with PD also have reduced metabolic activity in the occipital cortex that is correlated with nigrostriatal dysfunction and not retinal impairment (Bohnen et al. 1999) as well as cortical thinning in occipital cortex that is associated with increased disease duration (Jubault et al. 2011). Further, cortical pathology (Lewy bodies, cortical thinning) has been reported for occipito-parietal areas, including unimodal visual cortex (Tinaz et al. 2011).

Studies on altered visual motion perception (as described in the next section) have demonstrated selective impairments in processing higher-order motion mediated by the dorsal visual stream (Castello-Branco et al. 2009; Ezzati et al. 2010). In addition to cortically mediated perceptual impairments, subcortical neural changes contribute to vision difficulties in PD. Saccade abnormalities in PD are thought to arise from excessive inhibition of the superior colliculus by the basal ganglia (substantia nigra pars reticulate), resulting in disrupted connectivity between the superior colliculus and frontal eye fields, which is normally crucial for preparing and initiating saccades (Diederich et al. 2014; Hikosaka et al. 2000; White et al. 1983). The ability to modulate the perception of bistable figures appears to depend on multiple brain regions, as well as being subject to neurotransmitter modulation (Díaz-Santos, Cao, Mauro et al. 2015a; Díaz-Santos, Cao, Yazdanbakhsh et al. 2015b). Together, these findings implicate cortical and subcortical abnormalities in additional to retinal dopamine in the visual perceptual changes in PD.

Diederich and colleagues (2014) recently proposed an innovative theory to unify these seemingly diverse visual symptoms in PD. They suggested that in PD, the primary visual pathway (geniculo-striate) connecting the retina to the lateral geniculate nucleus of the thalamus and primary visual cortex, and responsible for conscious vision, is intact. By contrast, two pathways responsible for non-conscious vision (the retino-colliculo-thalamo-amygdala pathway, which is the tecto-pulvinar pathway extended to the amygdala, and the retino-geniculo-extrastriate pathway, which is a structurally and functionally distinct pathway through lateral geniculate nucleus directly to extrastriate cortex) are dysfunctional and serve as the underlying neurobiological mechanism for altered visual perception in PD. Diederich et al. suggested that dysfunctional signaling in the retino-geniculo-extrastriate pathway could lead to the erroneous perception of static or moving beings and inappropriate guessing of stimuli in the periphery, resulting in hallucinatory experiences. A deficit in the retino-colliculo-thalamo-amygdala pathway may contribute to impaired emotional face recognition, particularly for negatively valenced emotional faces, which is commonly observed in PD (Alonso-Recio et al. 2014; Clark et al. 2008; Kan et al. 2002; Saenz et al. 2013).

9.5 Relation of Visual Perception to Cognition in Parkinson Disease

Some of the visuospatial cognitive impairments seen in PD may be related to changes in basic visual abilities. First, how egocentric visual motion, or optic flow, information is processed may affect spatial cognition. Optic flow displays can mimic flow field motion as it is experienced in everyday life and include visual information about our own movement (ego-motion) as well as the environment we are moving in Dukelow et al. (2001) and Durant and Zanker (2012). Functional MRI and psychophysical experiments have identified human cortical areas that are

selective to visual motion processing, including the MT complex, MT+ (Duffy 2009; Tootell et al. 1997). Area V6, located in the dorsal parieto-occipital sulcus, has been described as selectively responding to expanding egocentric flow field visual motion information in young adult humans (Cardin and Smith 2010; Pitzalis et al. 2006, 2010).

In addition to MT+ and V6, several other regions responsive to egocentric coherent motion in the parietal lobes have been identified. These include the cingulate sulcus visual area (CSv) (Cardin and Smith 2010; Fischer et al. 2012; Wall and Smith 2008) and vestibular regions thought to process visual input, such as the parieto-insular vestibular cortex (PIVC) and putative area 2v (p2v) (Cardin and Smith 2010). Areas of the parietal lobe and parieto-occipital sulcus are affected by PD pathology (Levin et al. 1991; Vaugoyeau and Azulay 2010), and behaviorally, individuals with PD have shown optic flow perceptual deficits that were associated with veering and navigation error (Davidsdottir et al. 2008; Young et al. 2010). Recently, we established that individuals with PD showed diminished activity compared to age-matched control participants, particularly within visual motion area MT+ and the visuo-vestibular region CSv, and that activation in CSv was associated inversely with disease severity (Putcha et al. 2014) (Fig. 9.2). These findings suggest that impairments in optic flow perception and visuospatial performance, as documented by behavioral testing, may result from abnormal neural processing within visual motion and visuo-vestibular regions in PD.

It is noteworthy that our behavioral testing of optic flow perception (Davidsdottir et al. 2008) indicated side-of-onset effects: LPD tended to perceive speed of flow in the left visual field as slower than in the right visual field, whereas RPD and healthy age-matched control participants perceived speed asymmetry in the opposite direction. The task was to adjust flow speed in one hemifield until the observer perceived that it matched that of the speed-constant hemifield—the point of subjective equality across hemifields (Fig. 9.3). The same LPD individuals perceived their egocentric midline to be right of center, which is reminiscent of what is experienced in unilateral hemispatial neglect, in which the perceived midline is shifted towards the ipsilesional hemispace (e.g., Chokron and Bartolomeo 1997; Karnath 1997; Karnath et al. 1991; Richard et al. 2004). Data from our imaging study of optic flow perception in PD described above came from a smaller sample and hence we were unable to examine brain activation patterns for LPD and RPD subtypes.

Of possible relevance to interpretation of perceptual effects in PD was our finding, with the same research participants, that both LPD and RPD were more visually dependent that healthy adults. That is, they were less able to disregard visual environmental information (when attempting to set a tilted line to horizontal). LPD were more visually dependent than RPD. Those who were more visually dependent showed a trend toward more bumping into doorways, by subjective report, and for the RPD group, the more visually dependent demonstrated more leftward lateral drift (veering when walking). These findings accord with longstanding evidence that PD patients rely on visual guidance when walking and for performing tasks with significant perceptual demands. They are also supported by our recent

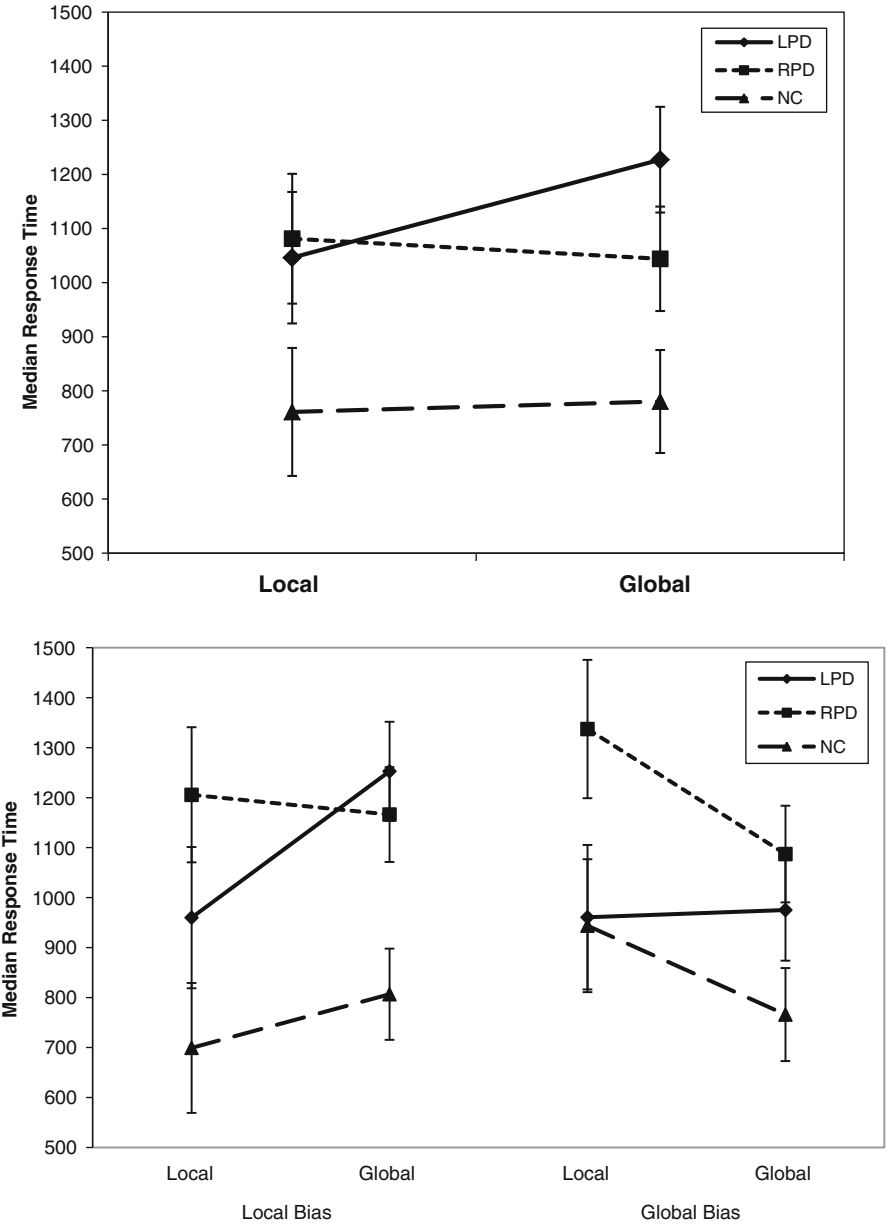

Fig. 9.2 Hierarchical pattern perception results. (*Top*) Median RTs (ms) for the LPD, RPD, and control (NC) groups in the no-bias condition. (*Bottom*) Median RTs (ms) for the LPD, RPD, and NC groups in the biased-attention conditions. The left half of the graph represents median RTs to targets occurring at the global or local levels in the local-biased attention condition. The right half of the graph represents median RTs to targets occurring at the global or local levels in the global-biased attention condition. (From Schendan et al. 2009; *Behavioral Neuroscience, 123,* American Psychological Association)

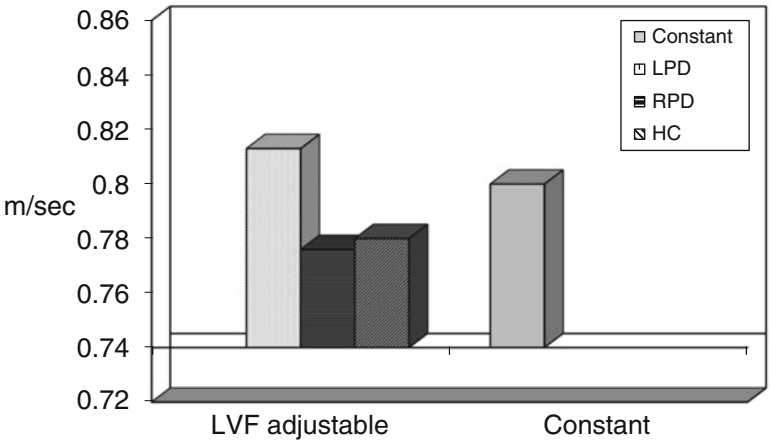

Fig. 9.3 When optic flow speeds were equal in the two hemifields, RPD and HC (healthy control) perceived the speed of optic flow in the left visual field (LVF) to be faster than the speed of optic flow in the right visual field (RVF); that is, they thought the LVF flow speed should be slower in order to reach the point of subjective equality (PSE) with respect to constant flow speed in the RVF. By contrast, LPD tended to perceive the speed in the LVF as slower than the speed in the RVF; that is, they thought the LVF speed should be faster in order to attain the PSE with respect to the constant speed in the RVF. (From Cronin-Golomb 2010, *Neuropsychology Review, 20*, Springer)

report that those with PD are able to use appropriate low-level visual cues to enhance their ability to hold one percept of a bistable figure (Díaz-Santos, Cao, Mauro et al. 2015a).

Returning to egocentric midline perception, there have been a number of studies of hemifield biases relatively specific to LPD, including bisecting lines right of center (Lee et al. 2001), stimulus exploration that begins on the right rather than the left side (Ebersbach et al. 1996), and perception of objects on the left but not the right as smaller than their actual size (Harris et al. 2003). Our recent psychophysical investigation found no evidence of perceived spatial compression or reduced contrast discrimination (weakening of the visual signal) in the left visual field to explain rightward perceptual bias (Norton et al. 2015). In another study, we found no correlation of LPD line bisection bias with thinning of the retinal nerve fiber layer, as measured with optical coherence tomography, or with retinal function, as measured with frequency doubling technology (Laudate et al. 2013). In the latter study, eye movement recordings suggested that LPD explored the right side more than the left side of the line to be bisected (Fig. 9.4). Taken together, these results suggest that observed rightward perceptual bias in LPD presumably arises not from retinal or low-order cortical dysfunction, but rather from higher-order attentional difficulties. We have also found more fixations in the right visual field by PD patients (not LPD specifically) than a control group when categorizing the emotion of faces (fear) (Clark et al. 2010), suggesting that hemifield biases may not be restricted to LPD (as also discussed in Norton et al. 2015).

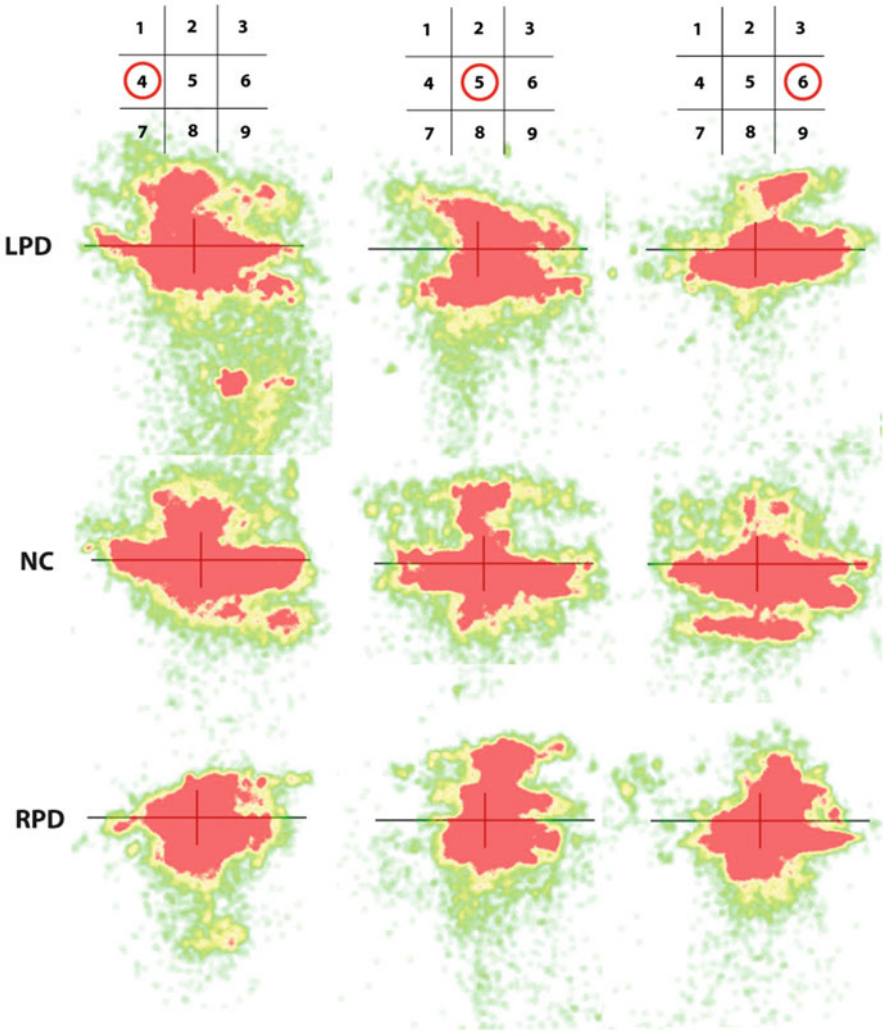

Fig. 9.4 Eye tracking "heat map" representations for horizontal line bisection at left, center, and right visual field positions. See schematics at top of columns for positions, which is where participants looked while performing the line bisection task. Colors closer to the red end of the spectrum indicate the most time spent looking at those areas, and "cooler" colors indicate progressively less looking time. At center and right positions, LPD scanning appeared to be shifted rightward compared to the control group (NC). RPD exhibited compression of the scanning area along the line. *NC* normal control participants, *LPD* left body-onset Parkinson's disease, *RPD* right body-onset Parkinson's disease. (From Laudate et al. 2013, *Behavioral Neuroscience, 127, 151–163*, American Psychological Association)

9.6 Perception-Action Coupling in PD

As reviewed above, visual perception deficits are common in PD. The perception of human movements and actions in particular may be altered in PD because of the close association of motor function and visual perception, referred to as perception–action coupling. Researchers have investigated the role of the subthalamic nucleus (STN) in action observation in individuals with PD who underwent deep brain stimulation surgery. These studies revealed that oscillatory activity in the STN is modulated by action observation, and that observing and executing movements are associated with similar changes in STN electrical activity and coherence between the STN and neocortex (Alegre et al. 2010; Marceglia et al. 2009). These findings suggest a role for cortico-basal ganglia-thalamocortical loops in the perception of human actions.

It is reasonable to postulate that in individuals with PD with disrupted activity in the STN (i.e., who have not had deep brain stimulation surgery), action observation and understanding may be affected by altered synchronous neural activity. Indeed, behavioral evidence indicates dysfunction in perception–action coupling in PD. Healthy adults show motor facilitation when executing an action that is congruent with a previously observed action (visuomotor priming), as when viewing the motion of a hand (an index finger moving up or down) and then having to perform the same hand motion themselves; individuals with PD do not show this facilitation (Poliakoff et al. 2007). This lack of perception–action facilitation appears to be specific to movements that are no longer in the PD motor inventory. In one study, observers with PD viewed another person (who either did or did not have PD) grasping an object, and then had to grasp the object themselves. Grasping was improved only after the PD observers viewed the same action performed by an individual with PD, suggesting that visuomotor priming occurs only when the observed action is in the PD observers' motor repertoire (Castiello et al. 2009). The literature is not consistent in providing evidence for such a perception–action link in PD, however. Our group found that although biological motion perception was impaired in PD (Jaywant, Shiffrar et al. 2016 in regard to walking; Jaywant, Wasserman et al. 2016 in regard to social gestures), the deficit was not associated with PD motor symptoms, but was more likely related to difficulties in the integration of visual form and motion cues. In an intervention study, absence of visual–motor learning was suggested by the finding that perceptual training to discriminate normal from parkinsonian gait did not result in objective improvement in walking, though it did lead to self-reported increases in functional mobility (Jaywant, Ellis et al. 2016).

Together, these studies suggest that changes in action observation in PD may be related to basal ganglia-mediated motor dysfunction, but may also arise from altered processing in cortical areas that support visual perception. Further understanding perception–action coupling as it relates to pathways supporting complex visual perception will be important in designing and refining targets for intervention.

9.7 Concluding Remarks

In this chapter, we have discussed neural network organization in PD, as well as changes in cognition and in the sensory and perceptual processes that affect cognitive abilities in PD. The ubiquity of some degree of cognitive impairment in PD underscores the urgency of the need to develop treatments. Not only does quality of life suffer as a result of direct cognitive problems, but these problems are also relevant to gait and falls in PD. The consequences of gait impairments are substantial and include increased disability, increased fall risk, and reduced quality of life (Shulman 2010). Gait abnormalities are exacerbated under dual-task conditions requiring the simultaneous performance of cognitive tasks (Fuller et al. 2013). Dual-task walking deficits in PD, including reduced gait speed, step length, alterations in cadence, and increased gait variability, have been associated with impairments in executive function, set-shifting, and attention (Lord et al. 2010; Plotnik et al. 2011; Rochester et al. 2004). This is particularly important in PD where there is a need for increased reliance on cognitive resources to control gait and posture due to the reduced movement automaticity associated with basal ganglia dysfunction (Kelly et al. 2012; Takakusaki et al. 2004). When two tasks are performed concurrently in persons with PD, competition for limited resources results in dual-task interference and deterioration in performance of one or both tasks (Power et al. 2012; Woollacott and Shumway-Cook 2002).

To date, interventions for cognitive deficits in PD include pharmacologic and, more recently, cognitive training. PD medications for motor symptoms largely do not reduce cognitive impairments, and although acetylcholinesterase inhibitors have shown some encouraging results (Seppi et al. 2011), none have proven effective for those with mild cognitive disturbance (Barone et al. 2011). They also have significant side effects (e.g., nausea, vomiting, and weight loss) and may be quite expensive to maintain over the duration of the disorder (Bond et al. 2012).

Cognitive training programs that aim to enhance specific cognitive processes through repeated practice are inexpensive and have no significant side effects. Additionally, they can be individually tailored, performed at home, and allow for remote supervision by a clinician/therapist. This approach may be particularly relevant in PD because cognitive training has been associated with increased dopamine release (Backman et al. 2011). Though only a handful of cognitive training studies have been performed in PD (reviewed in Calleo et al. 2012), the preliminary reports have been positive. For example, Sinforiani and colleagues (2004) had PD patients perform a 6-week program aimed at improving attention, abstract reasoning, and visuospatial ability. Participants showed improvement on some tasks, which remained stable for 6 months, but there was no control group, and training failed to enhance inhibition, set shifting, or working memory, key aspects of executive functioning deficient in PD. Paris and colleagues (2011) had individuals with PD perform a 4-week program targeting selective attention, working memory, processing speed, psychomotor speed, executive functioning, and visuospatial processing. Compared with the control group who performed speech therapy, the

experimental group improved on standard tests of attention, processing speed, memory, visuospatial processing, and executive functions, but not on self-reported cognitive difficulties in activities of daily living, and there was no follow-up to assess the longevity of the effects. Edwards and colleagues (2013) conducted 3 months of speed of processing training (SOPT) with 87 individuals with PD. Compared to a test–retest control group, SOPT improved PD performance on useful field of view (a measure of visuospatial processing and speed of processing). There was no alternative training or active-placebo condition to contrast with SOPT, and the improvements did not generalize to executive functions or everyday life (Chou and Cronin-Golomb 2013). In sum, although cognitive training programs show promise, there is a need for both additional interventions that target key PD cognitive impairments and better-designed studies such as those that include matched active control training conditions.

Greater attentional capacity and control with flexible allocation of attention between tasks could potentially improve performance in both cognitive and gait domains (Kelly et al. 2012). Because deficits in sustained attention (i.e., continuously engaging in attention-demanding tasks over a period of minutes and avoiding distraction) and inhibitory control (i.e., stopping an automatic behavior) are quite common in PD (Luque-Moreno et al. 2012; Obeso et al. 2011), and because these capacities may underlie higher aspects of attention, executive functioning, and cognitive ability in general (Sarter et al. 2001), these deficits may modulate many other PD cognitive impairments. For example, task switching (e.g., as measured by Wisconsin Card Sorting Task) may require the inhibition of competing stimulus-response links specified by the now inappropriate task (Rogers and Monsell 1995). Furthermore, decreased ability to sustain attention has been linked to deficits in visuospatial processing in healthy individuals (Matthias et al. 2009) as well as in individuals suffering from severe visuospatial deficits such as spatial neglect (Robertson et al. 1997). In a proof-of-concept study, we recently reported a case series of four individuals with PD who underwent training of sustained attention, which reduced spatial bias on a visual search task (DeGutis et al. 2016). Hence, enhancing inhibitory control and sustained attention in PD could improve several cognitive domains beyond these specific processes as well as tasks that require cognitive–motor integration.

Finally, the use of noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have gained increasing traction as neuromodulatory approaches to enhance cognition in neurological disorders (Fregni and Pascual-Leone 2007). With respect to PD, one study used tDCS to increase cortical excitability over the dorsolateral PFC, while adults with PD completed an n-back working memory task, and found improved working memory performance following electrical stimulation as compared to a sham stimulation condition (Boggio et al. 2006). Another investigation found that tDCS over bilateral dorsolateral PFC led to a sustained 1-month improvement on the Trail Making Test part B (a measure of executive function, set shifting, and working memory) compared to sham stimulation (Doruk et al. 2014). The use of noninvasive brain stimulation coupled with the cognitive training interventions described above may hold particular promise for improving cognitive function in PD.

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Chapter 10
The Basal Ganglia and Language: A Tale of Two Loops

Anastasia Bohsali and Bruce Crosson

10.1 Introduction

Interest in basal ganglia language functions began in the 1800s and was often associated with writings about aphasia. Among the first to propose a role for the basal ganglia in language, Broadbent (1872) suggested that words were generated as motor acts in the basal ganglia. Wernicke (1874), one of the fathers of modern aphasiology, thought that destruction of the left lenticular nucleus caused aphasia, and he attributed this aphasia to convergence of frontal fibers on the basal ganglia. Marie (1906) believed that language structures include the "quadrilateral zone," extending deep into the left hemisphere and subsuming the basal ganglia. There was some resurgence of interest regarding the basal ganglia and language in the 1950s and 1960s when investigators reported aphasia accompanying dominant pallidectomies for Parkinson's disease (e.g., Allen et al. 1966); Cooper (1959), Gillingham 1960; Svinnilson et al. 1960). However, it was the use of computed tomogaphy (CT) scans in the late 1970s and 1980s allowing clinicians and investigators to visualize basal

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ganglia infarcts and hemorrhages that gave speculation about linguistic functions of the basal ganglia considerable momentum (Alexander and LoVerme 1980; Alexander et al. 1987; Basso et al. 1987; Cappa et al. 1983; Damasio et al. 1982; Fisher 1979; Fromm et al. 1985; Hayashi et al. 1985; Knopman et al. 1984; Lieberman et al. 1986; Metter et al. 1983; Murdoch et al. 1989; Naeser et al. 1982; Ramsburger and Hillman 1985; Robin and Schienberg 1990; Tanridag and Kirshner 1985; Wallesch 1985; Yamadori et al. 1984).

Nonetheless, in 2002, Hillis and colleagues cast serious doubt on the proposition that the basal ganglia were involved in aphasia (Hillis et al. 2002). They showed that aphasia occurred acutely (<24 h of onset) in ischemic lesion of the left basal ganglia only when accompanied by left cortical hypoperfusion. The dynamics of this hypoperfusion have been covered extensively elsewhere (Hillis et al. 2002; Nadeau and Crosson 1997; Weiller 1993). Briefly, ischemic lesions of the basal ganglia and surrounding white matter are most commonly caused by obstruction of the initial segment of the middle cerebral artery or the internal carotid artery (Weiller et al. 1993). Relative sparing of cortex in the middle cerebral artery distribution in these cases is due to end-to-end anastomotic circulation from the other major arterial territories (Nadeau and Crosson 1997). Often anastomotic circulation is adequate to prevent cystic infarction seen on older CT scans but not adequate to support normal cortical function. In some cases, ischemic neuronal dropout led to some chronic aphasias, which were invisible to the imaging technology of the late 1970s and 1980s (Nadeau and Crosson 1997). What Hillis et al. (2002) could see with perfusion-weighted and diffusion-weighted MRI (Magnetic Resonance Imaging) images that their predecessors could not see was the cortical hypoperfusion in cases of aphasia. Indeed, when the cortical perfusion deficits were reversed in these cases, the aphasia disappeared. Hence, the bottom line was that lesions confined to the basal ganglia and surrounding white matter did not cause aphasia.

At this point, the reader is justified in asking, "Why, then, write a chapter about the role of the basal ganglia in language?" Our reply is the following: Even though the basal ganglia are not involved in the type of basic language functions whose interruption by lesion causes aphasia, there is ample evidence that the basal ganglia play some role in language. For example, Copland's studies of ischemic lesion and Parkinson's disease suggest that the basal ganglia play a role in the controlled (top-down) processes supporting lexical–semantic processing (Copland et al. 2000a, b; Copland 2003). Crosson et al. (2003) showed that generating words from either a category or a rhyme cue engaged a pre-SMA–caudate basal ganglia loop, while generating nonsense syllables did not do so. In numerous studies, Grossman and colleagues have shown that patients with Parkinson's disease have difficulty processing complex syntax (e.g., Grossman et al. 2003; Lee et al. 2003), and Sambin et al. (2012) findings suggest that there may be a truly syntactic deficit in Huntington's disease, another disease of the basal ganglia. Although this chapter is focused on language in human studies, it is also worth mentioning that mutations of the gene responsible for Huntington's disease disrupt vocal sequences in the songbird (Tanaka et al. 2016).

The question, then, becomes "If the basal ganglia do not play a role in the type of language functions whose interruption causes aphasia, what function do they serve in language?" This question is still debated in the literature, and the purpose of this chapter is to explore its potential answers. We begin with a discussion of anatomy. In general, we will use the concept of basal ganglia loops as elaborated by Alexander et al. (1986) to frame the discussion. Specifically, we will discuss the anatomy of a Broca's area–basal ganglia loop and of a pre-supplementary motor area (pre-SMA)–basal ganglia loop and the anatomic relationship between them. Subsequently, we will explore evidence regarding the role of each of these loops in language processing. Then, we will reflect upon the functional relationship between these loops as well as the parallels between their roles in language. Finally, our concluding remarks will explore remaining questions regarding the basal ganglia and language, with an eye toward what might be some productive next steps in research.

10.2 Anatomy

Much of recent discussion of basal ganglia functions has revolved around basal ganglia loops, and the concept is compelling enough to provide the conceptual foundation for our current discussion. Hence, we begin with a general consideration of basal ganglia loops. One of the first discussions of basal ganglia loops of which we are aware is an article regarding athetosis and tremor in which Bucy (1942) diagrammed and discussed the basic loop structure for the basal ganglia. All of the structures currently included in the consideration of basal ganglia loops were included in Bucy's diagrams though they can be viewed as missing some of the critical connections. Buckingham and Hollien (1978) were among the first to consider the function of basal ganglia loops in language, and Crosson (1992) gave the subject an in-depth treatment. By the time he wrote his book in 1992, Crosson had noted several other theories of subcortical functions in language. In the most notable of these, Wallesch and Pagagno (1988) suggested that basal ganglia loops were involved in choosing from among several cortically generated alternatives which response (word) would be executed. However, it was the seminal and exhaustive review of Alexander et al. (1986) that put meat on the anatomic bones of the basal ganglia loops and gave impetus to consideration of their function in countless empirical and conceptual works to follow.

Basal ganglia loops are commonly conceptualized to originate and terminate in a given area of cerebral cortex that has direct connectivity with the striatum (caudate nucleus, putamen, or archistriatum) (Alexander et al. 1986; Middleton and Strick 2000). Loops can be identified by these cortical origination/termination areas, which are usually but not always located in the frontal lobe. Figure 10.1 is a diagrammatic example of a basal ganglia loop associated with the pre-supplementary motor area (pre-SMA).

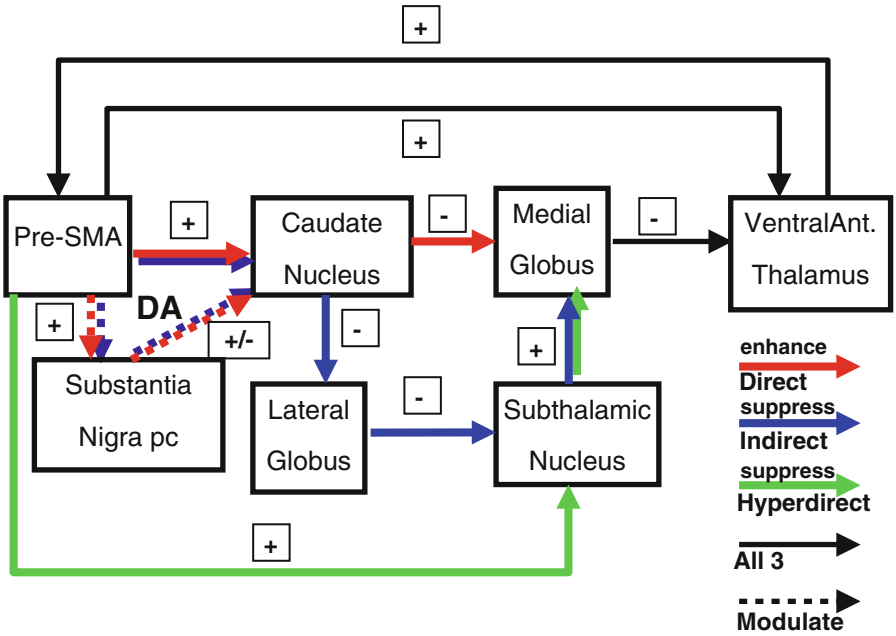

Fig. 10.1 The three cortico-basal ganglia loops originating in pre-SMA are shown. Pathways unique to one loop or shared by two loops are represented by the following colors: *red* for the "direct" loop, *blue* for the "indirect" loop, and *green* for the "hyperdirect" loop. Pathways shared by all three loops are represented in *black*. Excitatory pathways are indicated by a "+", and inhibitory pathways are indicated by a "−". Pathways that are modulatory, those involving the substantia nigra pars compacta (substantia nigra pc), are indicated by a *dotted line*. The "direct," "indirect," and "hyperdirect" loop structure is assumed to be replicated for all cortical–basal ganglia loops. *Lateral globus* globus pallidus externus, *Medial Globus* globus pallidus internus. Other abbreviations: *Ventral Ant. Thalamus* ventral anterior nucleus of the thalamus, *Pre-SMA* pre-supplementary motor area

Our recent conceptual work in this area has emphasized three types of basal ganglia loops, each having some common components with others originating from the same cortical area (Crosson et al. 2007). The "direct" loop starts in one of several areas of cortex that share direct connectivity with a striatal component. From the striatum, these loops project to the medial globus pallidus, and from the medial globus pallidus to a thalamic nucleus (ventral anterior, ventral lateral, or dorsomedial). The thalamic nucleus projects back to the area of cortex from which the loop originates. Corticostriatal and thalamocortical connections are excitatory (glutamatergic), and striatopallidal and pallidothalamic connections are inhibitory (GABAergic) (Gerfen 1992). For a more detailed description of the anatomy of the basal ganglia, the reader is also referred to Chaps. 1–5 in this volume.

"Indirect" and "hyperdirect" loops also begin in a specific area of cortex. For the "indirect" loops, the cortex projects to the striatum, similar to "direct" loops (glutamatergic/excitatory connections). However, in this loop, the striatum projects to the lateral globus pallidus (GABAergic/inhibitory connections), which in turn, projects to

the subthalamic nucleus (GABAergic/inhibitory connections). Then, the subthalamic nucleus projects back to the medial globus pallidus (glutamatergic/excitatory connections). The medial globus pallidus projects to one of the thalamic nuclei mentioned above (GABAergic/inhibitory connections), and finally, the thalamus projects back to the cortical component from which the loop originated (glutamatergic/excitatory connections).

Like the "direct" and "indirect" loops, the "hyperdirect" loop originates in one of the cortical areas projecting to the basal ganglia, but it differs from these loops by bypassing the striatum (Nambu et al. 2002). Instead, the cortical component of the loop projects directly to the subthalamic nucleus (glutamatergic/excitatory connections). In turn, the subthalamic nucleus projects back to the medial globus pallidus (glutamatergic/excitatory connections). The medial globus pallidus projects to one of the thalamic nuclei mentioned above (GABAergic/inhibitory connections), and completing the loop, the thalamus projects back to the cortical component from which the loop originated (glutamatergic/excitatory connections).

It should be noted here that on the basis of tractography using constrained spherical deconvolution of diffusion-weighted magnetic resonance images, Milardi et al. (2014) have suggested that direct corticopallidal connections exist and may constitute a fourth loop. We would feel more comforted in adopting this assumption if there were strong tracings of such a pathway in macaques or other primates. Thus, for the time being, we will assume three as opposed to four basal ganglia loops for each cortical component.

A couple of points about these loops should be emphasized: (1) Generally, for all cortical areas projecting to the basal ganglia, it has generally been assumed that each of the three loops mentioned above are represented. In this discussion, we have adopted this assumption. Basal ganglia models often suggested that loops associated with functionally distinct cortical areas should project to separate and nonoverlapping regions within basal ganglia (Alexander et al. 1986; Middleton and Strick 2000) implying that loops are segregated from one another. Additional studies, however, provide evidence that some basal ganglia loops are integrative allowing cross-communication between discrete functional networks (Selemon and Goldman-Rakic 1985; Haber et al. 2006). Specifically, a recent nonhuman primate tracer study by Haber and colleagues has demonstrated convergence within the striatum for basal ganglia loops originating in cingulate/orbitofrontal cortex and loops originating in the dorsolateral prefrontal cortex (Haber et al. 2006). The authors proposed that this convergence may enable the striatum to mediate reward-based learning by integrating internal reward representation with appropriate behavioral output to the reward. A human tractography study by Draganski et al. showed areas of spatial overlap within striatum for projections from the orbitofrontal, medial prefrontal, and dorsolateral prefrontal cortical areas suggesting integration between reward-processing circuits (Draganski et al. 2008). Similarly, it should be recognized that cortical regions from one set of loops have ample opportunities to interact directly with at least some cortical components from other loops. For example, we will demonstrate this to be true later in this section for the two sets of loops we are considering (Ford et al. 2010). (2) A simple arithmetic trick can be used to determine whether the net

effect of the loop projecting back to the cortical component is excitatory or inhibitory. If one replaces excitatory connections by +1 and inhibitory connections by −1 and multiplies all of the resulting values in the loop, then the product will represent whether the net effect of the loop is excitatory or inhibitory. This simple trick seems to work well in experiments addressing the net impact of activity of one structure on another within these loops (e.g., see Mitchell et al. 1989; Nambu et al. 2000). However, the three loops are thought to impact different cortical processes and neural assemblies. Further, the substantia nigra pars compacta (or the ventral tegmental area in the case of the archistriatum) sends dopaminergic projections to the striatal component of each "direct" and "indirect" loop. The nature of the influence over the striatum may depend on the dopamine receptor subtype on which these connections terminate (Gerfen 1992). We will address this issue below, as we turn to exploration of two distinct cortical–basal ganglia loops believed to be involved in language processing.

10.2.1 Broca's Area–Basal Ganglia Loops

In the recent decades, evidence supporting the notion of Broca's area–basal ganglia loops has been gaining considerable momentum (Brunner et al. 1982; Ullman 2001, 2004, 2006). Functional neuroimaging studies measuring regional blood flow effects associated with task performance implicated Broca's area and the basal ganglia to support an overlapping set of language functions (Ullman 1997, 2001, 2004; Friederici et al. 2003; Crosson et al. 2003). Specifically, both regions are thought to be involved in lexical selection and retrieval (Alexander 1997; Desmond et al. 1998), syntax (Moro et al. 2001; Friederici et al. 2003), phonology (Friederici et al. 2002), as well as higher order language processing (Ullman 2001, 2004). Functional connectivity studies modeling modulatory relationships between patterns of activation in distinct gray matter regions showed direct functional connectivity between Broca's area and putamen potentially supporting articulatory control and identification of phonological representations of lexical items (Booth et al. 2006). Indirect evidence supporting the existence of a Broca's area–basal ganglia circuitry also comes from nonhuman primate tracer studies that show structural connectivity between basal ganglia and ventral premotor cortex (location of the potential primate Broca's area homologue) (Middleton and Strick 2002). Although similar types of tracer studies are impossible to be replicated in humans, recent advances in noninvasive neuroimaging methods have allowed us to gain valuable insights into human white matter architecture in vivo (Catani et al. 2002; Catani and De Schotten 2008). Specifically, diffusion-weighted MR imaging tractography is a technique that infers white matter organization within the brain based on diffusion characteristics of the underlying neural tissues (Basser et al. 2000). Using this technique a number of studies inferred white matter connectivity between the human inferior prefrontal cortex and the striatum (Lehéricy et al. 2004b; Croxson et al. 2005; Leh et al. 2007; Draganski et al. 2008; Catani et al. 2012; Ford et al. 2013). Using the caudate and

putamen as regions of interest Lehericy and colleagues found pathways between caudate/putamen and inferior frontal gyrus (Lehericy et al. 2004a, b). Using the same approach, Leh et al. showed connectivity between the caudate and ventral lateral prefrontal cortex, while putamen connectivity was restricted to primary motor and premotor cortical regions (Leh et al. 2007). The Croxson and Draganski studies used a two-regions of interest approach where the caudate and putamen masks served as seed (or the start point for tracking) and prefrontal cortical areas (that encompassed Broca's area and surrounding prefrontal cortex) as targets (or end points for diffusion tracking). Using this approach, these studies identified connectivity between ventral prefrontal cortex (containing Broca's area) and both caudate and putamen (Croxson et al. 2005; Draganski et al. 2008). These findings make it clear that, not unlike anterograde/retrograde tracer methods, location and number of regions of interest used to guide white matter tracking in diffusion tractography greatly influences the trajectories of the resulting pathways. Applying a two-regions of interest approach (as in Croxson and Draganski et al.) and using known anatomical landmarks to exclusively delineate Broca's area (defined as pars triangularis and pars opercularis), we carried out a tractography study to investigate potential connectivity between Broca's area and basal ganglia (Ford et al. 2013). Our results identified two pathways connecting Broca's area with the striatum and the thalamus. Specifically, we found pathways connecting pars triangularis and pars opercularis with anterior one-third of the putamen. To perform our tractography analysis we first computed pathways connecting the entire brain (i.e., whole brain tractography). We then intersected the whole brain tracking results with pars opercularis and putamen (to delineate pars opercularis–putamen pathways) and also pars triangularis and putamen (to identify pars triangularis–putamen tracts). Since pars opercularis/triangularis also share connections with the thalamus (see below), we applied thalamic mask as an exclusion mask to eliminate pathways traveling between Broca's area and the thalamus.

Pars opercularis/pars triangularis–putamen fibers inferred using the above tracing method course medially away from the cortex wrapping over and around the circular sulcus. The tracts then pass the insula and then take a wide-angle turn in the posterior-inferior direction to pass through the anterior superior portion of the anterior limb of the internal capsule and finally descend down to the anterior putamen (see Fig. 10.2). It is important to note that pathways connecting pars triangularis with the putamen and pars opercularis–putamen pathways seem to converge within a largely overlapping location in the anterior putamen. These findings are in agreement with recent animal tracer and human tractography studies demonstrating that some basal ganglia loops are integrative at the level of basal ganglia nuclei (Haber et al. 2006; Draganski et al. 2008).

The acquisition resolution of our diffusion-weighted data did not allow us to trace interconnections within the basal ganglia nuclei. Therefore, we were not able to visualize this part of the Broca's area–basal ganglia circuitry and could not identify the "direct" or "indirect" basal ganglia loops. Subthalamic nucleus connectivity was not investigated in our study due to the data resolution constrains, and we were not able to visualize the potential "hyperdirect" loop. However, since these three

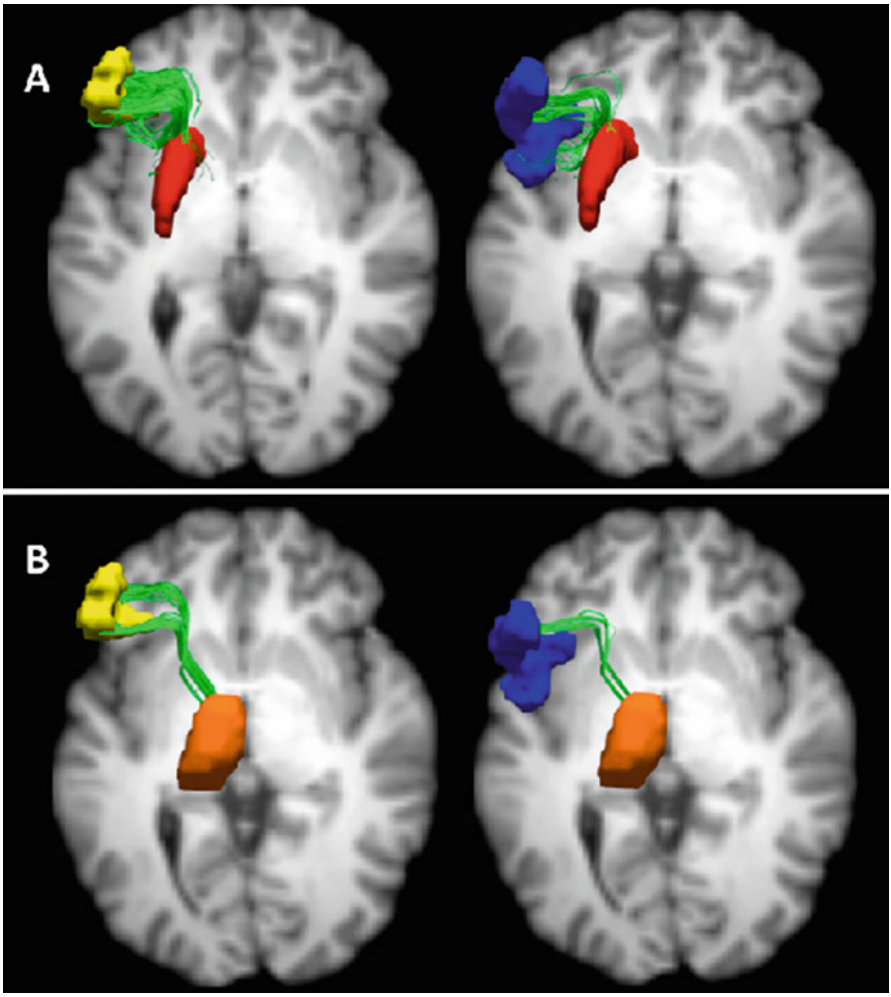

Fig. 10.2 Pathways connecting Broca's area (pars triangularis (*yellow*) and pars opercularis (*blue*)) with putamen (*red*) (**a**) and thalamus (*orange*) (**b**) in a representative participant from Ford et al. (2013). The figure represents a three-dimensional view of the pathways with the participant's structural scan as a background image for the ease of viewing

loops are represented for other cortical–basal ganglia circuits, the prevailing consensus suggests that it would be reasonable to presume that these loops are also likely to be represented for Broca's area.

We were not able to clearly identify potential Broca's area–caudate nucleus pathways in our study. Instead we observed that some of the pathways connecting Broca's area and thalamus traveled very close to and in some cases approached the dorsal lateral extent of the caudate. However, these pathways were eliminated when the thalamus mask was applied as an exclusion mask. Thus, based on these findings

we could not definitively conclude whether Broca's area shares structural connectivity with the caudate in addition to putamen. Other recent tractography studies report, though variable, connections between BA 44 (posterior Broca's area) and caudate as well as putamen using a two-regions of interest approach (Mandelli et al. 2014). Taking together the results from our and others' studies, it appears that Broca's area may have at least three potential pathways connecting it with the striatum: (1) pars triangularis–anterior putamen (from Ford et al. 2013), (2) pars opercularis–anterior putamen (Ford et al. 2013), and (3) pars opercularis (corresponding to BA 44)–caudate (Lehericy et al. 2004a, b; Mandelli et al. 2014).

Our study (Ford et al. 2013) identified connections between pars opercularis, pars triangularis, and the thalamus. As in the case of Broca's area–putamen pathways, connections between pars opercularis/triangularis and the thalamus travel medially, then take an obtuse angle to travel posteriorly within the anterior limb of the internal capsule and enter the ventral anterior nucleus of the thalamus (see Fig. 10.2). These pathways potentially represent the corticothalamic (or thalamocortical) component of the Broca's area–basal ganglia circuitry.

10.2.2 Pre-SMA–Basal Ganglia Loops

One of the first bits of evidence regarding a pre-SMA–basal ganglia loop involved in language came from the study of Crosson et al. (2003). These authors had subjects generate category members for categories that had both larger and smaller numbers of items as determined by a pilot study. For example, subjects might be asked to generate as many "birds" as they could in 17.4 s, to which they might reply "sparrow, wren, hawk …" To determine whether activity was attributable to the semantic nature of this task, subjects also generated words that rhymed with a cue word. For example, subjects might be asked to generate as many words as they could in 17.4 s that rhymed with "rat," to which they might respond "bat, hat, fat …" Finally, to determine whether activity was unique to the lexical nature of the task, subjects generated as many nonsense syllables as they could that began with a beginning and ending consonant blend. For example, for "str_mp," a subject might say "stramp, stremp, strump …" The baseline condition for all of these tasks was visual fixation. For generating words either to a category or to a rhyming cue, pre-SMA, the dorsolateral caudate, and the ventral anterior nucleus of the thalamus were all active.

The pallidal component of this "direct" loop was missing probably because of the tendency for accumulation of paramagnetic materials there, which create signal voids. Nonetheless, there is good anatomic evidence from monkeys for this loop, including the pallidal component. Inase et al. (1999) traced fibers in the macaque from pre-SMA to the gray bridges between the caudate and putamen that span the anterior limb of the internal capsule, as well as to the lateral caudate and medial putamen on either side of the gray bridges. The caudate activity in Crosson et al. (2003) would correspond roughly to the more caudal caudate projections shown by

Inase et al. (1999). Akkal et al. (2007) used retrograde transsynaptic transport of a strain of the rabies virus to trace projections from the medial globus pallidus to pre-SMA in the *Cebus* monkey. Pre-SMA was found to receive projections (via the thalamus) from the rostral portion of the globus pallidus. The anterior pallidum projects (via the thalamus) more to association than motor cortices. (The caudal pallidum projects more to parts of the thalamus projecting to motor cortex.) Regarding the thalamic component of the loop, Wiesendanger and Wiesendanger (1985) showed that the ventral anterior thalamus projects to the portion of the medial frontal cortex now known as pre-SMA. Indeed, the parvicellular portion of ventral anterior nucleus is known to receive fibers from the rostral medial globus pallidus and to project to pre-SMA (Nakano 2000). This thalamic location is consistent with the location of activity in the Crosson et al. (2003) study. Finally, Inase et al. (1999) demonstrated projections from pre-SMA directly to the subthalamic nucleus in the macaque, indicating the requisite initial connection for a "hyperdirect" pre-SMA loop. Hence, we assume that all three basal ganglia loops ("direct," "indirect," "hyperdirect") exist for pre-SMA.

A diffusion tensor imaging (DTI) study with humans has also provided evidence for pre-SMA to striatal connectivity (Lehericy et al. 2004a). Pathways from pre-SMA to the mid-putamen (i.e., intermediate between the rostral and caudal putamen) and the dorsal caudate nucleus were visualized. The caudate mask used to derive the tract for the caudate nucleus appears to have been truncated about as the head transitions into the body of the caudate nucleus, and the anterior limb of the internal capsule containing the gray bridges between the caudate and putamen was not included in the mask. Nonetheless, the pathways are roughly consistent with expectations based on Inase et al. (1999). Further, the more caudal portion of the projections is consistent with the position of activity seen by Crosson et al. (2003).

10.2.3 Connections Between Pre-SMA and Broca's Area

The evidence supporting Pre-SMA's role in language makes a strong case that this region is involved in a number of aspects of linguistic processing some of which have also been attributed to Broca's area (Jonas 1981; Picard and Strick 1996; Binder et al. 1997; Crosson et al. 2001, 2003). Since functionally related neural regions typically share structural connectivity, it would be therefore reasonable to suppose that such connectivity may be present between Broca's area and pre-SMA. Indirect evidence from macaque tracer studies shows that areas 44 and 45 of the left ventral lateral frontal lobe (believed to be the primate homologue of human Broca's area) do indeed share connections with the medial area 6 (pre-SMA) (Petrides and Pandya 2002). We investigated this connectivity in humans using diffusion tractography (Ford et al. 2010) and found that the posterior extent of Broca's area (including pars opercularis and in some cases posterior dorsal pars triangularis) does share connectivity with pre-SMA. Other dissection and tractography studies have also confirmed our findings (Lawes et al. 2008; De Schotten et al. 2012),

showing that this pathway is left-lateralized in right-handed participants (Catani et al. 2012; Kinoshita et al. 2012) and providing evidence that this pathway is important in verbal fluency (Catani et al. 2013; Mandelli et al. 2014). Additionally, Kinoshita and colleagues (2015) showed positive correlation for distance between Broca–pre-SMA pathways and resection cavity for patients undergoing gliomal resections and verbal fluency scores. Specifically, patients in whom the lesion was closer to the Broca's area–pre-SMA pathways (or the greater involvement of the pathway by the lesion) performed worse on verbal fluency tasks postoperatively (Kinoshita et al. 2015). Moreover, electrical stimulation of the pathways prior to the surgery resulted in interruption of speech, which the authors believe resulted from a virtual dissection of the Broca's area–pre-SMA pathways. These pathways were also implicated to be involved in word selection and sequencing during speech (Chung et al. 2005; Alario et al. 2006; Nachev et al. 2008; Kim et al. 2010). Mandelli and colleagues (2014) implicated this pathway in syntax production in patients with primary progressive aphasia of non-fluent variant.

Connectivity between Broca's area and pre-SMA presents a plausible structural interface for interaction between basal ganglia loops involving these cortical areas. The clear role of Broca's area in speech production (Broca 1865; Hagoort 2005; Eickhoff et al. 2009) and pre-SMA's involvement in word selection (Crosson et al. 2003) would suggest that these basal ganglia loops supporting different aspects of language output (see discussion below) may interact in patterns of modulation/feedback to ensure the optimal level of speed and accuracy in discourse. Broca's area–pre-SMA connectivity would be a likely candidate for this mechanism. We will further expand this discussion in the upcoming sections of this chapter.

10.3 Function

Although speculation about basal ganglia language functions dates to the 1800s, as we noted in the opening paragraph of this chapter, much of the modern theory around basal ganglia functions has focused on how basal ganglia loops, like the ones discussed above, function and contribute to behavior. There have been common threads that run through the earliest speculations to the present day. Bucy (1942) was one of the first to address this topic. He saw the basal ganglia as serving a suppressor function with respect to motor behavior and ascribed choreiform movements and tremor as due to interruption of this suppressor function. Buckingham and Hollien (1978) were among the first authors to consider basal ganglia loops in language functions, and Crosson (1992) suggested that basal ganglia loops regulate the release of preformed language segments. Mink (1996) hypothesized that cortical representations of an activity involved a central focus of a selected activity, the "center," and related but unselected activities, the "surround." According to Mink, the "center" is excited by activity of the "direct" loop, and the "surround" is suppressed by the activity of the indirect loop.

Nambu (Nambu 2003; Nambu et al. 2002) expanded upon Mink's center–surround concept by adding the "hyperdirect" loop and by imposing a sequence of participation of the different loops derived from his earlier work (Nambu et al. 2000). According to his theory, the first action from the basal ganglia subserving initiation of behavior is a broad inhibition of behaviors by the "hyperdirect" loop, followed quickly by an excitation of the selected behavior by the "direct" loop (the "center" to Mink 1996). Finally, competing behaviors (the "surround" to Mink 1996) are inhibited so that only the selected behavior is performed. Crosson et al. (2007) adapted Nambu's model to explain findings of Crosson et al. (2003) in pre-SMA loops with respect to word generation. We now turn to this explanation.

10.3.1 Pre-SMA–Basal Ganglia Loops

The anatomical and physiological evidence supporting Crosson et al.'s (2007) adaptation of Nambu's (2003) model to cover word generation is extensive. Hence, only a portion of it has been provided above. The reader wishing to gain a full appreciation for this evidence is referred to Crosson et al. (2007). The physiological evidence presented by Nambu et al. (2000) also is well worth reading since it leads directly to Nambu's later theory (Nambu 2003; Nambu et al. 2002).

The reader will recall from the anatomic discussion of the pre-SMA loop above, that Crosson et al. (2003) found activity in "direct" components of the pre-SMA loops when subjects generated series of words that were members of a specific category or rhymed with a word they were given (Fig. 10.3), but no activity occurred in this loop when subjects generated nonsense syllables given a beginning and ending consonant blend. From this evidence, these authors concluded that the pre-SMA loops were involved in generating lexical items with pre-existing representations but not involved in generating nonmeaningful syllables with no pre-existing representation.

In their work, Crosson et al. (Crosson et al. 2007; Crosson 2013) used Nambu's theoretical work (Nambu 2003; Nambu et al. 2002) as a scaffold onto which to develop an explanation for their earlier findings (Crosson et al. 2003). For generating category members, the explanation is as follows: Pre-SMA first stimulates its "hyperdirect" loop, which broadly suppresses all words from previous activities. This signal acts to reset word production processes so that no one word is preferentially activated to the extent it would be produced easily over other words. Within a few milliseconds, activity from the "direct" loop enhances the word selected for execution, and prior to execution, the "indirect" loop suppresses other category members so that only the selected category member is produced. As the subject moves on to the next word, it is necessary to suppress the word just given, and the cycle starts again when the "hyperdirect" loop resets the system so that a new category member may be chosen. Selection of words to a rhyming cue occurs in a similar fashion.

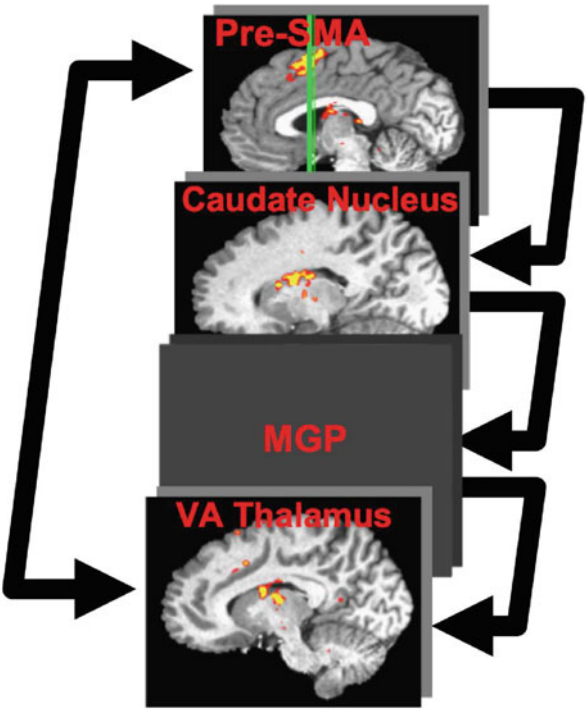

Fig. 10.3 Activity in the "direct" pre-SMA–basal ganglia loop is shown for category-member generation (vs. visual fixation) from the Crosson et al. (2003) study. Activity was detected in pre-SMA, the dorsal caudate nucleus, and the ventral anterior nucleus of the thalamus (VA thalamus). The empty box for the medial globus pallidus (MGP) indicates that activity could not be measured in this nucleus, most likely because of deposits of paramagnetic materials (manganese, iron). Activity for generation to a rhyming cue occurred in the same structures, with little variability in location, but generating nonsense syllables did not evoke activity in this pre-SMA loop. Thus, the activity can be considered related to activating pre-existing lexical representations as opposed to the semantic or phonological nature of the task

At this point, a couple of questions may occur to the reader. Since the three pre-SMA loops are more or less closed loops, do word representations reside in pre-SMA? The simplest answer, that these representations are a function of pre-SMA, seems unlikely for a variety of reasons, including the fact that unilateral lesions of medial frontal cortex alone frequently do not cause permanent deficits in language expression (Damasio et al. 2012). A more likely possibility, and one more in keeping with current systems approaches to neurocognitive functions, is that the lexical representations involved in word generation are a function of a distributed set of structures with each playing some unique role. This analysis begs the question of what other structures might be involved and how, and we shall address this question shortly when we talk about interactions between pre-SMA and Broca's area. It should be pointed out, however, that in order for different structures to play a role in a common

process, such as lexical selection, they must share some code with respect to that process, whether it be neural connections, patterns of activity, or more likely both.

The second question is if the basal ganglia play a role in language, why don't ischemic lesions of the dominant basal ganglia cause aphasia without cortical hypoperfusion (Hillis et al. 2002)? Or, why do we not see aphasia in Parkinson's disease? We have contended that the answer relates to the nature of the role of the basal ganglia in language. Rather than playing a primary role in language, they play a role of sharpening contrasts between words selected for production and those not selected in such a way as to increase the signal-to-noise ratio and improve neural efficiency (Crosson 2013; Crosson et al. 2007). Hence, what one might expect from basal ganglia lesion or dysfunction would be some loss of accuracy or the speed with which one finds words as opposed to a devastating loss of word-finding ability of the type commonly seen in aphasia. This being said, we also should note that patients with basal ganglia lesions in addition to cortical lesions have more lasting aphasias than patients with cortical lesions alone (e.g., Mazzocchi and Vignolo 1979; Brunner et al. 1982). Finally, something should be said about the function of the basal ganglia in loops with cortical components other than pre-SMA, which is the topic of the next section.

10.3.2 Broca's Area–Basal Ganglia Loops

Simonyan and colleagues (2013) provide an interesting account of potential functional implications of the Broca's area–basal ganglia circuitry in speech. Specifically, the authors combine positron emission tomography (PET), fMRI (functional MRI), and diffusion tractography to investigate endogenous dopamine release (PET) within the striatum coupled with cortical activation patterns (fMRI) associated with sentence production. They found that dopamine release was increased in the left anterior putamen, left dorsal posterior putamen, as well as in the bilateral dorsal anterior and left dorsal posterior caudate nucleus (Simonyan et al. 2013). When dopamine activity was correlated with fMRI activity clusters during sentence production, only the left anterior putamen showed significant relationship between speech-induced dopamine binding and fMRI activity. Importantly, one of the fMRI activation clusters associated with sentence production and correlating with dopamine activity in the left anterior putamen was inferior frontal gyrus (containing Broca's area). Diffusion tractography also confirmed structural connectivity between these regions. Based on these findings the authors conclude that the left anterior putamen may represent the basal ganglia site for speech production as it shares both structural and functional connectivity with cortical areas known to be involved in this task (i.e., Broca's area). Using dynamic causal modeling, Booth and colleagues (2007) demonstrated that Broca's area was modulating activity in the putamen (unidirectional functional connectivity) during a rhyming judgment task. The authors suggest that these findings may implicate the basal ganglia (specifically the putamen) to be involved with speech initiation/articulation and cortical initiation

of phonological representations of lexical items (Booth et al. 2007). Indeed, articulatory control of speech and phonological processing were previously shown to engage the putamen (Wise et al. 1999; Wildgruber et al. 2001; Devlin et al. 2003; Tettamanti et al. 2005; Seghier and Price 2010). Direct electrical stimulation of this region resulted in temporary speech deficits (Robles et al. 2005) and single word repetition associated with putamen activation (Wise et al. 1999; Wildgruber et al. 2001). Broca's area is crucially involved in articulatory and phonological processing (Friederici 2002; Devlin et al. 2003; Amunts et al. 2004; Hagoort 2005), and thus it is plausible that the Broca's area–basal ganglia loops involving putamen may support phonological/articulatory processing. Specifically, phonological representations are likely to be activated within Broca's area–auditory association areas network (Catani and Jones 2005; Glasser and Rilling 2008) based on contextual content (established by the temporal and inferior parietal cortical networks). The basal ganglia may be sharpening the signal-to-noise ratio of the most contextually appropriate lexical items, their phonological representations, and corresponding articulatory motor programs (via the direct loop), while suppressing competing phonological items (via the indirect loop). The hyperdirect loop could be resetting the system after the most appropriate phonological representation has been selected. Broca's area–basal ganglia loops likely act in concert with other basal ganglia loops, specifically the pre-SMA loop (via projections between Broca's area and pre-SMA). This functional interaction likely ensures accuracy of speech production so that verbal output matches what the speaker intended to say and improves the processing speed to ensure fluidity of speech. We continue our discussion of this topic in the next section to further examine the relationship between pre-SMA and Broca's area loops.

10.3.3 Interactions Between Pre-SMA and Broca's Area Loops

In the earlier sections of this chapter, we discussed potential functional contributions specific to Broca's area and pre-SMA basal ganglia loops in language processing. In addition, we examined anatomical connectivity between these cortical regions that would enable potential functional interactions between the loops. Although this structural connectivity presents a specific anatomical mechanism to allow interactions between Broca's area and pre-SMA basal ganglia loops, functional implications of these interactions remain largely unclear. In this section of the chapter, we consider language-related processes that may be jointly supported by these loops and propose potential theoretical considerations of the functions of these interactions. We must caution the reader that these theoretical considerations do not represent a comprehensive view of language functions supported by Broca's area and pre-SMA loops, and future research is crucial to fully understand the significance of these networks.

To further examine the role of potential interaction between Broca's area and pre-SMA basal ganglia loops, we revisit the study by Crosson and colleagues (2003) to address what happens in lateral frontal cortices. Functional activity within

pre-SMA-basal ganglia loops was observed during tasks engaging lexical processing (i.e., rhyme generation, fast and slow category-member generation). The authors concluded that this activity indicated potential involvement of the pre-SMA–basal ganglia loops in search and retrieval of lexical items from pre-existing lexical stores (Crosson et al. 2003). In addition to left pre-SMA circuitry, left lateral cortical areas also showed significant activity during word and nonword generation tasks. Specifically, classically defined Broca's area (restricted to cortex within pars opercularis and triangularis of the inferior frontal gyrus) showed activity during fast and slow category-member generation tasks implicating the involvement of this area in semantic aspects of word generation.

In contrast, lateral premotor cortex along precentral sulcus (posterior to pars opercularis) also showed robust activation during the nonsense syllable and the rhyme generation tasks (Crosson et al. 2003). This finding suggests that this region is involved in phonological processing during speech generation. Indeed, a meta-analysis of functional neuroimaging studies revealed that the lateral premotor cortex directly posterior to pars opercularis commonly activates during tasks involving phonological processing (Vigneau et al. 2006). Based on this evidence, linguists proposed conceptual expansion of Broca's area (pars triangularis and opercularis) to a larger region, termed Broca's region, to include lateral premotor cortex as well as pars orbitalis (Hagoort 2005). This larger cortical zone, i.e., Broca's region, can be regarded as the language unification hub within the brain (Hagoort 2005). Language unification represents the combination and interaction of syntactic, semantic, and phonological aspects of language processing to ensure fluidity and efficiency of speech. Specifically, syntactic unification represents combination (or binding) of lexical items to form multi-word statements according to the rules of grammar (e.g., subject, verb, direct object word order in English language) (Vosse and Kempen 2000; Hagoort 2003). Broca's region is thought to dynamically link lexical items into phrasal combinations (i.e., complete sentences) (Hagoort 2005). Each selected phrasal combination typically has competing alternates, for example, the words "horse," "eat," and "hay" can be grouped (with function words) into: "The horse ate the hay" or "The hay was eaten by the horse." Broca's region is thought to participate in selection of the most appropriate phrasal combination based on speaker's intent, while simultaneously suppressing competing alternatives (Hagoort 2005).

In addition to syntactic unification, semantic and phonological unification concepts were also proposed (Hagoort 2005). Semantic unification is thought to be the selection of the most fitting meaning of a lexical item based on the established context (for example, *bank* of a river as opposed to *bank* as a financial institution). Phonological unification is accomplished by unifying lexical items into intonational phrases translating speaker's intent to highlight specific portions of a sentence. For example, individual lexical items within the phrase "how are you?" are highlighted based on the conversation order between two speakers. The first speaker highlights the word "are," while the second speaker after responding to the question will highlight the word "you." The speaker may select either of these intonational profiles, and it is thought that Broca's region aids in the selection of the intended profile and suppresses the competing one.

The three language unification components are not distributed throughout Broca's region in a random fashion, but rather seem to follow an anterior-to-posterior functional gradient. Specifically, evidence suggests that anterior portions of Broca's region (corresponding to pars orbitalis and triangularis) are involved in semantic unification (Bookheimer 2002; Hagoort et al. 2004), middle portion (pars triangularis and opercularis) is important for syntactic unification (Bookheimer 2002; Petersson et al. 2004), while the posterior portion (pars triangularis, pars opercularis, and lateral premotor cortex) is thought to support phonological unification (Bookheimer 2002; Hagoort 2005). Thus, subareas of Broca's region support different aspects of language unification and likely work in concert to ensure fluidity and speed of language expression.

At this point the reader is probably wondering how do Broca's area and pre-SMA basal ganglia loops fit in with the language unification hypothesis? One potential answer based on the evidence presented in the earlier sections of this chapter could be that the pre-SMA–basal ganglia circuitry, rather than exclusively Broca's region, may be involved in lexical search and selection of lexical items from pre-existing stores. Structural connectivity between Broca's area and pre-SMA likely enables information transfer between these regions regarding the selected lexical items and the intent to initiate speech production so that (1) the appropriate/intended meaning (semantic unification) could be assigned to selected items, (2) the items are combined together in grammatically correct phrasal combinations (syntactic unification), (3) appropriate intonation features are assigned based on contextual information, and (4) matching phonological and articulatory representations are activated to ensure successful speech production (phonological unification). These unification and articulatory functions are likely to be accomplished by Broca's region, rather than classically defined Broca's area. Specifically, based on the established functional gradient within Broca's region it would seem that the semantic unification process of selecting the most appropriate lexical items based on intended meaning would engage anterior aspects of Broca's region corresponding to pars orbitalis and pars triangularis. Assembly of selected lexical items into grammatically correct phrasal components and sentences would likely involve pars triangularis and opercularis, while phonological and articulatory unification would likely recruit posterior Broca's region, including pars triangularis, pars opercularis, and lateral premotor cortex. Thus, lexical item selection presumably accomplished within the pre-SMA–basal ganglia loops may influence language unification processes potentially supported by the ventral lateral cortical areas. Further research is crucial to determine whether such information transfer is plausible and whether it is accomplished via Broca's region connectivity with pre-SMA. Current research in the first author's laboratory is examining structural connectivity between subareas of Broca's region and other prefrontal cortical areas including pre-SMA. Improved understanding of structural connectivity between Broca's region and pre-SMA will allow us to determine the plausibility of a structural mechanism for information transfer between these cortical areas and their basal ganglia loops. In addition, studies investigating functional connectivity between these regions and potential influence of one region onto the other (i.e., studies employing dynamic causal modeling

methods, structural equation modeling, or other techniques examining directionality of connections within neural networks) would provide invaluable insights into functional implications of this connectivity and whether pre-SMA does indeed modulate activity within ventral lateral cortical regions.

It is important to note that the three language unification processes and articulatory motor programming discussed above would require mechanisms enabling selection of the appropriate linguistic entity (e.g., word meaning, sentence structure, or articulatory representation), suppression of competing items, and a reset of the system so that each process can start all over. Following our discussion of potential involvement of basal ganglia loops in language processing from earlier sections of this chapter, it would seem plausible that loops engaging particular regions within Broca's area (and/or Broca's region) may be involved in these tasks. Specifically, the direct loops would be engaged during item selection, while the indirect loops would suppress completing alternatives. The hyperdirect loops would then reset the system. In keeping with evidence that the basal ganglia do not perform more basic language functions (Hillis et al. 2002; Nadeau and Crosson 1997), we suggest that the role of the basal ganglia in these processes is to enhance the signal-to-noise ratio in cortical processes, thereby enabling greater speed and efficiency of language production during semantic, lexical, and phonological unification.

The current chapter also discussed evidence of structural connectivity between subregions of Broca's area (pars opercularis and pars triangularis) with basal ganglia and thalamus (Ford et al. 2013). Future studies investigating potential connectivity between sub-portions of Broca's region (including pars orbitalis and lateral premotor cortex) with basal ganglia and thalamus are necessary to determine whether basal ganglia may be also involved in language unification processes discussed here.

Observations drawn from patients with neuroanatomical abnormalities resulting from vascular accidents or neurological disease often provide additional insights into functions supported by the impaired neural regions. A patient population relevant to our discussion of potential functions supported by the pre-SMA and Broca's area (and/or Broca's region) basal ganglia loops is transcortical motor aphasia. Transcortical motor aphasia is a language disorder characterized by non-fluent verbal output with relatively preserved repetition (Lichtheim 1885). Patients with this disorder are often able to repeat sentences and to produce highly overlearned material (for example, letters of the alphabet) (Alexander 2003), while being severely impaired in word generation tasks (such as category-member generation or letter category generation) (Gold et al. 1997; Robinson et al. 1998; Cox and Heilman 2011). In addition, the defining characteristic of transcortical motor aphasia is the overall difficulty in initiating internally guided verbal expression, which is why this disorder is often termed "dynamic aphasia" (Bormann et al. 2008; Costello and Warrington 1989; Crescentini et al. 2008; Luria 1970; Robinson et al. 1998, 2005, 2006), or more fitting, "adynamic aphasia" (Gold et al. 1997). This language disorder is typically associated with lesions to (1) the ventral lateral prefrontal cortical areas, particularly pars opercularis and lateral premotor cortex (Freedman et al. 1984), (2) cortex surrounding supplementary motor area (SMA) including pre-SMA (Alexander and Schmitt

1980; Freedman et al. 1984), and (3) white matter connecting these cortical regions (Mega and Alexander 1994; Alexander 2002). Medial frontal cortical areas, particularly pre-SMA, are thought to be involved in speech production based on internal contingencies, i.e., the intent of the speaker (Goldberg 1985). Crosson and colleagues (2001) observed changes in pre-SMA activity as a function of the amount of external guidance provided during word generation tasks. Specifically, the greatest degree of pre-SMA activity was present during a category-member generation task (e.g., generate members of the "birds" category), which required the participants to engage the highest degree of internal guidance. As the degree of external guidance was increased, first by imposing an additional restriction on potential category members (for example, generate members of the "birds" category that are "red"), and subsequently prompting word repetition, the activity within pre-SMA gradually decreased (Crosson et al. 2001). Similarly, activity within Broca's area also gradually decreased as the tasks changed from most to least internally guided word production. This finding further suggests a network or a system view of the interaction between pre-SMA and Broca's area. Crosson and colleagues (in press) propose that the structural connectivity between pre-SMA and Broca's area may enable pre-SMA to convey the impetus for speech initiation to Broca's area, perhaps by initiating/enabling the search for and retrieval of existing lexical representations. As we discussed above, Broca's area (as well as Broca's region) plays an important role in semantic, phonological, and syntactic aspects of language production (Hagoort 2005). Thus, the connectivity between pre-SMA and Broca's area (and potentially Broca's region if this connectivity exists) may allow this system to translate the impetus to speak (supported by pre-SMA) into semantic, phonological, and syntactic aspects of language production supported by Broca's area/region. In the context of transcortical motor aphasia, patients suffering lesions to medial frontal cortex, Broca's area, and/or white matter pathways connecting these regions may experience deficits in verbal fluency because (1) the impetus for lexical search and retrieval is not efficiently conveyed to the ventral lateral language zones (due to damage to the medial frontal cortex or white matter pathways), and/or (2) intended speech output is not represented accurately in terms of its semantic, syntactic, and phonological components (due to damage to Broca's region). These lesions would result in varying degrees of verbal fluency deficiencies (depending on the size of the lesion), while leaving repetition relatively unaffected, as lexical selection is externally imposed in repetition and places few demands on search and retrieval of lexical items.

How does transcortical motor aphasia fit into our discussion of the potential roles of the pre-SMA and Broca's area (and/or Broca's region) basal ganglia loops in language processing? Lesions to the medial frontal cortex or Broca's region would affect language processing not only within the medial frontal–ventral lateral network, but also the basal ganglia loops involving these regions. Specifically, patients with lesions involving pre-SMA may perform poorly on a category-member generation task due to the difficulty to successfully enhance the intended lexical item, while suppressing competing alternatives, and/or resetting lexical search once one member of a category was generated. Thus, partial damage to the direct, indirect, and/or hyperdirect pre-SMA basal ganglia loops could result in decreased verbal

output due to loss of efficiency in lexical selection while preserving the ability to repeat as it is supported by anterior and posterior regions and their connectivity.

Lesions involving Broca's region resulting in Broca's aphasia acutely and later evolving into transcortical motor aphasia may interrupt semantic, syntactic, and/or phonological aspects of language production depending on lesion location (specifically, the anterior to posterior extent of the lesion). Broca's area–basal ganglia loops involving the putamen may become less efficient in enhancing appropriate phonological and articulatory representations of lexical items and suppressing competing alternatives following damage to Broca's area. Additional studies are necessary to expand our knowledge concerning structural and functional connectivity between Broca's region and the basal ganglia, with the goal of examining further potential involvement of the basal ganglia loops in language unification processes.

10.4 Conclusions

In conclusion, our chapter provides an overview of the current evidence for basal ganglia's involvement in language processing and considers two basal ganglia loops engaging frontal language regions. Specifically, we discuss the pre-SMA and Broca's area basal ganglia loops, and their potential functions and interactions. We propose that the pre-SMA–basal ganglia circuitry is involved in internally guided lexical selection where the direct loop enhances activation of the intended lexical item and the indirect loop suppresses competing alternatives. The hyperdirect loop is likely resetting the lexical selection process after an item has been generated so that the process can be repeated. Broca's area–basal ganglia loops involving the putamen could be involved in selection of appropriate phonological and articulatory representations of lexical items selected via the pre-SMA–basal ganglia circuitry. In addition, structural connectivity between pre-SMA and Broca's area enables information exchange between the cortical components of the two sets of basal ganglia loops. This connectivity may convey the impetus to speak, in the form of lexical search and retrieval, from pre-SMA to Broca's region, and subsequently initiating phonological and articulatory processing of intended lexical items.

Recent evidence suggests that cortical areas outside Broca's area are crucially involved in language production processes. This evidence prompted a number of linguists to expand the notion of Broca's area to Broca's region to include pars orbitalis and lateral premotor cortex. Broca's region is thought to support language unification, where ventral lateral language eloquent cortex is involved in semantic, syntactic, and phonological aspects of speech production. It would seem plausible that the areas comprising Broca's region would share structural connectivity with pre-SMA and future studies are necessary to examine this connectivity. In addition, areas within Broca's region outside of pars triangularis and pars opercularis may share connectivity with the basal ganglia. Indeed, semantic, syntactic, and phonological unification processes attributed to Broca's region seem to involve selection, suppression, and resetting components that could be mapped onto the direct, indirect, and hyperdirect basal ganglia loops.

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Chapter 11
The Basal Ganglia Contribution to Controlled and Automatic Processing

Estrella Díaz, Juan-Pedro Vargas, and Juan-Carlos López

11.1 Automatic and Controlled Processes: A Historical View

One of the most interesting issues in psychology and neuroscience is how animals automate behavior. That is, how our attention is progressively reduced when performing a task repeatedly. Cognitive or automatic control of behavior was the subject of much debate during the first quarter of the twentieth century. For all this period, two opposing positions existed regarding the essence of associative learning. From the stimulus–response (S-R) perspective (e.g. Guthrie 1935; Hull 1943), learning involves the development of habits, which establish direct associations between environmental stimuli and responses. From a more cognitive approach (Tolman 1932), it was considered that knowledge and goal were the determinants of behavior. Although many experimental results as latent learning (Tolman and Honzik 1939), sensory preconditioning (Brodgen 1939), mediated conditioning (Holland 1981), or the effects of the revaluation of stimuli (e.g. Rescorla 1973) support the representational conception of associative learning, current theories of learning have incorporated new concepts about the processes that determine the declarative and/or procedural control of behavior.

11.2 Controlled Versus Automatic: A Continuum Processes?

The most common idea about learning is that prolonged training produces an automation of learned behavior (Dickinson 1980). Classical conditioning is a type of associative learning where a neutral stimulus is associated with an unconditioned

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stimulus (US). When this activity is repeated, the original neutral stimulus becomes a conditioned stimulus (CS), that is, it will generate a response similar to the unconditioned response. During this process, the CS loses the ability to activate a representation of unconditional stimulus (US), and therefore such learning would be automatically controlled through the development of habits or S-R associations. For example, we are able to learn the association of the sight and the smell (CSs) of chocolate with the taste of chocolate (US)) by classical conditioning. Thus, when we see it or smell it, we activate a representation of its taste. In this regard, the CSs activate the salivation response. In addition, with extensive training, the CSs are able to produce the salivation response without the representation of the flavor. That is, the CSs activate the output of the US without perceptual processing mechanisms. This implies that the sight of chocolate might generate the salivation response without activating either the odor or the flavor of the chocolate (S-R learning). However, experimental results, such as the sensitivity of Pavlovian-conditioned response (CR) to reinforce revaluation with extended training, are inconsistent with this view (Holland 1998).

11.2.1 Learning Based on the Predictive Value of a CS

To explain these results, new theoretical models of learning are based on the concept of the predictive value of CS. Shiffrin and Schneider (1977) proposed that stimuli with high predictive value would be automatically processed, and therefore it would be more difficult to generate a new learning. One of the most representative models of this type of approach is that developed by Pearce and Hall (1980). This model assumes that learning depends on the CS processing. Thus, the more predictible is a value of a stimulus, the less attention we pay to it. Therefore, attention and associability to the CS decrease as it becomes a reliable predictor of the US. This loss of associability of the CS involves the transition from one type of controlled processing (which requires the subject to make an effort to process new information) to an automatic one, in which the subject does not perform any effort (LaBerge 1975; Schneider and Shiffrin 1977; Shiffrin and Schneider 1977). Controlled processing of the CS is necessary in the early stages of the training, in which the predictive value of the US (and therefore its associative strength) is low. However, extended training produces predicted consequences by the CS, and this is the reason that the associability decreases, bringing about strategies for automatic processing. The model assumes that the loss of associability affects the learning but not the performance, therefore the CS would continue controlling the CR though it would have lost its capacity to generate new learning. From a broader perspective, we could consider that brain mechanisms and processing of the stimuli change with the progress of learning. In this regard, Holland (2005) has suggested that the distinction between stimulus–stimulus (S-S) and S–R associations would be determined by the portion of US-path activity that comes to be controlled by the CS. At the beginning of training, the CS would trigger a representation of sensory, motivational, and

motor properties of US. That is, the CS might activate the whole representation of the US. However, the extended training determines that the representation of the CS exclusively activates the downstream portions of the US path processing. This means that it does not encode the perceptual processing of US, although it maintains access to motivational processes. One of the most interesting aspects of this approach is that it would not be necessary to postulate the existence of a linear model of automatic versus controlled processing. Instead of this, it might be possible to set different levels of CS links with several kinds of US representations throughout the training. This process would imply a different type of processing (such as acquisition and performance) controlled by several brain systems. That way, when the US is presented (for instance, food), its sensory, perceptual, and motivational characteristics are processed, activating sensory, motivational, and motor systems. Thus, food activates flavor, odor, texture, hedonic value, and salivation response. The association between a tone (CS) and the food (US) endows the tone with the capacity to activate the representation of the food. Therefore, the tone might activate the perceptual, motivational, and motor processing mechanisms previously activated by the food. We propose that all these mechanisms, which are controlled by different brain systems, are activated by the CS presentation. The expression of a response controlled by one of these systems will take precedence over the others depending on certain parameters such as interstimulus interval, length of training, etc. Thus, if the tone precedes the food for a long time, preparatory responses associated to the motivational system (seeking or nearing behaviors) will take precedence over consummatory responses (salivation response).

11.2.2 The Operant as a Tool for the Study of Goal-Directed and Automatic Responses

The introduction of an operant has greatly facilitated the study of controlled and automatic processes, transforming the former into goal-directed actions and the latter into habits (see Box 11.1). In this regard, instrumental conditioning involves two

Box 11.1: Experimental Procedures to Get Controlled and Automatic Processes

The acquisition of a response controlled by the outcome versus an automatic response is relatively simple to show experimentally. Fixed-ratio schedules have been used to promote goal-directed behaviors. These learning programs include the reinforcement of the animal's behavior after a fixed number of responses. This allows a contingent control of the animal's response. Interval schedules provide a different relationship between the response and the outcome. The reward is achieved at the first response after a variable period.

(continued)

Box 11.1: (continued)
This process implies that the relationship between action and reward is variable, facilitating S–R associations.

Recent findings point to the dorsal striatum as a structure anatomically divided into functional domains and essential in the acquisition and expression of habits and goal-directed behavior. On the one hand, S–R processes have been linked to the most lateral domain (the area mostly corresponding to putamen in primates and the dorso-lateral striatum in rodents); on the other hand, the medial zone (the area mostly corresponding to primate caudate and the dorso-medial striatum in rodents) has been linked to controlled processes (R-O). These facilitate the behavioral shift when required by external contingencies (Yin et al. 2005b). Acting sequentially or in parallel, both divisions would compete for access to the expression of behavior.

different processes: one is a goal-directed behavior in which the consequences of an outcome (or R–O association) are codified; and the other is characterized by S–R associative processes (Balleine 2001, 2005; Balleine and Dickinson 1998a, b; Balleine and Ostlund 2007; Dickinson and Balleine 1993, 1994, 2002). The S–R associations differ from R–O ones in the role of reward in the control of behavior. For instance, R–O behaviors are directly motivated by the result of the actions; while S–R behaviors are defined as the performance under certain circumstances in the absence of a reinforcing expectation (Dickinson and Balleine 1993; Balleine and Dickinson 1998b). This implies that R–O behaviors tend to be sensitive to changes in reward value, while S–R ones are not (Dickinson and Balleine 1994; Dickinson et al. 1995; Grahn et al. 2008).

In several studies about automatic and goal-directed processes, Yin et al. (2004, 2005a, b) showed that these two processes could be controlling the acquisition and the performance of an instrumental conditioning task (Balleine et al. 2009; Dickinson 1989; Dickinson et al. 1995; Yin and Knowlton 2006; Yin et al. 2004, 2005a, b). In the beginning, during the acquisition phase, animals would express the goal-directed behavior. After a long period of training, a change in the behavioral control would be observed, where the animal's performance could be under the control of the antecedent stimuli, that is, generating an automatic response (Horvitz 2009; Ragozzino 2007).

The most recent experimental studies suggest that the dorso-medial striatum (dms) network would be related to the expression of learning observed at an early stage (goal-directed), and with further training (automatic responses), the control of the expression would shift to the dorso-lateral striatum (dls) network (see Box 11.2). The reader is also referred to Chap. 18 for a discussion of the role of the dorso-medial and dorso-lateral striatum in learning. Electrophysiological studies have also reported similar results. Miyachi et al. (2002) found that neurons in the sensorimotor striatum showed a higher rate of responses after a repetitive sequence of motor

learning. Moreover, blocking this structure with muscimol did not interfere with the acquisition of new motor routines, but did interrupt the previously acquired ones (Miyachi et al. 1997). This effect is observed in several experiments where the reinforcer that motivates the animal action is devaluated. If the response is goal-directed, the actions will be significantly reduced when the reinforcer is previously devaluated. However, if the animal continues responding to the presence of discriminative stimulus after the devaluation, then we call it automatic response or habit (Yin et al. 2005a, b). The dissociation between controlled and automatic process becomes even more evident by blocking the activity of sensorimotor (dls) or associative striatum (dms). Lesions or inactivation of dls in rats facilitate goal-directed learning (Yin et al. 2004). That is, these animals significantly reduce their responses after the reward devaluation (R-O), irrespective of the learning program used (see Box 11.2). Blocking the activity of the dms causes the opposite effect, that is, increases the expression of S-R association.

As we stated above, the current models that address the issue of automatic control propose an alternative view to the sequential processes from controlled to automatic behavior. The theoretical models suggest the possibility of a simultaneous and parallel activation of different systems of learning and memory (Poldrack and Packard 2003). Balleine et al. (2009) point out that both, the sensorimotor and the associative loops, are involved in the learning process from the initial phase. Thus, expression of the response would be merely the result of interference processes between the sensory and associative system. Thereby, blocking the lateral area would facilitate the expression of the medial striatum activity, displaying a goal-directed behavior. Instead, lesions or blockade of the medial area would prevent the expression of a controlled process. In this case, the most relevant question to ask is when a type of learning is expressed.

Box 11.2: Basal Ganglia Network

The basal ganglia are a group of subcortical nuclei that have been usually associated with the expression of automatic movement sequences. The first models of functioning pointed to the caudate and putamen nucleus (dorsomedial and dorso-lateral in rodents) as target structure of cortical inputs, and the internal globus pallidus and substantia nigra pars reticulata as main output. This monosynaptic architecture was initially defined as direct pathway, while the polysynaptic projection including the external globus pallidum and subthalamic nucleus was called indirect pathway (Albin et al. 1989). Working together, both pathways coordinate motor activity through inhibition (indirect pathway) or facilitation (direct pathway) of the movement of the body.

However, recent data indicate that these circuits are more complex than originally described (Crossman 1987; DeLong 1990). A large number of intrinsic connections to these pathways point to the possibility of reverberating circuits. For example, the direct path projects not only onto the internal globus pallidus, but also as a feedback loop to the external globus pallidus. The same

(continued)

Box 11.2: (continued)
happens with the subthalamic nucleus, which also receives direct projections from the cortex and thalamus. Therefore, our current conception of striatum has changed considerably. Anatomically, it is divided into topographically organized functional domains. Such is the case of the different projections of the cerebral cortex, the main input source to the basal ganglia. Although the circuits show a high similarity at the structural level, they are involved in different behaviors, and not only and exclusively at the motor level.

The basal ganglia receive input from a large number of areas of the cerebral cortex, maintaining a functional relationship through cortico-striatal loops (Alexander et al. 1986; Parent and Hazrati 1995). According to this model, cortical projections converge onto the striatum and project again, through the pallidum, substantia nigra, and thalamus, to frontal and prefrontal cortical regions. At present, three possible networks or loops have been specifically described: the limbic, the associative, and the sensorimotor loop (Alexander et al. 1986; Alexander and Crutcher 1990; Houk and Wise 1995; Middleton and Strick 2000; Nakano et al. 2000; Nambu 2008). These three loops are important because of their relationship to associative learning processes. The limbic loop involves the nucleus accumbens, the ventral caudate, and ventral putamen. These regions receive inputs from the orbital and medial prefrontal cortex (Haber et al. 2000; Kunishio and Haber 1994; Nakano et al. 2000). The associative loop is composed of the head of the caudate nucleus and the most rostral region of the putamen. It is innervated by afferents from the dorsolateral prefrontal cortex (homologous to the pre-limbic cortex in rodents), supplementary motor area, and posterior parietal cortex (Parent 1990; Parent and Hazrati 1995; Utter and Basso 2008). Finally, the sensorimotor loop is comprised of the putamen, which receives innervation from the primary and supplementary motor areas and the somatosensory cortex (Alexander and Crutcher 1990). This organization of connections has been described in primates and rodents, and therefore the functional circuits of the basal ganglia appear to be present in different species.

11.3 Implications of Striatal Networks in Maladaptive Behavior

11.3.1 Drug Addition and Automatic Response to Environmental Stimuli

The switching of behavioral control is particularly visible in drug addiction. Studies of intravenous self-administration of cocaine have pointed to the ventral striatum, specifically the nucleus accumbens (Nac), as the neural substrate responsible for the reinforcing effects of these substances (Wise 2009). This nucleus is also a key component of the limbic system due its connections with structures such as the ventral area of the basolateral amygdala, the hippocampus, and the prefrontal cortex (Charara

and Grace 2003; Floresco et al. 2001a, b, c; Goto and Grace 2008; Groenewegen et al. 1999a, b; Gruber et al. 2009; Ito and Hayen 2011; O'Donnell and Grace 1995). The Nac integrates these afferents and project to other nuclei, such as the dorsal striatum (Groenewegen et al. 1999a; O'Donnell et al. 1997), especially to its sensorimotor and associative areas. This relationship has been described as hierarchical. At the beginning, the ventral striatum could play a central role in the acquisition and performance of the learning. During the course of the training, this activity could be delegated in the dorsal striatum (Atallah et al. 2007). More specifically, recent studies indicate that dorsal and ventral striatum have different roles in a conditioning task. The dorsal striatum would be responsible for performance. On the contrary, the ventral striatum would be responsible for both motivational processes and performance of the task (Atallah et al. 2007). This notion is of great interest and represents a major advance in our understanding of these behaviors and addictive states. Initially, sensitization to an addictive substance requires activation of glutamatergic projections from the prefrontal cortex to the Nac (core). However, increased dopamine in Nac is accompanied by a reduced prefrontal cortex activity (Goto and Grace 2008; Lewis and O'Donnell 2000; Miller and Buschman 2007; Pasupathy and Miller 2005; Rosencrantz and Grace 2001). This process has been associated with neuronal plasticity phenomena related to the process of sensitization (Robbins and Everitt 1999). These changes are moved from the Nac to the sensorimotor striatum, where the motor programs are consolidated into persistent and very stable behaviors in the form of habits (Berke and Hyman 2000). More specifically, it has been described that during the development of sensitization, drug seeking gradually becomes a habit; that is, an automatic activity controlled by environmental stimuli, that in the case of addictive substances are understood as an S-R pathologic adaptation (Belin and Everitt 2008; Everitt et al. 2001; Everitt and Robbins 2005; Redish 2004; Volkow et al. 2006). Although this behavior is initially goal-directed (focused on the R-O relationship), that is, that subjects acquire the substance in the first sessions for their reinforcing effects, after a few training sessions the behavior becomes dependent on the stimuli associated with drug availability (Everitt and Robbins 2005). This behavioral shift from goal-directed behavior to habit has been interpreted as a rapid change in the expression of activation loops from the limbic and associative circuitry to the sensorimotor circuitry of the striatum (Everitt and Robbins 2005; Vanderschuren et al. 2005).

11.3.2 Degenerative Diseases of Nigrostriatal System Support a Double Mechanism of Learning

This model also facilitates the understanding of the various processes observed in Parkinson's disease, although in this case the process is opposite to that seen in addiction. Animal models of Parkinson disease show that a phasic dopamine signal between the substantia nigra pars compacta (SNc) and the dorsal striatum is critical to habit formation. Dopamine depletion after a SNc lesion with 6-OHDA causes similar changes to those observed after a dls lesion, hampering the acquisition of

habits and facilitating the expression of goal-directed behaviors (Yin et al. 2004). Regardless of the possible involvement of deficient levels of dopamine in attentional processes, Parkinson's patients exhibit a clear inability to automate motor sequences or S–R learning. This impairment is illustrated by the finding that prolonged training does not facilitate the acquisition of a habit, perpetuating the training in a goal-directed process. That is, Parkinson's patients do not shift from a controlled process to an automatic one. This maintains learning under voluntary control parameters, slowing the response process and resulting in a much higher cognitive cost than that seen following the acquisition of S-R association. This effect also increases interference processes when Parkinson's patients perform a normal activity, since they are aware of all their decisions. This fact reduces its ability to respond, and although executive control problems might not exist in the initial stages of the disease, these factors significantly reduce the ability of patients to develop a normal activity

11.4 Striatal Networks and Interference Processes

Pathologies such as addiction to substances of abuse or Parkinson's disease point to the importance of automatic processes. Addictive states facilitate their expression, whereas degenerative conditions hinder it, causing a collapse of the cognitive system. Although all available data link the dls to motor learning, we do not know whether S–-S associations could be controlled by this structure when the learning has been automated. The findings about this kind of processes could help to understand the controlled and automatic responses and their relationship with dms and dls. Diazand coworker (2014) have reported some data about this possible relation. They focused on the analysis of the encoding of stimuli that the dls makes without the presence of a motor component in its response.

Box 11.3: Latent Inhibition and Cortico-Striatal Loops
One of the most interesting approaches to analyze the implication of the dls and dms, in both controlled and automatic processes, using the same stimulus is the latent inhibition. LI is a learning process observed when the acquisition of a CR (or CS–US association) to a stimulus paired with a reinforcer is retarded if the same stimulus has previously been pre-exposed in the absence of the reinforcer. Recent studies point to the striatal dopaminergic innervation, in addition to the dopaminergic activity of the Nac, as essential neural substrates for its expression. However, our knowledge of the LI is still sparse. There are conflicting data on the role of both mesolimbic and nigrostriatal systems. The Nac seems to be involved in the expression of LI, modulating the processes that underlie the changes in its expression, such as changes in the magnitude of the reinforcer or changes in the context (Quintero et al.

(continued)

Box 11.3: (continued)
2011a, b; Traverso et al. 2010; Weiner 2003). One recent direction to the study of the neural bases of the LI has been fostered by the inclusion of the dorsal striatum and its functional activity described as three cortico-striatal loops (Alexander et al. 1986; Houk and Wise 1995; Lehericy et al. 2004; Middleton and Strick 2000; Nambu 2008; Parent and Hazrati 1995). These three loops are associated with flexible goal-directed behaviors (dms) and the formation of automatic processes or habits (dls) (Balleine et al. 2009; Dickinson 1989; Dickinson et al. 1995; Yin and Knowlton 2006; Yin et al. 2004, 2005a, b). This view of the activity of the dorsal striatum is interesting when applied to the development of the LI. Although LI refers to Pavlovian conditioning, we can also understand it as the extension of two processes controlled by the dms and dls. Thus, we could attribute two clearly differentiated phases in the expression of LI. In the initial phase (pre-exposure phase), animals would develop the association between the future CS and the no-consequences. After several trials of repeated presentation of the stimulus, the response to the future CS could become controlled by the dls, given the habituation process to the future CS. However, during the conditioning phase, the CS–US association would be controlled by the limbic loop. The result observed during the test phase (delay conditioning) could be the result of the conflict between the limbic and sensorimotor systems. Díaz et al. (2014) analyzed the LI and dorsal striatum activity establishing two types of CS exposition. A group was exposed to a long presentation of the future CS without consequences (5 consecutive days), and the other one to a short one (2 consecutive days). A short exposition to the future CS involves the use of controlled processing strategies. These strategies allow the subject to learn about the characteristics of the stimuli and the relationship to the possible consequences. However, it is likely that a long-term exposure to future CS determines the shift from a controlled to an automatic processing. That is, once the associative relationship between the stimuli and their consequences is established, subjects would use an automatic processing strategy. To analyze in depth if automatic processing interfere or compete with controlled processing for its expression, Díaz et al. (2014) blocked the dls and dms activity in the test phase. The results showed a release of the limbic network (conditioning), impairing the LI expression. This effect of competition between different systems indicates that they compete during learning, and that the damage or blocking to one system could facilitate the expression of the other.

They used a latent inhibition (LI) procedure (see Box 11.3) with the aim to automate the processing to the future CS (pre-exposure learning). This allowed dissociation between the exposed CS (pre-exposure or initial exposure phase) and the novel consequences of same CS (conditioning phase). The hypothesis was focused in the type of processing of the future CS, that is, if the subjects learn two different associations to a CS and both should be under control of different striatal loops. If so,

A

Group / Hour	Pre-1 L	Pre-1 S	Pre-1 N	Pre-2 L	Pre-2 S	Pre-2 N	Pre-3 L	Pre-3 S	Pre-3 N	Pre-4 L	Pre-4 S	Pre-4 N	Pre-5 L	Pre-5 S	Pre-5 N	Cond	Test
10.00h	●	○	○	●	○	○	●	○	○	●	●	○	●	●	○	●	●
14.00h	●	○	○	●	○	○	●	○	○	●	●	○	●	●	○	○	○
18.00h	●	○	○	●	○	○	●	○	○	●	●	○	●	●	○	○	○

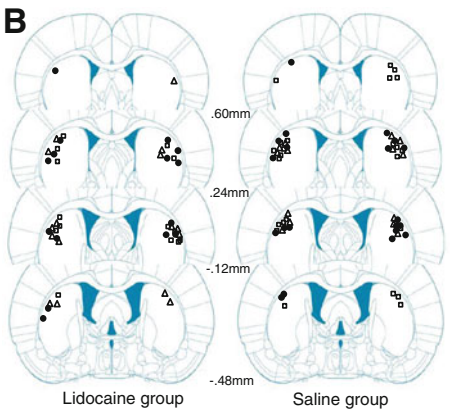

Fig. 11.1 Experimental procedure and results. (**a**) The figure shows the six experimental groups used for this experiment. Animals were tested in three different phases, pre-exposure, conditioning, and test. *Pre-exposition phase* (Pre-1–5) lasted 5 days. During this stage, all animals received three times per day a ten minutes period of access to water (*open circle*) or 0.04 % concentration of saccharine (*filled circle*). These were at 10.00, 14.00, and 18.00 h. The animals were assigned to three different conditions. Long pre-exposure groups (L) received three times per day exposure to saccharine for 5 days; Short pre-exposition groups (S) received three times per day exposition to saccharine only 2 days before the conditioning phase. The rest of days they consumed only water. The No pre-exposure groups (N) received water three times a day, without being pre-exposed to saccharine solution. *Conditioning phase* (Cond) consisted of a single session. All the animals received only saccharine at 10.00 h for 10 min, followed by an intra-peritoneal injection of LiCl (0.4 M, 0.5 % body weight). *Test phase* was run at 10.00 h the following day. During this phase all the subjects had access to the saccharine solution for 10 min. Saccharine consumption for this trial reflected the level of taste aversion. Before that, a microinfusion of either lidocaine 2 % or saline 0.9 % was carried out into the dls. (**b**) Reconstruction of the placement of the canulae within the dls displayed on standard coronal sections. *filled circle* L; *open square* S; *open triangle* N. (**c**) Effects of intra-dls application of lidocaine or saline on mean saccharine intake during the test phase. *Left*. The LI effect was more intense for the L condition and lower for S and both groups drank more saccharin than no pre-exposure group, indicating the presence of LI. *Right*. Lidocaine administration into the dls only affected the L group reducing the LI effect. No effects were observed in S group, showing a similar consumption of saccharine consumption. Finally, long group did not differ from the N group and drank significantly less than the short group (*$p < 0.05$; **$p < 0.01$)

then the future CS during the initial exposure phase might be controlled by the dms, given the relationship of this structure with attentional processes to novel stimuli. However, continued exposure to a stimulus without consequence may result in automatic processing by the subject, and in this case the processing of the future CS would be controlled by the dls. The limbic loop would play a role in the later conditioning phase (association CS–US) due to its relationship with motivational aspects. According to this hypothesis, they found in test phase a competition between the associations controlled by these systems (Fig. 11.1). Based on current theories of basal ganglia function, which propose that the dls is critical for motor habits, no effects of the dls blockade should have been observed during the test phase. However, and contrary to this expectation, they reported evidence in favor of the involvement of the dls in cognitive processes of learning and retrieval.

11.5 Dorsolateral Striatal Activity and the Increases in Conditioning: More Than an S-R Function

Studies on dls function have been restricted to purely motor tasks. Most studies have used an instrumental response in order to analyze the contribution of the outcome and reinforcer devaluation procedures. As discussed above, the devaluation of the stimulus does not appear to cause changes in the S–R relationship, only in the R–O relationship. Lesion and inactivation studies of dms and dls show a change in the associative structure that controls the instrumental response. Lesions to the dls facilitate the expression of R–O associations and the opposite effect was observed when the activity of dms is blocked. However, contrary to what is expected by this model, learning two different contingencies associated with the same stimulus (as in a LI procedure) suggests that the dls is an essential structure for other types of learning. This is not an original idea, since previous studies have also found an involvement of the dorsal striatum in LI. For example, Ellenbroek et al. (1997) found a significant reduction in LI after amphetamine administration. Using a conditioned taste aversion paradigm to evaluate LI, they administered several doses of amphetamine into the dorsal striatum and the Nac before the pre-exposed and conditioning phases. The results showed a significant decrease in LI after injections of amphetamine in dorsal striatum. However, the amphetamine administration in the Nac did not have any effects. The voltammetry results obtained by Jeanblanc et al. (2003) point in this direction. They showed a clear involvement of the anterior striatum in a conditioned olfactory aversion paradigm. Specifically, the conditioning phase was paralleled by a decrease in dopamine release in the dorsal striatum of no pre-exposed subjects, while dopamine levels in pre-exposed subjects approached those observed in non-conditioned animals (Jeanblanc et al. 2003). This release of dopamine appears to be necessary for the expression of LI. However, this phenomenon should be closely linked to other cortical processes. George et al. (2010) found support to this data. They trained two groups of rats in a press lever task with a

random interval schedule. In one of the groups, a noise was presented without consequences (future CS); in the other group, the noise was never presented. After conditioning (presentation of the noise with a shock), the conditioned emotional response used to test LI showed that lesions to the ventral prefrontal cortex elicited larger and more persistent LI effect. In this regard, it is possible that the ventral prefrontal cortex is involved in the process of habituation to stimuli observed during the pre-exposure phase; and after its lesion, the dorsal striatum would work without prefrontal feedback, facilitating an increase in the expression of the LI.

The last important question to discuss is the role of dms in this activity. In this regard, the dms could act as a mediator of the changes experienced by the S–O association. Díaz et al. (2014) found that the antecedent lesion of the dms hampered a habituation response in subjects with long pre-exposure to the future CS. Specifically, the interference effect observed in the lesioned subjects was similar to that in subjects without automatized processes, indicating that the dms is an essential structure for the development of automatic processing of stimuli. Moreover, a poor functioning of this structure could cause severe problems of attentional processes, since the subjects did not show a habituation to the same stimulus.

11.6 Theoretical Implications to Learning Models: Interference vs. Attentional Decreases

11.6.1 Recovery or Acquisition Failure?

Although our results show an important contribution of the dorsal striatum in LI, the mechanism involved in this processes remains unclear. Nowadays, there are different theories to explain LI processes. Regardless of the proposed mechanism, theories encompassed under the name "failure of acquisition" suggest that the processes taking place during the pre-exposure phase impair the establishment of the CS–US association during the conditioning phase (Mackintosh 1975; Pearce and Hall 1980; Schmajuk and Moore 1988; Wagner 1979). According to the theories called "recovery failure", both pre-exposure learning and conditioning would be carried out effectively. During the test phase, both types of learning compete for their expression. Therefore, the LI can be explained as a failure of the expression of CS–US association during recovery processes (Bouton 1993; Miller and Schachtman 1985).

In this regard, the failure recovery theory is able to explain the results obtained in the Díaz et al. (2014, 2015) study. This theory states that LI is due to a competition between CS–nothing learning (pre-exposure phase) and CS–US learning (conditioning phase) during the test phase. In Díaz et al. (2014), the effect of lidocaine during the recovery phase could change the probability of expression of one of the two associations, that is, the CS–no consequence association and CS–US association. These results could not be explained by traditional learning models, since they propose that the associability of the CS declines as it becomes a predictor of the

absence of the US. This loss of associability implies that the CS loses its ability to enter into new learnings (e.g. CS–US associations). However, if we consider the possibility of parallel processing, this decreased associability would not necessarily preclude the formation of new learning.

11.6.2 The Interference as an Action Mechanism in the Dorsal Striatum

We could consider that during pre-exposure, the animals learn a CS–no consequence association. As mentioned before, according to current theories, different systems of learning and memory could be interacting in either a competitive or integrative way in the development of this learning. Therefore, we could argue that certain neural structures including the dls and dms would support different processing pathways involved in this association. In this regard, the extended training becomes a key factor to determine which processing system gets more control over learning. The data suggest that with long- but not short-lasting training, processing based in the dls (or automatic process) gains greater control over the expression of this pre-exposure learning. From this perspective, learning the CS–US association could be developed effectively during the conditioning phase, since the development of this association could be supported by different processing systems.

These data are highly consistent with the theories of recovery failure in LI because they show that after a long pre-exposure to the stimulus, the subjects learn the CS–US association similar to subjects without pre-exposure to the future CS. However, we believe these models are compatible with theories based on the failure of acquisition and the integration of both theories into a parallel processing model would lead to a better understanding of the mechanisms of acquisition and recovery involved in the phenomenon of LI.

11.7 Conclusions

Current experimental behavioral data indicate that a poor functioning of the dms and/or the dls results in cognitive deficits. However, the mechanisms involved in these deficits are largely unknown. Anatomical and electrophysiological studies have analyzed the function of striatal and prefrontal circuits, emphasizing their important contribution to associative learning processes (Homayoun and Moghaddam 2009; Miller and Buschman 2007; Pasupathy and Miller 2005) and to disorders of these processes (Grace and Sesack 2010; Milad and Rauch 2012; Simpson et al. 2010; Vargas et al. 2016; Wise 2009). Additional neuroanatomical and behavioral studies are necessary to understand the functional relationships of cognitive processes and their neural substrata.

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Chapter 12
Striatal Mechanisms of Associative Learning and Dysfunction in Neurological Disease

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12.1 Introduction: Basal Ganglia Anatomy

The anatomy and circuitry of the basal ganglia are thoroughly discussed in other chapters in this volume (e.g. Chaps. 1–4) and we will present here only the major features relevant to our discussion. The basal ganglia are recognized today as an integral component of brain regions involved in higher-level processes to include emotion, motivation, and motor function. However, such functional attributions to the basal ganglia have occurred in relatively recent years and are based to a large extent on a better understanding of its underlying anatomical organization. In fact, it was only in 1786 that the French anatomist Vicq-d'Azyr made an anatomical distinction between the basal ganglia and the thalamus (discussed in Herrero et al. (2002). Further categorization of the basal ganglia into its components, the caudate nucleus, putamen, pallidum, subthalamic nucleus, and substantia nigra, did not occur until the 1900s.

The basal ganglia represent a group of grey matter nuclei located deep within the white matter of each cerebral hemisphere and is comprised of the striatum, the globus pallidus (or pallidum, which includes the internus and externus globus pallidus and the ventral pallidum), the substantia nigra, and the subthalamic nucleus (Lanciego et al. 2012). The striatum represents the input nucleus of the basal ganglia and primarily

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receives information from the cortex and the thalamus. The basal ganglia's output nuclei, the globus pallidus internus and substantia nigra, pars reticulata, project to the thalamus. Finally, the globus pallidus externus and the substantia nigra, pars compacta, are intrinsic nuclei, relaying information between the basal ganglia's input and output nuclei. The striatum, named for its grossly striped appearance when sliced, is the largest subcortical brain structure (Schröder et al. 1975). The striatum is divided into two parts. The dorsal striatum, comprised of the caudate nucleus and putamen, is thought to modulate working memory with the dorsal prefrontal cortex, while the ventral striatum, comprised of the nucleus accumbens and olfactory tubercle, is involved in reinforcement learning (Kreitzer and Malenka 2008). Interestingly, there are no cytoarchitectural or histochemical features that clearly demarcate the ventral and dorsal striatum (Haber and Knutson 2010); instead, the two regions are mainly distinguishable by their anatomical connectivity. There are four major types of neurons that comprise the striatum; however, the vast majority (about 95 %) are monosynaptic GABAergic medium spiny neurons (MSNs; Yager et al. 2015). MSNs that directly target the basal ganglia output nuclei express the D1 dopamine receptor and contribute to the 'direct pathway' of the basal ganglia, while those that indirectly target basal ganglia output nuclei via the globus pallidus externus express D2 dopamine receptors and contribute to the 'indirect pathway' of the basal ganglia (Albin et al. 1989; DeLong 1990). The direct and indirect pathways each have opposing effects on the basal ganglia output: direct MSNs cause a net excitement of the thalamus, while indirect MSNs cause a net inhibition of thalamic activity. Such connectivity is found in several functional subdivisions of the basal ganglia, including subdivisions associated with movement, executive function, and emotional processing.

The cellular connectivity of the basal ganglia in a well-defined cortico-striatal-thalamo-cortical loop circuitry contributes to the distinct motor functions of the basal ganglia. These pathways have been extensively studied due to their role in movement disorders such as in Parkinson's Disease (Calabresi et al. 2014). The cerebral cortex projects to the basal ganglia with glutamatergic excitatory projections to striatal MSNs. In the direct pathway, cortically stimulated D1-expressing MSNs release GABA to inhibit GABAergic neurons of the globus pallidus internus, a nucleus that represents one basal ganglia's output to the thalamus. Thus, activation of the D1-MSNs releases the inhibition of the ventral anterior and ventral lateral (VA/VL) nuclei of the thalamus, which subsequently project to the cerebral cortex to activate movement. In the indirect pathway, cortical activation results in the activation of GABAergic D2-expressing striatal MSNs, resulting in an enhanced inhibition of GABAergic neurons in the globus pallidus externus. This nucleus subsequently decreases its inhibition on the subthalamic nucleus and the globus pallidus internus, resulting in a net inhibition of VA/VL thalamic nuclei, and subsequently a reduction in motion. Thus, in terms of net functional outcomes, the cortico-striatal-thalamo-cortical loop is comprised of two pathways. In the first, direct striatal MSNs cause a net excitement of the thalamus, resulting in a positive cortical feedback loop, while the second, indirect striatal MSNs result in a net inhibition of thalamic activity.

A second well-described system involves the prefrontal association cortex, a region known for its role in working memory. Working memory is a higher-level function that allows information processing for the execution of complex cognitive tasks, such as mental arithmetic, problem solving, and language comprehension (Baddeley et al. 1986; Frank et al. 2001). The association loop shares a similar anatomical pattern with the motor pathway. Excitatory projections from the cortex synapse onto striatal direct and indirect pathway MSNs. Striatal MSNs then directly or indirectly control the basal ganglia's output nuclei, which send projections to the cortex by way of the thalamus (Galvan et al. 2015). The association circuit begins and ends primarily in the cortex surrounding Brodmann's areas 9 and 10, with additional cortical projections interconnected by cortico-cortical fasciculi that exist in the posterior parietal and premotor cortex (Alexander and DeLong 1986; Selemon and Goldman-Rakic 1985; Schmahmann et al. 2007). These cortical areas project to the dorsolateral head of the caudate nucleus, which further directs the signal through the tail of the caudate nucleus. In turn, the MSNs of the caudate nucleus project to the substantia nigra, pars reticulata, and dorsomedial globus pallidus internus. These signals project to the ventral anterior and ventral medial (VA/VM) nuclei of the thalamus, which complete the loop with neurons directed to the prefrontal cortex. Of note, studies examining the retrograde distribution of Herpes Simplex Virus (multi-synaptic labelling) after injection into premotor cortex and the basal ganglia nuclei demonstrate a topographic orientation well-maintained within each pathway (Middleton and Strick 2000). Such studies have demonstrated, for example, that Brodmann's area 12 stereotypically target specific regions of the globus pallidus internus, while Brodmann's area 9 projects to the substantia nigra, pars reticulata, to signal the down-stream thalamic nuclei. Furthermore, such topographic organization exists even within a single cortical area, with different subdivisions uniquely connected, in both afferent and efferent pathways, to either the globus pallidus internus or substantia nigra, pars reticulata. This well-defined topographic mapping demonstrates that the association loop consists of interconnected parallel pathways that, together, incorporate a wide area of projections from the premotor cortex and is ideally suited for integrating multi-modal streams of data from the environment.

The limbic system is essential to emotional memory, addiction, and motivation and is another well-studied basal ganglia circuit (Mogenson et al. 1980). This system consists of a broad range of anatomic structures, including the hippocampus, amygdala, hypothalamus, nucleus accumbens, and cingulate cortex; similar to the previous circuits, these structures are involved in a series of interconnected loops in which each component influences the activity of the other structures. Three of these components have historically been described as key structures involved in activating behaviors: the nucleus accumbens (involved in reward-motivated behaviors), the amygdala (involved in fear-motivated behaviors), and the prefrontal cortex (shown to regulate the overall intensity of response; Kluver and Bucy 1997; Olds and Milner 1954). The nucleus accumbens is considered a central component of behavioral function, shown in studies of drug abuse to stimulate downstream pathways by

releasing dopamine from cell bodies located within the ventromedial mesencephalon (Ikemoto and Panksepp 1999). While the ventromedial nucleus accumbens (the 'shell') targets the amygdala, lateral hypothalamus, and ventromedial portion of the ventral pallidum, the dorsolateral nucleus accumbens (the 'core') projects primarily to the dorsolateral ventral pallidum and substantia nigra (Kalivas and Volkow 2005). The ventral pallidum in turn projects to the mediodorsal thalamus, which serves as a signal relay to the prefrontal and cingulate cortex. The amygdala can be divided into two components, the central and basolateral amygdala, based on its efferent targets. While the central amygdala projects to the brainstem, the hypothalamus, and dopaminergic neurons of the ventral tegmental area to integrate autonomic and endocrine processes with environmental stimuli, the basolateral amygdala projects to the prefrontal cortex and nucleus accumbens to coordinate complex behavioral responses. Finally, the cingulate cortex is likely involved in preventing responses to inappropriate stimuli by regulating the strength of a behavioral response to environmental inputs and projects to the core of the nucleus accumbens (Cardinal et al. 2002).

12.2 Basal Ganglia Models

In addition to the significant advances in our understanding of basal ganglia anatomy over the past century, further development of our understanding of its functional circuitry has paved the way for the treatment of debilitating neurodegenerative diseases, most notably Parkinson's disease, with deep brain stimulation (Alexander et al. 1990). There are many models to explain the basal ganglia computational architecture. These models are based on knowledge of the anatomy, physiology, and neurochemistry of the basal ganglia and incorporate data gathered at one of many levels, from a molecular to a neuronal population-level. The wide spectrum of models at the cellular level can be divided into three broad categories: models of reinforcement learning, models of serial processing, and models of action selection (Gillies and Arbuthnott 2000; Joel et al. 2002). The reader is referred to Chaps. 5, 18 and 19 in this volume for a more detailed description of computational models of the basal ganglia. For a more detailed discussion of mechanisms of associative learning, the reader is also referred to Chaps. 5, 11, 18, 19 in this volume.

Models of reinforcement learning stem from the observation that behaviors can be reinforced with rewards obtained after a task has been completed. One such model of reinforcement learning is the Actor-Critic model, in which there are two main components: an actor, which produces behavioral responses based on environmental cues, and a critic, which provides reinforcement signals to the actor based on behavioral outcomes (Joel et al. 2002). In the basal ganglia, the actor is represented by the striatum, while the critic is represented by the substantia nigra, pars compacta, which produces reinforcement by way of dopamine release. In this model, the

actor requires immediate feedback from its response to environmental cues to learn a behavior, and a delay in reinforcement from the critic results in the failure of the actor to associate its action with a reward. This 'temporal difference problem' must be solved by the critic, which must learn to predict reward and provide reinforcement in a timely fashion based on environmental cues. The Actor-Critic model is able to accurately predict empirical data, correctly predicting that dopamine release decreases when an expected reward fails to occur at an expected time. However, the model assumes a temporal association of cue onset to reward, and that this association is represented in the cortical representation of the cue. These models also assume that the critic, or the substantia nigra, receives primary input from the environment. Neither assumption has yet been confirmed by currently available experimental data. Furthermore, reinforcement models do not provide a clear definition of the role of the indirect pathway of the basal ganglia.

A second category of computational models describing basal ganglia function are models of serial processing, derived from the anatomical observation that the basal ganglia are involved in cortical-basal ganglia-thalamic-cortical loops. Movement control and planning require processing and analysis of sequential events, both of which are offered by a serial processing model that involves this basal ganglia loop. In serial processing models, cues for the next item in the sequence can be presented by either the environment or internal representations in the prefrontal cortex; for example, one model describes the basal ganglia as an encoder of serial events to the prefrontal cortex, in which the caudate MSNs represent the basal ganglia detectors of cues (Beiser and Houk 1998; Pasupathy and Miller 2005). Thus, in models of serial processing, the prefrontal cortex processes stimuli from the environment, activating certain striatal MSNs in order to disinhibit thalamic neurons, subsequently activating cortical neurons. This pattern of activation changes as the prefrontal cortex receives new environmental cues, allowing serial stimuli to generate unique cortical representations, and subsequently, provide an explanation for the basal ganglia's role in working memory. Of note, the nuclei involved in each serial processing model differ based on the function and temporal duration examined. While the vast majority of the models falling within the category of serial processing analyze long-term memory, loops involving the globus pallidus externus and subthalamic nuclei may be used to explain short-term memory.

The third broad category into which most computational models fall are models of action selection (Albin et al. 1989; DeLong 1990). Functionally, the basal ganglia's output nuclei provide a tonic inhibitory input on the thalamus, but the direct pathway facilitates activity in the thalamus through disinhibition. Thus, a specific activity might occur if a small component of the thalamus is disinhibited, while the rest remains inhibited by the subthalamic nucleus or the indirect pathway of the basal ganglia in a manner akin to the off-center, on-surround organization of the visual system. Computational models of this category can be quite complex and take into account detailed biophysical properties such as delays introduced by transmission speed and synapses.

12.3 Neuropsychological and Cellular Mechanisms of Learning

The basal ganglia have an increasingly well-defined role in learning. In 2005, Kao and colleagues described in songbirds that the anterior forebrain circuit, which includes the basal ganglia and forebrain, is a required component for complex song learning and plasticity, but not for the execution of learned song (Kao et al. 2005). Furthermore, it has been demonstrated that song maturation in juvenile songbirds, developed by introducing song variations and selecting the appropriate tune, is prevented by either lesions or pharmacological inhibition of basal ganglia-cortical loops (Kao et al. 2005; Olveczky et al. 2005). The process of learning has also been examined at the neuronal level, where basal ganglia neurons have been monitored in rats trained in reward-based tasks (Barnes et al. 2005). Before training, striatal projection neurons spiked sporadically to all stimuli encountered throughout the task, presumably a form of neuronal exploration that assumes all encountered stimuli are critical to the task. After training was complete, the striatal neuron firing was shown to cluster at the beginning and conclusion of each task, suggesting that this neuronal activity marks the boundaries of the behavioral process (e.g., initiation and termination of a learned behavior), but is not required for execution of the task. Such preclinical data have been translated to the human level—in functional MRI studies, the ventral striatum has shown a preferential increase in activity following immediate rewards, while dorsal striatal activity preferentially increased with delayed rewards, demonstrating the potential of the basal ganglia to contribute to learning at various time scales (Tanaka et al. 2004). Altogether, these experiments have contributed to the notion that the basal ganglia are involved in learning through reinforcement loops that help select the series of actions that contribute to a particular behavior (Frank et al. 2001; Graybiel et al. 1994).

Increases in basal ganglia activity in primate studies induced by high frequency electrical stimulation of the caudate nucleus are associated with a significant improvement in the ability to perform learned tasks (Williams and Eskander 2006; Nakamura and Hikosaka 2006). The functional improvement that results from electrical stimulation raises the question of which underlying biochemical processes may contribute to the selection of circuits involved in task learning. Gale et al. demonstrated that high frequency electrical stimulation of the caudate directly results in increased dopamine release in the anterior caudate, while low frequency electrical stimulation does not contribute to dopamine release (Gale et al. 2013). When paired with the empirical data demonstrating that only high frequency electrical stimulation improves task-directed learning, the authors suggest that increased dopamine secretion is likely a direct mediator of basal ganglia-mediated learning. This hypothesis is further supported by rodent studies that demonstrate dopamine receptor blockade with neuroleptics like pimozide or inhibition of dopamine release not only reduces reward-seeking behaviors, but results in learning dysfunctions (Wise et al. 1978; Parkinson et al. 2002).

These findings raise an important and conceptually poorly understood aspect of learning—motivation. Katnani and Patel recently explored the role of motivation in associative learning by extending the work of Williams and colleagues, namely that electrical stimulation in the caudate nucleus on correct, but not incorrect, trials can selectively enhance visual-motor associative learning in non-human primates (Williams and Eskander 2006). Katnani and Patel hypothesized that, in combination with intermittent caudate stimulation during the feedback period, associative learning could be even further enhanced by experimentally activating motivation circuits at the beginning of the trial. To do this, at the beginning of each trial, they applied intermittent high-frequency electrical stimulation in the nucleus accumbens, a region of the ventral striatum involved in the processing of reward salience and motivation. In addition, they applied high-frequency electrical stimulation in the caudate nucleus during feedback on correct trials. They found that by using a spatially and temporally distributed stimulation protocol, they could not only enhance the rate of learning (even more than caudate stimulation alone), but also enhance the monkey's overall performance, as measured by number of correct trials in each session (Katnani and Patel 2015).

Based on these and other data, dopaminergic neurons have increasingly been proposed to play an integral role in reward-motivated learning (Shohamy et al. 2008). In 2013, Stephenson and colleagues used a primitive lamprey to study the lateral habenula, a structure found in organisms of all evolutionary stages and located downstream of the pallidum in the limbic system. The habenula is thought to be involved in processing the motivational value of actions (Stephenson-Jones et al. 2013). Using electrophysiological and immunohistochemical techniques, the authors found a novel circuit involving dopaminergic neurons of the midbrain that regulates the globus pallidus projection to the lateral habenula. This circuit represents a key component in the processing of value assessment and basal ganglia-mediated action selection tasks in the lamprey.

Dopamine signaling in response to a reward has been proposed to select and prune basal ganglia neuronal synapses and optimize value-based learning (Schultz et al. 1997; Fiorillo et al. 2003). When animals receive an unexpected reward, for example, a strong dopaminergic response is elicited in the ventral tegmental area and substantia nigra, and if the reward is consistently preceded by a cue, the dopamine response to the reward is replaced by a strong response to the cue (Schultz et al. 1997). The authors propose that using these dopaminergic stimuli, a monkey is able to learn to immediately press a lever in response to a light in order to receive a reward. However, if the reward is not received after a learned cue, dopamine release is significantly lower than basal levels at the time of the expected reward. Dopamine release will once again closely associate with reward presentation until another cue becomes a consistent temporal marker for the reward. Rather than simply serving as a transient driver of a reaction to a stimulus, dopamine release is currently thought to create downstream cellular changes that underlie adaptive behaviors to an event (Fiorillo et al. 2003). Such physiological changes are thought

in part to result from the metabotropic nature of dopamine receptors that allows them to modulate changes in long-term plasticity, distinct from the fast changes initiated by ionotropic glutamate and GABA receptors (Zucker 1989; Descarries et al. 1996; Voulalas et al. 2005).

In a recent study, Howe and co-workers applied fast-scan cyclic voltammetry to measure dopamine release in the dorsal and ventral striatum of rats engaged in a T-maze learning paradigm (Howe et al. 2013). What the authors found was striking and challenges our understanding of dopaminergic signaling in the striatum. Based on the work of Schultz and others, evidence has suggested that positive and negative prediction error signals are encoded through the phasic modulation of dopaminergic activity, ultimately providing reinforcement signals to either strengthen or weaken behaviors to maximize rewards. This line of evidence arose by studying the electrophysiological activity of single neurons within midbrain dopaminergic circuits. Instead, by directly measuring dopamine release, Howe and colleagues found that dopamine release in the striatum is not phasic, but instead flexibly scales with both the proximity and size of rewards. This newly discovered form of dopamine signaling provides a continuous measure of how close animals are to attaining rewards and has implications for both understanding the role of dopamine in motivation and goal-directed behaviors as well as neuropsychiatric disorders such as major depression.

Finally, additional data suggests that the relative levels and timing of dopamine release are critical to feedback-based learning involving the basal ganglia (Cools et al. 2001). In vitro studies of primate brain samples have demonstrated that electrical stimulation results in a varying degree of dopamine release between individual striatal slices, lending credence to the hypothesis that basal ganglia-dependent learning is comprised of a series of dopamine-dependent parallel circuits (Cragg 2003). In fact, depending on the task, learning can either be enhanced or impaired in Parkinson's patients taking medications that globally enhance dopamine levels. The clinical implications of physiological imbalances in the basal ganglia are vast and will thus be discussed in a later section.

Although over the past few decades great strides have been made in elucidating mechanisms of associative learning in the basal ganglia, the overwhelming majority of experiments have been conducted in animal models. Despite the numerous benefits of studying these processes in animals, the question still remains: Are the same signals also observed in the human brain? Many tools exist to study physiological processes in the awake-and-behaving human, such as functional magnetic resonance imaging, electroencephalography, and magnetic encephalography. However, none of these approaches are suitable to measure brain activity at the level of individual neurons, which is a requisite to provide a mechanistic description of learning related-processes. One avenue for collecting single-neuronal activity in human subjects has arisen in recent years—intraoperative microelectrode recordings during deep brain stimulation surgery (Patel et al. 2013). Deep brain stimulation surgery is a neurosurgical procedure whereby a stimulating electrode is implanted within specific target brain nuclei. Most commonly, these electrodes are implanted within the basal ganglia for the treatment of movement disorders such as in Parkinson's

Disease. However, as a result of the clinical procedure, an opportunity arises to record neural activity in patients that are awake-and-behaving. To leverage this opportunity, researchers have developed methods to probe cognitive functioning in the operating room environment through computerized behavioral tasks. In this way, two studies have explored whether reward-processing signals in the basal ganglia are also found in humans.

Zaghloul and co-workers performed microelectrode recordings from dopaminergic neurons in the substantia nigra pars compacta of patients undergoing deep brain stimulation for Parkinson's Disease while engaged in a financial decision-making task (Zaghloul et al. 2009). They hypothesized that under certain conditions the dopaminergic spiking activity would represent prediction error signals for monetary rewards, similar to those first described by Schultz in monkeys for primary rewards. More specifically, Zaghloul and colleagues found that spiking activity in nigral neurons phasically increased when subjects expected a negative (omission of reward) outcome but received a reward—a positive prediction error signal. Conversely, they found that neurons phasically attenuated their firing rate when expecting a rewarding outcome, but received a negative outcome—a negative prediction error signal. This provided the first evidence that reinforcement learning signals existed and were mechanistically similar in the human brain.

The nucleus accumbens is classically thought of as the 'motor-limbic interface' because of its rich limbic afferents from the hippocampus, amygdala, and frontal cortices and its efferent projections to motor output centers in the basal ganglia (Mogenson et al. 1980). Given this anatomical connectivity, the accumbens is in a unique position to integrate a wide-range of information to modulate behavior. Furthermore, the nucleus accumbens receives widespread input from midbrain dopaminergic centers, thus placing it under the influence of reward centers. This combination makes the accumbens well-suited for processing reward information and guiding goal-directed behaviors. Patel and colleagues extended findings from Zaghloul and colleagues by performing microelectrode recordings from the nucleus accumbens in patients undergoing investigational deep brain stimulation for major depression or obsessive-compulsive disorder (Patel et al. 2012). Again, subjects were engaged in a financial decision-making task, and the authors found that neurons in the nucleus accumbens encoded both positive and negative prediction error signals during the feedback period. In addition to this, however, the authors also described a signal in the accumbens that predicted the upcoming choice on a trial-by-trial basis nearly 2 s before the choice was manifested through a button press. Taken together, this suggested that the activity of accumbal neurons represents both reinforcement learning signals, the actor and critic, at two different temporal windows. This provided the first demonstration of both hypothesized re-inforcement learning signals within the human brain. The authors later replicated these findings in the subthalamic nucleus and were able to demonstrate a causal relationship between these decision-encoding signals and behavior through the application of intermittent electrical stimulation during the specific temporal window in which the signal arose (unpublished data).

12.4 Dysfunctions of Associative Learning in Pathology

12.4.1 Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopamine (DA)-producing cells of the substantia nigra, pars compacta, which innervates multiple regions of the basal ganglia, including the striatum. Disruption of these nigrostriatal projections causes prominent motor symptoms of tremor, bradykinesia, and rigidity, but also may result in particular cognitive dysfunctions, with an estimated 20–30 % of PD patients meeting diagnostic criteria for dementia and an even greater proportion displaying mild cognitive impairment (Aarsland et al. 2005). There has been some debate regarding the etiology of the cognitive dysfunctions. Although early hypotheses emphasized the role of alpha-synuclein aggregation in the cortex, later studies failed to demonstrate a clear correlation between cortical Lewy body deposition and certain forms of cognitive impairment (Parkkinen et al. 2005; Weisman et al. 2007), and pathological studies confirmed that cognitive impairment in PD can occur without cortical alpha-synuclein deposition (Adler et al. 2000; Jellinger 2010). Together, these results suggested a subcortical locus of at least some cognitive symptomatology, especially early in the disease course. It has now become clear that the striatum may play a central role in the development of cognitive dysfunction in PD.

There is a vast body of literature dedicated to cataloging the various cognitive deficits in PD, with many excellent reviews available on the subject (Foerde and Shohamy 2011; Kudlicka et al. 2011; Dirnberger and Jahanshahi 2013). An important consideration in this literature is distinguishing the cognitive deficits arising from striatal dysfunction, which are secondary to the loss of DA neurons in the substantia nigra, from those arising from cortical pathology. These later deficits resemble symptoms of Lewy body dementia and are likely due to cortical alpha-synucleinopathy in PD. The so-called 'dual-syndrome hypothesis' formalizes this distinction by purporting two partially overlapping but hypothetically independent etiologies of cognitive dysfunction in PD, one arising from disruption of frontostriatal circuits and another primarily cortical syndrome (Kehagia et al. 2013). Frontostriatal circuitry can be neuroanatomically divided into three subsets, connecting the striatum with the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and the orbitofrontal cortex (OFC; Middleton and Strick 2000). Cognitive deficits in PD arising from striatal dysfunction can generally be attributed to one or more of these circuits (Zgaljardic et al. 2006). The striatal-DLPFC circuit is thought to mediate executive functions including working memory, associative learning, and set shifting; breakdown of striatal-DLPFC circuitry in PD accordingly manifests as deficits in tests of these cognitive abilities (Flowers and Robertson 1985; Vriezen and Moscovitch 1990). The striatal-ACC circuit mediates conflict monitoring, motivation, and response initiation, and patients with PD show corresponding deficits in these areas (Brown and Marsden 1991). Finally, the striatal-OFC circuit mediates stimulus-driven behavior, impulsivity, and mood;

accordingly, breakdown of this circuit in PD results in impulsivity, perseveration, and depression (Cummings 1992; Hozumi et al. 2002; Evans et al. 2009). These categories of deficits have been clustered into a proposed battery of tests to assess function of each of these frontostriatal circuits in PD (Zgaljardic et al. 2003).

Neuroimaging and electrophysiological studies have reinforced the contribution of striatal dysfunction in the cognitive deficits observed in PD. Volumetric analysis demonstrates significantly decreased putamen volume in early PD, with further decreases in caudate and putaminal volumes throughout disease course (Lisanby et al. 1993; Geng et al. 2006). Functional neuroimaging studies show decreased connectivity between the striatum and the thalamus, midbrain, pons, and cerebellum in PD, underlining the importance of brainstem innervation of the striatum and its role in the disease (Hacker et al. 2012). Functional techniques have also demonstrated a decrease in the activity and integrity of frontostriatal neural circuitry in PD. For example, in a sentence comprehension task, patients with PD showed decreased striatal recruitment compared to healthy controls (Grossman et al. 2003). Another fMRI study demonstrated decreased striatal activation during a working memory task in patients with PD who were clinically cognitively impaired compared to patients with PD without appreciable cognitive deficits (Lewis et al. 2003). Multiple electro/magneto-encephalographic studies have demonstrated frontostriatal coherence across multiple frequency bands, some of which appear to be dopamine-dependent (Williams et al. 2002; Litvak et al. 2011). Together, these data support the notion that striatal dysfunction is a key contributor to the etiology of cognitive deficits in PD.

The clinical effects of DA replacement therapy with L-3,4-dihydroxyphenylalanine (L-dopa) or DA receptor agonists such as bromocriptine in patients with PD provide further insight into basal ganglia function and striatal roles in cognition. While DA replacement therapy improves the motor symptoms of PD, it has differential effects on various cognitive manifestations of the disease, improving some and worsening others (Macdonald and Monchi 2011). Specifically, there is evidence that DA replacement therapy in patients with PD improves set shifting (Cools et al. 2001; Shook et al. 2005), spatial working memory (Mollion et al. 2003; Beato et al. 2008), verbal fluency (Gotham et al. 1988), prospective remembering (Costa et al. 2008), action planning (Hanna-Pladdy and Heilman 2010), motor movement chunking (Tremblay et al. 2010), time estimation (Jones et al. 2008), and motor timing tasks (O'Boyle et al. 1996; Harrington et al. 1988). These improvements might broadly be categorized as recovery of cognitive flexibility, planning, and temporal processing with DA replacement therapy in PD (Macdonald and Monchi 2011).

Conversely, DA replacement therapy negatively affects learning and impulse control. Patients with PD on DA replacement therapy performed worse in tasks of probabilistic associative learning (Shohamy et al. 2008; Jahanshahi et al. 2010), sequence learning (Tremblay et al. 2010), reversal of stimulus-reward associations (Swainson et al. 2000; Graef et al. 2010), and learning from negative feedback (Frank et al. 2004), compared to performance off medication, and frequently despite performing equivalently to controls off medication. Additionally, DA replacement therapy increases the risk of developing disorders on the impulsive-compulsive

spectrum, including gambling, hypersexuality, compulsive buying, and binge eating (Weintraub et al. 2010). Patients with PD show a tendency toward impulsive betting strategies in tasks of decision-making (Cools et al. 2003), and toward temporal discounting of rewards (Voon et al. 2011). Similarly, in healthy controls, DA agonists impair reward learning (Pizzagalli et al. 2008) and increase temporal discounting (Pine et al. 2010).

These differences in the effect of DA replacement therapy on various learning and cognition processes in PD likely relate to differences in dopaminergic input among areas of the striatum. Whereas the dorsal striatum (which includes most of the caudate and the putamen) primarily receives dopaminergic input from the substantia nigra, the ventral striatum (as defined here as including the nucleus accumbens and the ventral-most parts of the caudate and putamen) is mostly innervated by the ventral tegmental area. In PD, the substantia nigra is preferentially affected over the ventral tegmental area at all stages of disease (Kish et al. 1988; Fearnley and Lees 1991), which renders the dorsal striatum relatively more DA-deficient than the ventral striatum. Dopamine replacement therapy, which is frequently titrated to control motor symptoms, renormalizes DA signaling in the dorsal striatum, but also effectively overdoses the ventral striatum. The 'overdose hypothesis' suggests that excessive DA disrupts normal signaling in non-DA-depleted regions of the striatum, which underlies the cognitive deficits that emerge in patients with PD upon DA replacement (Gotham et al. 1986; Vaillancourt et al. 2013).

The 'overdose hypothesis' is supported by multiple studies of striatal lesions and functional imaging in healthy subjects who demonstrate differences in the role of the dorsal and ventral striatum in cognition. Lesions of the dorsal striatum result in deficits in set shifting, planning, visuospatial processing, and suppression of irrelevant stimuli, and neuroimaging studies show increased activation of the dorsal striatum in healthy subjects during tasks involving set shifting, time estimation, and visuospatial processing. Lesions of the ventral striatum are rare, but deficits in learning new verbal material and anger recognition have been reported. Functional imaging reveals activation of the ventral striatum in association with implicit learning of a motor sequence (Reiss et al. 2005), preferentially in cases of positive (reward) feedback over negative feedback. Increased activity of the ventral striatum has also been noted in association with impulsivity (Ernst et al. 2004; Matthews et al. 2004). These data may be generalized to indicate that the dorsal striatum is primarily involved in integrating multiple influences to select among various stimuli, whereas the ventral striatum is primarily involved in implicit learning, especially association with reward (Foerde and Shohamy 2011; Macdonald and Monchi 2011). This seems consistent with the notion of 'overdosing' the ventral striatum with DA replacement therapy in PD, which explains the improvement in some cognitive facilities, which may be referable to the dorsal striatum, with concomitant worsening of learning and reward processing, referable to the ventral striatum (Macdonald and Monchi 2011).

Although the overdose hypothesis explains the apparent preferential dysfunction of the ventral striatum with DA replacement in PD, it does not explain why DA overdose seems to inhibit some functions of the ventral striatum while enhancing

others. Increased activity of the ventral striatum is noted in association with implicit reward-associated learning and impulsive decision-making, but while DA overdose diminishes associative learning, it appears to enhance impulsivity. One recent hypothesis to explain this discrepancy relies on features of the ventral striatum that renders it sensitive to both phasic and tonic DA signaling (Macdonald and Monchi 2011). Cytoarchitectural studies show that there is a relatively low density of dopaminergic inputs to the ventral striatum, and neurons in the ventral striatum tend to be smaller and have sparser dendritic spines (Wickens et al. 2007). Furthermore, there is relatively low expression of DA transporter in the ventral striatum, which reduces the rate of clearance of DA from the synapse (Wickens et al. 2007). These characteristics result in graded, incremental activation in the ventral striatum in response to DA impulses and the ability to integrate multiple dopaminergic inputs across time, features that seem ideally suited for associative learning (Wickens et al. 2007; Zhang et al. 2009). DA overdose likely disrupts signaling ordinarily reliant on phasic DA input, which may explain the worsening in implicit associative learning with DA replacement therapy. Conversely, if impulsivity is instead mediated by absolute dopaminergic tone in the ventral striatum, DA overdose would be expected to pathologically enhance these behaviors, explaining why patients with PD on DA replacement therapy frequently develop disorders of impulsivity (Macdonald and Monchi 2011). Although this theory suggests intriguing functional differences between phasic and tonic dopaminergic signaling in the ventral striatum, further studies are required to test this hypothesis in humans.

12.4.2 Schizophrenia

Schizophrenia (SCZ) is a complex neuropsychiatric disorder with a prevalence of about 1 % in the adult population and represents a major cause of psychiatric morbidity, mortality, and socioeconomic burden across the world. Schizophrenia is typified by a combination of so-called positive, negative, and cognitive symptoms. Positive symptoms are generally pathological psychoses, including hallucinations, delusions, and thought disorders, but may occasionally include motor disturbances. Negative symptoms include disruptions of normal emotions or behaviors, including depressed mood, anhedonia, low motivation, and psychomotor retardation. Cognitive symptoms are present early in the disease, and interestingly, are largely resistant to current therapies. One of the most enduring neuropsychiatric etiological theories is the DA hypothesis of SCZ, which points to dysregulated dopaminergic signaling as the basis for schizophrenic symptomatology. It is now generally accepted that striatal dysfunction as a result of aberrant DA signaling plays a major role in the development of these symptoms.

The DA hypothesis has undergone three major reconceptualizations in its evolution. Initial evidence for the theory arose from the realization that the effectiveness of antipsychotic drugs was directly related to their affinity for the DA receptor (Seeman and Lee 1975; Creese et al. 1976). Thus, it was hypothesized that SCZ was

characterized by excessive dopaminergic signaling, and that antipsychotic drugs exerted their effect by blocking postsynaptic DA receptors and thereby renormalizing activity of these circuits (Snyder 1976). Two decades later, an emerging understanding of cortical–subcortical interactions from pathological, imaging, and animal studies, along with several experimental inconsistencies with the basic notion of excessive DA signaling as the sole driver of schizophrenic symptomatology, led to the proposal of regional specificity in brain dysfunction in the disease (Davis et al. 1991). It was postulated that, in general, the positive symptoms of SCZ arise from striatal hyperdopaminergia, whereas the negative symptoms arise from frontal hypodopaminergia. Interestingly, these two phenomena are probably not independent, as experimental lesions of frontal dopaminergic neurons elevate striatal DA levels (Pycock et al. 1980). A third reconceptualization emphasizes the role of presynaptic dopaminergic dysregulation as the primary site of pathology (Howes and Kapur 2009). In addition to suggesting multiple promising therapeutic targets for SCZ, the DA hypothesis also purports pathologically excessive DA signaling in the striatum as a core driver of symptomatology.

The cognitive deficits in SCZ are numerous and include deficits in semantic and episodic memory, as well as in attention, working memory, and executive function. Clinically, many of these deficits tend to closely resemble those apparent in patients with frontal lobe lesions; for example, patients with SCZ and patients with frontal lobe lesions both perform poorly on tests of frontal executive function, including the Wisconsin Card Sorting Test (WCST), the Stroop Test, the Tower of London test, and the N-Back Test (Kolb and Whishaw 1983; Pantelis et al. 1997). However, given multiple lines of evidence indicating that striatal hyperdopaminergia is a robust hallmark of SCZ, along with an emerging appreciation for the role of frontostriatal circuits in executive function, some have suggested that striatal dysfunction may be the core etiology of cognitive symptomatology in SCZ (Simpson et al. 2010). Consistent with this, numerous functional neuroimaging studies have reported diminished recruitment of the striatum and decreased frontostriatal connectivity during a wide array of cognitive challenges in patients with SCZ, which frequently correlate with symptom severity (Tu et al. 2012; Fornito et al. 2013; Quidé et al. 2013; Wadehra et al. 2013). Antipsychotic therapy may restore aberrant fronto-striatal functional connectivity (Sarpal et al. 2015). This is also congruent with cognitive studies that consistently report deficits of cognitive facilities quintessentially associated with the striatum, such as associative learning (Kemali et al. 1987; Martins Serra et al. 2001), reward processing (Gold et al. 2008; Schlagenhauf et al. 2009), and motivation (Strauss et al. 2014).

These findings support a role for the striatum in the cognitive symptoms of SCZ, but a growing body of evidence suggests that the striatum may also mediate positive and negative symptoms of the disease. One popular theory of psychosis is to describe it as a state of ‘aberrant salience’ or an inability to accurately distinguish between predictive (salient) stimuli and non-predictive (irrelevant) stimuli (Kapur 2003). This framework may apply to SCZ, as attention to irrelevant cues in a cognitive task correlates with the severity of positive symptoms in patients with SCZ (Morris et al. 2013). Preliminary data from functional imaging studies suggest that aberrant

striatal activity and connectivity are also associated with psychoses. For example, one diffusion tensor imaging study found that disruptions in left amygdala-nucleus accumbens white matter tracts correlated with frequency and severity of delusions and hallucinations in patients with SCZ (Bracht et al. 2014). An fMRI study found that putaminal signal aberrance with stimuli presented in an audiovisual movie correlated positively with delusion scores (Raij et al. 2015). A resting-state functional connectivity study found significantly enhanced nucleus accumbens functional connectivity with the left temporal superior gyrus, the cingulate gyri, and the ventral tegmental area in patients with SCZ who experience auditory hallucinations (Rolland et al. 2015). Another study found increased coherent intrinsic activity within the dorsal striatum during positive symptomatology, and, interestingly, increased activity in the ventral striatum in psychotic remission that correlated with negative symptoms, including emotional withdrawal and blunted affect (Sorg et al. 2013). Similarly, the ventral striatum showed reduced activation during presentation of reward-inciting stimuli in patients with SCZ compared to controls, which may contribute to negative symptoms such as apathy, anhedonia, and loss of motivation (Juckel et al. 2006). These results are intriguing, but preliminary. Further work is required to more clearly understand the role of the striatum in the development of positive and negative symptoms in SCZ.

12.4.3 Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a highly heritable neuropsychiatric illness characterized by intrusive, repetitive thoughts and ritualistic behaviors that together cause significant disability to patients, with an estimated lifetime prevalence of 2–3 %. Its symptomatology falls into two categories: obsessions, which are unwanted, recurrent impulses, and compulsions, which are repetitive behaviors conducted in relation to obsessions. Obsessive-compulsive disorder has a high coincidence with other disorders of the striatum, suggesting a striatal etiology of the disorder. This is perhaps unsurprising, given that the disorder involves the development of pathological motivations and learned habituation of compulsions, all cognitive facilities independently ascribed to the striatum. One of the earliest and most influential models of striatal involvement in OCD is the orbitofronto-striatal model (Menzies et al. 2008). Multiple lesional and functional imaging studies indicate that the OFC plays a key role in sensory integration, motivation, reward-associated learning, and critically, the inhibition of previously rewarding behaviors following reversal of reinforcement contingency (reversal learning) (Schoenbaum et al. 2002; Chudasama and Robbins 2003; Elliott and Deakin 2005; Kringelbach 2005). The OFC has well-described anatomic and functional connectivity with the striatum (Kringelbach 2005). The orbitofronto-striatal model postulates aberrance of this circuitry as the neurological etiology of OCD.

Converging lines of evidence suggest dysfunction of striatal function, including associative learning, is a component of the pathophysiology of OCD. Patients who

suffer focal lesions within the striatum occasionally develop profound obsessive-compulsive symptoms (Laplane et al. 1989), and deep brain stimulation of the ventral caudate may be effective in medically refractory OCD (Aouizerate et al. 2009). Furthermore, patients with OCD show cognitive deficits that are attributable to striatal dysfunction. For example, patients with OCD show impaired implicit sequence learning (Deckersbach et al. 2002; Rauch et al. 2007), habit learning (Marsh et al. 2004), and implicit procedural acquisition (Joel et al. 2005), all of which rely on striatal associative learning for optimal performance. A vast body of functional neuroimaging studies confirms orbitofronto-striatal pathology in OCD (Friedlander and Desrocher 2006). Overall, the data indicate that in the resting state, patients with OCD have enhanced activity in the OFC and caudate (Baxter et al. 1987; Nordahl et al. 1989), which is further increased during symptom provocation (Adler et al. 2000) and is reduced toward normalization with both behavioral and pharmacological treatment (Benkelfat et al. 1990; Schwartz et al. 1996). Although the association between orbitofronto-striatal dysfunction and OCD symptomatology is not precisely understood, some have suggested that these fronto-striatal loops might be 'cognitive pattern generators' involved with the formation of cognitive habits, whose activity is pathologically increased and unregulated in OCD (Graybiel and Rauch 2000).

Importantly, though the orbitofronto-striatal heuristic has been a useful model for understanding OCD and has significant support from cognitive and neuroimaging studies, it is unlikely to be complete in its explanation of OCD pathophysiology (Milad and Rauch 2012). Indeed, there are some cognitive studies suggesting involvement of frontal areas outside the orbitofrontal region in OCD; for example, patients also have deficits in response inhibition (Penadés et al. 2007), set shifting (Chamberlain et al. 2006), planning (van den Heuvel et al. 2005), and decision-making (Sachdev and Malhi 2005). Furthermore, the model does not account for known regional functional variation within the OFC (Kringelbach and Rolls 2004; Milad and Rauch 2007). Though these cognitive facilities likely have a striatal component, the relative contribution of striatal versus frontal dysfunction in these cognitive facilities is less clear.

12.4.4 Huntington's Disease

Huntington's Disease (HD) is a progressive, uniformly fatal neurodegenerative disorder caused by CAG nucleotide triplet repeat expansion in the huntingtin (HTT) gene, which encodes an abnormally long polyglutamine repeat in the huntingtin protein (Ano 1993). The characteristic clinical features of HD include the classic triad of dysfunctions manifesting as chorea, cognitive decline, and psychiatric disturbance, though the initial presentation and progression of these features is varied and inconsistent. Mutant HTT protein is prone to misfolding and gives rise to toxic N-terminal fragments when cleaved, which together cause intracellular pathology via incompletely understood mechanisms (Ross and Tabrizi 2011). Intranuclear inclusion bodies, which represent large aggregates of HTT, are pathognomonic of

HD. The abnormal HTT protein is widely expressed in the brain and other tissues of the body, but HD is characterized by massive striatal neuronal death, with up to 95 % loss of GABAergic medium spiny projection neurons (Halliday et al. 1998). However, HTT cytotoxicity is widespread and affects many other brain regions outside the striatum (albeit to a lesser degree), including the cerebral cortex, subcortical white matter, thalamus, and certain regions of the hypothalamus (de la Monte et al. 1988; Halliday et al. 1998). Thus, the precise striatal contributions to the symptomatology of HD are difficult to discern.

The cellular features that render striatal neurons highly susceptible to HTT cytotoxicity are poorly understood. One hypothesis postulates that striatal medium spiny neurons are uniquely susceptible to excitotoxicity, which is thought to play a role in neurodegeneration in HD, owing to persistently high expression of the NR2B subunit of the NMDA glutamate receptor in these neurons (Li et al. 2003; Cowan and Raymond 2006). Others have found that the small guanine-binding protein Rhes, which is highly localized to the striatum, induces sumoylation of mutant HTT, potentiating its cytotoxicity, and have suggested that the Rhes-mutant HTT interaction accounts for selectivity for the striatum in HD (Subramaniam et al. 2009). Yet others have found that wild-type HTT upregulates the transcription of brain-derived neurotrophic factor (BDNF), whereas mutant HTT does not (Zuccato et al. 2001). As cortical projections to the striatum supply large amounts of BDNF, which is critical for striatal neuronal survival, loss of cortical BDNF due to mutant HTT may explain selective striatal loss of neurons (Zuccato et al. 2001). The exact mechanism is not known, but may have profound therapeutic implications for preventing striatal death in HD.

The cognitive and behavioral deficits are well-characterized features of HD at all stages of the disease (Montoya et al. 2006). While some deficits appear insidiously and progress slowly beginning in the early prodromal stage of HD, others appear relatively abruptly much later in the disease course. Neuropsychological testing in asymptomatic mutation carriers demonstrates early deficits in attention (Claus and Mohr 1996), concentration, visuospatial processing (Ho et al. 2003), and emotional processing (Sprengelmeyer et al. 1996), all of which tend to worsen over time. In contrast, memory tends to precipitously decline around the time of clinical diagnosis (Snowden et al. 2002). Although this pattern of deficit progression is somewhat variable among patients, it is grossly consistent with a model of early striatal involvement in the prodromal phase of disease, followed by abrupt cortical pathology arising only after a critical threshold of striatal projections has been lost (Snowden et al. 2002). Furthermore, the neuropathological pattern of disease within the striatum begins in dorsal-most areas and extends ventrally as the disease progresses (Vonsattel et al. 1985). This dorsal–ventral progression of striatal involvement in HD has been hypothesized to underlie the pattern of cognitive deficits that arise in early HD. For example, extra-dimensional set-shifting, a function ascribed to the dorsal striatum, is impaired in early HD, but simple reversal learning, ascribed to the ventral striatum, is spared in early disease and arises later (Lawrence et al. 1996). This may also explain why apathy, which is classically associated with lesions of the ventral striatum and associated OFC circuitry, correlates strongly with disease stage and motor symptom severity, suggesting progressive ventral striatal dysfunction throughout the disease course (Thompson et al. 2012).

Neuroimaging studies have corroborated the notion of early striatal pathology in HD. Striatal volume begins to progressively decrease years before motor manifestations of HD (Bamford et al. 1995). The caudate appears to be affected first (Harris et al. 1996), but there is involvement of the putamen, globus pallidus (Aylward et al. 1997), thalamus (Jernigan et al. 1991), and eventually cortical white- and grey-matter regions as the disease progresses (Rosas et al. 2003; Poudel et al. 2014). Ultimately, there is widespread neuronal atrophy and decreased total brain volume by as much as 40 % (Rosas et al. 2003). The degree of striatal changes correlates well with the magnitude of cognitive deficits in early HD. For example, the volume of the caudate is significantly correlated with general cognition (Harris et al. 1992) and performance on tests of visuospatial processing (Bamford et al. 1995). Numerous studies have identified decreased metabolic activity (Kuhl et al. 1982), dopamine binding (Ginovart et al. 1997; Pavese et al. 2003), and spectroscopic markers of neuronal health in the striatum of patients with HD (Sánchez-Pernaute et al. 1999) in the resting state.

Functional investigations during the execution of neurocognitive tasks have confirmed the disruption of striatal regions and their functional associations with cortical brain regions, which also correlate with performance on neurocognitive tasks themselves (Clark et al. 2002; Kim et al. 2004; Voermans et al. 2004; Unschuld et al. 2012). One group used fMRI to demonstrate dysfunction of the ventral striatum in the form of altered reward and punishment processing in the Monetary Incentive Delay Task in presymptomatic HD gene carriers near expected symptom onset (mean age 40.9 years), but not in carriers further from symptom onset (mean age 34.5 years), reinforcing the model of dorsal-to-ventral striatal involvement in prodromal disease progression (Enzi et al. 2012). Interestingly, fronto-striatal disruption is occasionally accompanied by enhanced activation of other brain regions. For example, in the Porteus Maze Task, patients with HD show reduced activity in the caudate, but increased activity in the left postcentral and right middle frontal gyri (Clark et al. 2002). In a route recognition navigational test, patients with HD show decreased striatal activation but increased hippocampal signal (Voermans et al. 2004). Together, these data suggest that other regions of the brain can compensate for striatal dysfunction, particularly in early HD.

12.4.5 Other Disorders

Although we have limited our discussion to the above four disorders of striatal associative learning, there are many other neuropsychiatric diseases in which striatal cognition plays a central role. For example, pathological striatal learning processes are believed to play a key role in the development of addiction and addictive behaviors (Belin et al. 2009). Similarly, abnormal reward processing and anticipation by the striatum play a role in major depression (Schlaepfer et al. 2008; Smoski et al. 2009). We refer the reader to the many excellent reviews available on these and other disorders of striatal learning.

12.5 Future Directions and Conclusions

In this chapter, we have reviewed concepts of basal ganglia anatomy and physiology within the context of associative learning. We are increasingly uncovering the mechanisms by which we learn and are developing better models to describe and predict adaptive behavior. Reinforcement learning theory has proven to be a great stride in this direction; however, we will need to continue to update these models and reconceptualize frameworks to include new findings on the role of dopamine in reward processing within the basal ganglia. Certainly, the recent advent and adoption of new approaches will guide these novel discoveries, such as optogenetics, in vivo two-photon and calcium imaging, and advancements in noninvasive functional neuroimaging and invasive single-neuronal recordings. In addition, much of our current understanding stems from findings in non-human animal models, which pose certain limitations in making inferences to human learning. This, of course, proves to be a significant and important unmet clinical need, given the implication of motor and neuropsychiatric disorders on human learning performance.

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Chapter 13
Alcohol Effects on the Dorsal Striatum

Mary H. Patton, Aparna P. Shah, and Brian N. Mathur

13.1 Introduction

The dorsal striatum is the input nucleus of the basal ganglia, receiving glutamatergic inputs from the cortex as well as from the thalamus to drive its principal cell type, the medium spiny projection neuron (MSN). The dorsal striatum is also heavily innervated by dopaminergic inputs from the substantia nigra, pars compacta. Dopamine released from this nucleus acts on dopamine D1 or D2 type receptors to modulate striatal output. Multiple classes of interneurons are present in the dorsal striatum, including GABAergic parvalbumin-containing fast-spiking interneurons (FSI), low-threshold spiking interneurons (LTSI), somatostatin-containing interneurons (SSI), and large aspiny-cholinergic interneurons (CHI) (Ding et al. 2010; Gittis et al. 2010; Kawaguchi 1993; Mallet et al. 2005; Oldenburg and Ding 2011; Pisani et al. 2007). MSNs receive inhibitory inputs from these local interneurons (FSIs, LTSIs, and SSIs) in addition to projection neurons from the globus pallidus. Additionally, they receive cholinergic inputs from CHIs. Thus, MSN output is shaped by a plethora of excitatory, inhibitory, and modulatory inputs.

The dorsal striatum is functionally separated into two regions based on connectivity, protein expression, and behavioral representation. The rodent dorsomedial striatum (DMS) is roughly equivalent to the primate caudate and receives inputs from the associative cortices (Sesack et al. 1989). The dorsolateral striatum (DLS) of the rodent roughly equates to the primate putamen and receives inputs

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from sensorimotor cortices (Fu and Beckstead 1992; Wan et al. 1992). These two regions of the dorsal striatum mediate different forms of action learning; activity in the DMS is necessary for goal-directed behaviors, while activity in the DLS underlies habit formation (Packard and McGaugh 1996; Quinn et al. 2013; Yin et al. 2004, 2005).

Given the necessity of the dorsal striatum, and the DLS in particular, to the formation of habits, a significant amount of attention has been devoted to the impact of drugs of abuse on this structure. In particular, the effects of alcohol on DLS function have received substantial attention for its emerging role in promoting the expression of habitual action, including the compulsive drinking that occurs in alcoholism. Ethanol produces a myriad of physiological changes in dorsal striatal cell types. As such, ethanol studies are not only poised to provide novel routes to therapeutic intervention for alcoholism, but are also capable of informing us how particular changes in striatal circuitry underlie the expression of habits, thus providing mechanistic insights that would have otherwise gone undiscovered. This chapter covers the diverse physiological changes caused by acute and chronic ethanol exposure on the dorsal striatum. The functional implications of how ethanol promotes habitual behaviors are also discussed.

13.2 Effects of Acute Ethanol on Physiology in the Dorsal Striatum

While there is no single specific binding site for ethanol, various cellular components of neurons comprising specific circuits respond to ethanol to manifest its reinforcing effects. These components can include various neurotransmitter receptors, ion channels, and signaling molecules. Complicating matters further, effects of ethanol on signaling and circuitry shift with concentration, and, likely, duration of ethanol exposure (Deitrich and Erwin 1996; Valenzuela 1997). Thus, physiological effects of ethanol at central nervous system synapses are highly complex.

The striatum is the input nucleus of the basal ganglia and mediates action learning and performance and aspects of cognition (Herrero et al. 2002; Rolls 1994; Yin et al. 2004, 2005). Thus, ethanol-induced modifications of striatal circuitry are likely to contribute to alcohol seeking, intoxication, dependence, and withdrawal (Chen et al. 2011; Gerdeman et al. 2003; Robbins and Everitt 2002).

In non-tolerant humans and experimental animals, ethanol produces intoxication at concentrations up to approximately 100 mM (Lovinger and Roberto 2013). Thus, electrophysiological studies have explored the acute effects of ethanol on striatal *ex vivo* preparations typically using this concentration range. Excitatory synaptic inputs into the dorsal striatum originate primarily from the cortex and to a lesser extent from the thalamus, and drive MSN activity. As such, glutamatergic inputs to MSNs represent a key node of modulation by ethanol. To this end, Choi

et al. (2006) demonstrated that bath application of ethanol decreases electrically evoked excitatory postsynaptic current (EPSC) amplitude in the dorsal striatum in a concentration-dependent manner, with a half maximal inhibitory concentration (IC_{50}) of approximately 50 mM. This effect is also seen with EPSCs evoked by exogenous glutamate and is independent of GABA (Choi et al. 2006). Choi and colleagues (2006) went on to show that ethanol also decreases the amplitude of miniature EPSCs (mEPSCs). The frequency of mEPSCs and the paired-pulse ratio remain unchanged suggesting a postsynaptic mechanism of action. Previously, several studies had looked at ethanol effects on glutamatergic transmission in the ventral striatum, the striatal region associated with motivated behavior (Nie et al. 1993, 1994). The effects demonstrated by Choi et al. (2006) in the dorsal striatum are similar to those reported in the ventral striatum where ethanol inhibits glutamatergic transmission; however, the mechanism of ethanol action in the ventral striatum appears both presynaptic and postsynaptic (Nie et al. 1994; Zhang et al. 2005).

N-methyl D-aspartate (NMDA) receptors (NMDARs) are expressed on MSNs within the dorsal striatum and contribute to corticostriatal glutamatergic transmission. These receptors have a well-established role in plasticity (Malenka and Nicoll 1999; Martin et al. 2000) and trigger long-term potentiation (LTP) in the dorsal striatum (Calabresi et al. 1992b; Partridge et al. 2000; Shen et al. 2008). NMDARs are involved in many aspects of addiction such as dependence, withdrawal, and relapse (Krystal et al. 2003). More importantly, ethanol directly inhibits NMDA-activated currents (Lovinger et al. 1989). An inhibition of these receptors may explain the observed depressive effect of ethanol at the corticostriatal synapse. In this light, Wang et al. (2007) investigated the effects of ethanol specifically on NMDAR-mediated synaptic transmission at the corticostriatal synapse. NMDAR-mediated currents were measured in the presence of picrotoxin, NBQX, and a low concentration of Mg^{2+} in the external solution to block inhibitory synaptic transmission mediated by $GABA_A$ receptors, excitatory synaptic transmission mediated by AMPA/kainate receptors, and to release the Mg^{2+}-dependent blockade of NMDAR activity, respectively. As anticipated based on previous results (Lovinger et al. 1989), acute treatment of rat dorsal striatum with ethanol decreases the amplitude of NMDAR-mediated EPSCs. However, these EPSCs recover after ethanol washout, followed by an increase over baseline. This facilitation lasts for more than 30 min and is hence called long-term facilitation (LTF). In contrast to this LTF observed in the dorsal striatum, ethanol has an immediate depressive effect on EPSC amplitude in the ventral striatum, but fails to induce the LTF. Dorsal striatal LTF during washout occurs by a postsynaptic mechanism and is due to enhanced activation of the NMDA receptor subunit B (NR2B) subunit of the NMDA receptor (Wang et al. 2007). Ethanol activates a signaling pathway involving NR2B and Fyn, a kinase that targets NR2B (Wang et al. 2007). The compartmentalization of Fyn near or away from NMDAR determines the sensitivity of NMDAR to ethanol (Yaka et al. 2003). Fyn is localized in

close proximity to NR2B in the dorsal but not in the ventral striatum, which may explain the occurrence of LTF in the former but not in the latter subregion of the striatum (Wang et al. 2007).

While investigating ethanol effects, these studies did not differentiate the dorsal striatum into medial and lateral sub-compartments. However, these two areas, the DMS and DLS, are functionally distinct. The former is implicated in learning of goal-directed actions, whereas the latter is involved in habit formation (Yin and Knowlton 2004, 2006; Yin et al. 2004, 2005). In a follow-up study, Wang et al. (2010) established that LTF of NMDAR-mediated EPSC amplitude by ethanol is observed in the DMS but not in the DLS. This regional difference does not seem to be due to a difference in protein levels of NMDA receptor subunit A (NR2A) or NR2B subunits in these brain areas.

Consistent with effects observed in the hippocampus (Lovinger et al. 1989) and work by Wang and colleagues (2007, 2010), Yin et al. (2007) demonstrated that bath application of 50 mM ethanol reversibly inhibits NMDAR-mediated currents in the DMS. However, unlike the report by Wang et al. (2007), Yin et al. (2007) did not observe any facilitation upon ethanol washout. The reason for this inconsistency between the two studies is not entirely clear. Yin et al. (2007) also tested the effects of acute ethanol on NMDAR-dependent LTP in the DMS by carrying out field potential recordings. A high frequency stimulation (HFS) protocol was used to induce LTP. Baseline population spike (PS) amplitude is not affected by ethanol. Ethanol has a concentration-dependent effect when present throughout the duration of the experiment; 2 mM ethanol reduces LTP magnitude while 10 mM ethanol fully attenuates HFS-induced LTP. These effects of relatively low concentrations of ethanol show that DMS-LTP is more sensitive to ethanol than NMDAR-mediated plasticity seen in other areas of the brain. For example, LTP is inhibited at the hippocampal CA1 synapse by 50–100 mM (Izumi et al. 2005; Schummers et al. 1997) and at the perforant path-dentate gyrus synapse by 75 mM ethanol (Morrisett and Swartzwelder 1993). Interestingly, 50 mM ethanol (a concentration comparable to intoxicating blood levels) not only abolishes the HFS-induced LTP but also reverses it to a significant long-term depression (LTD) in the DMS (Yin et al. 2007). HFS-induced LTP is blocked in the presence of an NMDAR antagonist, APV. However, APV in combination with 50 mM ethanol results in significant LTD post-HFS. Therefore, the LTD seen post-HFS with 50 mM ethanol is not mediated by NMDARs, suggesting a different underlying mechanism. A well-established form of LTD observed in the dorsal striatum is mediated by endogenous cannabinoids (endocannabinoids, eCBs) and requires activation of cannabinoid type 1 receptor (CB1) and D2-like dopamine receptors. The LTD observed post-HFS in the presence of 50 mM ethanol appears to be similar to eCB-LTD as it is blocked by CB1 or D2-like dopamine receptor antagonists. Thus, 50 mM ethanol potentially enhances eCB release and signaling in this striatal subregion (Yin et al. 2007).

What signaling pathways downstream of NMDA might ethanol target to elicit these effects on HFS-induced LTP? Similar to LTP occurring in the hippocampal

CA1 region (English and Sweatt 1997; Rosenblum et al. 2002), NMDAR-dependent, HFS-induced LTP at the corticostriatal synapse in the DMS requires extracellular signal-regulated kinase (ERK) signaling (Xie et al. 2009). While transient ERK activation is required for the induction of LTP at this synapse, it is not necessary for maintenance of LTP. Ethanol impairs corticostriatal LTP in the DMS by attenuating ERK activation in a concentration-dependent manner. These changes in the levels of activated ERK correlate with the concentration-dependent impairment in LTP observed with ethanol (Xie et al. 2009). There is evidence that ERK is activated by Ca^{2+} entry through the NMDA receptor (Hardingham et al. 2001). In addition, Xie et al. (2009) showed that in slices treated with an NMDAR antagonist, levels of activated ERK decrease within 10 min post-HFS and return to baseline levels only 60 min post-HFS. These data suggest that NMDARs associated with ERK signaling mediate HFS-induced LTP in the DMS. Interestingly, with long-term exposure ethanol suppresses ERK-dependent corticostriatal LTD in the DLS by suppressing ERK activation. By contrast, striatal slices from animals that underwent withdrawal from ethanol for 1 day had potentiated ERK activation and LTD magnitude (Cui et al. 2011).

In addition to the DMS, ethanol also has effects on circuitry mediating habit formation in the DLS (Yin and Knowlton 2006; Yin et al. 2004). Adermark and colleagues (2011a) demonstrated the net effect of acute ethanol in this brain region in juvenile rats, by carrying out field potential recordings. They reported that bath application of 50 mM ethanol decreases the PS amplitude whereas lower (20 mM) or higher (80 and 100 mM) concentrations do not have this effect. This depression is not NMDAR mediated but is blocked by antagonists targeting glycine, acetylcholine, or $GABA_A$ receptors. It is postulated to be regulated by glycine receptors located on CHIs causing an elevation in cholinergic activity; increased levels of acetylcholine may lead to excitation of neighboring GABAergic neurons and net inhibition of striatal output (de Rover et al. 2002). Following washout of 50 mM or higher concentrations of ethanol, PS amplitude is enhanced. This facilitation is mimicked following washout of a glycine receptor agonist and blocked by nicotinic and muscarinic acetylcholine receptor antagonists. Interestingly, in brain slices from adult animals, PS amplitude is enhanced not only during the washout but also during 50 mM ethanol treatment itself, highlighting age-related differences in the effect of ethanol on striatal microcircuitry (Adermark et al. 2011a).

The striatum comprises mainly GABAergic MSNs that project to downstream nuclei of the basal ganglia. The striatum also includes a small population of GABAergic interneurons, FSIs and LTSIs, in addition to the CHIs mentioned above. The results reported by Adermark et al. (2011a) underscore the potential impact that ethanol can have on neurons other than MSNs. In an attempt to reveal a more complete picture, Blomeley et al. (2011) conducted a thorough study on the electrophysiological effects of acute ethanol exposure (50 mM) on these various neuronal subtypes in the DLS. Somewhat unsurprisingly, the effects of ethanol are highly cell-type specific. In striatal CHIs, ethanol reversibly decreases spontaneous (firing) activity. CHIs respond to salient stimuli with characteristic pauses in their activity

that may signal MSNs in situations that require alertness or shifts to alternate action sequences (Aosaki et al. 1994; Benhamou et al. 2014; Kimura et al. 1984). By altering CHI firing activity, ethanol may, thus, interfere with the responses of an intoxicated individual to alerting stimuli. Effects of ethanol on LTSIs are variable. However, overall, ethanol decreases the rate of spontaneous action potentials in almost all LTSIs tested (Blomeley et al. 2011). This inhibition of LTSIs potentially leads to a decrease in GABA and neuromodulators contained by LTSIs such as nitric oxide, somatostatin, and NPY (Gittis et al. 2010). In stark contrast to these effects, ethanol depolarizes FSIs and even induces spontaneous firing in some cells. Ethanol elicits these effects by potentiating Ca^{2+}-activated K^+ currents in CHIs and in a group of LTSIs, whereas one or more K^+ conductances are suppressed in FSIs. Ethanol does not have any apparent direct effect on MSN intrinsic excitability. However, there are indirect effects due to the action of ethanol on neighboring striatal cells. Ethanol application leads to a hyperpolarization of MSN resting membrane potential. This is due to a decrease in cholinergic tone in the striatum that elicits a decrease in tonic activation of M1 receptors on MSNs. Activation of M1 receptors suppresses currents through inwardly rectifying K^+ (specifically, Kir2) channels (Shen et al. 2007). Hence, a decrease in activation of these receptors increases Kir2 currents in MSNs. Further, ethanol reduces evoked GABAergic currents and impairs thalamic gating of corticostriatal inputs in the MSNs (Blomeley et al. 2011). Thalamic gating of corticostriatal inputs may be crucial to shift attention and redirect behavior (Ding et al. 2010). These effects of ethanol on MSNs, taken together with the reduction in glutamatergic responses (Choi et al. 2006; Wang et al. 2007) and decreased cholinergic activation, demonstrate that ethanol may act at various targets within dorsal striatum microcircuitry and possibly make striatal output less responsive to external stimuli (Blomeley et al. 2011). Until recently, the effects of ethanol on specific synapses in the dorsal striatum had not been investigated. Using optogenetics and whole-cell patch-clamp recordings from MSNs in the DLS, Patton et al. (2016) demonstrate that 50 mM ethanol depresses both MSN and FSI inputs onto MSNs. This ethanol-induced LTD at the FSI-MSN synapse is mediated by activation of a presynaptic delta opioid receptor that acts to decrease GABA transmitter release. These results are consistent with other work that suggests activation of dorsal striatal delta opioid receptors is necessary for drinking (Nielsen et al. 2012).

So far, we have reviewed effects that are elicited by ethanol targeting various channels and receptors within the dorsal striatum (summarized in Table 13.1). An additional level of complexity arises from the ability of ethanol to affect nonclassical modulatory neurotransmitters. eCBs, briefly mentioned earlier, are lipid-derived neurotransmitters that act as retrograde signals to decrease the probability of neurotransmitter release (Gerdeman et al. 2002). Due to the widespread expression of CB1 receptors in the brain, eCBs play an important modulatory role in a variety of circuits and related behaviors. eCB-mediated LTD in the dorsal striatum occurs at GABAergic as well as glutamatergic synapses onto medium spiny neurons (MSNs) (Adermark et al. 2009; Gerdeman et al. 2002; Mathur et al. 2013). CB1 is heavily

Table 13.1 Physiological effects of acute ethanol on the dorsal striatum

Brain region	Synapse/cell type	Ethanol concentration	Effect	References
Dorsal striatum	Corticostriatal synapse	10, 50 mM	No effect on EPSC amplitude	Choi et al. 2006
Dorsal striatum	Corticostriatal synapse	100 mM	Decreases mEPSC amplitude	Choi et al. 2006
Dorsal striatum	Corticostriatal synapse	100, 200 mM	Dose dependently decreases EPSC amplitude	Choi et al. 2006
DMS	Corticostriatal synapse	40, 50, 100 mM	Decreases NMDAR-mediated EPSC and EPSP amplitudes	Wang et al. 2007; Wang et al. 2010; Blomeley et al. 2011
DMS	Excitatory synapse	2–88 mM	Dose dependently inhibits LTP expression	Yin et al. 2007; Xie et al. 2009
DMS	Excitatory synapse	50 mM	HFS-induced LTP reversed to LTD	Yin et al. 2007
DLS	Excitatory synapses	50 mM	Decreases DLS output in juveniles	Adermark et al. 2011a
DLS	Excitatory synapses	50 mM	Increases DLS output in adults	Adermark et al. 2011a
DLS	Excitatory synapses	20, 80, 100 mM	No effect on DLS output	Adermark et al. 2011a
DLS	Inhibitory synapses	20, 50 mM	Dose dependently eliminates disinhibition of DLS	Clarke and Adermark 2010
DLS	Cholinergic interneuron	50 mM	Decreases firing rate	Blomeley et al. 2011
DLS	Low-threshold spiking interneurons	50 mM	Hyperpolarizes membrane; decreases firing rate	Blomeley et al. 2011
DLS	Fast-spiking interneurons	50 mM	Depolarizes membrane; induces bursts of action potentials	Blomeley et al. 2011
DLS	Medium spiny neurons	50 mM	Hyperpolarizes membrane; decreases input resistance	Blomeley et al. 2011
DLS	Inhibitory synapses	50 mM	Decreases IPSC amplitudes	Blomeley et al. 2011
DLS	MSN-MSN; FSI-MSN	10, 50, 80 mM	Decreases IPSC amplitudes	Patton et al. 2016

EPSC excitatory postsynaptic current, *mEPSC* miniature excitatory postsynaptic current, *DMS* dorsomedial striatum, *NMDAR* N-methyl D-aspartate receptor, *EPSP* excitatory postsynaptic potential, *LTP* long-term potentiation, *HFS* high-frequency stimulation, *LTD* long-term depression, *DLS* dorsolateral striatum, *IPSC* inhibitory postsynaptic current, *MSN* medium spiny neuron, *FSI* fast-spiking interneuron

expressed in the striatum and, thus, eCBs are positioned to strongly influence striatal output (Atwood et al. 2014; Lovinger and Mathur 2012). Release of eCBs is regulated by neuronal activity and the amount of activity required for LTD at excitatory synapses is greater than that required for LTD at inhibitory synapses (Adermark and Lovinger 2007b; Adermark et al. 2009; Uchigashima et al. 2007). As such, a low-frequency stimulation protocol induces LTD at inhibitory synapses, rather than the high-frequency induction necessary for LTD at excitatory synapses, and consequently increases PS amplitude leading to long-lasting disinhibition (DLL) of striatal output (Adermark et al. 2009). Clarke and Adermark (2010) investigated the effects of acute ethanol on DLL of striatal output. DLL was induced by low-/moderate-frequency stimulation. To ensure the observed effect was due to DLL and not LTP at excitatory synapses, slices were treated with an NMDAR antagonist, AP-5. In slices pretreated with ethanol for 20 min and maintained in ethanol during field recordings, DLL is completely blocked. This lack of DLL in ethanol-treated slices is due to changes at the presynaptic level, downstream of eCB mobilization and release. Synapse specificity of this phenomenon was confirmed by analyzing the effect of ethanol on evoked EPSCs and inhibitory postsynaptic currents (IPSCs) in MSNs. A stimulation protocol was used to elicit eCB-signaling and induce a depression of EPSC amplitude. The same protocol induced a robust depression of IPSC amplitude at inhibitory synapses. Ethanol reduces the extent of this depression of IPSC amplitude but has no enhancing effect on the stimulation-induced depression of EPSC amplitude (see Table 13.1). Consistent with this observation, field potential recordings show that ethanol does not enhance HFS-LTD (Clarke and Adermark 2010). Ethanol exposure enhances eCB-signaling in other brain regions such as the hippocampus (Basavarajappa et al. 2008) and basolateral amygdala (Perra et al. 2008). If ethanol had this effect in the dorsal striatum, one would expect a depression of baseline synaptic transmission at eCB-sensitive inhibitory synapses with a net enhancement of PS amplitude. However, PS amplitude is only moderately reduced after acute ethanol exposure, and this reduction is not prevented by CB1-antagonist treatment. Thus, ethanol-mediated changes in baseline striatal output cannot be explained by changes in eCB-signaling (Clarke and Adermark 2010).

13.3 Effects of Chronic Ethanol on Dorsal Striatum Physiology

Alcoholism is characterized by excessive levels of drinking and increased vulnerability to relapse (Edwards and Gross 1976). Over the years, the development of rodent models that model these characteristic features were hindered by a lack of ethanol self-administration in rats in quantities large enough to attain blood alcohol levels that cause intoxication (Becker and Ron 2014). Therefore, better models were developed that accurately model the disease. These models include selective

breeding for high alcohol preference, schedule-induced polydipsia, and variations in schedules for ethanol exposure with periods of deprivation or intermittent ethanol access and have been reviewed in detail by Becker (2013) and by several others (Barkley-Levenson and Crabbe 2014; Becker and Ron 2014; Bell et al. 2014; Carnicella et al. 2014; Colombo et al. 2014; Ford 2014; Griffin 2014; Hopf and Lesscher 2014; Lopez and Becker 2014; McBride et al. 2014; Thiele and Navarro 2014; Vendruscolo and Roberts 2014; Vengeliene et al. 2014). Voluntary consumption of ethanol in rodents is achieved by initiation procedures such as water/food deprivation or sucrose fading (Samson and Pfeffer 1987). However, ethanol intake is then dependent on the presence of these initiation factors and is reduced if these are removed (Becker and Ron 2014); besides, these initiation factors may have unwanted neurobiological effects of their own. Another approach involves providing unlimited access to ethanol, in some cases along with an alternative liquid, usually water. Procedures with intermittent access to ethanol were developed several decades ago (Wayner et al. 1972; Wise 1973). These investigators demonstrated that alternating periods of alcohol access with periods of withdrawal over weeks led to an increase in ethanol consumption and preference to the extent that levels of blood ethanol concentration (BEC) achieved were higher than those reached with continuous access. This approach has received due attention in the last decade because it simulates various aspects of alcohol addiction such as binge-drinking, alcohol seeking and relapse, and relevant neuroadaptations that foster these behaviors (Carnicella et al. 2014).

As with rodent studies, various ethanol administration regimens and dosing schedules have been explored in non-human primates to induce alcohol self-administration (see Barr and Goldman 2006). The genetic, neuroanatomical, and social similarities with humans emphasize the importance of non-human primate models for studying alcohol dependence. As is evident from literature focusing on various brain regions, the most extensively studied effects of chronic ethanol exposure are on the glutamatergic and GABAergic systems. Cuzon Carlson et al. (2011) conducted a 3-year longitudinal study to investigate these effects in the primate caudate and putamen using a model of prolonged ethanol drinking interspersed with abstinence periods. Monkeys were induced to drink water followed by increasing doses of ethanol using a schedule-induced polydipsia procedure based on previous reports (Grant et al. 2008; Vivian et al. 2001) and then maintained on an ethanol self-administration protocol for 14 months. They were then given an additional 16 months (divided into three 4–6 month phases) of the same (free access to ethanol) with three 28-day periods of abstinence after each phase. This procedure led to progressive increases in BECs with average values of approximately 100, 125, and 150 mg/dL during the three phases of ethanol consumption. The overall pattern of ethanol drinking observed with this procedure resembles that seen with human alcohol dependence. Cuzon Carlson and colleagues (2011) found that while a history of ethanol drinking has no effect on spine density in the caudate (or DMS), it increases spine density in the putamen/DLS. Whole-cell recordings showed an increase in the frequency of glutamatergic mEPSCs in putamen MSNs of ethanol

drinkers with no changes in mEPSC amplitude, area or rise, and decay times. This suggests that a presynaptic change rather than a postsynaptic one occurs. The increase in mEPSC frequency may be explained by an increase in the number of glutamatergic synapses (as indicated by increased spine density) or by increased glutamate release probability. By contrast, the frequency of GABAergic miniature IPSCs (mIPSCs) onto MSNs is decreased in the putamen of ethanol-drinkers, suggesting a reduction in the number of synapses or in GABA release probability. Interestingly, the frequency correlates inversely with BECs during the last ethanol-drinking phase. Further, the amplitude and area of the mIPSCs are also decreased implying a potential postsynaptic effect in addition to the presynaptic effect. However, rise and decay times of mIPSCs do not differ between controls and ethanol drinkers eliminating the possibility of a change in receptor subunit composition, which would alter kinetics.

As ethanol can alter MSN intrinsic excitability, MSN membrane properties were also analyzed. MSNs from the putamen of ethanol-exposed monkeys have a small but significant reduction in input resistance; more depolarized resting membrane potentials and, thus, decreased action potential thresholds making these cells more excitable. Altogether, this noteworthy study showed that this long-term intermittent alcohol exposure decreases GABAergic transmission, increases glutamatergic transmission and increases intrinsic excitability of MSNs in the primate putamen, leading to an overall activated DLS (Cuzon Carlson et al. 2011).

A more recent study that addressed similar questions related to chronic ethanol effects on the dorsal striatum was conducted by Wilcox and colleagues (2014) using a chronic intermittent drinking paradigm in mice. In 2005, Rhodes et al. (2005) developed an intermittent ethanol self-administration for mice protocol called "drinking in the dark" (DID). This protocol induces binge-like drinking and generates pharmacologically relevant BECs (>80 mg/dL) (Rhodes et al. 2005, 2007). Wilcox et al. (2014) employed a similar paradigm involving repeated episodes of DID over 6 weeks with a weekly schedule of 2–4 h sessions of ethanol access for the first 4 days followed by 3 days of abstinence. Striatal synaptic physiology was studied at least 48 h after the last DID session. The DID protocol does not affect spontaneous glutamatergic transmission in the DLS or DMS. Further, it does not alter spine density in the MSNs of the DLS. GABAergic transmission is reduced in the DLS and DMS as indicated by a decrease in mIPSC frequency. Wilcox et al. (2014) report no significant correlation between mIPSC frequencies and mean BECs for each mouse; however, there is a trend for a positive correlation in the DLS. In other words, MSNs from animals with higher blood ethanol concentrations display frequencies closer to values for MSNs from water-drinking controls, a possible sign of compensatory adaptations that may occur at higher BECs. The amplitude, area, and kinetics of mIPSCs remain unchanged. Wilcox et al. (2014) also tested the effects of acute ethanol exposure to striatal slices from ethanol-drinkers and water-drinking controls. Acute application of ethanol to control striatal slices decreases mIPSC frequency in the DLS while increasing it in the DMS. This frequency enhancing effect of ethanol in the DMS is similar to that seen in other brain regions

such as ventral tegmental area (Melis et al. 2002), central nucleus of amygdala (Roberto et al. 2003), cerebellum (Carta et al. 2004), and hippocampal CA1 region (Li et al. 2006) among others (see Kelm et al. 2011). Interestingly, in animals that have a history of ethanol drinking, the effect of acute ethanol on mIPSCs is absent in the DLS and reversed in the DMS, where instead of an increase in mIPSC frequency, a significant decrease is noted (Wilcox et al. 2014).

The observations from the rodent study (Wilcox et al. 2014) for GABAergic transmission are consistent with those seen in the primate study (Cuzon Carlson et al. 2011). However, there is an inconsistency in observations for glutamatergic transmission. This can possibly be explained by various differences in the study designs, starting with the species itself. A key difference may lie in the ethanol concentration achieved or the time period over which the animals were exposed to ethanol. Nonetheless, both studies provide evidence suggesting that ethanol drinking enhances striatal output, particularly of the lateral subdivision.

As mentioned earlier, eCB-mediated synaptic plasticity is the predominant form of plasticity within the striatum. Acute ethanol exposure disrupts eCB-mediated plasticity at inhibitory synapses and prevents DLL of striatal output (Clarke and Adermark 2010). The effect of CIE treatment on eCB-mediated DLL was also tested in rats that voluntarily consumed ethanol (Adermark et al. 2011b). *Ex vivo* field recordings in striatal slices from CIE-exposed rats showed that similar to acute ethanol, CIE consumption impairs DLL of striatal output. A potential explanation for the lack of DLL could be elevated cholinergic activity, which can inhibit eCB-signaling (Partridge et al. 2002) and can reduce the opening of L-type Ca^{2+} channels that are required for LTD (Adermark and Lovinger 2007a; Wang et al. 2006). However, inhibition of muscarinic receptors does not rescue DLL. Another possible cause for the loss of DLL could be reduced $GABA_A$ receptor tonic activation in ethanol-treated animals. With lower GABAergic tone, eCB-LTD at the inhibitory synapse would not be sufficient to cause a net disinhibitory effect on striatal output. However, in addition to blocking DLL, CIE exposure impairs eCB-dependent LTD induced by HFS; although, with the caveat that this LTD is also impaired in isolated controls. This form of stimulation affects not only inhibitory but also excitatory synapses to induce overall depression of striatal output. Pharmacological manipulation with a CB1 agonist revealed that CIE leads to inhibition of eCB signaling downstream from CB1 activation (Adermark et al. 2011b). Therefore, both acute and chronic exposure to ethanol disrupts eCB-signaling in the DLS, which may impair DLL (Adermark et al. 2011b; Clarke and Adermark 2010).

It is likely that ethanol modulates circuitry by inducing structural changes in neurons over time. The potential effect of chronic ethanol on DLS neuronal morphology was investigated in mice using a chronic intermittent ethanol exposure (CIE) paradigm; where unlike voluntary consumption in DID, animals were passively exposed to ethanol vapor (DePoy et al. 2013). This paradigm induces a significant increase in overall amount of dendritic material in DLS neurons as compared to air exposure, with an increase in number and length of terminal dendritic branches. This dendritic remodeling is limited to neurons in the DLS and not

observed in several other brain regions that were studied including cortical and limbic regions. In addition to the structural changes, ethanol exposure also induces substantial functional changes in the DLS. As alluded to earlier, activity of MSNs within the dorsal striatum is largely governed by converging cortical inputs that are glutamatergic. Plasticity changes at this corticostriatal synapse heavily influence basal ganglia output controlling motor activity and skill learning. As previously mentioned, delivery of HFS to this synapse induces LTD of excitatory neurotransmission in the DLS (Calabresi et al. 1992a; Lovinger et al. 1993). This phenomenon is mediated by dopamine D2 receptor activation, which enhances release of eCBs. Released eCBs act as retrograde signals and activate presynaptic CB1 receptors, suppressing glutamate release, hence inducing striatal LTD (Gerdeman et al. 2002). Adermark and colleagues (2011b) showed that CIE impairs HFS-induced, eCB-mediated LTD in rats. DePoy et al. (2013) investigated the effects of CIE on this HFS-induced LTD in mice. They also demonstrated that CIE prevents induction of LTD in the DLS. A follow-up study showed that a more prolonged ethanol exposure of 16-bouts, as compared to 8-bouts in the current study, has the same effect (DePoy et al. 2015). This loss of LTD in the DLS of CIE-exposed mice is explained by a reduction in CB1 functional binding. This down-regulation of CB1 may also explain the dendritic hypertrophy, an effect that has been reported previously (Hill et al. 2011). Further analysis revealed that CIE exposure increases DLS levels of 2-arachidonoylglycerol, an eCB that binds to CB1. It is suggested that this increase in 2-arachidonoylglycerol results in a compensatory down-regulation of CB1-signaling, ultimately accounting for loss of corticostriatal LTD (DePoy et al. 2013).

The glutamate receptor, NMDAR, has been extensively studied in the context of synaptic plasticity and has been implicated as a major target that mediates the adverse effects of ethanol (Lovinger et al. 1989; Ron and Wang 2009). As described earlier, Wang et al. (2007) reported acute effects of ethanol on the activity of NR2B-containing NMDA receptors in the dorsal striatum. They also tested the effects of repeated ethanol administration on these receptors (Wang et al. 2010). Rats were administered ethanol (2 g/kg, i.p.) systemically for 7 or 14 days and NMDA activity was measured 16 or 40 h post the last injection. Whole-cell recordings from the DMS revealed that repeated administration of ethanol increases NMDA-induced currents and synaptic NMDA-EPSCs. Similar to the acute effects, the underlying mechanism involved phosphorylation of NR2B by activation of Fyn. This leads to increased forward trafficking of the NR2B-NMDARs to the synaptic membrane and increased function of the NR2B-NMDARs in the DMS of animals treated repeatedly with ethanol. Similar electrophysiological and biochemical changes were seen in rats that have intermittent access to high levels of ethanol. Interestingly, NMDAR activity as measured by amplitude of NMDA-mediated currents and of NMDAR-EPSCs in the DMS is also increased after 1–9 days of withdrawal from excessive ethanol intake (Wang et al. 2010). Further, increased NMDAR activity in response to acute ethanol and repeated systemic administration leads to NR2B-NMDAR-dependent facilitation of LTP of AMPA-mediated synaptic responses in the

DMS. Ethanol facilitates LTP by inducing a long-lasting increase in synaptic localization of AMPA receptors containing GluR1 and GluR2 subunits in the DMS (Wang et al. 2012).

Collectively, acute and chronic studies show that ethanol causes long-lasting changes in striatal synaptic output. Various ethanol-mediated changes are reported in both dorsal and ventral striatum. Adermark et al. (2013) investigated the time points at which these striatal region-specific ethanol effects occur over long-term consumption. These investigators carried out a 10-month study to assess effects of voluntary ethanol consumption on DLS and nucleus accumbens shell plasticity in rats. Singly housed animals had continuous access to two bottles, one that contained water and the other, 6 % ethanol. Field potential recordings were carried out after 2, 4, and 10 months of continuous access to ethanol. The half-maximal striatal PS amplitude is significantly depressed at the 2-month time point. Striatal output, measured by plotting PS amplitude as a function of stimulation strength, is also reduced at the 4- and 10-month time points. Interestingly, this effect of ethanol observed at all three time points is seen only in the DLS and not in the nucleus accumbens. The $GABA_A$ receptor antagonist, bicuculline, disinhibits striatal output. Slices from rats that have consumed ethanol for 2 months display a slower progression of bicuculline-mediated disinhibition in the dorsal striatum as compared to slices from water-drinking controls. Further, bicuculline-induced disinhibition is reduced in the dorsal striatum at the 4-month time point as well as in the ventral striatum at the 2-month time point, suggesting that ethanol has already disinhibited the striatal complex. Pharmacological manipulation showed that glycinergic transmission is well preserved in both dorsal and ventral striatum in these animals. The results of this study highlight that consumption of relatively low levels of ethanol can alter synaptic output of the DLS within 2 months and also emphasize the regional differences of ethanol effects (Adermark et al. 2013).

Collectively, the results for the effect of chronic ethanol treatment on the DMS are somewhat mixed. Wilcox et al. (2014) report no change in glutamatergic transmission in this striatal subregion, whereas Wang et al. (2010, 2012) demonstrate that repeated ethanol exposure enhances NMDAR-activity (specifically NR2B-containing receptors). It should be noted, however, that the Wilcox et al. (2014) study did not assay NMDA-mediated currents per se, but rather (largely) AMPA-mediated mEPSCs. On the inhibitory side, GABAergic transmission within the DMS is reduced (Wilcox et al. 2014) (see Table 13.2). In the DLS, CIE treatment increases glutamatergic transmission (Cuzon Carlson et al. 2011), decreases GABAergic transmission (Cuzon Carlson et al. 2011; Wilcox et al. 2014) and impairs eCB-mediated LTD (Adermark et al. 2011b; DePoy et al. 2013). It may then be considered that ethanol has an overall activating effect in the striatum, with a relative preference for activation of the DLS versus the DMS (see Table 13.2 and Fig. 13.1). In the next section, the specific behaviors attributed to the DMS and DLS are covered with regard to both healthy and alcohol exposed states. Finally, the behavioral effects of ethanol are considered in light of the aforementioned physiological findings.

Table 13.2 Physiological effects of chronic ethanol exposure on the dorsal striatum

Brain region	Synapse/cell type	Ethanol administration protocol	Effect	References
Caudate (DMS)	Medium spiny neuron	CIE: oral self-administration (3 years)	No change in spine density	Cuzon Carlson et al. 2011
Putamen (DLS)	Medium spiny neuron	CIE: oral self-administration (3 years)	Increases spine density; increases intrinsic excitability	Cuzon Carlson et al. 2011
Putamen (DLS)	Excitatory Synapses	CIE: oral self-administration (3 years)	Increases mEPSC frequency	Cuzon Carlson et al. 2011
Putamen (DLS)	Inhibitory synapses	CIE: oral self-administration (3 years)	Decreases mIPSC frequency, amplitude and area	Cuzon Carlson et al. 2011
DMS	Excitatory synapses	Drinking in the dark (6 weeks)	No change in spontaneous EPSCs	Wilcox et al. 2014
DMS	Inhibitory synapses	Drinking in the dark (6 weeks)	Decreases mIPSC frequency	Wilcox et al. 2014
DLS	Medium spiny neuron	Drinking in the dark (6 weeks)	No change in spine density	Wilcox et al. 2014
DLS	Excitatory synapses	Drinking in the dark (6 weeks)	No effect	Wilcox et al. 2014
DLS	Inhibitory synapses	Drinking in the dark (6 weeks)	Decreases mIPSC frequency	Wilcox et al. 2014
DLS	Medium spiny neuron	CIE: vapor (2 or 4 weeks)	Increases number and length of dendritic branches	DePoy et al. 2013; DePoy et al. 2015
DLS	Corticostriatal synapse	CIE: vapor (2 or 4 weeks)	Eliminates LTD	DePoy et al. 2013; DePoy et al. 2015
DLS	Excitatory synapses	CIE: oral self-administration (7 weeks)	Eliminates LTD	Adermark et al. 2011b
DLS	Inhibitory synapses	CIE: oral self-administration (7 weeks)	Eliminates disinhibition of DLS	Adermark et al. 2011b
DMS	Excitatory synapses	Systemic administration (7 or 14 days)	Increases NMDAR-mediated EPSCs; facilitates LTP	Wang et al. 2010; Wang et al. 2012

DMS dorsomedial striatum, *CIE* chronic intermittent exposure, *DLS* dorsolateral striatum, *mEPSC* miniature excitatory postsynaptic current, *mIPSC* miniature inhibitory postsynaptic current, *EPSC* excitatory postsynaptic current, *LTD* long-term depression, *NMDAR* N-methyl D-aspartate receptor, *LTP* long-term potentiation

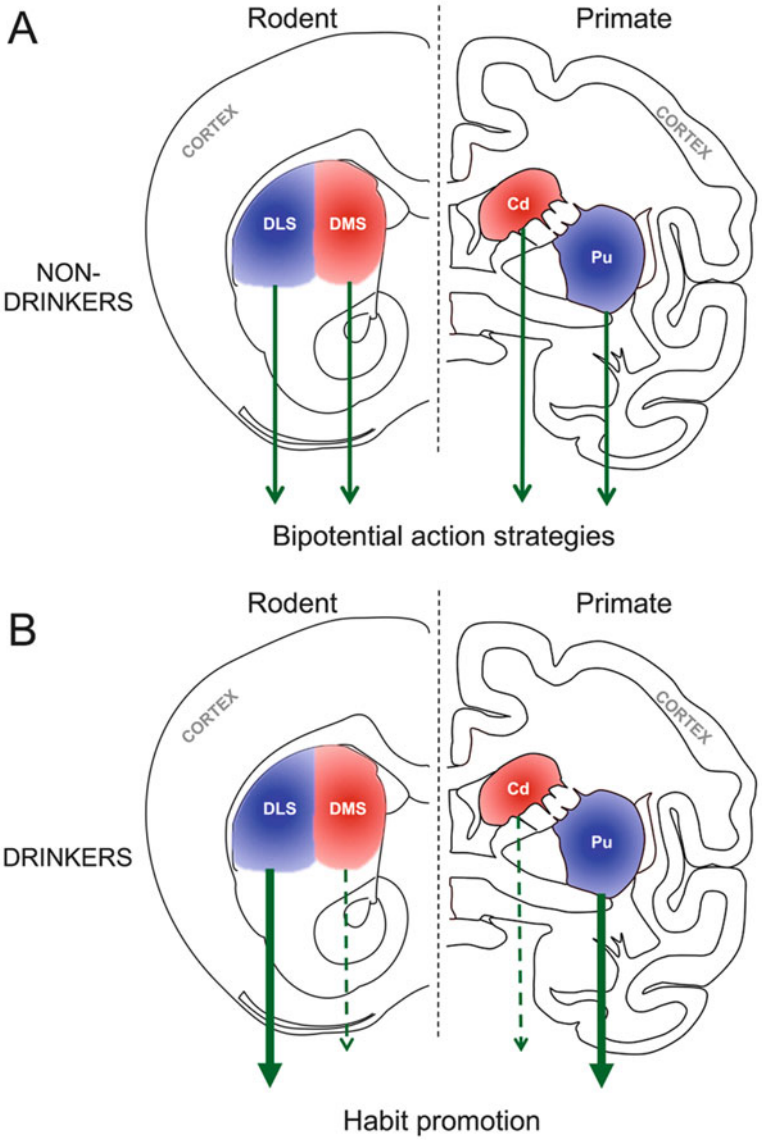

Fig. 13.1 Effect of repeated ethanol consumption on dorsal striatum-mediated behaviors in rodents and primates. (**a**) In alcohol naive animals (non-drinkers) both subregions of the dorsal striatum process information concurrently, allowing for the execution of bipotential behavioral strategies. (**b**) In alcohol drinkers, DLS/Pu output is disinhibited relative to the DMS/Cd, promoting a habitual action strategy. *DLS* Dorsolateral striatum, *DMS* Dorsomedial striatum, *Cd* Caudate, *Pu* Putamen

13.4 Effects of Ethanol on Striatal-Mediated Behaviors

Distinct learning systems exist in the human brain (Packard et al. 1989; Packard and McGaugh 1992); declarative and procedural learning. Declarative learning encompasses explicit knowledge gained from learning, or "text-book knowledge." In declarative learning, facts can be explicitly stated, while procedural learning is action based, and therefore unable to be verbally declared. Studies of amnesic and Parkinson's patients, conditions with damage in differing brain regions, demonstrate that separate brain structures mediate declarative and procedural learning. Parkinsonian individuals, with nigrostriatal degeneration, are unable to acquire a procedural-learning task, but perform a declarative memory task well, unlike amnesic patients with damage to the hippocampus (Knowlton et al. 1996). These findings implicate the basal ganglia in action-based learning strategies.

The dorsal striatum, specifically, is central to procedural learning. This form of learning encompasses two different behavioral strategies: habitual and goal-directed learning (Dickinson et al. 2002; Packard et al. 1989; Packard and McGaugh 1992). Procedural learning is initially guided by action-outcome contingencies. Stated differently, the outcome following a certain action dictates the amount of learning that occurs. In contrast, habits are defined as repetitive actions that persist in the face of reward devaluation. Unlike goal-directed behaviors, habits require little conscious thought, freeing up valuable cognitive resources for novel circumstances that may require attention while executing a habitual action (Adams 1982; Gasbarri et al. 2014). Habits can be beneficial. For instance, driving the same route to work each day allows the driver to pay attention to unexpected hazards that may arise, instead of consciously deciding which road to take at each turn. Occasions in which habits become awry, however, can lead to neuropsychiatric disorders such as addiction.

In a seminal study, Packard and McGaugh (1996) demonstrated that activity in the DLS, specifically, is necessary for habitual responses using a T-maze paradigm. While it was understood the dorsal striatum is involved in action selection (Knowlton et al. 1996), the exact role was unknown until this time. In the T-maze, animals are trained to make a turn at the end of a runway to obtain a reward. Animals may use extra-maze cues to employ a spatial learning strategy or behavioral responses from previous trials to get rewarded. Following training, animals are probed to see which behavioral response strategy is being employed. When tested early in training, animals preferentially employ place strategy, a response mediated largely by the hippocampus, and probing on a later day shows animals respond in a habitual manner. DLS inactivation abolishes the use of habitual responses and promotes the use of place strategies, indicating that a functional DLS is necessary for a habitual response (Packard and McGaugh 1996). Habit learning can be shifted in multiple directions when manipulating the DLS: inactivating the region diminishes habit formation, but activating it promotes response learning (Packard 1999). Glutamatergic activation of the DLS promotes response learning at an earlier time point than controls on the T-maze, indicating activity in the DLS bidirectionally controls habit formation.

Further, neural activity of principal MSNs in the DLS is correlated with speed and accuracy of running a T-maze (Barnes et al. 2005). During the initial learning of the T-maze, overall neural activity is high in the DLS and not synchronized to specific events, as if all parts of the task are salient. As training progresses, MSN activity redistributes to occur at the beginning and end of the maze runs. Additionally, when behavior is extinguished on the maze, striatal neurons increase firing to the same degree as when the animal first learned the task.

While the dorsolateral striatum (DLS) is involved in habit learning, the dorsomedial striatum (DMS) appears to mediate goal-directed learning (Quinn et al. 2013; Yin et al. 2004, 2005) (For further discussions on the role of the DSL and DSM in learning, the reader is also referred to Chaps. 11 and 18 in this volume). With sufficient repetition, a goal-directed behavior eventually shifts to form a habit, but learning occurs simultaneously in both systems (Dezfouli and Balleine 2012; Hart et al. 2014). Thus, during the initial acquisition of a task, both dorsal striatal subdivisions are believed to process actions in parallel, despite behavior being predominantly goal directed. In an elegant study, Yin and colleagues (Yin and Knowlton 2004) demonstrated that both action strategies are encoded simultaneously in rats. In the task, rats are overtrained to press a lever for a reward. In order to probe what type of response strategy is being used, the reward is devalued and the resulting behavior is used to infer the strategy: goal-directed animals will stop responding for a devalued reward, but habitual animals will not. Animals trained on this task received DMS or DLS lesions, and following the lesions rewards were devalued and the behavioral strategy was assessed. Animals with DMS lesions continue to respond for the devalued reward, indicating a habit response, while DLS lesions stopped responding for the reward, despite overtraining (Yin and Knowlton 2004). These results give insight into the functional separation between subregions of the dorsal striatum and underscore the belief that the transition from a goal-directed to a habit strategy occurs on a continuum. The transfer between goal-directed and habitual behaviors relies on other brain regions such as the prefrontal cortex or orbitofrontal cortex to execute the shift (Coutureau and Killcross 2003; Gremel and Costa 2013; Killcross and Coutureau 2003). Importantly, the transition from goal directed to habit can be expedited by drugs of abuse like alcohol (Corbit et al. 2012; Dickinson et al. 2002; Lesscher et al. 2010).

Alcohol and other drugs of abuse slide behavioral responses on the continuum toward habitual responses, a mechanism that likely contributes to the addictive nature of these substances. When trained to lever press for food pellets or ethanol in an instrumental conditioning task, rats respond less frequently for devalued food pellets but continue to respond for the devalued ethanol (Dickinson et al. 2002). These findings indicate that the animals form a habit for alcohol consumption before forming a habit for food. Corbit and coworkers (2012) similarly demonstrate that ethanol intake promotes habit formation by training rats to press for ethanol or sucrose and testing their response strategies at various time points during training. Animals stop responding for ethanol and sucrose with limited training (2 weeks) following devaluation of each substance. With continued training (4–8 weeks),

however, devaluing ethanol does not decrease responding, unlike devalued sucrose. These findings suggest that increased exposure to ethanol leads to habitual consumption of this substance. Animals that drink more are less sensitive to ethanol devaluation, further demonstrating that increased ethanol exposure promotes the shift to habit formation.

Repeated ethanol exposure also causes inflexible ethanol drinking behaviors. Inflexible consumption is measured by adding quinine, a bitter and aversive flavor to ethanol to create a conditioned taste aversion. Control animals are initially sensitive to the bitter taste of quinine and will stop its consumption (Fachin-Scheit et al. 2006; Lesscher et al. 2010; Whitney and Harder 1994). However, when mice are given a two-bottle choice test between ethanol-only and ethanol plus quinine, animals that had access to ethanol for 8 weeks prior no longer preferentially choose the ethanol-only bottle, rather they do not discriminate at all (Lesscher et al. 2010). This finding suggests that greater ethanol exposure leads to an increase in habitual ethanol consumption, despite the addition of an aversive substance. Additionally, adding quinine to ethanol does not decrease overall ethanol consumption and this indifferent drinking behavior occurs even after 2 weeks of ethanol exposure (Lesscher et al. 2010).

Studies in human patients with alcohol dependence report similar findings as rodent studies. For example, heavy drinkers show an increase in dorsal striatal activation using functional magnetic resonance imaging (fMRI) following alcohol cue-induced activity as compared to light drinkers (Vollstadt-Klein et al. 2010). Additionally, activity decreases in the ventral striatum as drinking becomes compulsive; supporting the hypothesis that activity shifts in a ventro-dorsal manner in the striatum during the progression of addiction (Vollstadt-Klein et al. 2010). Importantly, an overreliance on habitual responding is also seen in alcoholics. Sjoerds and colleagues (2013) demonstrated an altered balance of activity between goal-directed and habit regions using fMRI scans in alcohol-dependent participants. Specifically, they show that recruitment of the ventromedial prefrontal cortex and anterior putamen, brain regions commonly associated with goal-directed learning, is decreased while increased engagement of habit centers such as the posterior putamen during an instrumental learning task is observed (Sjoerds et al. 2013).

The shift from goal-directed to habitual actions is also associated with a shift in activity of the principal MSNs of the dorsal striatum in rodents. Electrophysiological single unit recordings of activity from MSNs in the DMS and DLS during various training schedules for ethanol self-administration in rats reveals DMS firing is time-locked to the delivery of ethanol while DLS activity remains elevated throughout the task (Fanelli et al. 2013). Thus, activity in the DMS is associated with goal-directed behaviors; increased firing rate is time-locked with the presentation of the lever associated with ethanol reward. The lack of time-locked neural activity in the DLS during instrumental conditioning denotes the importance of this region for stimulus–response actions, as habitual behaviors are not strongly associated with outcomes.

Manipulations to various molecular and transmitter systems in the dorsal striatum provide some insight into the necessary components underlying alcohol's ability to shift goal-directed behaviors to habitual actions. For example, AMPA and dopamine D2 receptors in the DLS are necessary for increased self-administration of ethanol in rodents (Corbit et al. 2014). Following training on ethanol self-administration, inhibiting AMPA or D2 receptors in the DLS at the time of ethanol devaluation shifts behavior to be goal directed in a paradigm that normally produces habitual behavior. This finding indicates that excitatory inputs from the cortex or thalamus, as well as dopaminergic inputs from the substantia nigra pars compacta are necessary for compulsive ethanol responding. These data are further supported by previous work demonstrating a lack of habitual responses in a Parkinson's disease model in which dopaminergic projections from the substantia nigra to the dorsal striatum are compromised (Faure et al. 2005; Knowlton et al. 1996).

These studies provide evidence that glutamatergic and dopaminergic signaling is important for habitual ethanol consumption, but it is not the complete picture. Pharmacologically blocking adenosine adenosine 2A receptors in the DMS increases ethanol consumption compared to controls (Nam et al. 2013). Furthermore, knocking out the equilibrative nucleoside adenosine transporter in mice also causes a compulsive ethanol drinking phenotype, suggesting that adenosine signaling may be important for promoting goal-directed ethanol consumption, which is an important early step in habit formation (Nam et al. 2013). While those effects are specific to the subregions of the dorsal striatum, pharmacological blockade of delta opioid receptor signaling in the entire dorsal striatum decreases ethanol consumption even after 6 weeks of ethanol exposure in rodents (Nielsen et al. 2012). Furthermore, injecting an agonist to the delta opioid receptor increases ethanol consumption in these animals. Finally, blocking the delta opioid receptor in the dorsal striatum before chronic exposure to ethanol prevents high ethanol consumption, providing strong support for this receptor's role in ethanol self-administration (Nielsen et al. 2012). In addition to the various receptors that are shown to be necessary for ethanol consumption, self-administration of ethanol increases levels of the modulatory neurotransmitter brain-derived neurotrophic factor (BDNF) in the DLS but not in the DMS (Jeanblanc et al. 2009). Decreasing BDNF levels in the DLS using siRNA decreases ethanol but not sucrose consumption (Jeanblanc et al. 2009). Taken as a whole, these studies suggest a multitude of transmitter and molecular systems are in play to promote the habitualization of ethanol consumption.

13.5 Conclusions

The studies described here show ethanol exerts a wide range of physiological and molecular effects in a concentration and cell-type specific manner in the dorsal striatum. These effects collectively support the hypothesis that ethanol acts to shift

striatal activity in favor of the lateral subdivision to promote a shift to habit formation. Acute ethanol wash in the DMS disrupts synaptic plasticity onto principal MSNs, particularly at glutamatergic synapses (Wang et al. 2010; Xie et al. 2009; Yin et al. 2007). Depressing these inputs onto MSNs decreases the relative excitation of these cells and decreases their overall output. Thus, it can be concluded that ethanol decreases DMS drive.

The effects of acute ethanol wash in the DMS are quite different from those in the DLS. Ethanol incubation eliminates disinhibition of the DLS that is known to occur through CB1 activation, suggesting that disinhibition has occurred secondary to ethanol exposure (Clarke and Adermark 2010). Further, this study demonstrates that ethanol disinhibits the DLS by acting downstream of CB1 (Clarke and Adermark 2010). These results are important, as they begin to show a mechanism of action of ethanol-induced disinhibition. In accordance, other studies show that ethanol wash decreases inhibitory inputs onto MSNs in the DLS (Blomeley et al. 2011), providing further evidence that ethanol disinhibits the DLS. The diverse mechanisms of action that ethanol has in these two key brain regions point to the role ethanol plays on striatal-mediated behaviors: ethanol promotes the shift to habitual responses, and likely largely accomplishes this through MSN disinhibition.

While the previously reviewed studies demonstrate the importance of understanding the specific physiological effects of acute ethanol exposure in the dorsal striatum, it is additionally important to understand if *in vivo* ethanol consumption is capable of altering physiology in these subregions to promote habit formation. While ethanol has no effect on spontaneous excitatory events onto MSNs in the DMS (Wilcox et al. 2014), evoked currents mediated by NMDA are dampened (Wang et al. 2010, 2012). In future studies, it will be important to understand what the overall effect these changes have on DMS MSN output. Regardless, it is apparent that chronic ethanol exposure produces a host of diverse physiological changes in the DMS, with the specific outcome likely depending on the duration and pattern of exposure to particular concentrations of ethanol.

Taking the physiological and behavioral effects of ethanol on the dorsal striatum together, a picture is emerging that describes a role for ethanol in promoting habits through relative activation of the DSL over the DMS (Fig. 13.1). Multiple studies across species demonstrate ethanol exposure decreases inhibition onto MSNs in the DLS/putamen (Cuzon Carlson et al. 2011; Wilcox et al. 2014). Changes in dendritic morphology are also seen, indicating long-term ethanol exposure causes long lasting synaptic changes (Cuzon Carlson et al. 2011). Furthermore, ethanol increases putamen MSN drive, through synaptic and intrinsic excitability changes (Cuzon Carlson et al. 2011; Wilcox et al. 2014). The combined attenuation of inhibition onto DLS/putamen MSNs and enhanced excitation of these cells likely contributes to the behavioral effects of ethanol in the dorsal striatum (Fig. 13.1). Thus, ethanol-induced remodeling of dorsal striatal synaptic weights and excitability is positioned to promote the switch to a cognitively dampened behavioral strategy underlying compulsive alcohol drinking.

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Part IV
Motivation, Decision Making, Reinforcement and Addiction

Chapter 14
The Subthalamic Nucleus and Reward-Related Processes

Christelle Baunez

14.1 Introduction

After Bergman and colleagues had shown that lesioning the subthalamic nucleus (STN) could alleviate some parkinsonian signs in a monkey model of Parkinson's Disease (PD) (Bergman et al. 1990), Benazzouz and colleagues showed that in monkeys that were rendered hemiparkinsonian with the selective neurotoxin MPTP, unilateral High Frequency Stimulation (HFS) of the STN alleviated the muscular rigidity observed in the contralateral forelimb (Benazzouz et al. 1993). This pioneering work was actually at the origin of the idea of applying HFS, which had initially been used on the thalamus (Pollak et al. 1993), to the STN in PD patients. In the intact monkey, it was also shown that STN HFS could induce hyperkinetic movements similar to the hemiballism observed after STN lesions (Beurrier et al. 1997). In contrast to what was described after STN lesions, STN HFS did not seem to induce hyperkinetic movements in MPTP-treated monkeys when applied at a specific voltage. This also contrasted with the dyskinesia-inducing effects of L-DOPA (Benazzouz et al. 1996). Application of STN HFS in PD patients was first performed by the group of Benabid in Grenoble, France (Limousin et al. 1995) and is currently used worldwide with great success. However there are remaining questions regarding its mechanism of action, which are still under investigation in both human clinical populations and animal models (Gubellini et al. 2009). In 1997, while STN deep brain stimulation (DBS) was spreading as a strategy for motor treatment, we showed that STN lesions in rats could increase motivation for sweet food as a reward (Baunez and Robbins 1997) and clinical case reports describing hyperphagia or hypersexuality and mood exaltation in patients suffering from an

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infarct of the STN (Trillet et al. 1995; Absher et al. 2000; Barutca et al. 2003) supported the involvement of the STN in motivational processes.

Although PD is considered by some authors as a psychiatric disorder (Agid et al. 2003), little consideration was initially given to the possible non-motor side effects of DBS because the basal ganglia were mainly considered as motor structures. Investigating the non-motor effects resulting from STN inactivation highlighted its involvement in motivational processes. Many PD patients subjected to STN DBS exhibit apathy and a general lack of motivation. The apathetic state affects the quality of life of these patients (Martinez-Fernandez et al. 2016) and supports the hypothesis that the dopaminergic system or the STN itself is involved in the expression of motivational and emotional dysfunction. There is now evidence that the STN alone can contribute to the apathy developed by these patients (Le Jeune et al. 2009; Lhommee et al. 2012) and that STN DBS modulates motivation in patients (Sauleau et al. 2009). For a more detailed discussion of the role of dopamine and the STN in apathy in Parkinson's disease, the reader is referred to Chap. 16 in this volume. This chapter will discuss current data available regarding the role of STN in motivation.

14.2 Anatomy and Connectivity of the Subthalamic Nucleus: From a Motor Relay Structure to a Limbic Structure

In the rat brain, the STN is a small, dense, and vascularized nucleus localized between the zona incerta (ZI) dorsally, the cerebral peduncle ventrally, the lateral hypothalamus medially, and the substantia nigra caudally. Phylogenetically, the STN has evolved from an open to a closed structure from rodents to primates. In the rat, it is considered open, since its neuronal dendrites extend into the ZI, lateral hypothalamus, and cerebral peduncle (Afsharpour 1985a, b). In contrast, in the cat, monkey, and human, the dendrites are restricted to the STN. In the human and non-human primate, the STN is divided in three functional territories. The dorsolateral part is sensorimotor, the medioventral part is associative, while the most medial tip is the limbic territory. In the rodent, the boundaries of these functional territories are less obvious since the dendritic arborization of STN neurons spreads across the entire nucleus (Afsharpour 1985a; Groenewegen and Berendse 1990; Parent and Hazrati 1995; Joel and Weiner 1997; Hamani et al. 2004).

The rat STN contains 25,000 neurons in a 0.8 mm^3 volume. The size of the cell bodies ranges from 10×25 μm to 19×88 μm (Hammond and Yelnik 1983). These neurons are mostly glutamatergic, giving the STN the status of the sole excitatory structure of the basal ganglia. The existence of interneurons within the STN remains controversial. The presence of GABAergic neurons, possibly inhibitory interneurons, has been shown in the human STN (Levesque and Parent 2005). Electrophysiological studies highlight a wide variability in neuronal properties within the STN, suggesting there might be various types of neurons (Lardeux et al. 2009; Breysse et al. 2015).

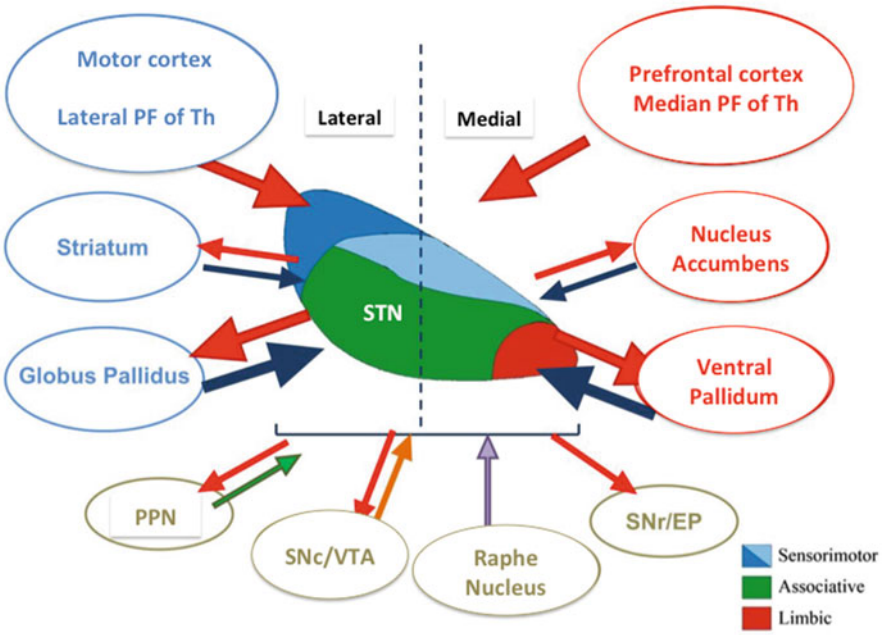

Fig 14.1 Schematic representation of the various inputs and outputs of the subthalamic nucleus with regard to its medial/lateral subterritories. The *arrows* represent projections from one structure to another. The *color* indicates the nature of the neurotransmitter involved: *blue* for GABA (inhibitory), *red* for glutamate (excitatory). As illustrated here, the STN is well positioned to integrate prefrontal, incentives, action, and habit information. *EP* entopeduncular nucleus (equivalent of the GPi: internal segment of the Globus Pallidus), *GPe* external segment of the Globus Pallidus, *PF of Th* Parafascicular nucleus of the thalamus, *PPN* pedunculopontine nucleus, *STN* subthalamic nucleus, *SNc* substantia nigra pars compacta, *SNr* Substantia nigra pars reticulata, *VTA* ventral tegmental area

14.2.1 Inputs to the STN

The STN receives glutamatergic inputs from various cortical territories (motor cortex to the lateral STN, prefrontal cortex to the medial STN) and the parafascicular nucleus of the thalamus (Fig. 14.1). It also receives GABAergic inputs from the globus pallidus (GP) and the ventral pallidum; dopaminergic inputs from the substantia nigra, pars compacta (SNc), and the ventral tegmental area (VTA); cholinergic inputs from the pedunculopontine nucleus (PPN); and serotoninergic inputs from the dorsal raphe (for review Parent and Hazrati 1995).

The existence of a direct cortico-STN projection, the so-called "hyperdirect pathway," is now well documented in the rat and the monkey (Künzle and Akert 1977; Monakow et al. 1978; Kitai and Deniau 1981; Afsharpour 1985b; Bevan et al. 1995; Nambu et al. 1996; Inase et al. 1999; Takada et al. 2001; Haynes and Haber 2013). These projections are organized according to the various functional territories

(motor, associative, and limbic). In the rat, the motor cortex projects to the lateral STN, the anterior cingulate cortex projects to the associative STN, while the prelimbic and medial orbital cortex project to the limbic part of the STN (Kita et al. 2014). A recent study has confirmed a similar organization in the monkey (Haynes and Haber 2013).

Recently, inputs from the superior colliculus have been highlighted (Coizet et al. 2009), conferring to the STN a possible role in the transmission of sensory information.

14.2.2 Outputs from the STN

The main target structure of the STN is the external segment of the GP (GPe or GP in rodents). These projections also follow the functional topography of the STN. The neurons of the limbic STN project to the ventral pallidum, while neurons of the motor STN project to the GP (Groenewegen and Berendse 1990; Parent and Hazrati 1995; Joel and Weiner 1997).

The other major targets of the STN are the so-called "output structures" of the basal ganglia: the internal segment of the GP (GPi or entopeduncular nucleus in rodents) and the SNr. The topography of these projections follows the functional territories of the STN (Kita and Kitai 1987; Groenewegen and Berendse 1990; Smith et al. 1990; Parent and Hazrati 1995; Joel and Weiner 1997).

STN neurons innervating the SNr also make contacts with DA neurons of the SNc (Nauta and Cole 1978; Ricardo 1980; Van Der Kooy and Hattori 1980; Kita and Kitai 1987; Groenewegen et al. 1990; Parent and Hazrati 1995). Interestingly for the present chapter dedicated to motivational processes, the STN also projects to the VTA (Groenewegen et al. 1990).

Other structures receive projections from the STN: the pedunculopontine nucleus (PPN) (Hammond et al. 1983; Smith et al. 1990), the raphe (Kita and Kitai 1987), and the cortex (orofacial, sensorimotor, prefrontal) (Jackson and Crossman 1981; Kita and Kitai 1987; Degos et al. 2008).

As described above, the topographic organization of the basal ganglia functional loops indicates that the STN is not only involved in motor processes, but is also in a position to be involved in associative and limbic functions. For a detailed review of the "limbic" organization of the basal ganglia, the reader is referred to Chap. 2 in this volume.

14.2.3 STN in the Reward Circuit

The traditional view of the reward circuit does not incorporate the STN. In the review written by Mogenson positioning the nucleus accumbens (NAc) as the key structure to integrate motivation to action (Mogenson et al. 1980), the STN is part

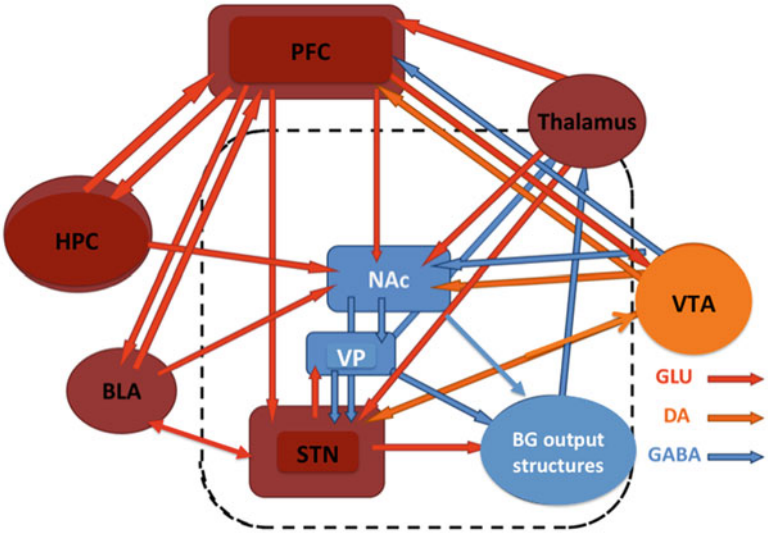

Fig. 14.2 Schematic representation of the reward circuit implemented with the subthalamic nucleus (STN). *BG* basal ganglia, *BLA* Basolateral Amygdala, *HPC* hippocampus, *NAcc* nucleus accumbens, *PFC* prefrontal cortex, *STN* subthalamic nucleus, *VP* ventral pallidum, *VTA* ventral tegmental area, *DA* dopamine, *GABA* gamma aminobutyric acid, *GLU* glutamate

of a box labeled "motor output." This was not changed in the revised version proposed by Wolf (Wolf 2002). Taking into account the various data regarding STN connectivity listed above, it appears that the STN shares many commonalities with the NAc. Since it receives inputs from the prefrontal cortex and the VTA and is connected with the basolateral amygdala (BLA), the thalamus, and the ventral pallidum, the STN is also a possible candidate to be a key node in the translation from motivation to action (Fig. 14.2).

14.3 Subthalamic Nucleus and Primary Processes of Motivation: Consumption

14.3.1 Food Consumption

We provided original evidence that bilateral STN lesions increased the number of visits in the food magazine in rats performing an attentional task for food reward (Baunez and Robbins 1997). This effect was reduced when rats were given ad libitum access to food before the session, indicating that the impact of STN lesions did not involve a change in hunger. Several experimental manipulations have then been conducted since and confirmed that STN lesions do not induce hunger (Baunez et al. 2002). Indeed, when given unlimited access to food, whatever the type of food

(standard lab chow, or more palatable food such as chocolate cereals, liquid sucrose solutions at various concentrations) and whatever the internal state of the animals (deprived or sated), rats with STN lesions did not eat more than control animals (Baunez et al. 2002; Lardeux and Baunez 2008). Inhibition of the STN by muscimol injections was also found not to affect feeding behavior in sated rats, although mu-opioid receptor agonists increased intake of sweetened fat food (Pratt et al. 2012).

When given the choice between a sweet solution with no caloric interest (i.e., saccharine) and an unsweetened but caloric solution (i.e., glucose), normal rats choose saccharine while rats with STN lesions reduced their choice for saccharine over glucose (Pelloux et al. 2014). This result suggests that the interest for the caloric supply is enhanced after STN lesions and is predominant over the hedonic pleasure of sweet taste.

In PD patients subjected to STN DBS, weight gain has been reported to be frequent and sometime spectacular (Barichella et al. 2003; Visser-Vandewalle et al. 2005; Macia et al. 2004; Tuite et al. 2005; Novakova et al. 2007; Montaurier et al. 2007; Bannier et al. 2009; Strowd et al. 2010; for review Rieu et al. 2011). Although some eating disorders directed towards sweet food and snacks are sometimes reported and might account for this gain, it has also been shown that basal energy expenditure decreases under DBS (Montaurier et al. 2007) with no change in hormonal levels (Novakova et al. 2011). The weight gain in PD patients seems to be correlated with the position of the electrode in the medial STN (Růžička et al. 2012).

Interestingly, in obsessive-compulsive (OCD) patients subjected to STN DBS, there was one case of dysphagia reported (Mallet et al. 2008), while in additional OCD patients, one out of four gained weight (Chabardes et al. 2013).

14.3.2 Alcohol Consumption

In nonselected strains of rats, such as Long-Evans rats, whatever the concentration of alcohol, STN manipulation has no effect on forced alcohol consumption (the animals are water-deprived and presented a bottle of ethanol), nor on choice between ethanol and water, between Pastis (anis-flavored alcohol) and water, or between Pastis and nonalcoholic Pastis (Lardeux and Baunez 2008). However, as assessed with manganese-enhanced magnetic resonance imaging, long-term alcohol drinking has been reported to increase activity in the STN including other structures related to the DA mesocortico-limbic system (Dudek et al. 2015).

14.3.3 Drug Consumption

In self-administration procedures, continuous reinforcement or fixed ratio 1 (FR1) allows measurement of drug consumption in a manner equivalent to what is done for other rewards, as there is no effort nor cost to obtain the drug. We have shown

that STN lesions, as well as STN HFS, do not affect cocaine intake in a FR1 schedule of reinforcement (Baunez et al. 2005; Rouaud et al. 2010) and this has been further confirmed with lesions (Uslaner et al. 2005) or lidocaine infusions in a second-order schedule of reinforcement (Kantak et al. 2013). In contrast, STN lesions decrease heroin intake (Slone-Murphy, Baunez, Cador, data unpublished), so does STN HFS (Wade et al. submitted).

14.4 STN and Secondary Processes of Motivation

14.4.1 STN and Reward-Related Information: Electrophysiological Data

The first motivational neuronal correlates in the STN have been observed in the monkey (Matsumura et al. 1992). In this study, monkeys performing an oculomotor task were recorded in the STN and some STN neurons were activated only when the target presentation was followed by a reward delivery. A more recent monkey study showed that STN neurons respond either during the reward anticipation phase or after the reward delivery (Darbaky et al. 2005). More recently, we have further shown that STN neurons respond differently to cues predicting various rewards when they are followed by a choice for the monkey (Espinosa-Parrilla et al. 2015). In contrast, in the rat, neuronal responses to the stimulus predicting the reward and to the reward delivery have also been shown, independently of a choice to make (Teagarden and Rebec 2007; Lardeux et al. 2009, 2013; Breysse et al. 2015). We have performed electrophysiological recording of STN neurons in rats revealing that they can encode the value of the reward (Lardeux et al. 2009, 2013). We designed a task where the rat had to press and hold a lever down for 1 s. Halfway through the holding period, a stimulus predicting which one of the two possible rewards will be delivered at the end of the trial was briefly presented. We have shown that STN neurons could be categorized into subpopulations responding differently to the various rewards. One subpopulation responded exclusively to the cue predicting a 4 % sucrose solution, but did not respond to the cue predicting the other reward (32 % sucrose solution). The other subpopulation responded to the cue predicting 32 % sucrose, but not to the cue predicting 4 % (Lardeux et al. 2009). In other studies, we further showed that this dissociation is also observed when the two rewards are sucrose and cocaine (Lardeux et al. 2013) or sucrose and an aversive reinforcer such as quinine (Breysse et al. 2015) (Fig. 14.3). These studies showed that the STN encodes the reinforcing properties of a reward and possibly the relative value and preference for the rewards available. The various manipulations carried out also demonstrated a role for STN neurons in reward prediction error (Lardeux et al. 2009, 2013; Breysse et al. 2015). We have also shown that some STN neurons, that we called “oops” neurons, encode behavioral error depending on the expected reward.

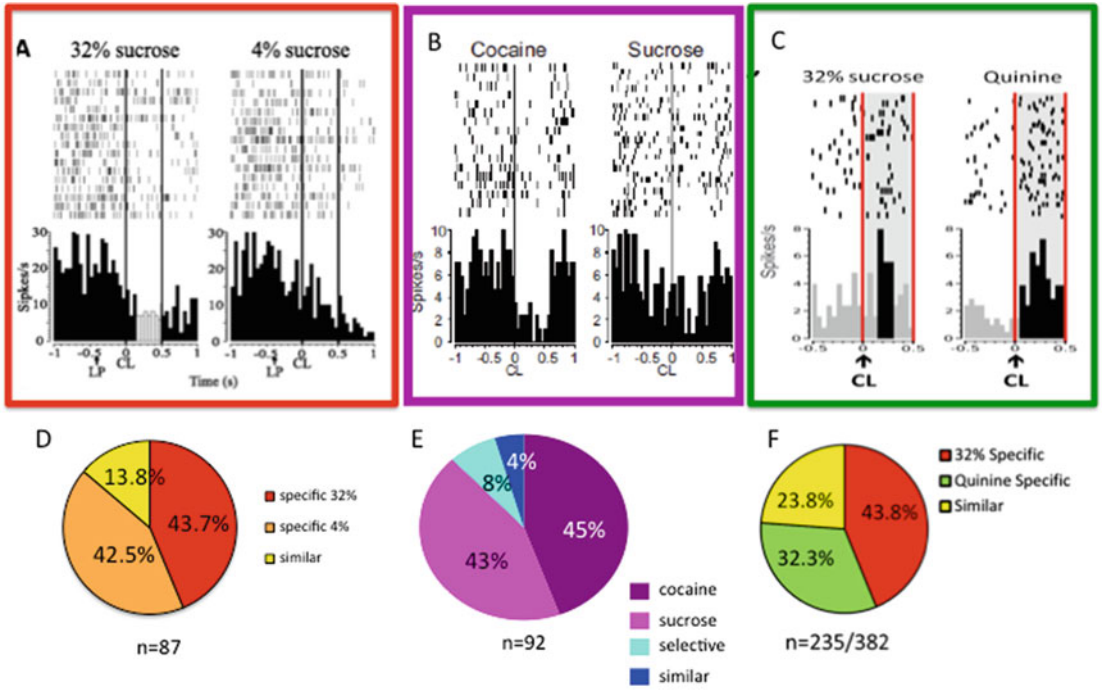

Fig. 14.3 STN response to predictive cue lights in correct trials. (**a**–**c**) Example of the firing pattern of three STN neurons (one "specific 32 % sucrose" (**a**) showing selective inhibition for the light predicting sucrose 32 % (*grey bins*), one "specific cocaine" (**b**) showing a specific inhibition to the light predicting cocaine and one specific quinine (**c**)) to cue light predicting the various rewards indicated above the raster plot. Rasters are centered on the occurrence of the cue light (CL, $t=0$) that lasted 100 ms. *Top*: raster plot of spike firing on each trial with the top row of dots corresponding to the first trial. *Bottom*: mean firing rate across all trials, bin size is 50 ms. The *arrows* indicate the time of the lever press (LP) and the tone (T). (**d**–**f**) Distribution in percentage of the neuronal population responding to the cue light when the light indicates either sucrose 4 % versus 32 % (**d**), sucrose versus cocaine (**e**) or sucrose versus quinine (**f**)

These electrophysiological results showing a differential encoding depending on the nature and on the preference for a reward are in line with behavioral results and are consistent with a role of the STN in motivation with regard to the nature of the reward, its valence, and also to the preference for it. Since the encoding of the relative preference for a reward has been observed in the orbitofrontal cortex (OFC) of the monkey (Tremblay and Schultz 1999), it might well be possible that this role of the STN is under the control of the OFC via the so-called "hyperdirect pathway." The direct cortical influence on STN activity may also explain the existence of "oops neurons" that share properties with neurons recorded in the monkey anterior cingulate cortex (Amiez et al. 2005).

Recent recordings in the STN of PD patients have also confirmed the involvement of STN in motivation, in particular in response to cues associated with reward (Zenon et al. 2016).

14.4.2 Incentive Motivation

14.4.2.1 Food Reward

Although as described above, STN manipulations fail to affect consummatory behavior, they increase motivation for stimuli associated with reinforcers, as assessed in several behavioral tasks. The conditioned locomotor activity procedure allows measurement of locomotor activity when animals anticipate food delivery. During conditioning, rats with STN lesions had a progressively higher locomotor activity during the waiting period, indicating a higher level of expectation for the food (Baunez et al. 2002). Furthermore, in a conditioned reinforcement task in which a lever is associated with a conditioned stimulus (CS, i.e., a light previously paired with food), STN lesions increased the number of responses on the lever associated with the CS. These results show that STN lesions do not affect the association between the CS and the unconditioned stimulus (US, i.e., the food), but that they increase the motivation for the reward, enhancing incentive motivation (Baunez et al. 2002). Further studies using other behavioral tasks have confirmed the role of the STN in food motivation. Indeed, in a conditioned place preference task, STN lesions increased the time spent in the compartment associated with food (Baunez et al. 2005). In this paradigm, animals learn to associate a particular environment with a particular reward, while another environment serves as control. After conditioning, in the absence of the reward, an increase in the time spent in the environment associated with the reward indicates an increase in its incentive motivation. In addition, in an autoshaping or a sign-tracking task, in which a visual stimulus or a lever is presented as a CS when the reward is delivered, STN lesions increased the number of approaches to the stimulus or lever presses on the lever associated with reward delivery and not on the control lever (Winstanley et al. 2005; Uslaner et al. 2008), thus confirming the increased motivation for stimuli associated with sweet

food after STN lesion (Baunez et al. 2002). Finally, although the food consumption measured in a continuous schedule of reinforcement (fixed ratio 1, FR1), in which one lever press leads to the delivery of one sucrose pellet, is not affected by STN lesions (Baunez et al. 2002), the willingness to work for food was increased by STN lesions as shown in the progressive ratio task where the lesion increases the last ratio completed (Baunez et al. 2005). This result has been replicated by other groups (Uslaner et al. 2005; Bezzina et al. 2008). In this task, the number of lever presses required to receive the same reward increases within the session until the animal stops responding for the reward, thereby reaching its breaking point (or last ratio completed). This paradigm allows direct measurement of the motivation to exert effort to obtain a particular reward (Hodos 1961). It is possible that the STN lesion impaired the perception of the "cost of the reward," as observed after excitotoxic lesion of the nucleus accumbens (Bowman and Brown 1998). However, this could hardly explain the results observed in the conditioned place preference since this task does not involve any effort or cost.

14.4.2.2 Drugs and Other Rewards: Towards Addiction

Cocaine and Psychostimulants

In contrast to the results obtained with sucrose or food reward, we found the opposite effects when the reward was cocaine, highlighting a possible role for the STN as a modulator of the reactivity of the reward system with regard to the nature of the reward involved (Baunez et al. 2005). Indeed, in both conditioned place preference and progressive ratio tests, STN lesions, like STN DBS, reduced the incentive motivation for cocaine in the conditioned place preference and progressive ratio tests (Baunez et al. 2005; Rouaud et al. 2010) (Fig. 14.4). The mechanisms through which STN inactivation could modulate motivation in an opposite manner depending on the reward remain to be elucidated. However, cellular analyses after STN DBS (Hachem-Delaunay et al. 2015) or STN inactivation with lidocaine (Kantak et al. 2013) associated with cocaine injections have provided some interesting results. STN DBS has been shown to reverse increased c-fos levels in the striatum induced by cocaine, while arc (activity-regulated cytoskeleton-associated protein) expression was further increased in the nucleus accumbens shell (Hachem-Delaunay et al. 2015). These cellular changes suggest that the effects of STN manipulations on cocaine motivation might result from changes in striatal activity induced by cocaine. By modulating striatal activity, STN inactivation may reduce the rewarding efficacy of cocaine by reducing its impact on the striatum. However, it is also important to note that a transient inactivation of the medial STN by lidocaine was found to have no significant consequence on c-fos levels induced by cocaine in the nucleus accumbens shell, while increasing it in the core (Kantak et al. 2013).

It is also important to note that there are conflicting studies showing that STN lesions can increase motivation for cocaine (Uslaner et al. 2005) and acquisition of

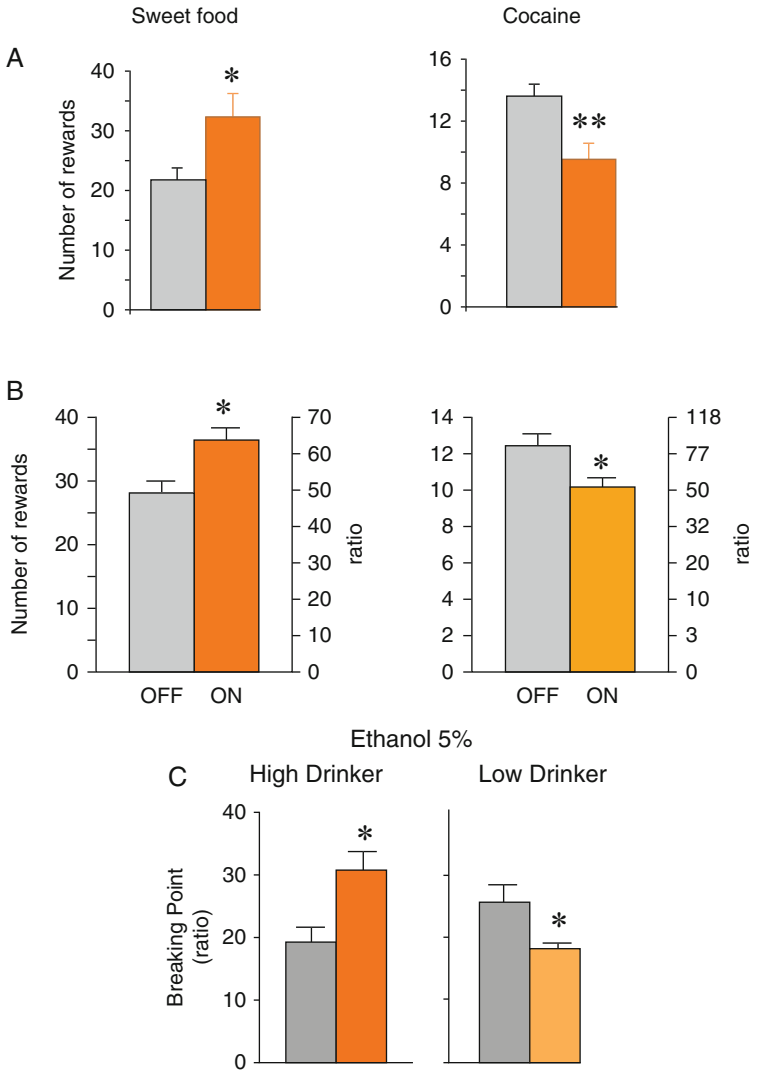

Fig 14.4 Effects of STN lesion (**a**, **c**) and DBS (**b**) on motivation for sweet food (**a**, **b**, *left panel*), cocaine (**a**, **b** *right panel*), and alcohol (ethanol 5% in high drinker and low drinker rats) (**c**), as assessed in the progressive ration schedule of reinforcement. In this task, the number of lever presses required to obtain the same reward increases progressively until the animal decides to stop producing an effort for it (i.e., breaking point: the maximal ratio to which the rat is willing to work). The motivation is expressed in terms of either the number of rewards earned (food pellets or cocaine injections) or the breaking point (last ratio) reached. STN lesion/DBS rats (*orange bars*) show increased motivation for sweet food and alcohol in high drinkers, but reduced motivation for cocaïne and alcohol in low drinkers when compared to sham control animals (*grey bars*). *, **: $p < 0.05$ and 0.01, respectively

responses to a cue associated with cocaine (Uslaner et al. 2008). The results on motivation in the progressive ratio could be easily explainable by the poor level of cocaine self-administration before the assessment of motivation and therefore the facilitation effect could be related to learning. In the latest study on sign tracking, the effects of STN lesions have only been tested on acquisition, but not afterwards (Uslaner et al. 2008), and might therefore again be an effect on learning, that would be consistent with the former study.

Oxytocin receptor mRNA is expressed in the STN (Vaccari et al. 1998). Oxytocin within the STN has been demonstrated to play a role in the regulation of DA-related reward processes. It has first been shown that systemic injection of oxytocin reduces methamphetamine-induced c-fos levels in the STN (Carson et al. 2010). These data suggest that oxytocin in the STN could block the effects of methamphetamine and thus reduce its rewarding efficacy. Indeed, it has also been shown that infusions of oxytocin into the STN reduce conditioned place preference induced by methamphetamine (Baracz et al. 2012). DA injected directly into the STN can induce conditioned place preference (CPP) and this effect is prevented by the coadministration of oxytocin (Baracz and Cornish 2013). These results not only show an important role for oxytocin in the STN in reward-mediated processes, but they also suggest that blocking the STN itself could be sufficient to prevent DA-mediated reward effects.

Alcohol

When testing the effects of bilateral STN lesions on motivation for alcohol, as assessed with conditioned place preference and progressive ratio, we have further shown that alcohol could also affect motivation in an opposite manner depending on the initial preference of the animals for the reward. STN lesions increased motivation for alcohol in "high drinker" rats, while they decreased it in "low drinkers" (Lardeux and Baunez 2008) (Fig. 14.4).

Heroin

We have recently shown that STN lesions decrease motivation for heroin (Slone-Murphy, Baunez, Cador, data unpublished). In another recent experiment, we have also shown that bilateral STN DBS reduces motivation for heroin in a progressive ratio (Wade et al. submitted). In former heroin-dependent subjects, heroin cues have been shown to elicit activity in the STN (Zijlstra et al. 2009).

Sex

As indicated above, an infarct at the level of STN has been reported to induce hypersexuality (Absher et al. 2000). STN DBS can also induce hypersexuality in PD patients (Akakin et al. 2014). Regarding responses to sexuality-related cues,

it has been shown that STN DBS increases responses to erotic cues (Serranová et al. 2013).

Conclusions

Taken together, these behavioral results show that STN lesions affect incentive motivation depending on the nature of the reward, but also on the initial level of preference for the reward. This latter observation highlights how critical presurgery assessment of the patients can be, in order to prevent or better anticipate some of the possible side effects of STN DBS (for example, in a patient with history of alcoholism, STN DBS could lead to relapse). These results also position the STN as an interesting target for a possible use of DBS as a treatment for addiction since the aim is to diminish the motivation to take the drug without diminishing motivation for everything else while even restoring motivation for natural rewards (Pelloux and Baunez 2013).

14.5 STN and Addiction

As mentioned above, the various results discussed in this chapter support the notion that the STN can be a possible DBS target for the treatment of addiction. However, all the experimental tests carried out so far have not been performed in models mimicking addiction. Recently, we have used the model of escalation of drug intake (Ahmed and Koob 1998). This model, using extended access to the drug (6 h per day) after short access sessions (1–2 h), leads to increased levels of drug intake. We have shown that STN lesions can prevent the escalation of cocaine intake, suggesting that STN inactivation prevents the loss of control over drug intake (Pelloux et al. in preparation)) (Fig. 14.5). Furthermore, we have recently shown a curative effect of STN DBS in rats that had previously escalated their heroin intake (Wade et al. submitted). Moreover, in human subjects with alcohol use disorders, STN connectivity is different to that of binge drinkers, highlighting a specific role of STN in addict-like subjects (Morris et al. 2015).

It thus occurs that STN DBS could be a potentially interesting treatment for drug addiction. There are currently no data available in human addicts, but there are interesting data from PD patients subjected to STN DBS. Indeed, some PD patients become addicted to their dopaminergic treatment (mostly to L-DOPA), a symptom called DA dysregulation syndrome (Lawrence et al. 2003). It is therefore interesting to determine how STN DBS can affect this addictive behavior in those patients suffering from DA dysregulation syndrome. In most studies looking specifically at this aspect, the results are supportive and show that STN DBS can decrease addictive behavior towards DAergic treatments (Witjas et al. 2005; Knobel et al. 2008; Lim et al. 2009; Lhommee et al. 2012; Eusebio et al. 2013).

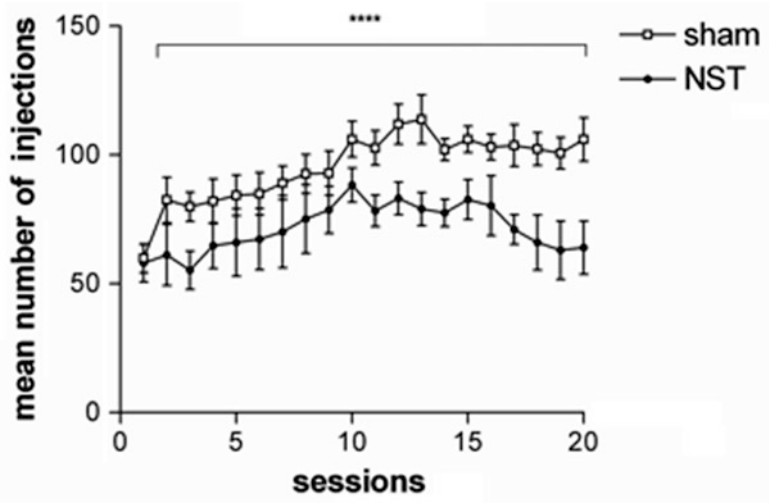

Fig 14.5 Effect of subthalamic nucleus lesion on the number of cocaine injections during 6 h self-administration sessions (mean ± SEM) (extended access) (*open squares*: sham group, $n = 10$; *filled circles*: STN group, $n = 6$) (**** $p < 0.0001$, STN group compared to sham group). While the sham control animals exhibit an escalation in their drug consumption, the STN lesion rats show a stable intake along the course of the experiment. *NST* subthalamic nucleus lesion group

14.6 Conclusions

The data discussed in this chapter position the STN as an interesting brain region where dissociation between motivation for a drug versus other types of rewards can be made. This dissociation seems to be more than solely based on the nature of the reward as it also seems to be based on the value of the reward. Indeed, electrophysiological data obtained in various species have shown that STN neurons exhibit specific and different responses to various types of rewards, but they also seem to encode the relative value of a reward (relative preference). This may explain why such dissociable effects can be observed after STN inactivation. However, it is also possible that the critical interaction with the DA system as well as the influence of the direct inputs from the cortex (the hyperdirect pathway) play a role in the properties of STN, but the mechanisms are unclear and will require further investigations. At present, it is only possible to speculate that the STN acts as a gate control where the action leading to obtain the preferred reward can be selected.

Underestimated for a long time in the field of motivation and addiction, the STN should now be considered as an important potential target for a treatment of addiction. Further investigations using established animal models of addiction are necessary however to validate the hypotheses discussed in this chapter and develop novel strategies to target the STN in a clinical setting.

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Chapter 15
The Basal Ganglia and Decision-Making in Neuropsychiatric Disorders

Sule Tinaz and Chantal E. Stern

15.1 Introduction

We are constantly confronted with multiple alternatives in our everyday lives and forced to make choices in order to move towards a goal. The nature, importance, value, and time scale of these choices vary widely from deciding what to have for breakfast to figuring out the course of a career path. The process of choosing the appropriate series of goal-directed actions is called "decision-making." Our decisions are informed by our past (memory), dependent on the current situation (context), and are motivated by rewards. Basic reward features including magnitude, probability, and time play a central role in decision-making processes.

There is an extensive literature on the role of basal ganglia-cortical circuits and dopamine in decision-making in healthy people and individuals with neuropsychiatric disorders. In this chapter, we first provide an overview of terms used in decision-making research and an overview of the behavioral and neural correlates of decision-making. In the second part of this chapter, we describe how different aspects of decision-making are affected in a number of neuropsychiatric conditions that have an impact on the basal ganglia, including Parkinson's disease (PD), Attention deficit hyperactivity disorder (ADHD), Obsessive Compulsive Disorder (OCD), Tourette syndrome (TS), Schizophrenia, and Mood disorders.

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15.2 Definitions

15.2.1 Decision-Making

Decision-making is a multidisciplinary topic that has been approached from different angles in various research fields including psychology, neuroscience, and economics. Here, we start by providing a brief overview of key components that have emerged from this multidisciplinary research and constitute the decision-making process (for a comprehensive review, see Miyapuram and Pammi 2013).

15.2.2 Reward

Approaching rewards and avoiding threats are fundamental elements of goal-directed human behavior and are directly related to decision-making. Basic reward parameters include magnitude, probability, and delay. An ideal reward would be the one with the greatest magnitude, highest probability, and shortest delay (Sugrue et al. 2005).

15.2.3 Expected Value

Reward values have a probability distribution. For instance, when flipping a coin one would expect two possible outcomes, heads and tails, with equal probability, namely 50 %. In other words, the expected value of a reward refers to the anticipated mean of the probability distribution of the reward.

15.2.4 Expected Utility

Expected value alone is not sufficient to determine choice behavior. The value or utility an individual assigns to a reward depends not only on the magnitude of the reward, but also on the situational context. For example, a sandwich will have more value for someone who has not eaten for many hours compared to another person who has just had a full meal.

15.2.5 Prediction Error

This is a measure of deviations from previous reward expectations. It is a requirement for further or new learning of stimulus-reward associations in order to make optimal future choices. In other words, if a reward is fully predicted by the stimulus/

cue, then the association between the two will always be preferred over others. Thus, new associations will not be learned.

15.2.6 Uncertainty, Risk, and Ambiguity

Decisions are made based on the predicted outcome, and predictions are not always perfect because we live in a constantly changing environment and some decisions depend on the behavior of others. As a result, decisions are made in the face of varying degrees of uncertainty. When there are two possible outcomes (e.g., reward or non-reward), an expected outcome with 50 % probability has the highest uncertainty. When this 50 % probability is known in advance, then the decision can be called a "risky" decision. On the other hand, when the probabilities are unknown, then one has to make an "ambiguous" decision.

15.2.7 Prospect Theory

This theory (Kahneman 2003) suggests that risk attitudes regarding an outcome are determined by the sensitivity to gains and losses. In general, individuals demonstrate a preference for outcomes with certainty and avoid risky or uncertain outcomes. Individuals tend to show a preference for a sure gain of a smaller amount as opposed to an unsure gain of a larger amount (i.e., risk-averse for gains). They also demonstrate a preference for a sure loss of a smaller amount as opposed to the probability of losing a larger amount (i.e., risk-averse for losses).

15.2.8 Temporal Discounting

There is usually a delay between a decision leading to a choice/action and the subsequent outcome/reward. Temporal discounting refers to the decrease of the reward utility over time. Individuals tend to choose a small but immediate reward over a larger but delayed reward, if the rewards do not differ too much in magnitude. This same behavior is observed when the larger reward is delayed for too long. However, these preferences are not fixed over time. For example, one might prefer a small but immediate reward today as opposed to a slightly larger reward tomorrow, yet this preference would be reversed, if both rewards were still 1 day apart but a year from now. In other words, the temporal discounting rate is not steady, but decreases over prolonged delays (Berns et al. 2007).

15.3 Neural Correlates

In this section, we discuss the neural correlates of the basic elements of decision-making as defined in the previous section. We focus specifically on the role of distinct cortical-basal ganglia loops (for reviews, see Dreher 2013; Miyapuram and Pammi 2013).

15.3.1 Reward Magnitude, Probability, Delay, and Reward Prediction Error

The role of the dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SN) in reward processing is well known (Schultz 1998). In stimulus-reward association tasks, dopaminergic neurons respond in a phasic fashion to the reward itself as well as to the stimulus that predicts the reward. This phasic response is scaled according to the magnitude, probability, and delay of the reward. The response to the conditioned stimulus increases linearly with the magnitude and probability of the reward (Tobler et al. 2005) and decreases with the delayed delivery of the reward (Kobayashi and Schultz 2008). The opposite response pattern is observed at the time of reward delivery, namely, increased response with delay and decreased response with higher reward probability (Fiorillo et al. 2003).

Dopaminergic neurons also encode the reward prediction error, displaying a positive phasic response to unexpected reward (or omission of expected punishment) and negative phasic response to worse-than-expected reward (or unexpected punishment) (Schultz et al. 1997; Berns et al. 2001; McClure et al. 2003; Abler et al. 2006; Dreher et al. 2006; Matsumoto and Hikosaka 2009).

The dopaminergic neurons project to the striatum and prefrontal cortex (PFC) and relay reward-related signals to distinct parts of these structures. The ventral striatum/nucleus accumbens (VS/NAc) neurons activate during reward anticipation. Neuroimaging studies demonstrated increased VS activity with higher reward magnitude and probability. The VS also demonstrates sustained activity that scales with reward uncertainty, indicating that this region encodes not only reward, but also risk associated with the reward (Dreher et al. 2006).

Neurons within the orbitofrontal cortex (OFC) encode the motivational value of rewards (Padoa-Schioppa and Assad 2006), and respond to reward-predicting cues and reward delivery (Tremblay and Schultz 2000; Peters and Büchel 2010). The medial and lateral parts of the OFC play distinctive roles in reward processing. The medial OFC specializes in representing rewards, gains, and appetitive states, whereas the lateral OFC is associated with punishment, loss, and aversive states (Elliott et al. 2000; O'Doherty 2007; Seymour et al. 2007). The OFC also represents reward prediction error together with the VS when a reward is omitted or delivered unexpectedly (O'Doherty et al. 2003). The anterior insula (AI) also represents losses or aversive events. The amygdala processes aversive and fear-inducing

stimuli; however, it seems to play a more general role in processing the intensity of both appetitive and aversive stimuli (Baxter and Murray 2002).

In addition to the basic reward-processing network, there seems to be an additional network that encodes the salience of events in the same way regardless of their hedonic value. This network includes the core structures of the salience network, namely the anterior cingulate cortex (ACC) and AI, and the putamen. Activity in these regions correlates with the prediction error of appetitive and aversive outcomes (Metereau and Dreher 2013).

In summary, the midbrain, VS, and medial OFC constitute the basic network underlying reward processing. Additionally, regardless of the hedonic value, the AI and ACC are thought to encode the salience of the outcome, while the amygdala is thought to encode the intensity of the stimulus.

15.3.2 Reward Uncertainty

Midbrain dopaminergic neurons display tonic activity during the delay between a stimulus and reward that correlates with the degree of reward uncertainty, showing the highest tonic response to maximal uncertainty (i.e., 50 % reward probability) (Preuschoff et al. 2006). The dorsal striatum, on the other hand, demonstrates activity for risky choices (Hsu et al. 2005). The lateral OFC activation (together with the amygdala) correlates with degree of ambiguity (Hsu et al. 2005). Risk-aversion is also associated with lateral OFC activity, whereas medial OFC is involved in risk-seeking behavior (Tobler et al. 2007). The ACC and AI are involved in choice uncertainty. Activity in the ACC and AI correlates with risk levels (Christopoulos et al. 2009; Grinband et al. 2006; Huettel et al. 2005). More specifically, the rostral parts of the ACC are associated with risky, whereas the dorsal parts with ambiguous decision-making processes (Krain et al. 2006; Xue et al. 2009). A similar dissociation was also observed in the PFC and parietal cortex. The lateral PFC activity was associated with ambiguity, whereas the posterior parietal cortex was involved in risk in a gambling task (Huettel et al. 2006).

The hippocampus is involved in processing the uncertainty of stimulus-reward associations. Hippocampal recordings obtained from epileptic patients while they learned stimulus-reward associations with varying reward probabilities demonstrated that the amplitude of the hippocampal negative event-related potentials covaried with outcome uncertainty. This response had an inverted U shape, demonstrating maximum response to 50 % probability and minimal response to 0 or 100 % probability suggesting that gain or loss did not matter (Vanni-Mercier et al. 2009).

The hippocampus has also been shown to be recruited during a spatial navigation task that required decision-making under ambiguous conditions. Participants navigated through well-learned virtual mazes to reach a target location, and some of these mazes shared hallways with another maze. Disambiguation of the overlapping hallways compared to navigating through nonoverlapping ones resulted in

higher functional connectivity between the hippocampus, caudate, and OFC (Brown et al. 2012).

In summary, the network consisting of the midbrain, VS, AI, ACC, lateral OFC, and hippocampus is thought to be critically involved in uncertainty/risk processing.

15.3.3 Reward Context

The OFC, VS, and amygdala represent the relative, as opposed to absolute, value of a reward depending on the individual preferences and availability of other alternatives (Tremblay and Schultz 1999; Cromwell and Schultz 2003).

Studies have demonstrated activity within the medial OFC in response to relative rather than absolute value of financial rewards. Amygdala activity increased when a choice was safe and framed as a gain, and decreased when it was risky and framed as a loss (De Martino et al. 2006). The dorsal ACC demonstrated the opposite pattern: Increased activity for risky choices that are framed as gains and decreased activity for safe choices that are framed as losses (De Martino et al. 2006). More recent studies have shown that loss aversion correlates with amygdala activity (Sokol-Hessner et al. 2012), and patients with bilateral amygdala damage exhibit reduced loss aversion despite intact value and risk sensitivity (De Martino et al. 2010).

The cost of a decision, in the form of delay or effort, also impacts the decision-making process. The ACC, OFC, and VS all play a role in cost representation (Rushworth et al. 2007; Walton et al. 2006). A delay/effort-discounting task in humans demonstrated recruitment of different neural circuits depending on the type of cost. The VS and ventromedial PFC represented the increasing subjective value of the reward during the delay, whereas the ACC and AI represented the decreasing value of the reward that required higher effort (Prévost et al. 2010).

In addition, the hippocampus has been shown to process environmental contextual cues in decision-making during spatial navigation, as discussed in the previous section (Brown et al. 2012).

15.4 Problems with Decision-Making in Neuropsychiatric Disorders

In many neuropsychiatric disorders that have an underlying pathology in distinct cortical-basal ganglia loops, patients display specific problems with decision-making in addition to the characteristic cognitive and behavioral deficits associated with the disorder. In this section, we discuss the decision-making deficits associated with these neuropsychiatric disorders, which include Parkinson's disease, Attention deficit hyperactivity disorder, Obsessive Compulsive Disorder, Tourette syndrome, Schizophrenia, and Mood disorders.

15.4.1 Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms caused by nigrostriatal dopamine depletion, and cognitive and behavioral symptoms associated with dysfunction of the respective cortico-striatal loops (Kish et al. 1988; Grahn et al. 2008). The dorsal striatum is more affected by the pathological burden than the VS, especially in earlier stages of the disease course. Patients with PD show specific deficits in decision-making. Two underlying mechanisms seem to play a basic role in these decision-making deficits, including problems with (1) the processing of reward prediction errors and (2) the evaluation of outcome based on feedback. The first mechanism is sensitive to the medication status of the patient, whereas the second mechanism is sensitive to the type of feedback (see Ryterska et al. 2013 for a review).

The VS activity scales with reward magnitude, probability, and anticipation. Tasks that rely on learning stimulus-reward associations (e.g., probabilistic classification learning and probabilistic reversal learning tasks) recruit the VS. Dopaminergic treatment in patients with PD tends to worsen performance in these types of tasks. For example, PD patients on dopaminergic medication show limited learning of cue–outcome associations in the Weather Prediction Task, a probabilistic classification task in which participants are required to predict the outcome (rainy or sunny weather) based on a combination of cards (Knowlton et al. 1996; Wilkinson et al. 2008; Witt et al. 2002). Similarly, PD patients have difficulty in probabilistic reversal learning tasks. In these tasks, participants gradually learn to choose the stimulus with the highest probability of a positive outcome on a trial-and-error basis. The probabilities are then changed without warning, and the participants are expected to adjust their choices accordingly. Patients with PD on dopaminergic treatment fail to adjust their choices and demonstrate a tendency to stick to the initial reward contingencies (Cools et al. 2002, 2006; Peterson et al. 2009). On the other hand, performance on cognitive tasks that are known to recruit the dorsal striatum (e.g., working memory, planning, task-switching) improve with dopaminergic treatment in PD (Cools et al. 2001; Macdonald and Monchi 2011).

Given that the processing of many basic reward properties (e.g., magnitude, probability, prediction error) depends on phasic dopamine signals, one would expect improved, not worsening, performance in associative stimulus-reward learning tasks with dopaminergic treatment in PD. According to the "dopamine overdose" hypothesis, this discrepancy can be explained by the different degrees of pathology affecting the dorsal and ventral parts of the striatum (Agid et al. 1993; Kish et al. 1988). The more affected dorsal part is more severely deprived of dopamine and functions more optimally with dopamine replacement, whereas the less severely affected ventral part is overwhelmed by dopamine replacement and functions suboptimally (Cools et al. 2001, 2003; Gotham et al. 1988).

The other important factor that seems to impact decision-making skills in individuals with PD is the feedback structure of the task. Impaired performance of PD patients in feedback-based tasks might reflect a difficulty in properly evaluating the

outcome based on the feedback that is provided on a trial-by-trial basis (Knowlton et al. 1996). For example, stimulus-reward association learning tasks provide discrete feedback about whether or not a single trial is correct or incorrect, but no additional information about the rules between these associations, outcome probabilities, etc. is provided. Therefore, these rules can only be learned incrementally over time, by trial-and-error. This task structure may challenge the working memory capacity of PD patients (Shohamy et al. 2004a, b). On the other hand, tasks that use cumulative feedback about the outcome over many trials provide information about the rules governing the cue–outcome relationships. Patients with PD can discover and learn these rules by tracking their ongoing performance over time (Osman et al. 2008; Witt et al. 2006).

Patients with PD also exhibit deficits in decision-making under risk and uncertainty. In gambling tasks that explicitly present the rules for gains and losses and probabilities (e.g., Game of Dice task, Cambridge Gambling task), PD patients on dopaminergic medication tend to choose the riskier options (Brand et al. 2004; Euteneuer et al. 2009). On the other hand, in the absence of immediate feedback on the outcome, the risky behavior normalizes, suggesting a deficit in outcome evaluation (Labudda et al. 2010). The abnormal betting behavior of PD patients on dopaminergic medication has also been observed in the form of quicker bets, suggesting impulsivity. Yet, when off dopaminergic medication, these same patients exhibit abnormally high costs when switching between two tasks, reflecting attentional inflexibility (Cools et al. 2003). In addition, dopaminergic treatment in PD (especially with dopamine receptor agonists) may result in impulsive and compulsive behavior including pathological gambling (Dodd et al. 2005; Driver-Dunckley et al. 2003) and steeper temporal discounting (Housden et al. 2010; Milenkova et al. 2011), indicating impulsivity and/or delay aversion. These findings also support the importance of medication status and task feedback structure in decision-making in individuals with PD.

The decision-making performance of PD patients in tasks of uncertainty that do not provide explicit information about the rules for gains and losses (e.g., Iowa Gambling task-IGT, Bechara et al. 1994) has been variable. Some studies have demonstrated more disadvantageous selections in PD patients compared to controls (Perretta et al. 2005), whereas others did not find a difference between the two (Euteneuer et al. 2009).

Finally, deep brain stimulation (DBS) surgery in PD also has cognitive and behavioral consequences, some of which directly affect decision-making processes. For instance, it has been recently demonstrated that PD patients who underwent DBS surgery of the subthalamic nucleus (STN) and consequently were able to reduce the dose of their dopaminergic medications drastically, showed significantly improved postsurgical performance on the IGT compared to their pre-surgical performance. This finding is also consistent with the dopamine overdose hypothesis (Castrioto et al. 2015).

DBS of the STN also has been shown to result in a unique problem in decision-making using a probabilistic selection task. In this task, positive feedback learning was indicated by choosing the stimulus in a pair that had the highest probability of

positive outcome, whereas negative feedback learning was indicated by avoiding the stimulus in a pair that most likely led to a negative outcome. There were also high-conflict pairs in which the stimuli had very close reinforcement values. Patients on dopaminergic medication (without DBS) were selectively impaired at negative feedback learning, whereas those off medication performed equally well as matched controls. Within the surgical group, having DBS on versus off did not affect the positive or negative feedback learning. Controls and patients on and off medication slowed down in high-conflict trials. However, when DBS was on, patients became more impulsive and failed to slow down in high-conflict trials, and this premature responding led to suboptimal choices (Frank et al. 2007). Anatomically, the STN is the input nucleus on the hyperdirect pathway and provides a global no-go signal to the thalamocortical neurons, which is then overcome by the dynamic interplay between the direct and indirect pathways, and a fine-tuned go cue is produced (center-surround inhibition model of basal ganglia functioning). With DBS, the fine-tuning of this interplay is impaired and an excessive go signal is relayed to the thalamocortical neurons, which is thought to cause the resulting impulsivity (Frank 2006).

15.4.2 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset disorder characterized by inattention, hyperactivity, and impulsivity. Symptoms may persist into adulthood. Dysfunction in the dopaminergic and noradrenergic systems and frontostriatal circuits are implicated in the pathophysiology of ADHD. It has also been associated with deficits in decision-making and learning. These deficits are thought to be due to impulsivity and altered sensitivity to reinforcement in individuals with ADHD.

One study investigating the neural substrates underlying impaired processing of reward prediction errors in adolescents with ADHD demonstrated abnormal activity in the medial PFC using fMRI and EEG. A probabilistic reversal task was used in which participants had to learn the stimulus with a higher outcome probability on a trial-and-error basis. The reward probabilities were reversed occasionally, and the participants were expected to learn the reversed contingencies. The ADHD group exhibited a more rigid learning pattern compared to controls and showed less sensitivity to changes in reward contingencies. These deficits were attributed to abnormal activation patterns in the medial PFC during cue and outcome presentation (Hauser et al. 2014). Reduced activity in the VS during reward anticipation (Carmona et al. 2012) and in the medial OFC in response to higher incentive reward delivery (Wilbertz et al. 2012) has also been shown in adults with ADHD.

Feedback also plays a critical role in decision-making in ADHD. Adolescents with ADHD and matched controls performed a probabilistic choice task in which outcomes and probabilities were explicitly provided. In the absence of feedback, the ADHD group and controls performed similarly, whereas in the feedback condition,

the ADHD group made unfavorable choices more frequently than controls (Pollak and Shoham 2015).

Another study, this time in adults with ADHD, demonstrated similar learning deficits in a feedback-based rapid-decision gambling task using event-related potentials. Compared to controls, the ADHD group was found to be impaired in learning by feedback and insensitive to reward magnitude. A source location analysis revealed reduced responses within the cingulate cortex to reward valence and magnitude in the ADHD group (Ibanez et al. 2012).

The role of impulsivity in decision-making in ADHD has been studied extensively. One consistent finding is that children and adolescents with ADHD have difficulty delaying gratification, and show significantly greater temporal discounting of delayed rewards compared to matched control participants (Barkley et al. 2001; for a review, see Lee 2013). Stimulant medication (methylphenidate) improves temporal discounting in children with ADHD (Shiels et al. 2009), suggesting a dopaminergic mechanism. However, temporal discounting has not been demonstrated consistently and does not seem to be an issue in adults with ADHD (Mowinckel et al. 2015).

Gambling tasks have been used frequently to assess impulsivity and reward sensitivity in ADHD. In fact, there is evidence demonstrating a link between ADHD and problem gambling. Adults with ADHD were found to be more likely to meet the criteria for problem gambling than controls, and their ADHD-related symptoms were correlated with gambling-related cognitions and behavior. Moreover, adults with ADHD were more impulsive than controls based on their temporal and reward probability discounting scores. Probability discounting alone was found to be associated with gambling-related measures, suggesting a relationship between impulsivity and risk proneness and problem gambling in this population (Dai et al. 2013). Medication status in ADHD (being unmedicated) seems to plays an additive role in this impulsivity. For example, in a computerized version of the IGT, participants were expected to maximize the favorable outcome based on positive and negative reinforcement for good and bad bets. Unmedicated adults with ADHD and pathological gambling performed worse than adults who were pathological gamblers without ADHD (Abouzari et al. 2015).

Dysfunction in the reward-related OFC-VS circuit has also been implicated in impulsive and risky behavior in ADHD. Medication-naïve adults with ADHD were tested using Go-NoGo and monetary incentive delay tasks using fMRI. The former task assessed response inhibition, specifically focusing on inferior frontal gyrus activity, and the latter evaluated reward sensitivity/impulsivity, focusing on VS activity. The ADHD group demonstrated reduced bilateral VS activity compared to controls during reward anticipation, but there was no difference between the groups in inferior frontal gyrus activity in the Go-NoGo task. Furthermore, activity in the VS, but not in the inferior frontal gyrus, correlated negatively with severity of hyperactivity/impulsivity (Carmona et al. 2012). Another fMRI study examined the neural substrates of reward processing combined with the physiological response to risky decision-making using the game of dice task in adults with ADHD. Both ADHD and

control groups showed comparable activation in the ventral and dorsal striatum and the medial OFC during the delivery of high-incentive rewards. However, the encoding of the motivational change from low to high-incentive rewards was not as strong in ADHD group as it was in controls. In addition, this dysfunctional medial OFC activity in the ADHD group was paralleled by their risky decision-making process and the associated physiological arousal response (Wilbertz et al. 2012).

Taken together these results suggest that impulsivity in ADHD is related to problems with reward processing within the OFC-VS circuits rather than frontal (specifically the inferior frontal) response inhibition mechanisms.

15.4.3 Obsessive Compulsive Disorder

Obsessive Compulsive Disorder (OCD) is characterized by ruminative thoughts and compulsive behavior. Selective difficulties with decision-making and goal-directed behavior are also frequently observed. Most of these decision-making difficulties seem to arise from excessive subjective uncertainty, abnormal valuation of reward, and impaired cognitive flexibility.

The OFC has been strongly implicated in OCD. Anatomically, the OFC receives rich affective information from the limbic areas (e.g., amygdala) (Baxter et al. 2000). Functionally, it maintains reward history and participates in biasing choices among multiple alternatives. Positively reinforced choices appear to be facilitated, whereas negatively reinforced ones are inhibited. Increased metabolism in the OFC in the setting of provoked obsessive symptoms has been consistently found in neuroimaging studies (Menzies et al. 2008). Lateral PFC, ACC, insula, amygdala, and caudate activations have also been observed in symptom provocation studies in OCD (Breiter et al. 1996; Nakao et al. 2005).

In the context of decision-making, the dorsolateral PFC plays a role in online retention and manipulation of goal-related information in working memory and deliberation of actions. The ACC is implied in processing uncertainty and conflict and for monitoring the determination of a choice. Abnormal activations in the OFC, dorsolateral PFC, and ACC in OCD have been associated with abnormal valence assignment to rewards, prolonged deliberation and/or repetition due to excessive doubt, and delayed closure of decision-making, respectively (Sachdev and Malhi 2005).

Prolonged deliberation in OCD is often associated with excessive uncertainty and worry about the accuracy of a performed action and the quality of outcome. Decision-making under ambiguous conditions is especially difficult for patients with OCD. For instance, adult patients with OCD showed impaired performance on decision-making under ambiguous conditions, but not under risk (Kim et al. 2015). In an fMRI study investigating the neural substrates of decision-making in OCD under varying degrees of uncertainty, OCD patients demonstrated more activation in the limbic/paralimbic areas including the ventromedial PFC, OFC/insula,

parahippocampus, and amygdala compared to controls, even in the "no uncertainty" condition. They also rated themselves as more uncertain in this condition. However, there were no performance or activation differences between patients and controls in uncertainty conditions. These findings suggest that hyperactivation in decision- and reward-related limbic/paralimbic regions might contribute to the subjective sense of uncertainty in OCD patients (Stern et al. 2013).

Reduced cognitive flexibility and compulsive behavior are also factors in impaired decision-making in OCD. Patients with OCD were tested using a Go-NoGo task that measures the ability to respond to relevant and inhibit the response to irrelevant targets. The OCD patients did not show any significant difference in their response patterns compared to controls, suggesting that appropriate responding and response inhibition were not an issue. However, the task also included switch blocks in which the response contingencies were reversed from the previous block. The OCD group responded excessively to the previously rewarded stimulus category when they were required to reverse response categories on switch blocks. They also demonstrated selective deficits in attentional set shifting tasks. Taken together, these results are consistent with diminished cognitive flexibility in OCD (Watkins et al. 2005).

15.4.4 Tourette Syndrome

Tourette syndrome (TS) is a childhood-onset disorder characterized by motor and vocal tics and psychiatric comorbidities including ADHD and OCD (Freeman et al. 2000). Symptoms can persist into adulthood. Tics are defined as repetitive, stereotyped movements, and vocalizations. The pathophysiology of TS is thought to involve functional, neurochemical, and structural changes in multiple parts of cortico-striato-thalamo-cortical circuits (Leckman et al. 2010). Excessive dopaminergic tone within these circuits has also been implicated (Singer et al. 2002; Wong et al. 2008; Yoon et al. 2007).

This increased dopaminergic tone plays a role in reinforcement learning issues in patients with TS. A subliminal instrumental learning task with monetary gains and losses was administered to unmedicated PD patients and medicated TS patients (i.e., both in hypodopaminergic condition). Both groups were found to be impaired in reward learning, but not in punishment learning (Palminteri et al. 2009). Conversely, unmedicated TS patients (i.e., in hyperdopaminergic state) showed selectively enhanced motor performance in a reward-based motor skill learning task, whereas those who were medicated were impaired in this task (Palminteri et al. 2011). Finally, the comorbidities associated with TS have also been shown to contribute to reward-based learning problems. An fMRI study demonstrated reduced reward-related activity in the ventromedial PFC and VS in a probabilistic instrumental learning task, only in TS patients who had comorbid OCD (Worbe et al. 2011).

15.4.5 Schizophrenia

The dopamine hypothesis has been the prevailing view of the primary pathology in schizophrenia. An earlier version of this theory postulated excess transmission at dopamine receptors, as well as prefrontal hypodopaminergia and subcortical hyperdopaminergia. According to the revised version, irregular dopamine release ascribes "aberrant salience" to irrelevant stimuli, while on the other hand, it causes an inadequate response to relevant reward cues leading to positive and negative symptoms of schizophrenia, respectively (Howes and Kapur 2009). The aberrant salience model also applies to reward learning deficits in schizophrenia (Whitton et al. 2015). For example, in an fMRI study of reward prediction, activity in the VS in control participants correlated with prediction errors, whereas schizophrenic patients demonstrated exaggerated responses to expected outcomes and blunted responses to unexpected outcomes (Morris et al. 2012), in line with the abnormal salience model. Consistent with this, schizophrenic patients, compared to controls, have also shown reduced activity in the striatum related to reward prediction error in an instrumental reward learning paradigm (Gradin et al. 2011).

Schizophrenic patients also show deficits in both positive and negative feedback learning. In a probabilistic Go-NoGo task, schizophrenic patients were found to be impaired in flexibly switching their choices based on negative feedback and incrementally adjusting their choices according to positive feedback across multiple trials (Waltz et al. 2011). In a probabilistic selection task, the preference of subjects for choosing the most rewarded stimulus and avoiding the most punished stimulus was tested. Schizophrenic patients displayed a decreased preference for the most rewarded stimulus, yet were unimpaired at avoiding the most punished stimulus (Waltz et al. 2007). In a similar task, schizophrenic patients showed a learning deficit from both negative and positive feedback, and this deficit persisted across extended trials suggesting that it is specific to reinforcement learning rather than reflecting a general slowness in learning (Cicero et al. 2014). Behavior in schizophrenic patients after receiving a big penalty has also been investigated using the IGT with and without certainty. In the absence of certainty, schizophrenic patients failed to switch their choices from the disadvantageous to the advantageous card deck (Matsuzawa et al. 2015).

Finally, schizophrenic patients with positive (e.g., psychosis) versus negative (e.g., apathy) symptoms demonstrate different patterns of deficits in feedback-based learning tasks. For example, using a feedback-based dynamic reward task, belief formation, and belief perseveration in schizophrenic patients with relatively low and high levels of psychosis was examined. Reward sensitivity of both groups was found to be lower than that of controls. Schizophrenic patients also updated their reward values more rapidly than controls, indicating low perseverance which was more prominent in the high-psychosis group (Li et al. 2014). In addition, schizophrenic individuals were tested in an effort-based decision-making ("effort discounting") task in which they could exert physical effort on a handgrip to obtain a proportionate monetary award, or could choose not to exert any effort and obtain a

default monetary award. Patients did not differ from controls in effort discounting, i.e., the relative subjective value of the award decreased with increased effort comparably in both groups. However, patients demonstrated a significant correlation between effort discounting and apathy (Hartmann et al. 2015).

All of these findings of abnormal reward sensitivity and impaired feedback learning in schizophrenia are consistent with the aberrant salience version of the dopamine hypothesis. However, the inhibitory circuit in which the lateral habenula (LHb) has a critical function opposite from the dopaminergic system is also worth mentioning as another potential mechanism mediating these deficits. Anatomically, the habenula is a structure within the caudal and dorsal aspect of the dorsal thalamus and is also associated with the pineal gland. Stimulation of the LHb induces a GABA-mediated inhibition of the midbrain dopaminergic neuron firing (Hikosaka et al. 2008). Research has shown that LHb neurons show increased activity in response to punishment or reward omission and decreased activity in response to rewarding cues (Hikosaka 2010). In addition, there is postmortem and in vivo neuroimaging evidence that abnormal regulation of dopaminergic neurons by the LHb might be a potential mechanism contributing to the problems in schizophrenic individuals in both positive and negative feedback learning and decision-making (Stopper and Floresco 2015).

15.4.6 Mood Disorders

Regulation of emotional behavior is mediated by complex interaction within a functional network that includes the medial PFC and OFC, amygdala, bed nucleus of stria terminalis, hippocampus, VS/ventral pallidum, mediodorsal thalamus, hypothalamus, periaqueductal gray, and several brain stem regions. Dysfunction in discrete parts of this network has been demonstrated to lead to impairment in autonomic regulation, emotional behavior, and cognition, and may constitute the neural basis of mood disorders including anxiety, depression, and bipolar disorder in humans (Drevets et al. 2008). Many of these regions are also involved in decision-making processes, as reviewed in previous sections, and individuals with mood disorders demonstrate distinct deficits in decision-making tasks. In mood disorders, these deficits are characterized mainly by abnormalities in reward response, motivation, and effort; and are related to dysfunction in underlying neural circuits (Price and Drevets 2010). For example, imaging studies have shown increased activity within the subgenual cingulate cortex in individuals with major depressive disorder (MDD). The subgenual cingulate cortex is an area in the medial PFC and a hub of the default mode network. It is known to be involved in emotion processing and self-referential thinking, both of which are important in decision-making processes. Specifically, increased resting-state functional connectivity between the subgenual cingulate cortex and the thalamus has been demonstrated in individuals with MDD compared to controls. Additional work has shown that the length of a depressive

episode also correlates positively with increased functional connectivity in the subgenual cingulate area (Greicius et al. 2007).

A major component of depression is anhedonia. Anhedonia is defined as an inability to experience pleasure and to respond to rewarding stimuli, and is an important contributor to problems with decision-making. Studies have suggested that dysfunction of the subgenual cingulate cortex coupled with amygdala hyperactivity may contribute to anhedonia in individuals with MDD (Drevets et al. 2008; Gorwood 2008). Striatal pathology may also play a role in anhedonia; and trait anhedonia severity was found to correlate negatively with the volume of the anterior caudate and VS (Harvey et al. 2007).

Anhedonia and abnormalities in reward expectation/response are intimately linked in MDD and impact goal/reward-directed behavior and decision-making. In a monetary incentive delay task, unmedicated individuals with MDD showed significantly reduced activity in the left NAc and bilateral caudate specifically in response to monetary gains. In addition, anhedonic symptoms and depression severity have been shown to correlate with reduced bilateral caudate volume (Pizzagalli et al. 2009).

Individuals with varying degrees of anhedonia were tested in a temporal discounting paradigm. Increasing levels of anhedonia correlated negatively with delay discounting rate, indicating that anhedonic individuals tended to choose the larger, but delayed reward. This result suggests that anhedonic individuals make future decision that is ultimately advantageous, possibly due to their decreased responsiveness to immediate rewards (Lempert and Pizzagalli 2010). Medicated patients with MDD have also been tested using the classic and modified version of the IGT. In the classic version, advantageous card decks are associated with an immediate small reward but even smaller future punishment. In the modified version, advantageous decks are associated with immediate large punishment but even larger future reward. It has been shown that patients with MDD are impaired in the classic version and tend to choose from the disadvantageous decks offering high immediate reward. However, they were found to be unimpaired on the modified version, namely, they did not change their behavior in the face of negative feedback. This decision-making pattern suggests that patients with MDD have difficulty integrating reward feedback with future behavior, and focus on the immediate outcome with higher reward on the short term. Patients with MDD also seem to expect future punishing consequences to be more likely to occur than immediate rewarding ones (Must et al. 2006, 2013).

Anatomically, this tendency to expect a negative outcome and/or reduced sensitivity to reward in MDD is also associated with LHb dysfunction (Proulx et al. 2014). Increased habenula activity has been implicated in the etiology of MDD (Shumake and Gonzalez-Lima 2003). LHb neurons show increased activity in response to punishment or reward omission and induce a GABA-mediated inhibition of the midbrain dopaminergic neuron firing (Hikosaka et al. 2008; Hikosaka 2010). An overactive LHb would possibly lead to less activity and motivation, and reluctance to explore options, which are core symptoms of MDD (Proulx et al. 2014).

In addition, serotonin has been shown to play a critical role in depression as well as in decision-making. Serotonin is involved in the prediction of aversive events and behavioral inhibition in light of predictions of aversive outcomes. In a simplified reinforcement learning model, the role of serotonin has been described in terms of pruning a tree of possible decisions (i.e., eliminating those choices that have low or negative expected outcomes). According to this model, decreased serotonin levels result in large negative prediction errors and a shift towards aversion (Dayan and Huys 2008). Therefore, depressed individuals would expect a lower reward rate from their actions due to deficient pruning of negative expected outcomes as a result of insufficient serotonin. The LHb is also important in regulating serotonin neurotransmission. It conveys both "value change" and "value state" signals downstream selectively directed to dopaminergic and serotoninergic neurons, respectively. The phasic firing of dopaminergic neurons in response to reward encodes the value change, and the tonic changes in activity of serotoninergic neurons after the reward value is updated encode the value state. Dysfunction in these systems may partly constitute the neural mechanisms of decreased "liking" and "wanting" in MDD (Proulx et al. 2014). "Liking" and "wanting" are indeed distinguishable (Berridge et al. 2009). Liking is a consummatory response to hedonic stimuli, whereas wanting refers to the approach behavior of the organism as a result of the incentive salience of a reward. Liking has been linked to the opioid/endocannabinoid systems, whereas wanting is mediated by the dopaminergic system. Similar to wanting, reward-based learning is also dopamine mediated. Reduced reward sensitivity (i.e., liking) and reduced striatal response to reward in MDD might also be related to deficits in the striatal opioid/endocannabinoid systems (Chen et al. 2015).

An objective measure of wanting is the level of effort the individual is willing to make to obtain the reward. A PET study of healthy individuals showed that willingness to expend greater effort for larger reward correlates with dopamine functioning in the left striatum and ventromedial PFC (Treadway et al. 2012a). Individuals with MDD are less willing to expend effort for the reward compared to controls (Treadway et al. 2012b), and anhedonia correlates negatively with willingness to expend effort (Treadway et al. 2009). Even individuals with subsyndromal depression show decreased willingness to make effort for rewards. This decreased willingness correlated with reduced anticipatory and consummatory pleasure in individuals with MDD, whereas the correlation was limited to anticipatory anhedonia but not consummatory anhedonia for individuals with subsyndromal depression (Yang et al. 2014).

Individuals with bipolar disorder (BP), on the other hand, exhibit a behavioral pattern that is at the end of the spectrum opposite MDD. Impaired decision-making in BP is characterized by impulsivity and risk taking, and different subtypes of BP show variations in the expression of impaired decision-making (Whitton et al. 2015). An fMRI study of individuals with euthymic BP demonstrated hyperactivation of the VS and OFC compared to controls in response to anticipation of rewarding monetary outcomes, but not during the outcome, in a card guessing paradigm (Nusslock et al. 2012). There was no difference in brain activity between the groups

during loss anticipation. These results suggest increased sensitivity to reward-relevant cues in BP. Another fMRI study investigated the neural correlates of reward valuation and its relation to risk taking in euthymic individuals with BP in a Roulette task (Mason et al. 2014). The anticipation and outcome stages of the task with different reward probabilities and magnitude were examined separately. The BP group showed hyperactivation relative to controls in the VS both during anticipation and experience of rewards. The anticipatory response in the left VS was higher for high reward probability gambles. The BP group also demonstrated hyperactivation relative to controls in both VS and ventromedial PFC when processing reward outcomes. Control group preferentially activated the dorsolateral PFC for high-probability relative to low-probability rewards both during anticipation and delivery stages. In contrast, the BP group preferentially activated the dorsolateral PFC for low-probability (i.e., more risky) rewards. The dorsolateral PFC activity was positively correlated with that of ventromedial PFC in controls; however, these two regions were negatively correlated in the BP group. These results are consistent with impulsivity and risk-taking traits in BP and are related to decreased ability to integrate reward valuation with higher order goals.

15.5 Conclusion

As reviewed here, extensive research has explored the elements of decision-making in detailed computational models and demonstrated the potential neurophysiological mechanisms for decision-making using functional neuroimaging. This basic research provides a framework for analyzing potential pathological mechanisms within the basal ganglia that contribute to decision-making deficits across different neuropsychiatric disorders. In particular, disturbances in dopaminergic pathways and the regulation of these pathways could contribute to alterations in decision-making in disorders including PD, ADHD, OCD, TS, schizophrenia, and mood disorders.

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Chapter 16
Motivational Deficits in Parkinson's Disease: Role of the Dopaminergic System and Deep-Brain Stimulation of the Subthalamic Nucleus

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16.1 Introduction

Parkinson's disease (PD) is traditionally viewed as a motor disorder involving the degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNc) (Samii et al. 2004). However, in addition to the cardinal motor symptoms of PD that includes hypokinesia, rigidity, and resting tremors, a plethora of non-motor symptoms may occur, including sleep disturbance, cognitive impairments, psychosis, anxiety, depression, apathy, and impulsive/compulsive disorders (Aarsland et al. 2009b; Chaudhuri et al. 2006; Chaudhuri and Schapira 2009; Voon et al. 2011). This cluster of symptoms, which was largely neglected in the past, is now recognized as a major contributor to morbidity, severely impairing the patient's quality of life (Chaudhuri et al. 2006; Chaudhuri and Schapira 2009).

Apathy, in particular, appears to be a major neuropsychiatric feature of PD (Aarsland et al. 2009b; Chaudhuri and Schapira 2009). Apathy is classically defined as a motivational deficit (see below) and its frequency varies from 16.5 to 70 %, depending on the assessment scale used and the population studied (Aarsland et al. 2009b; Dujardin et al. 2008; Levy and Dubois 2006). It is, however, now considered that apathy probably affects 30–50 % of PD patients (Dujardin et al. 2008; Lhommee et al. 2012), and that most PD patients will develop apathy during the progression of the disease (Aarsland et al. 2009b; Pedersen et al. 2009; Starkstein and Brockman 2011). In addition, apathy is viewed as a major postoperative complication of deep brain stimulation of the subthalamic nucleus (STN-DBS) (e.g., Houeto et al. 2002; Starkstein and Brockman 2011). As such, during the last decade, the medical and scientific communities have shown increased interest in understanding the pathophysiology of apathy.

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16.2 Nosology and Pathophysiology of Apathy

16.2.1 Nosology of Apathy

A clear definition of apathy is lacking in the current psychiatric classification systems. For instance, the term apathy in the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders IV*) is only used in the context of a specific subtype of personality change due to a general medical condition or as an associated feature of dementia or of the negative symptoms of schizophrenia (APA 1994), while the ICD-10 does not include apathy at all (WHO 2010). More recently in the fifth edition of the DSM (APA 2013), apathy was also referenced as a frequent associated feature of major or mild neurocognitive disorder due to Parkinson's or Huntington's disease, like anxiety and depression, two affective impairments that are prevalently associated with apathy in these neurodegenerative disorders (Aarsland et al. 2009b; Chaudhuri et al. 2006; Craufurd et al. 2001; Thobois et al. 2010; van Duijn et al. 2007). Apathy may therefore be regarded as a non-specific symptom, emerging from a general degradation of cognitive functions, with negligible implications for assessment or treatment. Several evidences, however, suggest that apathy is a true clinical construct (Drijgers et al. 2012; Marin 1990), with interesting transnosographic aspects (Brown and Pluck 2000; Del-Monte et al. 2013; Pluck and Brown 2002).

Robert Marin in the early 1990s proposed that apathy could manifest in neurological disorders as a symptom or a distinct psychiatric syndrome (Marin 1990; Marin et al. 1991). He was the first to propose diagnostic criteria for a syndrome of apathy based on the construct of *deficits in goal-directed behaviors*[1] *or a primary lack of motivation* (Marin et al. 1991). Marin structured the clinical expression of apathy around behavioral, cognitive, and emotional domains that were operationalized as follows:

1. *Diminished goal-directed behavior*, with a lack of effort, energy, initiative, and productivity.
2. *Diminished goal-directed cognition*, with decrease interests, lack of plans and goals, and lack of concern about one's personal problems.
3. *Diminished emotional concomitants of goal-directed behavior*, with a flattened effect and lack of emotional response to positive or negative events.

It was also stated that the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Since the seminal work of Marin, several psychometric scales of apathy were developed, especially for PD (e.g., Lhommee et al. 2012; Sockeel et al. 2006; Starkstein et al. 2009). They basically all rely on the behavioral and cognitive dimensions of apathy, but opinions differ on the inclusion of an emotional dimension.

[1] The term "goal-directed behavior" can be misleading and should be viewed as a "behavior directed toward a goal" and not as a "behavior directed by a goal", as the second has a strong theoretical connotation referring to a specific psychobiological process and putative functional subcompartmentalization of the dorsal striatum (Belin et al. 2009; Yin and Knowlton 2006).

Later, it was suggested by Levy and Dubois that apathy should not be defined as a lack of motivation, pointing out that such definition would be a psychological interpretation of a behavioral change (Levy and Dubois 2006). They instead proposed to define apathy as a quantifiable behavioral syndrome that consists in a quantitative reduction of self-generated voluntary and purposeful behaviors. This aspect of lack of self-generated action is of particular importance, as apathetic patients are able to function properly and to perform daily activities if they receive repeated external stimulation (Isella et al. 2002; Levy and Dubois 2006), indicating a clear deficit in their capacity to initiate and maintain behaviors toward a specific goal. Within this framework, they also argue against apathy as a unique syndrome and alternatively suggest multiple forms of apathetic states that are subscribed to different dysfunctions of the corticostriatal circuits involved in the complex chain of processes, which translate an intention into an adapted action (Levy and Dubois 2006). Interestingly, through this concept, a study using an implicit incentive task has recently reported an association of apathy in PD and non-PD patients, with a strong alteration in the motivational processes normally responsible for translating an expected reward into effort and action, with no change in the perception of reward value (Schmidt et al. 2008). Specifically, apathetic patients were unable to modulate hand-grip force in order to obtain a monetary incentive, in function of its size, while their sensitivity to the relative value of the incentive was preserved (Schmidt et al. 2008). The results of this study are in line with recent clinical observations suggesting that the apathetic state described in PD may be particularly linked to the anticipatory subcomponent of anhedonia, that is the lack of association between pleasure and a specific action, and not to a change in consummatory responses, which reflects the capacity of a subject to experience pleasure when engaged in an enjoyable activity (Der-Avakian and Markou 2012; Loas et al. 2012). Taken together, it strongly indicates that at least some forms of apathy in PD are related to dysfunctions of preparatory, but not consummatory subcomponents of motivated behaviors.

16.2.2 A "Two-Head" Pathophysiological Hypothesis of Apathy in Parkinson's Disease

Apathetic symptoms, such as fatigue and lack of interest or initiative, as well as mood disorders such as depression or anxiety, are often reported even before the onset of motor symptoms, or early in the disease, in untreated PD patients (Aarsland et al. 2009a; Pedersen et al. 2009; Poewe 2008). Apathetic symptoms also frequently worsen during STN-DBS (Houeto et al. 2002; Starkstein and Brockman 2011), particularly in cases of strong reduction of dopaminergic medication (Thobois et al. 2010), whereas they can be alleviated at different stages of the disease by treatment with the dopamine precursor levodopa or dopaminergic D_2/D_3 receptor (D_2/D_3R) agonists, such as ropinirole or pramipexole (Chaudhuri and Schapira 2009; Czernecki et al. 2002, 2008; Ishizaki and Mimura 2011; Leentjens et al. 2009; Thobois et al. 2010; Volkmann et al. 2010). Apathy in PD thus appears to depend on the dopaminergic state of the patients, suggesting an important role of

dopamine in the pathophysiology of this non-motor symptom (Chaudhuri and Schapira 2009; Krack et al. 2010; Volkmann et al. 2010). In line with this hypothesis, functional imaging studies in humans have reported an association between PD-related apathy, as well as anxiety and depression, and the extent of dopaminergic denervation in several brain regions, including the ventral and dorsal striatum and the prefrontal cortex (Remy et al. 2005; Thobois et al. 2010; Weintraub et al. 2005). This therefore suggests that the resurgence of apathy observed during STN-DBS is a dopaminergic withdrawal-like syndrome, secondary to the reduction of pharmacotherapies (e.g., Thobois et al. 2010).

Some investigators otherwise propose that postoperative apathy may be directly linked to STN-DBS (Drapier et al. 2006; Starkstein and Brockman 2011; Volkmann et al. 2010). In two longitudinal studies, Verin and coworkers found no association between the increase of apathy following STN-DBS surgery and the reduction in the dopaminergic medication dose, arguing against the aforementioned hypothesis (Drapier et al. 2006; Le Jeune et al. 2009; see also Kirsch-Darrow et al. 2011). In Drapier's study, electrodes were placed more ventrally in the STN of apathetic than non-apathetic DBS patients (Drapier et al. 2006), suggesting that apathy could be due to a diffusion of the electric current of the stimulation to the limbic-related territory of the STN (Le Jeune et al. 2010).

These conflicting data may be resolved if, as regarded by Levy and Dubois, apathy may result from different neurobiological dysfunctions and at least two types of apathy can be observed in PD: (1) a fluctuating apathetic state directly related to a hypodopaminergic state resulting from the dopaminergic neuronal loss, and that can be revealed by the decrease in dopaminergic medication associated with STN-DBS, and (2) a more protracted apathy, resistant to dopaminergic medication and observed in the chronic stage after surgery (Drapier et al. 2006; Starkstein and Brockman 2011; Voon et al. 2006). Nevertheless, the pathogenesis of apathy in PD remains elusive. For instance, there are no clear mechanisms of action of DBS on the basal ganglia loops that could account for a direct effect on mood and motivation, despite some interesting preclinical studies (reviewed in Krack et al. 2010; Temel et al. 2009). Moreover, it appears difficult to disentangle the specific role of the dopaminergic denervation and that of DBS since it has been reported that STN-DBS influences the dopaminergic function on its own (Deniau et al. 2010; Savasta et al. 2011).

Approaches relying on experimental models of PD and STN-DBS thereby can be useful tools to dissect the potential causal contribution of these two factors and their possible interactions.

16.3 The Dopaminergic Nigrostriatal System and Motivational Deficits in Parkinson's Disease

We first set out to determine the potential implication of the dopaminergic neurodegenerative process in the development of apathy. Investigating the neuropsychiatric dimension of PD in experimental models has remained a challenging issue because

of the difficulty in disentangling the potential motivational and mood-related deficits from the motor impairments characteristic of the disease (e.g., Lindgren and Dunnett 2012), as well as the relative contribution of the different subparts of the ascending dopaminergic pathways arising from the ventral tegmental area (VTA) and the SNc.

Most authors have linked apathy, and its related affective disorders, to the partial dopaminergic denervation of the mesolimbic system that frequently occurs in PD patients (Agid et al. 1984; Krack et al. 2010). Specifically, estimation of dopaminergic neuronal loss within the VTA in post-mortem studies varied from 30 to 60 % (Tong et al. 2000), leading to a ~50 % dopaminergic denervation of the ventral head of the caudate nucleus of PD patients (Kish et al. 1988). Interestingly, Torack and Morris (1988) found a partial dopaminergic loss in the mesolimbic system exclusively in depressed, but not in non-depressed PD patients. Functional imaging studies also suggest that apathy, anxiety, and depression in PD are associated with a dopaminergic hypofunction within the ventral striatum (Remy et al. 2005; Thobois et al. 2010). Others, however, suggest that the partial loss of dopaminergic neurons in the VTA is not severe enough, especially in the early stages of the disease, to induce strong neuropsychiatric symptoms (Levy and Dubois 2006). They instead hypothesize that Parkinsonian apathy directly stems from the loss of dopaminergic neurons in the SNc, the main nucleus initially affected in the disease, as, beyond its well-known role in motor functions, the dopaminergic nigrostriatal system is strongly implicated in the control of motivated behaviors (Belin et al. 2009; Bromberg-Martin et al. 2010; Palmiter 2008; Wise 1973; Yin and Knowlton 2006). Interestingly, depression and anxiety have been also found specifically associated with a greater putaminal dopaminergic denervation (Weintraub et al. 2005). Similar correlations between apathy and putaminal dopaminergic denervation were evidenced in patients with Alzheimer's disease and Lewy body dementia (David et al. 2008), suggesting that these neuropsychiatric symptoms involve a nigrostriatal dopaminergic dysfunction.

16.3.1 Functional Dissociation of the Dopaminergic Mesocorticolimbic and Nigrostriatal Systems

We developed a lesion-based model using stereotaxic bilateral injections of the neurotoxin 6-hydroxydopamine (6-OHDA) into discrete areas of the rat SNc or VTA, to selectively induce degeneration of the DA mesocorticolimbic and/or nigrostriatal systems. As shown in Fig. 16.1, VTA and SNc 6-OHDA lesions resulted in distinct, non-overlapping complementary patterns of dopaminergic denervation and dopamine loss throughout striatal territories (Drui et al. 2014; Favier et al. 2014). Importantly, infusion of the neurotoxin can lead to a 40–60 % tyrosine hydroxylase immunoreactivity (TH-IR) loss in the NAc (Fig. 16.1c), similar to the partial denervation of the ventral striatum observed in PD (Kish et al. 1988). Our study was aimed at determining whether such limited dopaminergic loss would impact motivational function, akin to complete dopaminergic mesolimbic

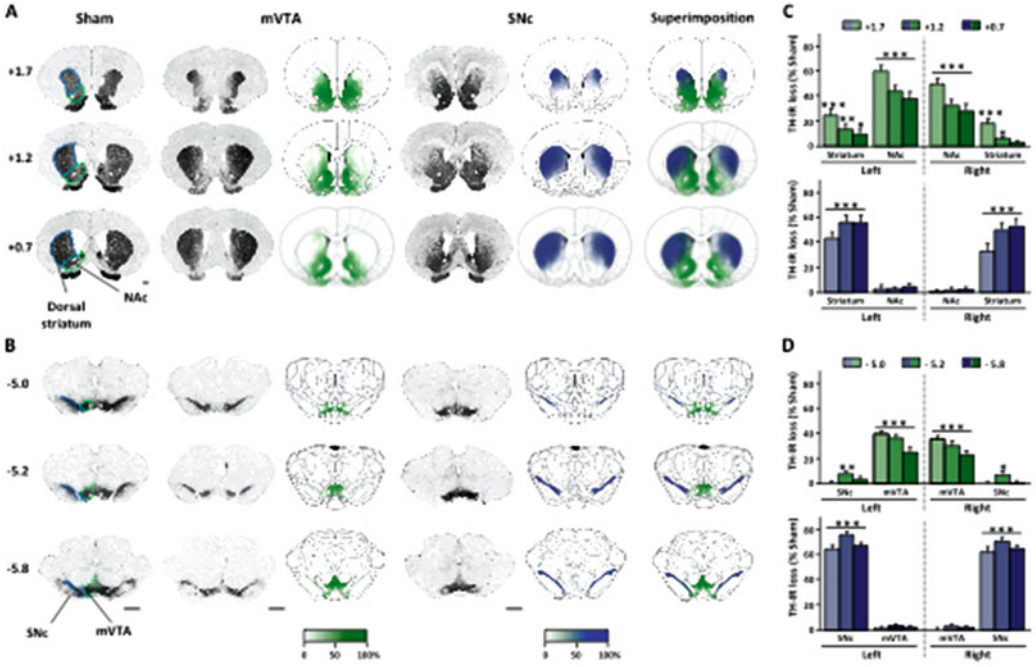

Fig. 16.1 Bilateral partial lesions of the VTA or SNc result in distinct, non-overlapping, complementary patterns of DA depletion throughout striatal territories. (**a**, **b**) Representative photomicrographs of coronal sections stained for TH in striatal (+1.7 to 0.7 mm anterior to bregma) (**a**) and mesencephalic (−5 to −5.8 mm posterior to bregma) (**b**) regions according to the stereotaxic atlas of Paxinos and Watson (1998). Scale bar = 1 mm. The gradient of color (*white* to *green* or *white* to *blue*) in schematic sections corresponds to the measured DA-lesioned area in the different brain structures studied for each lesion performed. VTA lesions are represented in *green* and SNc lesions in *blue*. The highest intensity of *green* or of *blue color* (100 %) indicates that all animals had lesions in the corresponding area, whereas the lowest color intensity (*white*, 0 %) corresponds to a non-lesioned or non-denervated area. (**c**, **d**) Quantification of the loss of TH staining in the different mesencephalic (**d**) and striatal (**c**) structures, expressed as percentage of the mean value obtained for sham-operated animals ± SEM. $n = 22–28$, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. From Drui et al. 2014. *VTA* ventral tegmental area, *SNc* substantia nigra pars compacta, *DA* dopamine, *TH* tyrosine hydroxylase

lesions (e.g. Berridge 2007; Le Moal and Simon 1991; Salamone et al. 2003). The SNc lesions also led to a partial dopaminergic denervation in the dorsal striatum (Fig. 16.1c). The loss of TH-IR was predominant in the lateral striatal portion (Fig. 16.1a), but remained below 80 % (Drui et al. 2014), leading to a 70 % decrease in basal extracellular dopamine levels in the dorsal striatum, with no changes in the NAc (Favier et al. 2014). This partial denervation was crucial for preventing the severe alterations of the motor functions that usually occur for denervation around or above 80 % (e.g., Brizard et al. 2006; Kirik et al. 1998). This approach allowed us to study specifically the role of the nigrostriatal DA system in motivational and affective processes, in the absence of the usual potential bias related to locomotor impairments. Using several tests, we consistently found that our partial dopaminergic SNc lesion did not induce significant motor impairments (Drui et al. 2014; Favier et al. 2014).

16.3.2 Bilateral Partial Dopaminergic Lesions of the SNc, but not of the VTA, Specifically Impair Motivated and Affective Behaviors

Because it is suggested that apathy in PD is related to preparatory, but not consummatory, behavioral deficits, we used various non-operant and operant tasks to distinguish between the potential effects of the lesions on these two subcomponents of motivated behaviors. For instance, we showed that partial dopaminergic lesion of the SNc, but not of the VTA, dramatically impaired operant responding for obtaining a sucrose solution (Fig. 16.2a). The absence of effect of the partial dopaminergic mesocorticolimbic lesion on motivation was confirmed under a progressive ratio schedule of reinforcement, when the workload required to obtain the reward increased exponentially (Drui et al. 2014). This result confirmed numerous data showing that complete lesions of this system are necessary to decrease motivated behaviors (Le Moal and Simon 1991; Nieoullon and Coquerel 2003). In addition, we found a robust negative correlation between operant performances and the loss of TH-IR within the dorsal striatum (Fig. 16.2b), supporting the implication of the dopaminergic nigrostriatal system in motivational processes. This reduced behavioral response of SNc-lesioned animals could not be attributed to an impairment in instrumental learning as, and despite a very low level of operant activity, their capacities to discriminate between a reinforced and non-reinforced lever were preserved (Drui et al. 2014). Moreover, this behavioral deficit was observed after the full acquisition of the instrumental task, confirming that a learning impairment did not account for this effect (Favier et al. 2014). Furthermore, the reduced behavioral response of SNc-lesioned rats could not be attributed to a decrease in the sensitivity to the rewarding properties of sucrose since rodents demonstrated a clear preference for the sucrose solution in a two-bottle choice procedure (Fig. 16.2c). This indicates that partial dopaminergic SNc lesions do not affect hedonic, consummatory processes, but selectively impair preparatory behaviors.

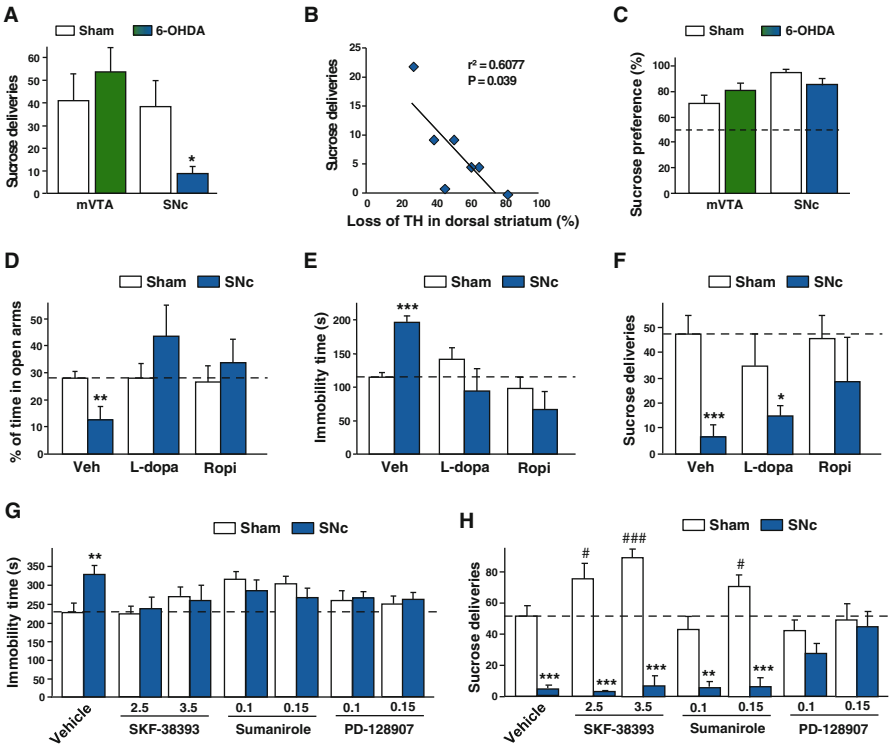

Fig. 16.2 Bilateral partial 6-OHDA lesions of the SNc, but not of the VTA, induced motivational and affective impairments that are reversed by dopaminergic agonists. (**a**) Number of sucrose deliveries (0.2 mL, 2 %) during an hour operant session, under a FR1 schedule of reinforcement (averaged from the last three sessions). (**b**) Linear regressions between three sessions-averaged sucrose deliveries and the loss of TH within the dorsal striatum for SNc lesions, $n = 6–9$. (**c**) Preference for a 2 % sucrose solution over water during 24 h two-bottle choice sessions, $n = 12–19$. (**d–f**) Effects of i.p. subchronic administration of L-Dopa (12.5 mg/kg), Ropinirole (Ropi, 1 mg/kg) or vehicle (veh) were evaluated in an elevated plus-maze (**d**), a forced-swim test (**e**) and in an operant sucrose self-administration procedure (**f**), $n = 6–11$. (**g**, **h**) Effects of i.p. subchronic administration of SKF-38393 (2.5 and 3.5 mg/kg), Sumanirole (0.1 and 0.15 mg/kg), PD-128907 (0.1 and 0.15 mg/kg), or vehicle were evaluated in an elevated plus-maze (**g**) and in an operant sucrose self-administration procedure (**h**), $n = 8–21$. Data are expressed as mean ± SEM. *Dotted lines* represent the mean of the behavioral performances of vehicle-treated sham animals. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$, sham-operated versus lesioned within the same treatment and $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ between the treatments for sham-operated and lesioned conditions respectively. Adapted from Drui et al. 2014 and Carnicella et al. 2014. *SNc* substantia nigra pars compacta, *TH* tyrosine hydroxylase, *i.p.* intraperitoneal

We also investigated whether similar effects could be observed with a non-ingestive, non-food-related, incentive reward. We therefore tested whether SNc, and also VTA, 6-OHDA lesions would affect novelty-seeking, operationalized by the acquisition of instrumental conditioning, reinforced only by the contingent presentation of a "novel" cue-light. As previously observed (Deroche-Gamonet et al. 2002), the cue-light acted as a robust positive reinforcer in control groups and VTA-

lesioned animals, but not in SNc-lesioned rats (Drui et al. 2014). In contrast, neither VTA nor SNc lesions impaired preference for a novel environment in a non-instrumental novelty place preference procedure (Drui et al. 2014). Again, a marked motivational deficit was observed specifically in animals with partial dopaminergic SNc lesions, when an instrumental preparatory action was required.

As aforementioned, apathy in PD is frequently associated with anxiety and depression. We therefore investigated affective-related behaviors and found that SNc-, but not VTA-, lesioned rats displayed reduced social interaction, anxiety-related behaviors in an elevated plus-maze, and a dark/light avoidance test, as well as a depressive-like behavior, as reflected by an increase in the time spent immobile in a forced-swim test (Drui et al. 2014); and see SNc-lesioned control groups of Fig. 16.2d, e.

16.3.3 Reversal of the Behavioral Deficits Resulting from Nigrostriatal Dopaminergic Denervation by Dopaminergic Medications: Implication of the Dopamine D3 Receptor

To further examine the role of dopamine and validate our experimental approach, we tested whether subchronic systemic administration of pharmacological dopaminergic agents classically used in PD could correct some of the behavioral impairments induced by partial dopaminergic SNc lesions. Anxiety- and depressive-like behaviors displayed by SNc-lesioned rats were fully reversed by L-Dopa and the D_2/D_3R agonist ropinirole, as indicated by a reversal of the reduction in time spent in the open arms of the elevated plus-maze and immobility in the forced swim-test (Fig. 16.2d, e) (Drui et al. 2014). In addition, ropinirole was the only pharmacological agent that significantly improved instrumental performances under a fixed- or progressive-ratio of reinforcement, in an operant sucrose self-administration procedure (Fig. 16.2f and Drui et al. 2014). The efficacy of D_2/D_3R agonists in reversing the motivational deficits induced by the SNc lesions was confirmed with the use of pramipexole in the same operant procedure (Favier et al. 2014). Importantly, discontinuation of pramipexole treatment led to the resurgence of motivational deficits (Favier et al. 2014), thereby mimicking the reemergence or worsening of apathetic symptoms when the dopaminergic medication is reduced or withdrawn in PD patients (Thobois et al. 2010).

The beneficial effects of D_2/D_3R agonists on the motivational deficits induced by dopaminergic SNc lesions are likely to be mediated specifically by the D_3R subtype. Indeed, while subchronic administration of a D_1R (SKF-38393), D_2R (Sumanirole), or D_3R agonist (PD-128907) fully reversed the anxiety- and depression-related behaviors induced by the SNc lesions (Fig. 16.2g and Carnicella et al. 2014), only the D_3R agonist reversed the deleterious impact of the SNc lesion on operant sucrose self-administration (Fig. 16.2h). The absence of effect of SKF-38393 and sumani-

role was particularly striking, as both agonists dose-dependently improved the instrumental performances of sham animals (Fig. 16.2h), indicating that the lack of effect was most likely not due to insufficient dosage. Moreover, the effect of PD-128907 in SNc-lesioned animals was selectively blocked by the D_3R antagonist SB-277011A, but not the D_2R antagonist L-741,626 (Carnicella et al. 2014), confirming the D_3R-mediated action of the agonist. Taken together, these data strongly suggest a pivotal role of D_3R in motivational processes. This is consistent with earlier evidence that this receptor contributes to the control of affective and motivated behaviors (Sokoloff et al. 2006) and mediates the therapeutic effect of dopaminergic medication on neuropsychiatric symptoms in PD.

16.3.4 Conclusions

By inducing partial and selective dopaminergic neuron loss in either the SNc or the neighboring VTA in rats, we provide new insights into the pathophysiological mechanisms underlying the neuropsychiatric symptoms of PD and the therapeutic action of dopaminergic agents. Specifically, our work suggests that motivational and affective deficits are core impairments in PD, which result from the loss of nigral dopaminergic neurons, the major neuronal group known to degenerate in this disease. This interpretation is consistent with a growing body of evidence documenting similar affective and cognitive impairments in other experimental rodent PD models (Bonito-Oliva et al. 2014; Chen et al. 2014; Santiago et al. 2010; Tadaiesky et al. 2008; Winter et al. 2007); but see (Branchi et al. 2008; Eskow Jaunarajs et al. 2012). Our work also highlights a critical role of the dopaminergic nigrostriatal system on motivation, a role that had been previously largely neglected and mainly attributed to the dopaminergic mesoaccumbal pathway (Wise 2009). On the other hand, our data are consistent with pioneering studies supporting a role of the nigrostriatal dopamine on motivation (Beninger and Ranaldi 1993; Fibiger et al. 1973; Ungerstedt 1971; Zis et al. 1974) or with more recent electrophysiological-based evidence in monkeys (e.g., Hollerman and Schultz 1998; Hollerman et al. 1998; and see for a review Bromberg-Martin et al. 2010). A role of the dopaminergic nigrostriatal system in reward, reinforcement, and motivation was also recently confirmed in two studies using selective optogenetic modulation of nigral dopaminergic neurons (Ilango et al. 2014; Rossi et al. 2013). However, the mechanisms underlying motivational deficits induced by the denervation of the dopaminergic nigrostriatal system remain to be investigated. Our results are in line with a role of dopamine in incentive mechanisms (Berridge 2007), as the SNc lesions disrupt "wanting" rather than "liking" behaviors. Although the theory of incentive motivation is generally centered on the dopaminergic mesoaccumbal system (Berridge 2007), it may be of interest to shift our focus toward the dorsal striatum, in keeping with its role in "motivational habit" (Sjoerds et al. 2014) or "incentive habit" (Belin et al. 2009, 2013), which has recently been proposed to explain the mechanisms of drug addiction. Our lesions affected predominantly the dorsolateral part of the striatum, but dopaminergic denervation also occurred in its dorsomedial part. Regarding

the respective role of the dorsomedial and dorsolateral striatum in goal-directed and habitual control of behavior (Belin et al. 2009; Yin and Knowlton 2006) (discussed in this volume: e.g. Chap. 18), we can speculate that, by affecting these two subdivisions of the dorsal striatum, our SNc lesions induce a catastrophic loss of motivational functions supported by various regions of the dorsal striatum. This mechanism has been indeed recently proposed to account for abulia and apathy in PD (Redgrave et al. 2010).

Although the data presented in the previous paragraphs point toward a critical implication of the dopaminergic neurodegenerative process in the induction of apathy in PD, they do not rule out that STN-DBS may also contribute to the occurrence of such neuropsychiatric symptoms. The possibility of a contribution of STN-DBS independent to dopaminergic mechanisms is discussed in the following paragraphs.

16.4 Motivational Deficits in Parkinson's Disease Patients Under Deep-Brain Stimulation of the Subthalamic Nucleus: Is the Dopaminergic System Implicated?

Based on very convincing experimental data obtained in the MPTP monkey, another gold standard model of PD, and demonstrating that STN-DBS improves parkinsonian motor symptoms in this model (Benazzouz et al. 1993), clinical trials using STN-DBS for the treatment of PD patients were initiated by Benabid and collaborators early in the 90s (Limousin et al. 1995a, b). Since then, STN-DBS has been widely developed and is now recognized as a well-established treatment for the main PD motor symptoms. This has led to decreasing L-Dopa requirement, and consequently, decreasing L-DOPA-induced dyskinesia (Bejjani et al. 2000; Benabid et al. 1998, 2000; Krack et al. 1998, 2003; Krause et al. 2001; Moro et al. 1999). Nevertheless, despite its remarkable clinical efficacy on motor symptoms, the precise mechanisms by which STN-DBS exerts its effects remain a matter of debate. Furthermore, numerous recent published works which report neuropsychiatric changes after STN-DBS, with onset or worsening of pre-existing disorders or, on the contrary, improvement of neuropsychiatric symptoms revive this debate (Temel 2010).

16.4.1 Non-motor Symptoms Associated with STN-DBS in PD Patients

Almost 10 years after the beginning of the therapeutic application of STN-DBS in PD patients, some clinical studies have reported the appearance of non-motor effects varying from a decline in executive functions to mood disorders (Funkiewiez et al. 2004). Concerning the later, acute effects most commonly observed are feelings of euphoria, characterized by disinhibition, hyperactivity, and increased

motivation. More rarely, this disinhibition might manifest as mania, impulsive behaviors, or intermittent explosive behaviors (Herzog et al. 2003; Krack et al. 2001; Mallet et al. 2007; Sensi et al. 2004; Ulla et al. 2011). Contrary to what is observed for the acute effects, apathy, depression, and anxiety constitute the long-term complications most often encountered after STN-DBS (Czernecki et al. 2008; Funkiewiez et al. 2004). Pioneering studies reporting that advanced PD patients experienced such symptoms after STN-DBS surgery were published at the end of the 90s (Kumar et al. 1999; Moro et al. 1999). Since then, these early reports have been widely confirmed by more recent clinical publications (Drapier et al. 2006; Dujardin et al. 2001; Funkiewiez et al. 2004; Gervais-Bernard et al. 2009; Houeto et al. 2002; Soulas et al. 2008; Voon et al. 2008; York et al. 2008). It is difficult to know the precise incidence of STN-DBS-associated long-term neuropsychiatric side effects. Discrepancies in reported frequency may reflect differences in time of assessment, instruments used, and strategy of dopaminergic treatment management (Voon et al. 2006). Apathy and depression have been reported as two of the most frequent symptoms (Funkiewiez et al. 2004; Krack et al. 1998, 2003; Czernecki et al. 2008; Drapier et al. 2006; Houeto et al. 2002; Saint-Cyr et al. 2000; Troster 2009), with an increase to about 25 % in the proportion of apathetic PD patients at the third postoperative year and 1.5–25 % in the proportion of individual episodes of postoperative depression (Voon et al. 2006).

16.4.2 Motivational and Affective Deficits and STN-DBS: What Can We Learn from Experimental Studies

The underlying mechanisms of long-term neuropsychiatric side effects associated with STN-DBS are not understood and clinical reports describing them are confusing (for details see discussion above). Complex neurobiological mechanisms including biochemical changes and neuroplasticity in terms of basal ganglia loops connectivity seem to be implicated in these side effects. However, as mentioned above, it is difficult to elucidate these mechanisms in a clinical context because of the various overlapping variables such as state of dopaminergic denervation, duration and doses of dopaminergic treatment, and STN-DBS conditions.

In this context, experimental studies performing STN-DBS in animal models have also reported clear-cut effects on cognitive and limbic functions and thus provide a significant advantage to study the underlying neurobiological mechanisms of these effects (Baunez et al. 2007; Desbonnet et al. 2004; Klavir et al. 2009; Temel et al. 2005). Indeed, animal models allow to experimentally dissociate the effects of STN-DBS from the modulation of the dopaminergic system, thus leading to a clear identification of the real impact of each treatment on motivational states.

The STN has long been recognized as a key structure for motor information processing in the basal ganglia (BG) (Kita and Kitai 1987; Kitai and Deniau 1981; Nambu 2004; Smith et al. 1998). But the cortico-BG-thalamocortical connectivity comprises five parallel loops (Alexander et al. 1986), and the STN is also a

component of the limbic loop involving the prefrontal cortex, the nucleus accumbens, and the ventral pallidum (Mathai and Smith 2011). Furthermore, the borders between the sensorimotor, associative, and limbic territories of the STN overlap (Haynes and Haber 2013). Thus, the STN should be considered as a structure involved in the processing of limbic and motivational information in addition to its role in motor activity (Parent and Hazrati 1995a, b). The earliest evidence of such an implication was provided by electrophysiological recordings of STN neurons in the monkey performing an oculomotor task, which revealed changes of activity when the animal was expecting a reward (Matsumura et al. 1992). Since then, the role of the STN in motivational functions has been widely confirmed (Baunez and Lardeux 2011; Baunez and Robbins 1997; Baunez et al. 2011; Darbaky et al. 2005; Temel et al. 2006; Winstanley et al. 2005; Witjas et al. 2005). Further electrophysiological explorations in monkeys and rats revealed that STN neurons not only respond during the expectation, but also during the delivery of the reward (Darbaky et al. 2005; Teagarden and Rebec 2007). Concomitantly, behavioral data obtained in rats have shown that a lesion of the STN differentially affects motivation for food, cocaine, and alcohol, depending on the nature of the reward or the preference for it (Baunez et al. 2005; Lardeux and Baunez 2008; Uslaner et al. 2005) (see Chap. 14 in this volume). These findings led to the conclusion that STN neurons can encode the salience and the value of different natural rewards (Lardeux et al. 2009). In this context, it can be expected that modulation of its activity by DBS should induce per se changes in motivational state. For further discussions on the role of the subthalamic nucleus in reward, the reader is also referred to Chaps. 14 and 17 in this volume.

Some animal studies have reported direct or indirect effects of STN-DBS on motivational behaviors, but the results are not totally consistent. One study performed in 6-OHDA-rats using unilateral STN stimulation has shown that STN-DBS applied with effective parameters to alleviate motor symptoms did not result in any effect on non-motor functions. Nevertheless and interestingly, the authors also reported that DA-depleted rats exhibited profound and long-lasting deficits in the operant task, among which was the inability to perform the task, which was not alleviated by STN-DBS. Even more, STN-DBS transiently impaired the ability of sham-STN-DBS animals to perform an operant task, but did so to a lesser extent than in 6-OHDA-lesioned rats (Darbaky et al. 2003). Using bilateral STN-DBS in dopamine-depleted and naïve animals, Baunez et al. have reported (Baunez et al. 2007) that STN-DBS did not alleviate or exacerbate the deficits induced by a lesion of dopamine neurons in a visual attentional task such as the latency to make correct responses or omissions, but did induce perseverative approaches to the food magazine. Similar effects were observed in sham-operated control rats. The authors hypothesized that an increased number of visits into the food magazine could be due to enhanced motivation. However, increased number of omissions induced by STN-DBS did not suit well with such hypothesis. To further explore this idea of an 'enhanced motivation' induced by STN-DBS, Rouaud and co-workers have used behavioral tests of reference to evaluate motivational state (continuous and progressive ratio of reinforcement in a self-administration procedure) in non-parkinsonian

rats under STN-DBS (Rouaud et al. 2010). They showed that STN-DBS increased motivation for a 'natural' reward such as food, but reduced it for drugs of abuse such as cocaine. Their results were obtained in normal food-restricted non-parkinsonian rats and the stimulation was applied during short periods.

Concomitantly to these studies of the effect of STN-DBS on motivated behaviors, other authors were interested in its effects on depressive behaviors and the results are coherent (Creed et al.; Temel et al. 2007). Using the forced swim test, a widely used and validated behavioral test of depression, Temel et al. (2007) have shown that bilateral STN-DBS induced acute and reversible depression-like behavior linked to a decrease in firing rate of 5-HT neurons in the dorsal raphe nucleus (DRN) of control and parkinsonian rats. This effect was prevented by a pretreatment with a selective inhibitor of the 5-HT transporter (Hartung et al. 2011; Tan et al. 2012; Temel et al. 2007). These data were strengthened by more recent ones also obtained in rats and showing that repeatedly applied STN-DBS impaired performance in the learned helplessness model of depression and that this impairment was associated with decreased levels of *zif268* gene expression in the DRN (Creed et al. 2013), further implicating 5-HT mechanisms in these STN-DBS-induced depressive-like effects.

16.4.3 Proposed Mechanism for the Motivational Deficits Associated with STN-DBS: The Role of the Dopaminergic System

The remarkable efficacy of STN-DBS for a range of treatment-resistant disorders is well-established, but it is still not matched by a comparable understanding of the underlying neural mechanisms. Experimental evidence collected so far allows for some conclusions to be drawn about the neural and systems level mechanisms of action of DBS. The effects of DBS do vary with the stimulation parameters (including frequency, amplitude, pulse width, and duration), with the intrinsic physiological properties of the stimulated region and the interactions between the electrode and the geometric configuration of the surrounding neural tissue and specific anatomy of the targeted region. Current evidence clearly shows that DBS affects multiple neural elements, but foremost myelinated axons and, to a lesser extent, cell bodies. The weight of the evidence has shown that the most likely mode of action for STN-DBS is through stimulation-induced modulation of brain activity (Kringelbach et al. 2007; McIntyre and Hahn 2010; McIntyre et al. 2004; Montgomery and Baker 2000; Vitek 2002), rather than synaptic inhibition (Dostrovsky et al. 2000), depolarization blockade (Beurrier et al. 2001), or synaptic depression (Garcia-Rill et al. 2014). Overall, the data suggest that for movement disorders DBS works by modulating the larger, closed loop networks of thalamocortical and corticostriatal connections, where sequential motor program commands are setup, passed on, and executed (Leblois et al. 2006; Li et al. 2007). Movement disorders can be conceptualized as subtle shifts or as a corruption of this distributed spatiotemporal information and, as suggested by computational models,

DBS works by specifically regularizing the interactions between diffuse but functionally related networks (McIntyre and Hahn 2010). The impact of such mechanisms on limbic and associative functions and associated neuropsychiatric disorders are still poorly understood (Czernecki et al. 2005; Drapier et al. 2006; Funkiewiez et al. 2004; Thobois et al. 2010). Clinical observations have led to propose two hypotheses to explain the apathy observed in patients under STN-DBS. Because the STN is a motor, cognitive, but also limbic structure (Peron et al. 2013), it was suggested that apathy induced by STN-DBS occurs as a result of stimulating the limbic cortico-subcortical loops (Le Jeune et al. 2010; Mallet et al. 2007) independently of a reduction in dopamine replacement therapy (DRT) (Denheyer et al. 2009; Drapier et al. 2006). Another hypothesis is that apathy observed in STN-DBS patients stems from the degeneration of the dopamine mesolimbic pathway that is unmasked by the DRT reduction (Thobois et al. 2010). Thus, apathy observed under STN-DBS appears to be a complex and multifactorial behavioral disorder, but there are still few experimental or clinical data that could explain the possible pathophysiological mechanisms.

Microdialysis studies in normal animals and in animal models of PD have provided strong evidence that STN-DBS increases striatal dopamine (DA) release and metabolism (Bruet et al. 2001; Lacombe et al. 2007; Meissner et al. 2001, 2002, 2003; Paul et al. 2000; Pazo et al. 2010) and that this increase is associated with an improvement of PD motor symptoms (Zhao et al. 2009). Although clinical studies have not yet provided definitive evidence that similar mechanisms occur in patients (Abosch et al. 2003; Hilker et al. 2003; Nozaki et al. 2013; Strafella et al. 2003), the hypothesis that changes in striatal DAergic activity contribute to the clinical benefits of STN-DBS is supported by evidence that STN-DBS is effective only against levodopa-sensitive motor symptoms and that DAergic medication levels can be reduced by up to 50 % in PD patients on chronic STN-DBS treatment (Benabid et al. 1998; Krack et al. 2003; Limousin et al. 1995a; Moro et al. 1999).

Recent studies performed in rats have reported that STN-DBS can also induce alterations in the dopaminergic limbic system (Carcenac et al. 2015; Winter et al. 2008). Indeed, using microdialysis, Winter et al. have demonstrated that acute STN-DBS increases release of DA in the nucleus accumbens (NAcc) of normal and 6-OHDA anesthetized rats. Then, using autoradiography, Carcenac et al. have provided original evidence that long-lasting STN-DBS reduced the expression of D_2 and D_3 receptors in the same structure and in the same animal model (Fig. 16.3). More experiments are needed to determine if the down-regulation of D_2 and D_3 receptors involves pre- or post-synaptic receptors. Nevertheless, DA in the NAcc is involved in motivation, reward, and emotion (Berridge 2007; Ikemoto et al. 1997; Salamone et al. 2012) and some of these aspects are mediated by D_2R and D_3R (Nowend et al. 2001; Salamone et al. 2007; Tran et al. 2002). Indeed, the blockade of D_2/D_3R in the NAcc decreases the willingness of rodents to work for a reward, leading the animals to shift from more effortful toward less effortful behavior (Nowend et al. 2001; Salamone et al. 2007). Furthermore, clinical PET data have shown that a decrease in D_2/D_3R signal in the NAcc of patients suffering from attention deficit hyperactivity disorders (ADHD) is correlated with their motiva-

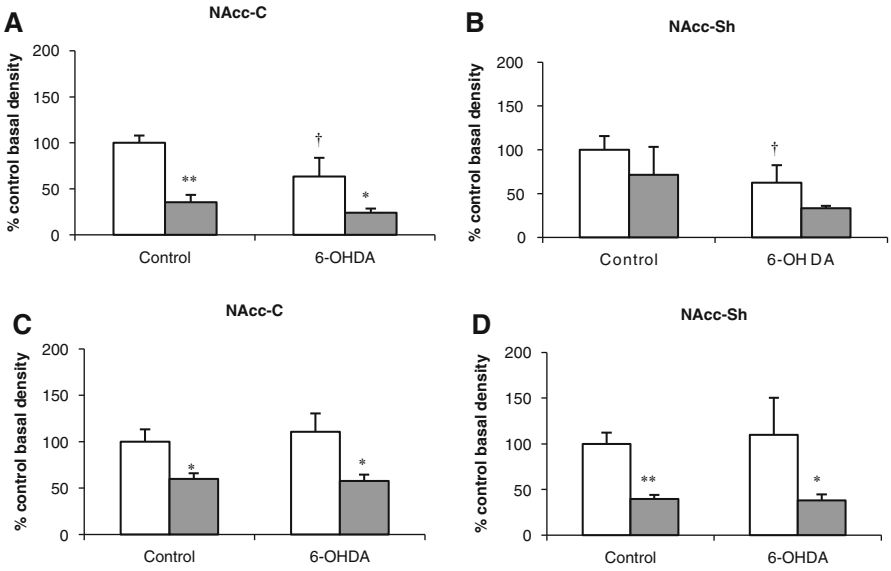

Fig. 16.3 STN-DBS decrease D_2R and D_3R density in the nucleus accumbens of normal and 6-OHDA rats. Density of D_2R (**a**, **b**) and D_3R (**c**, **d**) in control (*white bar*) and SNc-lesioned (*grey bar*) rats submitted (ON condition) or not (OFF condition) to STN-DBS and measured in the accumbens nucleus (core (**a**, **c**) and shell (**b**, **d**)). The binding was expressed in each condition (control STN-DBS ON group, lesioned STN-DBS OFF and ON groups) and for each brain region studied as a mean percentage ± SEM of basal levels of radioligand binding in control STN-DBS OFF group, defined as 100 %. $^{*}p < 0.05$ and $^{**}p < 0.01$, ON versus OFF; $^{\dagger}p < 0.05$ 6-OHDA versus control. *NAcc-C* accumbens nucleus core, *NAcc-Sh* accumbens nucleus shell

tional deficits (Volkow et al. 2011a, b). These results provide strong evidence for a direct facilitatory action of STN-DBS in postoperative apathy. Furthermore and in an interesting way, these data may also account for the responsiveness of postoperative apathy to treatment with DA agonists and D_2R/D_3R agonists in particular (Czernecki et al. 2008), thereby reconciling the two hypotheses put forward to explain apathy related to STN-DBS.

16.4.4 Conclusions

STN-DBS is a frequently performed surgical procedure to treat PD patients in their advanced stage. This therapy improves motor disability and the quality of life, but some patients have shown unexpected postoperative behavioral changes. These behavioral effects may be explained on the basis that the STN is interconnected not only with motor areas, but also with associative and limbic brain regions.

Thus, after 20 years of use of STN-DBS for treating motor symptoms in Parkinson's disease, the influence of STN-DBS on non-motor disorders observed in

PD is still largely unexplored. So, improving our understanding of STN-DBS mechanisms, especially those concerning non-motor disorders, represents a challenge for research in human behavior and appears essential to improve treatment.

16.5 Concluding Remarks

Recent experimental and clinical evidence clearly highlights a critical role of dopamine in apathy in PD. Whether apathy intrinsically results from the loss of dopamine in the nigrostriatal system or the progression of dopamine loss toward more limbic areas, or from other variables associated with STN-DBS, remains a matter of debate. However, in light of the recent data presented in this chapter, it may be proposed that different etiological factors all contribute to the development and occurrence of apathy, or of different forms of apathy, in PD. For instance, the dopaminergic dysfunctions resulting from neurodegenerative mechanisms may act synergistically with the DBS of STN regions associated with the nigrostriatal and the mesolimbic system to induce or to aggravate apathy. Moreover, although the present chapter focuses on the role of dopamine, it must be emphasized that the noradrenergic and serotoninergic systems are also likely to be involved in the pathophysiology of PD-related neuropsychiatric symptoms (e.g. Ballanger et al. 2012; Delaville et al. 2012; Politis et al. 2012; Temel et al. 2007). Some forms of apathy, non-responsive to dopaminergic medication, have also been found to be associated with executive dysfunction (Dujardin et al. 2009; Starkstein and Brockman 2011) or with atrophy of specific basal ganglia or cortical structures (Carriere et al. 2010; Reijnders et al. 2010). Therefore, apathy, and related affective impairments, in PD can be considered a complex and multifactorial entity.

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Conflicts of Interest none.

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Chapter 17
The Circuitry Underlying the Reinstatement of Cocaine Seeking: Modulation by Deep Brain Stimulation

Leonardo A. Guercio and R. Christopher Pierce

17.1 Introduction

Drug addiction is a major public health concern in the United States and worldwide. It is estimated that the total costs of substance abuse, including productivity, health, and crime-related costs, exceed $600 billion annually in the United States alone (National Drug Intelligence Center, 2011). Cocaine is the third most commonly abused illegal drug, after marijuana and prescription painkillers (SAMHSA 2012). In 2011, nearly five million Americans over the age of 12 used cocaine. In addition, there were 1.4 million regular cocaine users aged 12 and older, comprising 0.5 % of the American population (SAMHSA 2012). One of the major problems facing cocaine addicts is the discouragingly high rate of relapse, even after prolonged abstinence (Carroll et al. 1994; O'Brien 1997). Despite many years of preclinical and clinical research focused on understanding the underlying neurobiological and neurochemical basis of addiction, there are no FDA-approved pharmacotherapeutic interventions for the treatment of cocaine abuse and relapse.

Cocaine craving and relapse into cocaine-taking behavior in abstinent addicts can be precipitated by three major factors: stress, environmental stimuli previously associated with drug taking, or re-exposure to the drug itself (Wit and Stewart 1981; Jaffe et al. 1989; O'Brien et al. 1992; Sinha et al. 1999). In an effort to better understand cocaine taking and relapse of cocaine-seeking behavior in laboratory

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animals, researchers utilize the drug self-administration/extinction/reinstatement paradigm (Shalev et al. 2002; Shaham and Hope 2005; Bossert et al. 2013). This involves training an animal to self-administer cocaine via operant conditioning. After a period of self-administration (typically several hours per day for 14–21 days), the drug solution is removed and replaced with saline, which extinguishes cocaine seeking. Following extinction, a stressor, cocaine-associated cues, or a non-contingent priming injection of cocaine reinstate drug-seeking behavior; operant responding does not result in cocaine administration during the reinstatement session (Shalev et al. 2002). This model is invaluable for assessing the neurobiological underpinnings of drug addiction and craving-induced relapse of cocaine-seeking behavior.

The reinforcing and rewarding effects of cocaine are primarily mediated by the mesocorticolimbic dopamine system (Pierce and Kumaresan 2006). However, a large body of evidence indicates that cocaine craving and relapse is mediated by changes in glutamatergic transmission in these same nuclei (Schmidt and Pierce 2010). It is currently thought that long-term neural adaptations in both the dopaminergic and glutamatergic systems are involved in the drug-associated learning underlying cocaine reinstatement (Jones and Bonci 2005; Kauer and Malenka 2007). In this chapter, we will focus on dopaminergic and glutamatergic transmission underlying cocaine reinstatement, with a particular emphasis on how these changes can inform the use of deep brain stimulation (DBS) as a therapeutic intervention for cocaine craving and relapse.

17.2 Neuronal Circuitry Underlying Cocaine Reinstatement

Cocaine is a monoamine transporter inhibitor, exerting its effects on the dopamine, serotonin, and norepinephrine systems (Ritz et al. 1990). However, several studies have shown that dopamine is the critical biogenic amine underlying the reinstatement of cocaine seeking. Administration of a dopamine, but not serotonin or norepinephrine, reuptake inhibitors reinstated cocaine seeking (Schenk 2002; Schmidt and Pierce 2006). Dopaminergic neurons in the ventral tegmental area (VTA) richly innervate corticolimbic nuclei, including the nucleus accumbens, medial prefrontal cortex (mPFC), amygdala, hippocampus, and ventral pallidum (Berendse et al. 1992; Brog et al. 1993; Heimer et al. 1997) (Fig. 17.1). Several of these corticolimbic nuclei, including the medial prefrontal cortex (mPFC), hippocampus, and amygdala, send robust glutamatergic projections to the nucleus accumbens (Phillipson and Griffiths 1985; Friedman et al. 2002) (Fig. 17.1), which is segregated into two subregions, the shell and the core. The nucleus accumbens sends efferent GABAergic projections to the VTA and ventral pallidum (Heimer et al. 1991; Groenewegen et al. 1999), which in turn send efferent GABAergic projections to the mediodorsal thalamus (Groenewegen 2003). The mediodorsal thalamus sends glutamatergic projections to the mPFC, effectively closing this circuit.

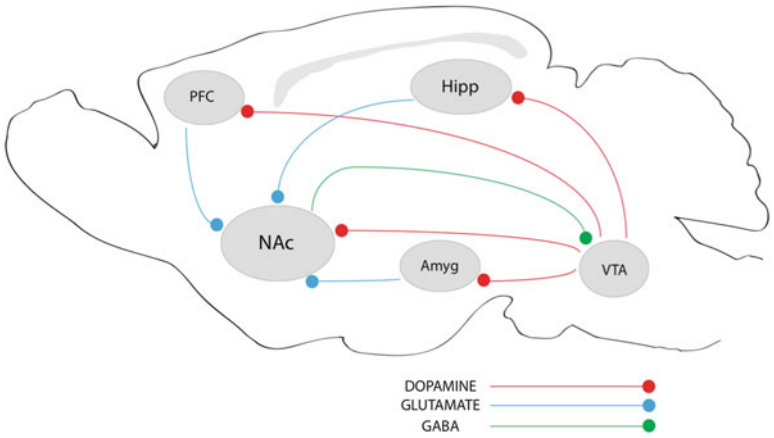

Fig. 17.1 Major nuclei and circuitry involved in cocaine reinstatement. *VTA* ventral tegmental area, *Hipp* hippocampus, *Amyg* amygdala, *NAc* nucleus accumbens, *PFC* prefrontal cortex

As mentioned previously, the nucleus accumbens can be further divided into two functionally segregated subregions, the medial shell and the lateral core (Meredith et al. 1992; Groenewegen et al. 1999). The nucleus accumbens shell, considered part of the limbic system, has been implicated primarily in the reinforcing and rewarding properties of drugs of abuse (Di Chiara and Imperato 1988; Pontieri et al. 1995; Carlezon and Wise 1996). The nucleus accumbens core, considered an extension of the basal ganglia, contributes to drug-associated, cue-induced drug seeking (Di Ciano and Everitt 2004; Fuchs et al. 2004; Ito et al. 2004). Therefore, the nucleus accumbens serves to integrate the motivational information from the limbic system with the basal ganglia to facilitate an appropriate behavioral response.

17.3 The Role of the Nucleus Accumbens in Cocaine Seeking

17.3.1 Priming-Induced Reinstatement of Cocaine Seeking in the Nucleus Accumbens

It is now clear that increased dopamine transmission in the nucleus accumbens promotes the reinstatement of cocaine seeking. Thus, intra-nucleus accumbens infusions of cocaine (Park et al. 2002) or dopamine (Cornish and Kalivas 2000) promoted the reinstatement of cocaine seeking in rats that previously self-administered cocaine. Co-administration of the nonselective dopamine receptor antagonist, fluphenazine, blocked the reinstatement of cocaine seeking precipitated by intra-accumbal infusions of dopamine (Cornish and Kalivas 2000). Dopamine transmission is mediated by a family of G-protein-coupled receptors, with five subtypes (D1–D5). These receptors subtypes can be further categorized as D1-like (D1

and D5) or D2-like (D2, D3, D4) based on their sequence homology and pharmacology (Missale et al. 1998; Beaulieu and Gainetdinov 2011). There is an extensive literature indicating that dopaminergic transmission through D1-like and D2-like dopamine receptors is critical for the reinstatement of cocaine seeking in the nucleus accumbens (Bossert et al. 2005; Schmidt et al. 2006).

Systemic administration of D1-like or D2-like dopamine receptor antagonists blocked the reinstatement of cocaine seeking (Self et al. 1996; Khroyan et al. 2000; Vorel et al. 2002). Peripheral injections of D2-like dopamine receptor agonists promoted cocaine priming-induced reinstatement (Self et al. 1996; Khroyan et al. 2000; De Vries et al. 2002). However, systemically administered D1-like dopamine receptor agonists failed to promote and actually attenuated cocaine reinstatement (Self et al. 1996, 2000; Khroyan et al. 2000), while intra-accumbal shell administration of D1-like dopamine receptor agonists promoted the reinstatement of cocaine-seeking behavior (Bachtell et al. 2005; Schmidt and Pierce 2006; Schmidt et al. 2006; Anderson et al. 2008). These results suggest that systemic administration of D1-like dopamine receptor agonists activate D1-like dopamine receptors in other brain regions, which counteract the reinstatement of cocaine seeking promoted by activation of D1-like dopamine receptors in the nucleus accumbens. It should be noted, however, that dopaminergic transmission in the core and shell subregions of the nucleus accumbens has differential effects on cocaine seeking. Administration of D1-like or D2-like dopamine receptor antagonists in the accumbens shell, but not the core, blocked priming-induced reinstatement of cocaine seeking (Anderson et al. 2003, 2005; Bachtell et al. 2005). Consistent with these findings, intra-accumbal shell, but not core, administration of D1-like and D2-like dopamine receptor agonists promoted the reinstatement of cocaine seeking (Schmidt and Pierce 2006). Collectively, these findings offer evidence that D1-like and D2-like dopamine receptors play a critical role in cocaine reinstatement and that D1-like dopamine receptors in other nuclei besides the nucleus accumbens shell may have differential effects on the reinstatement of cocaine seeking.

Although cocaine increases the extracellular concentration of dopamine, there is overwhelming evidence that chronic cocaine use also affects glutamatergic transmission, particularly in the nucleus accumbens, which can have profound effects on neuronal function and alter the behavioral effects of cocaine (Schmidt and Pierce 2010). While cocaine has no direct action on glutamatergic neurons or glutamate levels, withdrawal from repeated exposure to cocaine reduced basal extracellular levels of glutamate in the nucleus accumbens (Pierce et al. 1996), an effect due to decreased activity of the cysteine-glutamate antiporter (Baker et al. 2003).

Cocaine priming-induced reinstatement is associated with increased extracellular levels of glutamate in the nucleus accumbens (Cornish et al. 1999; Cornish and Kalivas 2000; Park et al. 2002; McFarland et al. 2003). In fact, systemic injections of N-acetyl cysteine, a pro-drug that increases the activity of the cysteine-glutamate antiporter, attenuated cocaine priming-induced reinstatement. Glutamate binds to *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid (AMPA), and metabotropic glutamate (mGluR) receptors, all of which play a role in cocaine reinstatement (for a review, please see Schmidt and Pierce 2010).

Intra-accumbal administration of AMPA or an AMPA receptor agonist reinstated cocaine seeking, whereas intra-accumbal administration of AMPA receptor antagonists attenuated cocaine priming-induced reinstatement (Cornish et al. 1999; Cornish and Kalivas 2000; Famous et al. 2008; Ping et al. 2008). These effects were observed in both core and shell subregions of the nucleus accumbens. AMPA receptors are heteromeric, ligand-gated ion channels expressed throughout the brain that are composed of four subunits: GluA1-GluA4, and are also permeable to Ca^{2+}, Na^{+}, and K^{+}. AMPA receptors have a unique feature where conversion of a glutamine (Q) residue to an arginine (R) on the GluA2 subunit renders GluA2-containing AMPA receptors impermeable to calcium (Hume et al. 1991; Rueter et al. 1995). Since most GluA2 subunits are edited in this matter, GluA2-containing AMPA receptors are considered calcium-impermeable (Tanaka et al. 2000).

Cocaine reinstatement is associated with the phosphorylation and trafficking of GluA1- and GluA2-containing AMPA receptors. Consistent with these results, suppression of GluA1 transcription in the accumbens blocked the reinstatement of cocaine seeking induced by a priming injection of cocaine (Ping et al. 2008). Cocaine reinstatement is associated with increased phosphorylation and surface expression of GluA1-containing AMPA receptors and of GluA1 in the accumbens shell, but not the core (Anderson et al. 2008). Consistent with this, preventing the transport of GluA1-containing AMPA receptors to the cell surface in the nucleus accumbens shell attenuated priming-induced reinstatement of cocaine seeking (Anderson et al. 2008). Additionally, extended withdrawal from cocaine self-administration increased surface expression of GluA1-containing, but not GluA2-containing, AMPA receptors in the nucleus accumbens (Conrad et al. 2008), which may contribute to the reinstatement of cocaine seeking. Cocaine reinstatement is also associated with increased phosphorylation and decreased surface expression of GluA2-containing AMPA receptors in the accumbens shell, but not the core (Famous et al. 2008). Disruption of trafficking of GluA2-containing AMPA receptors attenuated cocaine priming-induced reinstatement (Famous et al. 2008). Similarly, more recent studies have shown that withdrawal from cocaine self-administration and incubation of cocaine craving is associated with increased insertion of GluA1-containing, GluA2-lacking, calcium-permeable AMPA receptors (CP-AMPARs) in the nucleus accumbens (Mameli et al. 2009; Ferrario et al. 2010; McCutcheon et al. 2011). Taken together, these findings suggest that cocaine reinstatement is associated with increases in accumbal glutamatergic transmission, mediated in part by the differential trafficking of GluA1 and GluA2 subunits.

17.3.2 Cue-Induced Reinstatement of Cocaine Seeking in the Nucleus Accumbens

Relapse to drug-seeking behavior can be induced by re-exposure to environmental cues and contexts previously associated with drug taking (O'Brien et al. 1992). This can be modeled experimentally in three major ways: context-induced reinstatement

(Crombag and Shaham 2002), discrete cue-induced reinstatement (Meil and See 1996), and discriminative cue-induced reinstatement (Weiss et al. 2000). We will summarize behavioral findings from all three models; however, a recent review from Marchant et al. (2015) expertly details the corticostriatal circuitry underlying context-induced reinstatement.

As in priming-induced reinstatement, re-exposure to cocaine-associated stimuli resulted in increased glutamate levels in the nucleus accumbens (Hotsenpiller et al. 2001). Systemic administration of ceftriaxone, an antibiotic that enhances glutamate reuptake in synapses, attenuated cocaine cue-induced reinstatement (Sari et al. 2009; Sondheimer and Knackstedt 2011; Fischer et al. 2013). Consistent with this, ceftriaxone-mediated attenuation of cue-induced cocaine reinstatement was reversed by blockade of GLT-1, which is responsible for glutamate reuptake, in the accumbens core, but not the shell (Fischer et al. 2013).

Systemic or intra-accumbal core administration of baclofen and muscimol attenuated cue-induced reinstatement of cocaine-seeking behavior (Di Ciano and Everitt 2004; Fuchs et al. 2004). Additionally, excitotoxic lesions of the nucleus accumbens core, but not the shell, attenuated cocaine seeking induced by discrete cues (Ito et al. 2004). Consistent with these findings, systemic and intra-accumbal core administration of an AMPA receptor antagonist, or intra-accumbal core administration of an NMDA receptor antagonist, attenuated cue-induced reinstatement (Di Ciano 2001; Bäckström and Hyytiä 2006, 2007; Zavala et al. 2008)—however, these treatments had no effect when injected into the accumbens shell. Finally, cocaine seeking induced by cocaine-associated cues is associated with increased dendritic spines and synaptic potentiation in medium spiny neurons in the accumbens core, but not the shell (Gipson et al. 2013).

While the role of the accumbens core is well-established for cue-induced reinstatement of cocaine seeking, there is evidence that the accumbens shell also contributes to cue-induced reinstatement, particularly in context-induced reinstatement. Administration of baclofen and muscimol into the accumbens shell attenuated the context-induced reinstatement of cocaine seeking (Fuchs et al. 2008). Additionally, intra-accumbal shell administration of AMPA/kainate glutamate receptor antagonist CNQX attenuated context-induced reinstatement of cocaine seeking (Xie et al. 2012). It should be noted, however, that similar effects were observed in the accumbens core in both cases. Together, these findings suggest that the nucleus accumbens core, and to a lesser extent, the accumbens shell, is critical for cue-induced reinstatement of cocaine seeking.

17.3.3 Stress-Induced Reinstatement of Cocaine Seeking in the Nucleus Accumbens

Reinstatement to drug-seeking behavior can also be induced by stress (Sinha et al. 1999). Stress-induced reinstatement is typically triggered using an intermittent footshock (Shaham and Stewart 1995), but can also be triggered by acute food

deprivation (Shalev et al. 2000), administration of pharmacological stressors such as yohimbine, an α2-adrenergic receptor antagonist, or swim stress (Lee et al. 2004). However, the underlying neuronal circuits and mechanisms contributing to stress-induced reinstatement of cocaine seeking are not well-understood.

Administration of baclofen and muscimol into both the nucleus accumbens core and shell attenuated footshock-induced reinstatement of cocaine seeking (McFarland et al. 2004). A similar study found that footshock potentiated priming-induced reinstatement triggered by a sub-threshold dose of cocaine (Graf et al. 2013). Additionally, corticosterone potentiated the cocaine-induced increase in extracellular dopamine levels in the nucleus accumbens and pharmacological blockade of accumbal dopamine receptors blocked reinstatement triggered by a sub-threshold dose of cocaine (Graf et al. 2013). Interestingly, stress-induced reinstatement of cocaine seeking was also associated with increased glutamate levels in the nucleus accumbens core (McFarland et al. 2004). These findings, while sparse, suggest that the modulation of dopaminergic and glutamatergic signaling in the nucleus accumbens may contribute to stress-induced reinstatement of cocaine seeking.

17.3.4 Non-pharmacological Manipulations of the Nucleus Accumbens in the Reinstatement of Cocaine-Seeking Behavior

There have been several studies that have used non-pharmacological approaches to examine the role of the nucleus accumbens in cocaine priming-induced reinstatement; chief among them are DBS and optogenetics. It has been shown that DBS of the nucleus accumbens shell, but not the core or the dorsal striatum, attenuated cocaine priming-induced reinstatement (Vassoler et al. 2008, 2013). The reduction in reinstatement was not due to inactivation of accumbal medium spiny neurons as intra-accumbal shell infusions of GABA agonists, baclofen and muscimol, or lidocaine did not mimic these effects (Vassoler et al. 2013). However, baclofen/muscimol and lidocaine in the accumbens core attenuated cocaine priming-induced reinstatement (Vassoler et al. 2013). Additionally, DBS of the accumbens shell also attenuated cue-induced reinstatement of cocaine seeking (Guercio et al. 2015). A recent finding showed that DBS of the accumbens shell attenuated locomotor sensitization to cocaine, without any effect on general ambulatory activity (Creed et al. 2015). This helps to bolster support for the use of accumbal DBS as a potential therapeutic agent in the treatment of addiction.

The underlying mechanism of DBS is not very clear, especially since multiple neurotransmitter systems are involved and can have differential effects in the accumbens core and shell as described previously. Optogenetic inhibition of the accumbens core attenuated cocaine priming-induced reinstatement (Stefanik et al. 2013), an effect that seemed to be dependent on glutamatergic projections from the mPFC. Similarly, DBS of the accumbens shell promoted antidromic activation of

GABAergic interneurons in the mPFC (Vassoler et al. 2013). This is consistent with previous work that has shown that accumbal DBS inhibited activity of cortico-accumbal glutamatergic neurons via antidromic activation of GABAergic interneurons in the mPFC (McCracken and Grace 2007). Taken together, these findings suggest that the projections from the mPFC and potentially other corticolimbic structures contribute to the reinstatement of cocaine seeking.

17.4 The Role of the mPFC in the Reinstatement of Cocaine Seeking

17.4.1 Priming-Induced Reinstatement of Cocaine Seeking in the mPFC

The mPFC can be divided into three functional components: the anterior cingulate cortex, the prelimbic cortex, and the infralimbic cortex (Krettek and Price 1977), all of which receive dense dopaminergic projections from the VTA (Heidbreder et al. 2003). These regions can also be segregated into the dorsal mPFC, which includes the anterior cingulate cortex and dorsal prelimbic cortex, and the ventral mPFC, which includes the ventral prelimbic and infralimbic cortices (Graybiel et al. 1990; Steketee 2003). Notably, these regions have differential glutamatergic projections to the nucleus accumbens. The dorsal mPFC projects mainly to the nucleus accumbens core, whereas the ventral mPFC projects primarily to the nucleus accumbens shell (Berendse et al. 1992; Wright and Groenewegen 1995; Ding et al. 2001). While there is strong evidence for the role of the dorsal mPFC in the reinstatement of cocaine seeking, there is also evidence for the role of the ventral mPFC as well.

Infusion of dopamine or cocaine into the dorsal mPFC reinstated cocaine seeking (McFarland and Kalivas 2001; Park et al. 2002). Consistent with this, administration of baclofen and muscimol (McFarland and Kalivas 2001) or TTX (Capriles et al. 2003) into the prelimbic, but not infralimbic, cortex attenuated cocaine priming-induced reinstatement. Additionally, administration of nonspecific, D1-like, or D2-like dopamine antagonists into the prelimbic, but not infralimbic, cortex blocked cocaine reinstatement (McFarland and Kalivas 2001; Park et al. 2002; Capriles et al. 2003; Sun and Rebec 2006). These findings suggest a strong role for dopaminergic transmission in the mPFC in cocaine priming-induced reinstatement.

The glutamatergic projections from the mPFC to the nucleus accumbens, particularly the dorsal mPFC-accumbens core projections, play a critical role in the reinstatement of cocaine seeking (Kalivas and O'Brien 2008; Schmidt and Pierce 2010; Gipson et al. 2013). As mentioned previously, cocaine priming-induced reinstatement is associated with increased glutamate release in the nucleus accumbens, an effect that was blocked by pharmacological inactivation of the dorsal mPFC (McFarland et al. 2003). Consistent with this, reinstatement of cocaine seeking induced by administration of cocaine directly into the dorsal mPFC was blocked by

intra-accumbal administration of AMPA antagonists (Park et al. 2002). Additionally, repeated cocaine exposure increased the excitability of glutamatergic projection neurons in the prelimbic cortex (Hearing et al. 2013), which increased their responsiveness for cocaine (Sun and Rebec 2006).

While there is strong evidence for the role of the dorsal mPFC in cocaine reinstatement, there is also evidence, albeit conflicting, that the ventral mPFC plays a critical role as well. In one particular study, administration of baclofen and muscimol into the infralimbic cortex reinstated cocaine seeking, while microinjections of AMPA into this region attenuated cocaine seeking (Peters et al. 2008). This is inconsistent with the finding that administration of baclofen and muscimol into either the prelimbic or infralimbic cortices attenuated cocaine priming-induced reinstatement (Vassoler et al. 2013). It is difficult to draw conclusions on the role of the ventral mPFC and its connections to the nucleus accumbens shell in cocaine reinstatement. However, recent findings suggest that the infralimbic cortex is involved in the consolidation of memories for the extinction of cocaine-seeking behavior (LaLumiere et al. 2010). Collectively, these results indicate that increased dopamine transmission in the mPFC and glutamatergic transmission from the mPFC to the nucleus accumbens are critical for the reinstatement of cocaine seeking.

17.4.2 Cue-Induced Reinstatement of Cocaine Seeking in the mPFC

While the mPFC plays a critical role in the priming-induced reinstatement of cocaine seeking, its role in cue-induced reinstatement has been minimally explored. Re-exposure to cocaine-associated cues is associated with increased neuronal activity in the mPFC (Neisewander et al. 2000; Ciccocioppo et al. 2001), an effect that was blocked by administration of a D1-like dopamine receptor antagonist (Ciccocioppo et al. 2001). Consistent with this finding, TTX infusion into the prelimbic, but not infralimbic, cortex attenuated cue-induced reinstatement of cocaine seeking (McLaughlin and See 2003); similar results were found in a context-induced reinstatement model of cocaine (Fuchs et al. 2005). Additionally, administration of baclofen and muscimol into the prelimbic cortex attenuated cue-induced reinstatement (Gipson et al. 2013).

Recent findings using a cue-induced reinstatement paradigm shed some light on the role of the ventral mPFC and its projections to the nucleus accumbens shell in the reinstatement of cocaine seeking. Activation of AMPA receptors in the ventral mPFC attenuated cue-induced reinstatement of cocaine seeking, an effect that was blocked by co-administration of an AMPA antagonist in the nucleus accumbens shell (LaLumiere et al. 2012). Additionally, intra-accumbal shell injections of dopamine reversed the blockade of cocaine seeking induced by activation of AMPA receptors in the ventral mPFC (LaLumiere et al. 2012). This suggests that the ventral mPFC acts upstream of the mesocorticolimbic dopamine system to regulate cocaine seeking in the accumbens shell. Together, these findings suggest a role for

the mPFC in the cue-induced reinstatement of cocaine seeking; however, further studies are needed to more fully characterize the mechanisms by which mPFC contributes to cue-induced reinstatement.

17.4.3 Stress-Induced Reinstatement of Cocaine Seeking in the mPFC

Administration of baclofen and muscimol into the dorsal mPFC attenuated footshock-induced reinstatement of cocaine seeking (McFarland et al. 2004). However, there were no effects seen with administration of these agonists into the ventral mPFC. Administration of fluphenazine into the dorsal mPFC attenuated cocaine seeking induced by footshock (McFarland et al. 2004). Additionally, injections of a D1-like, but not D2-like, dopamine receptor antagonist into the prelimbic, but not infralimbic, mPFC attenuated footshock-induced reinstatement of cocaine seeking (Capriles et al. 2003). Consistent with these findings, stress-induced reinstatement of cocaine seeking is associated with a rise in dopamine and glutamate levels in the mPFC (McFarland et al. 2004). Interestingly, stress-induced reinstatement of cocaine seeking was also associated with increased glutamate levels in the nucleus accumbens core, an effect that was attenuated by administration of baclofen and muscimol in the dorsal mPFC (McFarland et al. 2004). These findings support the role of the mPFC in the stress-induced reinstatement of cocaine seeking.

17.4.4 Non-pharmacological Manipulations of the mPFC in the Reinstatement of Cocaine-Seeking Behavior

Non-pharmacological-based studies of the mPFC seem to support the role of glutamatergic projections from the dorsal mPFC to accumbens core in the reinstatement of cocaine seeking. However, there is also evidence that the ventral mPFC to accumbens shell projections may contribute as well. Optogenetic inhibition of the prelimbic mPFC or prelimbic cortical fibers in the nucleus accumbens core attenuated the reinstatement of cocaine seeking (Stefanik et al. 2013). Withdrawal from cocaine self-administration also increased the insertion of CP-AMPARs at mPFC-accumbal shell synapses (Pascoli et al. 2014). A similar investigation showed that extended withdrawal from cocaine self-administration led to accumulation in CP-AMPARs in the infralimbic-accumbens shell synapses and accumulation of non-CP-AMPARs in prelimbic-accumbens core synapses (Ma et al. 2014). Optogenetic reversal of this synaptic remodeling potentiated and inhibited cocaine seeking, respectively (Ma et al. 2014). Although these findings are generally consistent with the role of the prelimbic-accumbens core projections in cocaine reinstatement, they add complexity to the role of the infralimbic-accumbens shell projections. Additionally, DBS of the infralimbic, but not the prelimbic cortex, attenuated cocaine priming-induced

reinstatement (Vassoler et al. 2009). These findings suggest that dopaminergic projections to the mPFC and its afferent glutamatergic projections to the nucleus accumbens are critically involved in the reinstatement of cocaine seeking.

17.5 The Role of the Hippocampus in the Reinstatement of Cocaine Seeking

17.5.1 Priming-Induced Reinstatement of Cocaine Seeking in the Hippocampus

The hippocampus, a critical region for memory and reward-related behaviors, can be segregated into dorsal and ventral regions (Moser and Moser 1998). The dorsal hippocampus is critical for spatial memory (Moser et al. 1995), whereas the ventral hippocampus plays more important role in motivated behavior (Henke 1990). Additionally, these regions have different anatomical connections, with distinct inputs and outputs (Swanson and Cowan 1977). The ventral hippocampus is strongly innervated with dopaminergic projections from the VTA (Gasbarri et al. 1994a, b). Additionally, the ventral hippocampus is the major output region of the hippocampus (Groenewegen et al. 1987) with strong projections to the nucleus accumbens, particularly the accumbens shell (Fanselow and Dong 2010). Stimulation of the ventral hippocampus leads to increased extracellular dopamine levels in the nucleus accumbens, an effect that was abolished through blockade of glutamate receptors in the accumbens (Blaha et al. 1997; Taepavarapruk et al. 2000). There is strong evidence for the role of the ventral hippocampus in the reinstatement of cocaine seeking.

Inactivation of the ventral hippocampus with lidocaine blocked cocaine priming-induced reinstatement (Sun and Rebec 2003). Consistent with this, administration of baclofen and muscimol to the ventral hippocampus attenuated cocaine priming-induced reinstatement (Rogers and See 2007). Interestingly, neonatal rats with lesions to the ventral hippocampus showed increased cocaine taking as well as increased cocaine-seeking behavior following withdrawal as adults (Chambers and Self 2002). These results indicate a role for the hippocampus, particularly the ventral hippocampus, in the reinstatement of cocaine seeking.

17.5.2 Cue-Induced Reinstatement of Cocaine Seeking in the Hippocampus

There is strong evidence for the role of the dorsal hippocampus in context-induced reinstatement of cocaine seeking (Fuchs et al. 2005, 2007; Hearing et al. 2010; Xie et al. 2010, 2013), which is consistent with the role of the dorsal hippocampus in spatial memory (Moser et al. 1995). However, there is evidence that the ventral

hippocampus plays a role in the cue-induced reinstatement of cocaine seeking. Re-exposure to cocaine-associated cues is associated with increased neuronal activity in the ventral hippocampus (Kufahl et al. 2009). Administration of lidocaine into the ventral hippocampus attenuated the cue-induced reinstatement of cocaine seeking (Sun and Rebec 2003). Consistently, administration of baclofen and muscimol into the ventral hippocampus also attenuated cue-induced cocaine seeking (Rogers and See 2007). This effect was also seen in a context-induced reinstatement paradigm (Lasseter et al. 2010). Interestingly, neonatal rats with ventral hippocampus lesions exhibited potentiated cue-induced reinstatement of cocaine seeking compared to sham controls as adults (Karlsson et al. 2013). Collectively, these findings suggest that the hippocampus plays an important role in the cue-induced reinstatement of cocaine seeking.

17.5.3 Non-pharmacological Manipulations of the Hippocampus in the Reinstatement of Cocaine-Seeking Behavior

Brief theta-burst stimulation of the ventral hippocampus, which mimics its endogenous rhythms (Vinogradova 1995), reinstated cocaine-seeking behavior (Vorel 2001). Recent evidence showed that ventral hippocampal inputs to the accumbens shell are strongly potentiated following cocaine injections, and that in vivo, bidirectional optogenetic modulation of these inputs attenuated and enhanced cocaine-induced locomotion (Britt et al. 2012). Additionally, it was shown that mice optogenetically self-stimulated ventral hippocampal fibers in the nucleus accumbens shell, supporting the role of this nucleus in cocaine seeking (Britt et al. 2012). Additionally, DBS of the ventral hippocampus attenuated cocaine seeking (Guercio et al., *in prep*). Due to the fact that the ventral hippocampus receives strong dopaminergic projections from the VTA and projects strongly to the nucleus accumbens shell, coupled with the fact that disruption of the dorsal hippocampus may impair non-drug-related memories (Raybuck and Lattal 2014), the ventral hippocampus seems to be a critical nucleus for the reinstatement of cocaine seeking.

17.6 The Role of the Basolateral Amygdala in the Reinstatement of Cocaine Seeking

17.6.1 Priming-Induced Reinstatement of Cocaine Seeking in the BLA

The amygdala is another nucleus that plays a critical role in the reinstatement of cocaine-seeking behavior. Like the hippocampus and mPFC, it also receives dopaminergic projections from the VTA (Fallon et al. 1978) and sends glutamatergic

projections to the nucleus accumbens (Phillipson and Griffiths 1985). The amygdala can be divided into many subnuclei, several of which have been shown to be involved in various types of cocaine reinstatement, particularly cue-induced reinstatement of cocaine seeking (Grimm 2000; McFarland et al. 2004; Fuchs et al. 2005; Mashhoon et al. 2009; Stefanik and Kalivas 2013). The basolateral amygdala (BLA), however, has also been implicated in priming-induced reinstatement of cocaine seeking.

Administration of NMDA into the BLA reinstated cocaine seeking (Hayes et al. 2003). Consistent with this, lesions of the BLA attenuated cocaine priming-induced reinstatement (Yun and Fields 2003). However, inactivation of the BLA using lidocaine had no effect on priming-induced reinstatement of cocaine seeking (McFarland and Kalivas 2001). Antagonism of D1-like and D2-like dopamine receptors in the BLA attenuated cocaine priming-induced reinstatement (Alleweireldt et al. 2006; Di Ciano 2008). Additionally, pharmacological manipulations in the BLA that promote experience-dependent plasticity enhanced extinction and attenuated cocaine seeking (Xue et al. 2014). This is consistent with findings that immediate-early genes *arc* and *zif268* in the BLA were upregulated following priming-induced reinstatement of cocaine seeking (Ziółkowska et al. 2011). While these results indicate that the BLA is involved in the priming-induced reinstatement of cocaine seeking, further studies are required to elucidate the precise mechanisms by which this nucleus contributes to priming-induced reinstatement.

17.6.2 Cue-Induced Reinstatement of Cocaine Seeking in the Basolateral Amygdala

The amygdala plays a critical role in the cue-induced reinstatement of cocaine seeking. Excitotoxic lesions of the BLA abolished the abilities of discrete cues to reinstate cocaine seeking (Meil and See 1997). Administration of TTX or lidocaine into the BLA attenuated cue-induced reinstatement of cocaine seeking (Grimm 2000; Kantak et al. 2002; McLaughlin and See 2003; See 2005; Fuchs et al. 2006). Consistent with this, inactivation of the BLA using injections of baclofen and muscimol also attenuated cocaine cue-induced reinstatement (Gabriele and See 2010). Additionally, disruption of de novo protein synthesis in the BLA attenuated cue-induced reinstatement of cocaine seeking (Lee et al. 2006). This finding is in agreement with the results that cue-induced reinstatement of cocaine seeking is associated with upregulation of immediate-early genes *arc*, *zif268*, and *fos* in the BLA (Zavala et al. 2008; Ziółkowska et al. 2011; Zhou et al. 2014).

Re-exposure to cocaine-associated cues increased extracellular levels of dopamine in the BLA (Weiss et al. 2000). Administration of D1-like and D2-like dopamine receptor antagonists into the BLA attenuated cocaine cue-induced reinstatement (See et al. 2001; Alleweireldt et al. 2006; Berglind et al. 2006; Mashhoon et al. 2009). Consistent with these findings, administration of a D1 dopamine receptor agonist into the BLA potentiated cue-induced reinstatement of cocaine seeking

(Mashhoon et al. 2009). However, while high doses of a D2-like dopamine receptor antagonist attenuated cue-induced reinstatement, low doses potentiated reinstatement (Berglind et al. 2006), suggesting a more nuanced role of BLA D2-like dopamine receptors in cue-induced reinstatement.

Disruption of glutamatergic signaling in the BLA also affects the cue-induced reinstatement of cocaine seeking. Systemic administration of an AMPA receptor antagonist attenuated cue-induced reinstatement and decreased *fos* expression in the BLA (Zavala et al. 2008). Injections of an NMDA receptor antagonist into the BLA impaired the abilities of cocaine-associated cues to reinstate cocaine seeking (Feltenstein and See 2007). The BLA also projects directly to the prelimbic mPFC (Hoover and Vertes 2007). Disruption of BLA projections to the dorsal mPFC using either lidocaine or baclofen and muscimol attenuated cue-induced reinstatement of cocaine seeking (Fuchs et al. 2007; Mashhoon et al. 2010). Taken together, these findings suggest a critical role for the BLA and its projections to the mPFC in the cue-induced reinstatement of cocaine seeking.

17.6.3 Non-pharmacological Manipulations of the Basolateral Amygdala in the Reinstatement of Cocaine-Seeking Behavior

It was shown that mice optogenetically self-stimulated BLA fibers in the nucleus accumbens, supporting the role of this nucleus in cocaine seeking (Stuber et al. 2011). Consistent with this, optogenetic inactivation of the BLA, or its fibers in the accumbens core or dorsal mPFC, attenuated cue-induced reinstatement (Stefanik and Kalivas 2013). A recent finding showed that extended withdrawal from cocaine self-administration led to an insertion of CP-AMPARs in BLA-accumbens shell synapses and that optogenetic reversal of this synaptic remodeling attenuated cue-induced reinstatement of cocaine seeking (Lee et al. 2013). Collectively, these findings suggest that the BLA may be an important nucleus to target for DBS treatment of cocaine seeking, especially considering its projections to both the nucleus accumbens and mPFC. The reader is also referred to Chap. 14 in this volume for a discussion on the effect of DBS of the subthalamic nucleus on drug addiction.

17.7 Concluding Remarks

There is a large body of evidence implicating multiple brain areas in the reinstatement of cocaine seeking. While these areas contribute to cocaine seeking in similar ways, there is evidence suggesting these regions can have greater roles in certain forms of cocaine reinstatement and thus may present reasonable targets for DBS treatment. DBS in the nucleus accumbens shell, but not the core, or the dorsal striatum attenuated the reinstatement of cocaine seeking. Consistent with this, DBS of

the infralimbic, but not prelimbic, mPFC attenuated the reinstatement of cocaine seeking. Additionally, DBS of the ventral hippocampus, which projects nearly exclusively to the shell subregion of the accumbens, also blocked cocaine reinstatement. There may be mechanistic differences in how these nuclei mediate the reinstatement of cocaine-seeking behavior. However, changes in drug-adaptive synaptic plasticity seem to be a common shared mechanism. Further studies are needed to delineate the precise roles of these neural circuits and the molecular mechanisms by which they contribute to cocaine reinstatement. Ultimately, since the accumbens, particularly the shell subregion, can be highly reorganized by cocaine exposure, this nucleus and the nuclei that project to it are highly promising targets for DBS treatment.

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Part V
Computational Models and Integrative Perspectives

Chapter 18
Cognitive and Stimulus–Response Habit Functions of the Neo- (Dorsal) Striatum

Bryan D. Devan, Nufar Chaban, Jessica Piscopello, Scott H. Deibel, and Robert J. McDonald

18.1 Introduction: A Historical Perspective

In 1979, the book "*The Neostriatum*" (Divac and Öberg 1979b), sponsored by the European Brain and Behavior Society, reported on the proceedings of a workshop in which researchers of the time representing different specializations presented their latest findings on this particular part of the brain that has remained enigmatic even to this day. The Editors of the book, Ivan Divac and Gunilla Öberg, decided to focus the Vejle meeting in Denmark on the "basic experimental work" to complement two preceding meeting-based volumes (Cools et al. 1977; Yahr and Association for Research in Nervous and Mental Disease 1976) and deemphasize the topics of clinical and pharmacological research that was already prominently covered in the past decade. The goal seemed to be to integrate concepts like "cognitive functions" and call out proposals of the past to solve the functional puzzle(s) of the neostriatum within a broad context, with a rich description of the history involved (e.g., Divac and Öberg 1979a, pp. 215–230) and the divisiveness that had preceded decades prior to this meeting. Almost 15 years later, when we (RM and BD) were both beginning our work on multiple memory systems at McGill University, this work from the late 1970s caught our attention and provided inspiration on a different perspective that helped us understand some unexpected experimental findings, given our then present theoretical perspective on "the neostriatum" (or dorsal striatum, a.k.a. cortico-striatal circuits) as a stimulus–response associative system or

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"habit structure" in the mammalian brain (Hirsh 1974; Mishkin et al. 1984; Mishkin and Petri 1984; Petri and Mishkin 1994). Our view of the dorsal striatum was based on some very solid and exciting experimental groundwork (McDonald and White 1993; Packard et al. 1989; White et al. 2013), which has since garnered such praise and recognition to warrant reprint of the original article in the journal *Behavioral Neuroscience* (McDonald and White 2013) and is among the most cited findings in the field, the so-called "double" and "triple" dissociation experiments in rats using different radial maze tasks (McDonald and White 1993; Packard et al. 1989). However, some of the work using variations of the water maze task (McDonald and White 1994) did not seem to fit the model (Devan et al. 1996) and we sought out other research to explain our findings, including the contents of "*The Neostriatum*" as a complement to another influential source, O'Keefe and Nadel's "*The Hippocampus as a Cognitive Map*" published in 1978 (available online in open-access format at cognitivemap.net).

Part of the answer to our problem was obvious when we compared the placement of lesions within the striatum. Lesions of the dorsomedial striatum (DMS) seemed to produce thigmotaxis in the water maze (Devan et al. 1996, 1999), whereas that was not the case with lesions of the dorsolateral striatum (DLS) which did produce effects consistent with a simple stimulus–response (S-R) or habit memory system and parallel to the cognitive-map or "place" functional impairments described for the effects of hippocampal lesions (McDonald and White 1994). Additional work confirmed the functional differences between DMS and DLS lesions using variations of McDonald and White's (1994) competitive cue-place version of the water maze (Devan 1997; Devan et al. 1999; Devan and White 1999), further suggesting that, under certain conditions, the DMS may cooperate with the cognitive-based hippocampal system, while the DLS remained independent, parallel, and even competitive with the hippocampus (McDonald and White 2013). In one experiment, we even determined the interdependence of connectivity between DMS and hippocampus by showing that crossed-unilateral lesions had the same or similar effects to bilateral lesions of either structure alone (Devan and White 1999), very powerful evidence that connections between the structures constitute a functional circuit.

The water maze findings above combined with a non-unitary view of striatal function related to subregional lesion findings led us to a theoretical proposal based on associative learning theories with an expanded review of the literature, combined with new empirical findings related to the above groundbreaking radial maze work (Devan et al. 2011). For example, we report that DMS lesions facilitate radial maze cued win–stay behavior (Devan et al. 2011; Devan and White 1997), while previous studies show that larger lesions of the DLS clearly impair performance on the task (Devan et al. 2011; McDonald and White 2013; White et al. 2013). Our review of the literature in 2011 indicated that the associative learning function of the DLS was a form of simple S–R habit formation, whereas the DMS may contribute to a higher-order form of (S–S) –R function we referred to as "cognitive control" integrating the allo- and meso-cortical input to DMS with the reinforcement function of dopamine input to the dorsal striatum that could be combined with relational stimulus information directly conveyed to this region (e.g., López-Figueroa et al. 1995; McGeorge and Faull 1989).

Even as far back as Lashley's 1941 studies of the topographical projection to the striatum, visual inputs seemed to be restricted to the posterior parts of the structure (as cited in Iversen 1979). However, more recent studies show visual input projecting to longitudinal territories within the DMS of the rat (López-Figueroa et al. 1995), with pre-terminal fibers forming "fluffs" that correspond with weak calbindin staining and yet belong to the matrix compartment. Many association cortical areas project to longitudinal territories with restricted medial–lateral domains in the monkey with some interdigitation of terminal regions consistent with neurochemical compartmentalization (e.g., Selemon and Goldman-Rakic 1985).

Given the lack of direct visual input to the DLS, in 2011, we hypothesized that impairments of simple visual S–R tasks may rely on the reinforcement function of striatal dopamine evoked by unconscious visual sensory information via a phylogenetically older series of connections from the superior colliculus to the substantia nigra and striatum (via the thalamus) in both primates and rats (Coizet et al. 2003, 2007; May et al. 2009), providing a slow incremental strengthening of S–R associations over time, consistent with the longer time intervals to improved accuracy of discriminative behavior to develop for win-stay and other habit tasks. Redgrave et al. (2010) point out that the superior colliculus provides afferent signals to the other input nuclei of the basal ganglia, the dopaminergic neurons in substantia nigra, and to the subthalamic nucleus. Their recent electrophysiological data show that the afferent signals originating in the superior colliculus carry important information concerning the onset of biologically significant events to each of the basal ganglia input nuclei that may be crucial for the proposed functions of selection and reinforcement learning within the striatum.

Divac and Öberg (1979a) pointed out that many studies and theories tend to ignore or fail to appreciate the anatomical heterogeneity within the neostriatum, and we further suggested that the inconsistency in nomenclature over the years has contributed to the confusion, hence our proposal for distinguishing DLS and DMS subregions of the dorsal striatum after a fairly represented review of the neuroanatomical literature on the subject, integrating the re-defined anatomical/connectivity nomenclature to neurobehavioral findings—including lesion, electrophysiological, some pharmacological studies, and consideration of hippocampal and prefrontal relations to dorsal striatum along with a lengthy discussion of various conceptual frameworks, pointing out the strengths and weaknesses of different associative learning models and experimental protocols (e.g., stimulus devaluation studies and R–O and S–O learning processes), the details of which may be re-visited in our previous review.

Divac and Öberg (1979a) also claimed that "inhibitory" and "motor" theories of neostriatal function were too general and could be applied to many areas of the brain, thus rendering such "theories" less meaningful and useful for modern functional conceptions. As Iversen (1979) pointed out in her chapter, even the early anatomical studies in rats, rabbit, cat, and monkey showed that the striatum receives a highly organized projection apparently from all areas of the neocortex, leading to the logical conclusion that prior exclusive emphasis on motor functions missed the exciting and important alternative of cognitive functions, citing an influential statement by Lashley (1950; S.E.B. Symposium IV, pp. 454–482) that the conclusive

evidence in mammals showed that the basal ganglia are not an essential link in the patterning of learned activities (as cited in Iversen 1979, p. 195), a statement that is directly opposed to the current focus on learning functions of the striatum and for which much evidence has accumulated over the years (e.g., White 2009). In a tribute to Ivan Divac, Dunnett (1999) describes a classic experiment in which lesions of three different subregions of prefrontal cortex and the corresponding input subregion within the head of the caudate nucleus produce similar behavioral impairments on different learning tasks, demonstrating that cortico-striatal circuits mediate different learning functions, providing an early triple dissociation centered on subregions within the neostriatum.

Our historical perspective is offered to provide a strong background to integrate important unacknowledged advances in thought that have laid the groundwork for our current assessment of recent work. With our modern emphasis on new scientific findings using the latest state-of-the-art technique, whether tried and true or an artefactual data generation (e.g., Boubela et al. 2015) that becomes apparent after it's already "out there," the past is vulnerable, even likely to be lost, as the more recent work replaces what has come before. Arguably, the most important contribution of our previous review of the literature is the attention we gave to the historical context that came before with a chaotic, incoherent variety of theoretical proposals that, in the end (and beginning), tend to really have a level of organization that is amazingly ordered, structured, and almost entirely consistent with the emerging neuroanatomical data. Although theories are often sold as novel, different, and a significant advancement in science, truth be told, a step back to see the broader context can show a clearer and more coherent picture to increase our level of understanding. Consequently, we identified several theories in a nonexhaustive, but representative, table that showed two categories or themes that emerged from a survey of the theoretical and scientific review literature of the early work in the field. Using the general terminology common to the debate, we categorized theories as emphasizing motor or cognitive functions, though many were beginning to include elements of both, and some even distinguished regional variations in neuroanatomy.

The late 70s were an amazingly productive time where researchers considered all relevant ideas of their peers and acknowledged research to build upon the established literature and knowledge (e.g., Divac & Öberg, 1979a, b). We wish to continue this traditions by providing a critical analysis and integration of findings from more recent work in the field. In that tradition, we continue with the following new integration since 2011. Theory building could proceed like selling snake oil—what's unique that you must have to end the dilemma—or it could actually build, acknowledging the value and merit of "other" work, how it relates and also differs from your own, and attempt to tie it all together in a narrative that makes sense out of the seemingly disparate and incoherent arguments we have no doubt encountered in the past and that are often not even internally consistent.

The main point we try to make in the first section of this chapter is that there are similarities and differences between species in basal ganglia anatomy (focusing on circuit connectivity and neurochemical compartmentalization). Despite the differences, however, a general tripartite model enables functional specialization

between associative, limbic, and motor loops for parallel processing, while also allowing important interactions between subregions at the local cortico-striatal patch/matrix level (inter-digitation and cross boundary interactions by interneurons), and as recent research shows, through interactions between circuits via diverse mechanisms involving modulatory midbrain structures, thalamic relays, and cortical integration (open-circuit interactions) coordinating behavior to both build higher-order habits and to take such secondary automatisms off-line when cognitive control is required to deal with new situations in a flexible manner. The subsystems interact in such a way to build future habits when consistent reinforcement contingencies are stable over time to allow abstract relational (cognitive/spatial/configural) information to manifest as complex habits. In turn, prefrontal working memory function and other high-level cognitive resources engage new "hypothesis testing," or "vicarious trial and error," supporting dramatic shifts in performance that may result from new insight or the slow incremental buildup of cognitive–habit strength all along, forming a continuous interplay in problem-solving and associative learning. In the second half of the chapter, our goal is to emphasize several major directions the field is progressing toward, provide a critical evaluation that will hopefully ultimately lead to an integration of meritorious work to further clarify cortico-striatal functions, parallel processing and integration in order to further elucidate its role(s) in various disorders and to better understand at some level of coherence, states of function and often dysfunction, possibly leading to productive avenues for future research on neurodegenerative diseases and neuropsychological dysfunctions. Basic research has often proven to be an essential element in the step toward therapeutic intervention and drug discovery. The areas we will explore include: (1) an assessment of single-unit electrophysiological research in freely behaving rodents from the past and present and (2) an evaluation of some Bayesian computational approaches to understanding sensorimotor learning and the role of striatal regions.

As a Forerunner to Bayesian statistical approaches was David Hume's skepticism about cause and effect, which led him to attack some of Christianity's fundamental narratives (Mcgrayne 2011). Hume believed that we cannot be absolutely certain about anything based on cause and effect, traditional beliefs, testimony, habitual relationships, etc.; we can only rely on what we learn from experience. Our model (Devan et al. 2011) was built on specific scientific findings leading individuals to posit theories of striatal function (initial beliefs), which we have in a sense used in a Bayesian inverse probability problem to understand. Based on Bayes' original thought experiment idea of throwing balls on an even table with his back turned so as not to know the final resting place/outcome of any ball, only that it rested to the left or right of the original, we essentially ask—given the sampling of empirically based theoretical proposals "thrown on the table" so to speak (i.e., the Likelihood for the probability of other hypotheses) following the Prior for the probability of the original belief dating back to Thomas Willis' 1664 observation that the corpus striatum receive input from all sensory modalities, consistent with Aristotle's *sensorium commune*, how likely is it that striatal function is based on habit formation or a cognitive control function (i.e., Posterior for the probability of the newly revised belief)?

What we have essentially argued is that the original hypothesis or guess (Prior) possessing elements of each argument landed nearly smack in the middle of the table, with our or newly revised belief (Posterior), supporting an approximately equal number of subsequent instances of recent objective data (Likelihood) landing to the left and to the right of the Prior. In other words, both conclusions are correct and the myth that there must be a unitary original location or conclusion is, though conceptually appealing and parsimonious, is itself overly simplistic and possibly in error. Our conclusion is more in line with the superposition or 'spooky behavior' of elections and photons occupying multiple locations at once in quantum physics. All too many times have we been humbled in neuroscience when we think we have established a single new rule or principle of neural function and then soon thereafter realize the exceptions (e.g, action potentials can travel bi-directionally on dendrites). Mishkin and Petri (1984) have pronounced an end to the great debate among learning theorists, neuropsychology declares both the winners, as evidence shows that the mammalian brain contains multiple memory systems. The starting point of a process for Bayesian modeling that doesn't end, but rather builds on what has come before, effect before cause (see also, Hirsh 1974; Mishkin et al. 1984; Petri and Mishkin 1994).

To establish a beginning point, A PubMed search including all search fields for "striatum AND theory" and "basal ganglia AND theory" produced a combined number of 667 papers with duplicates removed and without any year restriction. Earlier, we highlighted 25 early proposals of the function(s) of basal ganglia in 2011, based on a systematic yet informal sampling of papers that we encountered frequently in the literature. The goal was not to present a comprehensive list, which by the standards outlined above would be quite large. Our point was to use the sampling of early studies to detect trends in categorical affiliation with motor or nonmotor cognitive forms of functional proposals. Based on our assessment, many theories had elements of both but differed in the emphasis placed on one of the two alternatives. Divac and Öberg (1979a) warned that although the neostriatum may appear homogeneous with more-or-less explicit assumptions of functional homogeneity unfortunately dominating main-stream conceptions at the time, we concluded that the homogeneous/unitary trend along with some attempts to integrate, still with a clear emphasis on one component or the other, continued up to the time of our review. The present trend toward expansion of theoretical ideas on the striatum, given the results of the PubMed search mentioned above, illustrates an exponential effort to understand the functions of the striatum, the lack of any unifying theory seems less tenable and even further beyond reach, though many theorists will tell you that they embrace a particular perspective until "sufficient" evidence to the contrary demands a new functional formulation and finally that the approaches used to address the theoretical issues have increased in a field that depends heavily on technological advances to generate new approaches or empirical data to attack the problems on several fronts, even if such techniques are blatantly flawed or provide only weak evidence at best that often is over-interpreted.

18.2 Neuroanatomy

The debate between cognitive and motor functions of the neostriatum is, to a large extent, of historical value given that functional neuroanatomy has resolved the issue by demonstrating both motor- and cognitive-related cortical afferents to different subregions within the striatum. Nevertheless, the debate continues based on biases arising from a focus on research in a restricted area. For example, a focus on the motor symptoms of Parkinson's disease or other related disorders would naturally lead one to conclude that the function of the neostriatum was primarily motoric in nature, given the symptoms of those diseases (Marsden 1980, 1981, 1982; Marsden and Olanow 1998; Öberg and Divac 1981) and some ambiguity concerning whether neostriatal function was dependent on or autonomous from the cortex in some species and stages of development (Divac 1980). It really took a broader consideration of the functional neuroanatomy to convince others that neostriatal function was not simply motoric in nature, but rather also included cognitive functions (Öberg and Divac 1979). Perhaps it is no small victory toward setting the record straight that a contemporary leader in the field of neuroanatomy recently included the striatum in a chapter on "the cognitive system" in his book entitled *Brain Architecture* (Swanson 2012).

Previously (Devan et al. 2011), we discussed the nomenclature associated with different basal ganglia structures, cytoarchitecture of the striatum, and connectivity of basal ganglia circuits. In terms of nomenclature, inconsistent usage and ambiguity of terms were considered to avoid previous problems and promote a consensus based on the spatial localization of subregional areas within the striatum corresponding to connectivity patterns with different cortical inputs (McGeorge and Faull 1987, 1989). The term *basal ganglia* invariably includes the globus pallidus, substantia nigra pars reticulata, caudate nucleus, and putamen (Wise 1991). In addition, a ventral extension of the basal ganglia includes the nucleus accumbens and olfactory tubercle. The term *striatum* includes the caudate nucleus, putamen, nucleus accumbens, and olfactory tubercle. The striatum is the major input structure to the basal ganglia. The term *neo-striatum* refers to the caudate nucleus and putamen (*neo-* indicating a more recent phylogenetic origin compared to the globus pallidus—*paleo-striatum*, and amygdaloid complex—*archi-striatum*) (Parent 1986; Webster 1979), but some authors include the nucleus accumbens and olfactory tubercle in their designation (e.g., Smith and Bolam 1990). Hence, the prefix "neo-" is unclear due to inconsistent usage. The term *dorsal striatum* (DS) is a more common alternative to neostriatum and specifically refers to the caudate nucleus and putamen (CPu) (The reader is also referred to Chap. 1 in this volume for a description of the nomenclature of major basal ganglia nuclei). These structures cannot be distinguished in rodents because the cortical fiber fascicles course diffusely through the nuclei rather than forming a distinct band of fibers (the internal capsule) that is clearly visible in other mammals, including cats, dogs, and primates. In popular atlases of the rat brain, the dorsal striatum is identified as the *caudoputamen* (Pellegrino and Cushman 1967; Swanson 2004) or *caudate-putamen* complex (Paxinos and Watson 2014). The term is synonymous with *dorsal striatum*, which is

often used to distinguish the CPu from the *ventral striatum* (VS) (i.e., nucleus accumbens and olfactory tubercle) and the pallidum (Heimer et al. 1985). Nauta (1979) observed a common internal histology within the CPu, even in species with a distinct internal capsule. Furthermore, Heimer and van Hoesen (1979) have suggested that the dorsal and ventral striatum do not differ in cytoarchitecture or biochemical composition. The latter conclusion is challenged by the neurochemical compartmentalization of the striatum, described below.

The dorsal striatum receives three main types of cortical input; neo-, allo-, and meso-cortical afferents (McGeorge and Faull 1989). In the rat, neocortical input includes sensorimotor afferents to the dorsolateral CPu and visual and auditory input to the dorsomedial subregion (Faull et al. 1986; López-Figueroa et al. 1995). The primary visual projection (V1) is directed to a longitudinal region bordering on the lateral ventricle and subcortical white matter (López-Figueroa et al. 1995). Interestingly, the pre-terminal fibers form fluffs poorly stained by calbindin yet belong to the matrix compartment (discussed below). The secondary visual areas also project to the dorsomedial region innervating the deeper tissue in the same area. Neocortical areas that surround the visual complex project to other regions, including a dorsolateral longitudinal region receiving somatosensory afferents (McGeorge and Faull 1987) and a dorsomedial caudal-half region receiving the auditory projection. Hence, to a large extent, the neocortical input to the dorsal striatum is segregated and the V1 projection, that is not present in cats and primates but is in other mammals, suggests significant differences in neocortical input to the dorsal striatum in several mammalian species (López-Figueroa et al. 1995).

Despite these differences, a tripartite model of cortico-striatal connections has been described for rats and primates (McGeorge and Faull 1989; Parent 1990). As shown in Fig. 18.1, three distinct cortico-striatal areas are identified in rats and monkeys. The main correspondence is between the "sensorimotor" cortical input to the DLS in the rat and the lateral and posterior regions of the putamen in the monkey. In addition, prefrontal "association" cortical afferents terminate in the medial CPu of the rat and anterior regions of the dorsal striatum along with some input to the posterior caudate nucleus of the monkey. The allocorical (archi-, periform, and entorhinal cortices) or "limbic striatum" (Beckstead 1979; Kelley and Domesick 1982) is centered on the ventral striatum and dorsomedial CPu in the rat, overlapping to a large extent with mesocortical (medial and lateral prefrontal) afferent projections to the CPu. However, in the monkey the limbic striatum is located primarily in the ventral striatum with minimal overlap with prefrontal association projections. Despite the apparent parallel organization and segregation originally described by Alexander and colleagues (Alexander and Crutcher 1990; Alexander et al. 1986, 1990), the limbic striatum may interact with the other two pathways in primates and rats (Joel and Weiner 1994, 1997, 2000). For example, Haber (2003, 2011) reviews evidence that limbic ventral striatal regions in primates may influence more dorsal striatal regions via spiraling connections between the midbrain dopamine cells and the striatum, and via thalamo-cortico-thalamic projections. Moreover, there may be "hot spots" of convergence between corticostriatal projections from different functional regions and integration of information via the thalamus that sends a mas-

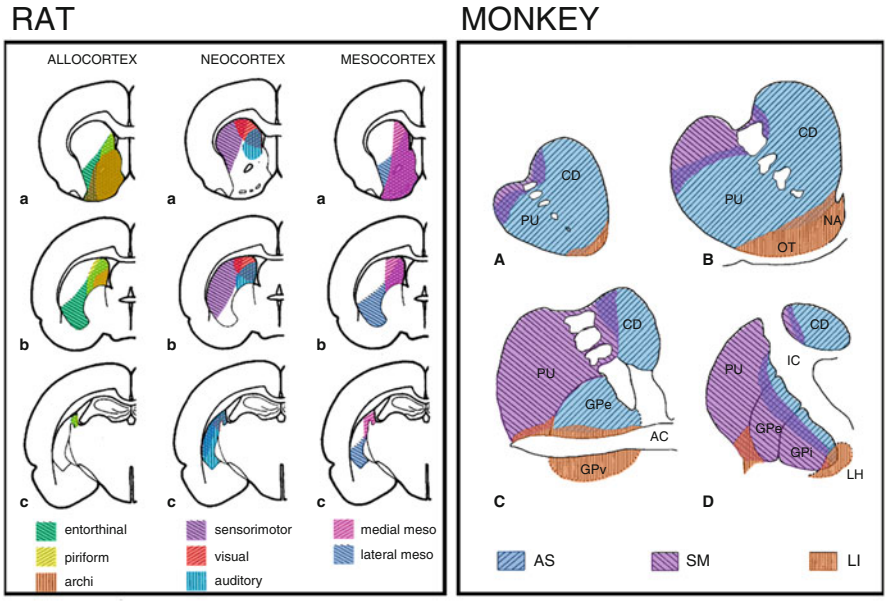

Fig. 18.1 Comparison of cortico-striatal terminations in the rat (adapted from McGeorge and Faull 1989) and monkey (adapted from Parent 1990). Associative/Mesocortex (*blue/pink*); Sensorimotor cortex (*purple*); Archicortex/Limbic (*brown*). Transparent colors were superimposed on the original figures to more easily discriminate striatal subregions with overlap areas. *CD* caudate, *PU* putamen, *Gpe* external globus pallidus, *Gpi* internal globus pallidus, *NA* nucleus accumbens, *IC* internal capsule, *OT* olfactory tubercle, *GPv* ventral globus pallidus, *AC* anterior commissure, *LH* lateral habenula, *AS* associative, *SM* sensorimotor, *LI* limbic

sive, topographically organized projection directly to the striatum, thus promoting the execution of learned behavioral responses based on inputs related to emotional, cognitive, and motor cortical functions (Haber and Calzavara 2009).

The dorsal/ventral striatal distinction has been questioned, putting a "spin" on the designation to include a dorsolateral and ventromedial subregion based on the connectivity discussed above and neurophysiological and behavioral evidence (Voorn et al. 2004). The distinction was further described as being in accordance with a mediolateral functional zonation imposed on the striatum by its excitatory cortical, thalamic, and amygdaloid inputs; hence, representing a synthesis between the dorsal–ventral distinction and the more mediolateral-oriented functional striatal gradient.

The main functional distinction that we previously described, between the DLS and DMS in rats, was based on the known anatomy and our neurobehavioral work and is in general accord with the more recent conceptual spin. However, the unique neocortical visual and auditory inputs to the DMS in rat suggest that the idea of a simple ventral extension of the limbic striatum into the dorsal CPu may fail to recognize local interactions between these sensory neocortical projections and limbic-related allocortical and cognitive-related mesocortical input (McGeorge and Faull 1989).

The longitudinal organization of cortical afferents to the dorsal striatum also applies to areas of association cortex in primates with topographic terminations exhibiting restricted medial–lateral domains (Selemon and Goldman-Rakic 1985). The ventromedial CPu receives input from superior temporal, orbitofrontal, and anterior cingulate cortices, the central region of CPu receives projections from dorsolateral and dorsomedial frontal cortices, and the dorsolateral CPu input is from posterior parietal and superior arcuate cortices. Selemon and Goldman-Rakic (1985) showed that convergence of associational input to CPu ranged from almost complete segregation of cortically linked areas (e.g., from dorsolateral prefrontal and orbital cortices) to extensive overlap of terminal domains (e.g., from frontal and temporal cortices), although inter-digitation rather than true convergence of overlap regions was observed.

The restricted medial–lateral domains and interdigitation of overlapping terminations characteristic of the longitudinal organization can be inferred from the serial coronal sections illustrating the tripartite model in Fig. 18.1. However, there are notable species differences in overlap regions of termination. As described above, in the rat there is extensive overlap in allocortical/mesocortical regions with visual and auditory neocortical areas. In the monkey, overlap is less prominent with a predominance of association projections anteriorly and a predominance of sensorimotor neocortical input posteriorly, and less dorsal extension from the ventral/limbic striatum. In general, Swanson's (1995) estimate of the total proportion of the cerebral cortex to basal ganglia in the rat brain is 31–7 %, respectively, for a ratio 4.43. In comparison, the total proportion of cerebral cortex to basal ganglia in the human brain is 77–4 %, respectively, for a ratio of 19.25. Assuming a constant proportion of cortical afferent input to the striatum, in general, one would expect to see more overlap in the primate, which is obviously not the case. Hence, the capacity for direct local interactions among overlapping functional subregions may be more prominent in rats than in primates, whereas indirect functional integration, as described by Haber and colleagues, may allow for necessary interactions across tripartite subregions (Haber 2003, 2011; Haber and Calzavara 2009; Haber et al. 1994).

18.3 Neurochemical Compartmentalization

The above discussion has focused on the regional differences in striatal afferent and efferent connectivity patterns and the parallel organization of cortico-striatal connectivity. However, these patterns represent only one level of striatal organization. A second level is evident in the patchy distribution of various neurochemical constituents of the striatum. These so-called patches, also known as striosomes (Graybiel and Ragsdale 1978) or islands (Goldman-Rakic 1982), appear in coronal sections as elliptically shaped areas set within a larger matrix field. The patch/matrix dichotomy was initially observed with catecholamine histofluorescence (Olson et al. 1972; Tennyson et al. 1972). Since then, several other

neurotransmitters, neuromodulators, and receptor subtypes have been differentially affiliated within patch or matrix compartments (see, Graybiel 1990; Groves et al. 1995 for review). For example, patches are commonly identified by ^{3}H-naloxone- and ^{3}H-diprenorphine-labeled opiate receptors (Desban et al. 1993; Herkenham et al. 1984; Herkenham and Pert 1981, 1982; Pert et al. 1976) and are associated with dopamine D1 and cholinergic M1 (muscarinic) receptor binding (Besson et al. 1988; Nastuk and Graybiel 1985). The matrix compartment is frequently identified by acetylcholinesterase (AChE) histochemistry (Butcher and Hodge 1976; Graybiel and Ragsdale 1978; Herkenham and Pert 1981) and is composed of neurons that contain a 28 kD calcium-binding protein, calbindin (Gerfen et al. 1985), and a rich plexus of somatostatin-immunoreactive fibers (Gerfen 1984). Other histochemical markers have a more diffuse distribution within the striatum (e.g., enkephalin immunoreactivity), despite the fact that their receptor binding sites are highly localized (Herkenham 1987). Although there are many possible explanations for such "mismatches" between receptor and neurotransmitter localizations, it is likely that some receptors may be sites of action for neurochemicals released from a distant source (Fuxe et al. 2013).

Three-dimensional reconstructions of patch/matrix compartments using serial coronal, horizontal, and sagittal sections have revealed that the patches form a tunnel-like system running predominately along the mediolateral axis in the rat CPu (Desban et al. 1993), and also along the rostrocaudal plane in the cat caudate nucleus (Desban et al. 1989; Groves et al. 1988). Patch compartments were more extensive and tended to converge at the mediorostral pole, while the matrix compartment dominated in the more lateral and caudal regions of the dorsal striatum. Medial-to-lateral gradients in receptor binding and neurochemical localizations within the striatum have been noted early on (Altar et al. 1991; Graybiel et al. 1986; Pert et al. 1976) as well as more recent rostrocaudal gradients in several species (Alakurtti et al. 2013; Rosa-Neto et al. 2004).

Krebs et al. (1991) quantified regional differences in striatal patch–matrix distributions, showing significantly more patch in the anterior and medial CPu, and significantly more matrix in posterior and lateral CPu. Further, when NMDA (*N*-methyl-D-aspartate) was infused into the different areas, it evoked a greater release of newly synthesized 3H-dopamine from presynaptic nerve terminals in the matrix-enriched posterior and lateral subregions than from the patch-enriched anterior and medial subregions. These findings show physiological effects related to both compartmental and subregional areas within the striatum.

Three-dimensional mapping of synaptic boutons, expressing vesicular glutamate (VGluT1 and VGluT2) and GABA transporters in relation to the patch-matrix topography, has revealed that the VGluT1 boutons increased along three axes: ventrolateral-to-dorsomedial, ventral-to-dorsal, and lateral-to-medial, with the highest densities in the dorsal one-third of the striatum and density "valleys" in the DMS coinciding with patch locations (Wouterlood et al. 2012). Both VGluT1 and VGluT2 bouton densities were higher in matrix than in patches in all striatal sectors and vesicular GABA transporters were more evenly distributed in the patch-matrix, with bouton density tending to increase from medial to lateral (Wouterlood et al.

2012). Higher VGluT1 bouton density in DMS correlated with inputs from prefrontal cortex and related thalamic regions, while enhanced VGluT2 in ventromedial striatum correlated with associated prefrontal, thalamic, amygdaloid, and hippocampal areas.

Neurons affiliated with the different striatal compartments develop at different embryonic time periods (Graybiel 1984; Graybiel and Hickey 1982; Johnston et al. 1991; Krushel et al. 1995; van der Kooy and Fishell 1987). The earliest neurons to leave the mitotic cycle are restricted to the patch compartment, whereas neurons that become post-mitotic at a later time preferentially join the matrix compartment (van der Kooy and Fishell 1987). Embryonic lesions of the substantia nigra do not prevent the segregation of patch/matrix neurons (van der Kooy and Fishell 1992), suggesting that early nigrostriatal connections are not critical for the basic compartmental organization of the striatum (see also Snyder-Keller 1991). However, despite the preservation of neuronal patch formation, embryonic substantia nigra lesions do block the patchy expression of dense opiate receptor binding (van der Kooy and Fishell 1992). This finding suggests that early nigrostriatal connections may be important for the maturation of certain phenotypic markers of the striatal compartments.

Findings suggest the existence of more than one system of compartments in the striatum. Dopamine-containing fibers projecting from the midbrain to the striatum form patches called "dopamine islands" during development (Olson et al. 1972; Tennyson et al. 1972). These dopamine islands correspond with AChE-poor striosomes in the dorsal caudate nucleus (Graybiel et al. 1981), but are not congruent with Nissl-stained cell clusters (Graybiel 1984). Moreover, there is an apparent shift in the compartmental localization of cholinergic interneurons during development. The distribution of choline acetyltransferase (ChAT) positive neurons changes from an early preference for the patch compartment to a late preference for an area of the matrix just outside of the patches (Van Vulpen and Van Der Kooy 1996). Three distinct ChAT-immunostained compartments have been identified in the human striatum (Holt et al. 1996).

In aged rats, reduced ChAT activity was found in the ventromedial and dorsolateral striatum compared to young rats, whereas no difference was found in the hippocampus (Colombo and Gallagher 1998). Aged rats with the most ChAT activity in the anterior ventromedial striatum performed well on place-learning and reference memory tasks, but made perseverative errors on a working memory task. Interestingly, young and aged rats with the most ChAT activity in the anterior dorsolateral neostriatum were those with the least accurate working memory and no relationships were found between ChAT activity in the hippocampus and spatial memory. These findings support the idea that the multiple co-factors approach described for conceptualizing the etiology of age-related dementia (Gidyk et al. 2015; McDonald 2002) should be considered along with the interactive multiple memory systems approach (McDonald et al. 2004a, b) towards understanding the contribution of changes in cholinergic integrity of subregions within the dorsal striatum to age-related cognitive impairments .

Although there are many neurochemical similarities between the limbic part of the dorsal striatum (ventral and medial CPu) and the ventral striatum (nucleus

accumbens), there are some subtle differences, as was the case for cortico-striatal connectivity. The cell clusters in the CPu are smaller and less distinct than those in the nucleus accumbens (Herkenham et al. 1984). Moreover, although the cell clusters in the CPu correspond with naloxone-defined patches, the dimensions are slightly different. In contrast, the cell clusters and naloxone patches in the nucleus accumbens form a more complete match (Herkenham et al. 1984). However, even within the nucleus accumbens, the histochemical organization of the core region differs from the shell, which in turn differs from the CPu (Jongen-Rêlo et al. 1993). These findings provide further evidence of a multicompartmental organization beyond a simple two-compartment dichotomy.

Although distinct neurochemical modules are not found in the matrix, Graybiel (1990) has suggested that modular units, called 'matrisomes', are nevertheless evident in the patchy distribution of sensorimotor inputs and striatopallidal/striatonigral outputs (see also, Flaherty and Graybiel 1993; Flaherty and Graybiel 1994). Flaherty and Graybiel (1994) found that multiple matrisomes in the squirrel monkey putamen receive input from a single area in the sensorimotor cortex (divergence), and in turn send output to a single site in the pallidum (reconvergence). This divergence-reconvergence pattern was found in both motor and somatosensory inputs, and in both the external and internal globus pallidal target sites. The lack of a phenotypic neurochemical marker of matrisomes does not necessarily mean that these modules are neurochemically homogeneous. Differences may exist in the relative distribution of a particular combination of neuropeptides, or there may be quantitative cellular differences among peptides in different matrix–neuron assemblies (Graybiel 1990).

18.3.1 Compartmental Interactions and Reinforcement Learning

In related theories of reinforcement learning, dopamine neuron activity serves as an effective reinforcement signal for learning of sensorimotor associations in striatal matrisomes (Suri et al. 2001), and a role for cholinergic mechanisms for neural plasticity was hypothesized to occur in modules assigned "responsibility" by a pause in tonically active neurons (TANs) related to "spatially selective learning" as a critical requirement of modular reinforcement learning (Amemori et al. 2011). Our understanding of the latter theory is that the proposed "responsibility" of modules, determined by errors in predictions of environmental features, is related to the "spatially-selective learning" that the authors assign responsibility to the striosomes/patches, which in turn convey information to matrisomes via local circuit interneurons, including the TANs. The tuning of spatial selectivity is likely not as specific as hippocampal place cell activity as previously described; however, it may provide the context-based information that the same group relates to vesicular acetylcholine transporter-mediated increases in acetylcholine that could be critical in exacerbating drug-induced stereotypic behaviors and promoting exaggerated

behavioral fixity (Crittenden et al. 2014). The stereotypy and "fixity," or lack of flexibility, is characteristic of enhanced reinforcement that accompanies the overt mechanisms of drug addiction based on reward-related (i.e., striosomal/patch) function in the ventral striatum (Haber 2011).

In a related proposal, Crittenden and Graybiel (2011) describe how basal ganglia disorders may result from imbalances between striosome and matrix neurochemical compartmental function. These authors suggest that the widely distributed striosomes interact at a global and local level with the surrounding matrix, in part through interneurons that bridge communication between the two compartments. The matrix is suggested to contain neurons of both direct and indirect output pathways that receive input from sensorimotor and associative input, whereas the striosome/patch neurons receive limbic input and send projections to dopamine neurons in the substantia nigra pars compacta. The authors suggest that striosomal-linked limbic input exerts control of the matrix, which directly mediates behavior driven by sensorimotor- and associative-linked inputs. Consequently, disorders such as Huntington's disease, dopamine-linked dyskinesias, dystonias, and drug addiction result from imbalances between striosome/matrix function.

18.3.2 Neurobehavioral Integration

The findings reviewed here suggest that local interactions between neurochemical compartments and cortico-striatal overlap regions may support different forms of associative learning, including simple stimulus–response learning and higher-order habits (Devan et al. 2011). Evidence for cortico-striatal divergence in matrisomes prevalent in the sensorimotor DLS subregion is consistent with neurobehavioral lesion data showing impaired stimulus–response learning on a win-stay task (McDonald and White 2013). More recent data suggests that the rodent DLS is involved in rapid response adaptation that is more sophisticated than that embodied by the classic notion of habit formation driven by gradual stimulus–response learning (Skelin et al. 2014). The local interaction of limbic and associative systems in striatum that may modulate DLS output is consistent with these findings.

Preliminary findings have used a behavioral variation of the competitive place task in the water maze (McDonald et al. 2005) with extensive place training in phase one (Acquisition), followed by mass place trials with a new location (Retraining) in phase two and a probe test (Competition) the following day in phase three (Fig. 18.2).

Bilateral infusion of the mu-opiate receptor antagonist naloxone in the dorsomedial CPu prior to phase 2 retraining resulted in fewer passes through the 'old' radial quadrant without influencing passes through the 'new' quadrant on the drug-free competition probe test the following day (Fig. 18.3). These findings implicate the striatal patch compartment within the dorsomedial CPu in overtrained spatial behavior and extend our previous findings on DMS lesions (Devan et al. 1999; Devan and White 1999) that showed spared place learning, but weakened place responding during a place–cue competition test in the water maze. The present findings utilized a

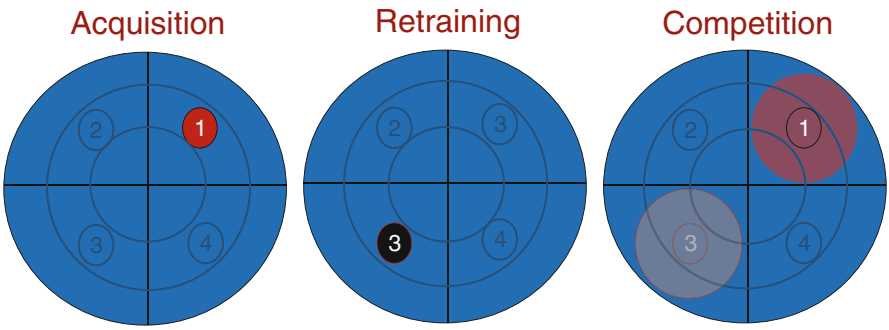

Fig. 18.2 Acquisition—hidden platform at location 1, 4 trials/day (16 days); Retraining—hidden platform moved to location 3, four trials following intra-striatal infusion (day 17); Competition—platform removed, 60 s probe test (day 18)

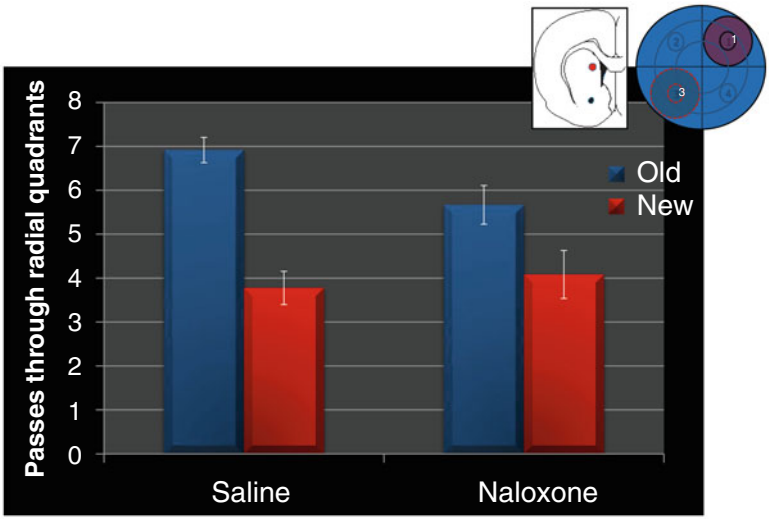

Fig. 18.3 *Upper right*—bilateral infusion site in the dorsomedial CPu; Water maze showing the old radial quadrant—3 versus the new radial quadrant—1; Bar graph showing the mean number of radial quadrant entries; [Group main effect $F(1,19)=5.35$, $p<0.05$; Old Radial Quadrant $t(1,19)=2.48$, $p=0.023$; New Radial Quadrant $t(1,19)=0.48$, $p>0.05$]

competition test between an overtrained old place response and more recently acquired new place information. Consequently, the striosome/patch compartment within the dorsomedial CPu may normally contribute to the expression of higher-order habit formation that allows cognitive place information acquired through hippocampal/limbic-striatal interaction to access matrix-related reinforcement/response processing under circumstances that promote a cooperative interaction between memory systems (Devan et al. 2011). The reader is referred to Chap. 13 for a discussion on the effects of alcohol consumption on the plasticity of the dorsomedial striatum.

18.3.3 Summary

Increasing evidence supports the idea that cognitive information is processed by parallel and partially segregated corticostriatal limbic and associative afferent input to the basal ganglia with integration occurring at multiple levels of organization reviewed above. Recent work supports the proposal that functional connectivity between remote brain regions is modulated by task learning and the performance of an already well-learned behavior. In a recent virtual water maze study (Woolley et al. 2015), the extent to which initial learning and stable performance of spatial navigation modulates functional connectivity between subregions of hippocampus and striatum was investigated using neuroimaging techniques. The first scan session represented initial learning and a second session represented stable performance. There was an increase in functional connectivity between the posterior hippocampus and dorsal caudate specific to the first session. The increase in functional connectivity was correlated with offline gains in task performance, suggesting that a cooperative interaction occurred between posterior hippocampus and dorsal caudate during awake rest following the initial phase of spatial navigation learning. These findings support earlier findings showing that activation of the hippocampus was strongly associated with the accuracy of knowing where places were located and navigating accurately between them, while performance in getting to those places quickly was strongly associated with activation of the caudate nucleus (Maguire et al. 1998). Hence, functional brain imaging combined with the use of virtual environments has revealed strong parallels between humans and other animals in the neural basis of navigation (Maguire et al. 1999).

18.4 In-Vivo Electrophysiological Techniques

In-vivo electrophysiological recording techniques in freely moving animals are one important experimental approach that has contributed important evidence in support of the idea that different regions of the dorsal striatum are involved in different functions. As the field moves forward and new techniques emerge, we believe that this is a potential “hotspot” of research that will provide important new information about the functions of the dorsal striatum. In particular, the increased use and development of high-density multi-site electrophysiological approaches combined with more sophisticated data analysis capabilities will reveal much about potential interactions between different portions of the dorsal and ventral striatum as well as dynamic interactions between these systems and other identified learning and memory systems like the hippocampus and amygdala. Below, we will remind the reader of some of the key electrophysiological findings implicating different portions of the dorsal striatum in different learning and memory functions, describe some recent work using more advanced techniques, and potential approaches for future researchers that might yield important empirical and theoretical advances.

In our recent review/theoretical paper that focused on dorsal striatal function, we reviewed some of this key evidence (Devan et al. 2011). Briefly, this work showed that neurons in the DLS and DMS (rat) and caudate/putaman (monkey) display evoked responses when a visual, auditory, or tactile stimulus is linked with a movement that is subsequently reinforced movement (Aosaki et al. 1994, 1995; Jaeger et al. 1995; Kimura 1986, 1995; Kimura et al. 1992, 1993; Lidsky and Schneider 1994; Rolls 1992, 1994; Romo et al. 1992; Schultz 1995; White and Rebec 1993). The activity of striatal neurons is sometimes related to the sensory stimulus, the movement, to both events or to neither event.

One early and important study investigated the neuronal activity of single neurons in the sensorimotor or putamen region of monkey subjects while they performed a stimulus–response task (Kimura 1986). The task required the monkeys to move a handle via different elbow flexion-extensions that were signaled by LED lights. Correct repetitions of these sensory-triggered movements were reinforced with fruit juice. The results showed an interesting pattern of findings with different types of cells encoding different aspects of the task parameters. Of particular interest for the present chapter is that one category of cells, Type IIa cells, recorded under these testing conditions showed phasic discharges before the first movement of a learned sequence that were triggered by the sensory cue presentation. This work represents early evidence for electrophysiological correlates of stimulus–response representations in the sensorimotor region of the monkey striatum.

Consistent with Kimura's (1986) results and interpretation is an early rodent study (White and Rebec 1993) in which the investigators recorded neural activity from the dorsal striatum on a stimulus–response task in which the subjects can avoid footshock by releasing a lever during a specific cue presentation (tone). Some of the neurons in the dorsal striatum responded to the conditioned stimulus, the response, or the combination of the two (stimulus–response cells). Interestingly, there was a regional specificity to the neuronal responses to the different task parameters with the conditioned stimulus neuronal activity found mostly in the DMS and the response-related activity in the DLS. Evidence for a direct functional connection between these neuronal responses and the stimulus–response behavior was obtained by peripherally administrating Haloperidol, a neuroleptic that blocks dopamine transmission, at a dose that impairs performance of the stimulus–response avoidance task and recording the neuronal activity in these same striatal regions during task performance. The results showed that this dopamine transmission manipulation of striatal function that impairs task performance also attenuated task-related neuronal activity without altering spontaneous firing rates.

Other important electrophysiological work on the dorsal striatum includes a classic series of experiments by Schultz and colleagues (Romo et al. 1992; Schultz 1995; Schultz and Romo 1992) who investigated the electrophysiological activity of neurons in the caudate and putamen subregions of the monkey striatum during reinforced cued motor responses and compared these responses to a reinforced self-initiated response experimental condition in separate blocks run each test day (Schultz and Romo 1992). One interesting aspect of the findings in this series of experiments was that of the 217 neurons that responded to the conditioned stimulus

presentation, 127 were found in the caudate and 90 were found in the putamen and three quarters of the 217 neuronal responses to the stimulus were conditional on the response being made. The demonstration that both of these dorsal striatal regions represent the conditioned stimulus on these kinds of stimulus–response tasks is consistent with the view presented in the previous anatomical section of this chapter suggestive of functional interactions between the two regions of the striatum.

18.4.1 More Recent Electrophysiological Approaches

Recent electrophysiological work using more sophisticated recording techniques including better separation of unit activity of specific neuronal subtypes (interneurons from projection neurons), higher density recordings, and analysis of these rather large data sets has yielded some interesting results.

Barnes et al. (2005) recorded from the striatal projection neurons (medium spiny neurons) in the DLS of rats during acquisition, overtraining, extinction, and reacquisition of a conditional discrimination T-maze task. Briefly, to obtain rewards and achieve high levels of performance on the discrimination, the rats had to learn to turn left at the choice point of the T-maze when one auditory cue was presented and to turn right at the choice point when another auditory cue was presented. The results showed several interesting firing characteristics of the MSN neurons in DLS. First, in the early stages of training, neuronal activity, of the cells active during the task, occurred throughout the trial from start point to goal site. By the time the subject had reached asymptotic levels of performance, the strongest neuronal firing rates were correlated with the start and end runs. Second, these activity patterns were partially reversed during extinction training and then the original pattern reinstated during reacquisition. Third, neurons that did not show phasic peri-event activity during any aspect of the task, but did show low rates of firing in and out of the task, reduced their activity during task training, suggesting some kind of sculpting of the relevant striatal neurons. These changes in neuronal activity distributions, response tuning, and task specificity were altered across the different components of the task elements (acquisition, extinction, re-acquisition).

This kind of approach is exciting and the results interesting, but there are several caveats and questions that remain. First, although not discussed by the experimenters, is the response tuning and task selectivity observed under these training conditions, which were dynamically reconfigured during the different phases of the task, unique to the DLS? What about the other regions of the striatum as well as other neural systems implicated in learning and memory processes like the amygdala, different parts of prefrontal cortex, hippocampus, parahippocampal cortex, thalamus, etc? Second, the authors use the pattern of data to suggest that this region is important for both exploration and exploitation. Although we understand these functional conceptualizations, we do not really see this pattern in the data. Third, it is not clear why during data analysis they did not establish perievent analysis during cue presentations and the specific left and right responses. Based on previous elec-

trophysiological work, reviewed above, this seems like an interesting analysis. Fourth, the demonstration that task relevant activity in striatum disappeared during extinction and then reappeared during re-training has huge implications for theoretical explanations for extinction in which it is claimed that the original association is not lost, but a new inhibitory representation is acquired. This finding should be pursued to assess its veracity and whether this is a common mechanism found during different forms of learning (stimulus–response, Pavlovian, spatial) or unique to instrumental tasks. Fifth, the behavioral task had both a stimulus–response solution and a spatial solution, which unfortunately contaminates the results if one is interested in the coding characteristics during a stimulus–response habit task.

Redish and colleagues (van der Meer et al. 2010) recorded from neurons in the dorsal striatum, ventral striatum, and hippocampus in different groups of rats. Electrophysiological recordings were undertaken during the acquisition of a multiple T-maze task. For this task, rats were allowed to select three "low cost" choice points with dead ends, which was followed by a "high cost" choice with a specific side of the maze rewarded during each session. Of specific interest for the present analysis, in comparison of perievent electrophysiological activity analyzed during various aspects of the multiple T-maze task, the results suggested that the dorsal striatum is not involved in encoding or representing rewards or future paths, but neurons in this striatal region did encode motoric components of the task.

Eichenbaum and colleagues (Berke et al. 2009) completed an interesting study in which they recorded simultaneously from dorsal hippocampus and different striatal subregion (DLS or DMS) projection neurons simultaneously in different groups of rats learning a win–stay task on a plus maze. For this task, the rats were trained to enter one of the four plus maze arms indicated by a flashing LED light to receive liquid reward. The activity of hippocampal CA1 cells was spatially selective, despite the fact that space was irrelevant to solving the task. Projection neurons from both the medial and lateral portions of the striatum were most active during selective portions of the task particularly when the rats executed a response choice at the entrance to arm locations.

Oddly, cue-specific neuronal responses in the striatum were not common. This latter finding is inconsistent with other earlier research described in this section (e.g., Kimura 1986; White and Rebec 1993) and may have something to do with early cueing that occurred while the subject was still in another arm. This same issue can be found in the Redish and Graybiel experiments (Barnes et al. 2005; van der Meer et al. 2010) described above because in both cases there is either no explicit cueing of reinforced responses or the temporal contiguity between the explicit cues and the responses is separated. Further research will be required to assess this idea.

The general pattern of data being generated with these more advanced electrophysiological studies is consistent with previous results and interpretations in some aspects and different in other ways. For example, various recent reports replicated previous work showing that DLS neurons encode stimulus–response associations (Fanelli et al. 2013; Stalnaker et al. 2010). Interestingly, one of these studies showed that neurons in the same region seem to encode information about associated out-

come as well. This same study showed that the DMS also encoded stimulus–response associations and information about associated outcomes. These results were interpreted as inconsistent with the idea of a strict division of the medial and lateral portions of the striatum simply involved in stimulus-outcome and stimulus–response associations, respectively. These results are consistent with the idea promoted in the current chapter that, although these regions are involved in different aspects of learning (cognitive vs. S-R), there is significant cross talk between the regions via an interesting anatomical design described in our neuroanatomical and neurochemical sections. However, it is important to note that even though neurons in the DLS encode aspects of associated outcomes, it is possible that this information is encoded and used differently than this information in DMS.

In our view, an important advancement for this kind of work will be simultaneous recordings from different neural regions suspected in learning and memory during acquisition of an instrumental task, like in the recent work by Berke et al. (2009), with the guidance of good theoretical work that make clear predictions about which neural systems should be encoding information during different components of the learning experience. On the theoretical side, Gruber and McDonald (2012) provide a good example of a dynamic model of learning in which different learning and memory systems are engaged during different aspects of instrumental learning. Several scenarios were presented indicating the type of cortico-limbic processing that is likely engaged. These circuits include neural systems responsible for variants of memory-based behavior including: (1) an emotional memory system involving the VS and related limbic and frontal cortical inputs that exerts early influences on behavior; (2) a cognitive control system centered on the DMS; (3) and a stimulus–response habit system mediated by a circuit that includes the DLS (see also, Devan et al. 2011).

Four learning scenarios that would be common experiences for a rodent, the neural circuits likely engaged, and the plasticity and control mechanisms implicated were presented in this theoretical paper including: (1) early in instrumental learning; (2) when a less than expected reinforcer is experienced; (3) the effects of presentations of a classically conditioned cue on instrumental responding; and (4) what is learned about the non-reinforced cue during discrimination learning.

For our purposes, the first example is the most illustrative for the type of task analysis and electrophysiological approach that will improve our knowledge base concerning how different memory-based behavioral systems gain control of behavior. In the first example, early in instrumental learning, we hypothesized that presentations of a conditioned stimulus (CS+) and the context in which it is presented early in instrumental learning would evoke activity in amygdala and the hippocampus triggering VS activity and elevated dopamine to engage general arousal, attention, approach which can be thought of as triaging responses to stimuli based on their associated affective value. At the same time, these early Pavlovian associations acquired by the emotional system invigorate non-specific activity so that the goal-oriented system can acquire contingencies and discover appropriate operant responses. Later in learning, the CS+ and context activates amygdala, hippocampus, and neocortex, resulting in activation of ventral striatal-projecting dopamine neu-

rons. Elevated dopamine in the VS biases SPN to hippocampal input and promotes direct pathway output to orient the animal and to trigger activity of dopamine neurons projecting to dorsal striatum. Elevated dopamine in the DS promotes activation of the direct pathway to invigorate actions mediated by a competition between the cognitive control systems involving the DMS and the stimulus–response habit system involving the DLS and the winner of these competitions is determined by various factors related to task parameters including the amount of training. So, for example, many repetitions of such stimulus–response pairings would lead to learned behavior mediated by the DLS similar to habitual responding.

18.4.2 Summary

Multi-site high density recordings in an experimental situation like the final experimental situation presented in this section would be quite revealing. Electrode clusters placed in several different combinations in areas VS, DMS, DLS, amygdala, and hippocampus in the same subjects would provide important electrophysiological correlational data concerning these different stages of instrumental learning and the contributions of these different regions to behavioral output. This kind of within-subject assessment of neuronal firing of clusters of cells in each region, while the subject learns or remembers a task, will be an important advancement. However, we reiterate the important caveat that any data collected using these techniques, no matter how advanced and complex, still represent correlational data and should be interpreted as such, failing to support strong causal inference when antecedent conditions are directly manipulated and precisely controlled.

18.5 Bayesian Computational Approaches

One stripe of system neuroscientists has long been interested in the neurobiological mechanisms and complex neural circuits that underlie memory-based behaviors. Their approach to this problem was to complete physiological studies (brain lesions and inactivations, pharmacological manipulations, electrophysiology, etc.) on simple and more complex learned behaviors and identify the necessary neural circuits and mechanisms necessary for these behaviors (Kapp et al. 1990; Sutherland and Hamilton 2004; Thompson 2013). This work was strongly influenced by the impressive foundational work done in the fields of associative learning, human neuropsychology and neurology, and physiological psychology or what was to become the field of behavioral neuroscience.

This pioneering work has led to a plethora of knowledge about different neural circuits mediating different types of learning, work that is strongly suggestive of the idea that these different memory-based behavioral systems use different algorithms to encode key features of an experience and these representations are proffered as

possible solutions in uncertain situations (for recent reviews see Devan et al. 2011; Gruber and McDonald 2012; White et al. 2013). This approach has been criticized (Glimcher 2003; Marr 1982). Marr argued for an alternative approach in which one would define modular goals that the brain should be able to accomplish and then develop mathematical models of those goals. The fruits of this computational work would guide neurophysiological and functional research. Essentially, the idea is that you need to understand the problem that the brain is trying to solve, not study the mechanics of the brain to understand how it solves a particular problem. Glimcher extended these ideas by suggesting several potential problems with Marr's approach that would improve the potential success of this research strategy. First, how would systems neuroscientists define the goals of behavior mathematically and how would you relate these mathematical models to neural circuits in the brain. Glimcher argues that these potential problems can be circumvented by defining the goals of behavior using an evolutionary approach, a field now called neuroeconomics, and then using neuroscientific methods to identify the neural circuits and mechanisms that solve these goals.

Clearly, we wholeheartedly disagree with Marr and Glimcher's criticism of the approach taken by behavioral neuroscientists like Thompson, Kapp, Sutherland, and many others. The progress made using this approach has been nothing short of miraculous. In fact, we would argue that now is probably a good time to combine this behavioral neuroscience approach with Bayesian computational approaches to make a great leap forward in our understanding of the neural systems and mechanisms supporting the complexities of memory-based behaviors. Our call for this approach is based on the fact that we currently know a significant amount of information about parallel neural circuits involved in different aspects of memory-based behavioral control, there has been significant progress in approaches using Bayesian computational techniques, and in combination we foresee significant reciprocal cross talk, which will improve information culled from both approaches leading to greater insights and advances in our understanding of memory-based behavioral systems in the mammalian brain. With these claims in mind, in the following section we will provide a basic review of the Bayesian approach and some examples of its use in trying to understand aspects of sensorimotor learning and dorsal and ventral striatal functions.

18.5.1 Thomas Bayes

The posthumously published manuscript by Thomas Bayes (1763, 1958) entitled "Essays Towards Solving a Problem in the Doctrine of Chances" has had an immense impact on those interested in understanding brain/behavior relationships. Briefly, his insight revolved around a fundamental problem. The problem is that we are faced with experiences that we have incomplete information about and are thus uncertain. Bayes' major contribution was that he developed an approach to

mathematically calculate inferences about the most likely values or properties of those events using inverse probabilities. Essentially, the idea is that I have knowledge or accumulated information about the world in this state, I have available to me online sensory data of the current world state, then precisely how likely is it the case, that the world is currently in this state. Essentially, the idea is that your predictions about the likelihood of previous states of the world given your current information are based on mathematical calculations.

18.5.2 Bayesian Approaches Applied to Sensorimotor Learning

A good example of the application of Bayesian computational approaches to the kinds of learning and memory processes thought to be mediated by the various striatal subregions is work being done my Wolpert and colleagues (Dimitriou et al. 2012; Franklin and Wolpert 2011a, b). Consistent with approaches to date, sensorimotor learning is broken down into multiple processes that interact in some unknown way at the neurophysiological and neural systems level. Wolpert's focus is on computational and behavioral approaches to understanding several fundamental processes including but not limited to: (1) how motor memories for different skills are organized with a specific focus on how these different motor memories for different skills can be separately stored and retrieved at the appropriate time; (2) issue surrounding online control of motor responses, how motor trajectories can be altered, and feedback control; (3) bidirectional interactions between sensorimotor control mechanisms and decision-making systems. This work has many attributes and revealed much about sensorimotor control in humans like providing evidence for how motor memories might be stored and protected by potential interference using elegant motor tasks that require the opposite motor responses (Wolpert 2014). However, Wolpert and others in this area have focused on the computational level and behavioral level, not at the neurophysiological and systems dynamics level.

The limitation of this work is the lack of integration of a large body of work showing that parallel neural circuits acquire and store different types of information during sensorimotor learning and make different contributions to behavioral output under different stages of training and during certain unexpected events (Devan et al. 2011; Gruber and McDonald 2012; McDonald and Hong 2004). For example, it has been argued that a significant amount of sensorimotor learning occurs early in life and so we have available to us, as adults, good representations of the skills necessary to move our arms, kick a soccer ball, and the movements necessary to ride a bike successfully. It is likely these representations are encoded and stored in the motor cortex and are likely a repertoire of fundamental movement categories (Graziano 2006). In other words, the motor cortex is a repository of movements that each species of animal can make. What we learn in adulthood, according to Wolpert, in situations using these movements and skills is the adjustments necessary due to differences in parameters like mass, friction, etc. We would argue that there are other

key forms of sensorimotor learning that occurs in adulthood in which the dorsal striatum plays a key role (e.g., see Hassler 1978). One theory is that one of the key functions of the dorsal striatum is linking fundamental movement categories that lead to reinforcement to specific cue and temporal conditions (Devan et al. 2011). These key aspects of adult sensorimotor learning and the role of identified parallel neural circuits centered on the striatum are not part of this approach or these models.

How could the strengths of these two approaches to understanding sensorimotor learning be combined in a fruitful way? One issue is the need to realize that, despite all the electrophysiological, computational, pharmacological, genetic, and functional work that has been completed, we still do not have a good understanding of what the algorithms are for key learning and memory structures like the hippocampus (Bannerman et al. 2014; McDonald et al. 2007; McNaughton et al. 2006). Even more concerning is that most of these models of hippocampus are based on evidence culled from dorsal hippocampal experimental manipulations. The same problem of lack of information about these different systems can be applied to current views of amygdala function (Cahill and McGaugh 1996; McDonald et al. 2007), striatal subregions (Devan et al. 2011; Yin et al. 2005), and prefrontal cortical regions (Quirk et al. 2000; Stalnaker et al. 2015; Zelinski et al. 2010).

The current situation suggests that it will be challenging to gain a relevant knowledge base in order to understand what algorithms and representations are available to the subject at any given moment during a learning experience. For example, in a recent paper by FitzGerald and colleagues (FitzGerald et al. 2014), this exact issue was raised and investigated. The idea is that an agent needs to not only make inferences about hidden variables and learn about various parameters, like the Wolpert approach, but must also determine what model to use. This would involve some kind of model comparison and one approach to this problem would be model averaging. This approach, in our view, gets even more complicated by the fact that these different models provided by multiple learning and memory systems sometimes appear to compete and sometimes synergistically interact. The future looks promising with these approaches in hand, but much needs to be done at the most basic level of understanding what algorithms these parallel memory-based behavioral systems are computing.

One strategy resembling this approach is the use of Bayesian computational models to understand goal-directed versus habit striatal learning and memory systems. This work will be the focus of the final sections of this chapter.

18.5.3 Which Learning and Memory System Controls Behavior?: Systems Behavioral Neuroscience Combined with Bayesian Approaches

Tolman (1932) suggested that animals have an internal representation of environments, and from these ‘cognitive map’ representations, actions can be associated with desired outcomes/goals. However, rats that had received extended training in a

spatial learning paradigm seemed to lose this flexible goal-directed strategy (Tolman 1949; Tolman et al. 1946). This was perhaps the first evidence that animals can employ different representations and strategies to solve the same problem and strategy selection can depend on the amount of training. Similarly, in instrumental learning, it has been argued that cognitive control of behavior and/or goal-directed responding dominates acquisition, whereas stimulus–response habit responding takes over after extended training (Balleine and Dickinson 1998b; Dickinson et al. 1995a, b).

Essentially what Tolman described is a flexible strategy that is sensitive to changes in states (internal or external) and an inflexible system in which a response is selected based on the previously acquired reward. These strategies are very similar to the stimulus–response and cognitive control of behavior, sometimes also referred to as habit- and goal-directed instrumental learning strategies. In stimulus–response habit learning, actions are selected based on their associations with stimuli, whereas in cognitive control of behavior actions are selected based on complex cognitive representations formed in hippocampus and higher-order association cortices like prefrontal and posterior cingulate cortex. A somewhat similar distinction is response-outcome (R-O) or goal-directed learning, where actions are selected based on their relationship with outcomes (Balleine and O'Doherty 2010).

There is one key distinction between the type of learning strategies that Tolman defined and those for instrumental learning: spatial learning strategies involve different types of information (place vs. response), whereas the instrumental learning strategies are differentiated in terms of how the information is used (Khamassi and Humphries 2012). Nonetheless, reinforcement learning theory and research has implemented these different learning strategies to try to explain, model, and identify the neural correlates of instrumental behavior.

The dichotomy between stimulus–response habit and cognitive control of behavior or goal-directed learning has been applied to the neural circuits that subserve these processes. Multiple memory systems theory suggests that there are different types of learning that are mediated by specific neural substrates (McDonald and White 1993; White and McDonald 2002). In an extensive review of the extant literature at the time (Devan et al. 2011), we argued that the DLS and associated circuits were essential for stimulus–response habit learning and memory processes and the DMS was a key part of a neural circuit critical for the cognitive control of memory-based behavior. Within the multiple memory systems theory, there is much speculation as to how these systems might interact to control behavior (Gruber and McDonald 2012). The claim is that there are many factors such as task demands, ongoing cognitive processing, and disease pathologies that are involved in determining which learning system controls on-going behavior in any given situation. Alternatively, it appears as though there are situations in which these systems are not mutually exclusive. The following section will review animal, human, and computational modeling data using Bayesian approaches regarding dorsal striatal functionality in instrumental learning.

18.5.4 Model-Free and Model-Based Controllers for Instrumental Learning: Bayesian Approaches

With the attempt of better understanding how these learning strategies work and are implemented, various computer algorithms have been created. Most of this work has focused on the habit and goal-directed instrumental learning distinctions. These algorithms can be broadly classified as model-free, which represent habit learning, or model-based, which represent goal-directed learning (Daw et al. 2005). For the duration of this section, model-free and habit will be used synonymously, as will model-based and goal-directed. These algorithms are being applied to spatial, Pavlovian, and instrumental learning (Dayan and Berridge 2014; Johnson et al. 2007; Khamassi and Humphries 2012; Zilli and Hasselmo 2008). As we are primarily focusing on the basal ganglia's role in instrumental learning, we will limit our discussion to the instrumental learning computational models. While there are many different computational models for instrumental learning, we will focus on several that we view as being integral to the field.

In the context of instrumental learning, the model-free controller selects actions that produce rewards (Daw et al. 2005; Otto et al. 2015). Information produced by various responses is cached and then used for future action selection (Dayan and Berridge 2014). These cached values gleaned from trial and error are combined into a single scalar number that takes into account all the future probabilities of receiving a particular reward (Daw et al. 2005; Dayan and Niv 2008). These scalar numbers can then be used to grade particular actions during action selection (Dayan and Niv 2008).

In contrast, the model-based representations are similar to the 'cognitive map' in that there is an internal representation of an environment that contains all of the possible actions and stimuli within it (Daw et al. 2005; Otto et al. 2015). One primary difference between the two models is that the model-based representation also considers an organism's internal states and motivations, while model-free representations do not (Balleine and Dickinson 1998a, b; Gasbarri et al. 2014; Gruber and McDonald 2012). Another way of looking at this is that the model-free controller gauges the value of actions solely based on trial and error and this model is blind to changes in the value of the reward or changes in internal states such as hunger or thirst (Daw et al. 2005).

The operation of these two models is inherently different as model-free computations are retrospective because they are contingent on the previous response, whereas model-based computations take into account all of the different possible states within the environment and thus are prospective (Daw and Dayan 2014; Daw et al. 2011; Dayan and Berridge 2014). Nonetheless, importantly these systems are both trying to achieve the same goal, which is to maximize the amount of rewards received.

18.5.5 Seminal Computations

Barto and his colleagues proposed a model-free algorithm called the actor/critic. In this model, there is an actor that selects the appropriate response based on an error signal received from the critic, which tells the actor if the outcome of the previous response was expected (Barto 1992, 1995; Sutton and Barto 1998). The error signal (often called temporal difference) employed by the critic closely resembles the dopamine reward-predicted error signal thought to underlie habit learning (Balleine and O'Doherty 2010). fMRI has also unveiled a temporal difference like signal in the ventral striatum; however, this may not support a pure model-free representation (discussed below; Daw et al. 2011).

Dayan and colleagues (Dayan 2002; Dayan and Balleine 2002) proposed a model that incorporated the actor–critic model-free controller that involves a temporal difference error and a flexible goal-directed component. Their aim was to create a model that encapsulated incentive evaluation that is characteristic of Pavlovian learning. Thus, their model is similar to the learning phenomenon called Pavlovian Instrumental Transfer (PIT) in that there are Pavlovian and habit controllers. For this task, subjects are first trained on an appetitively motivated pavlovian task and then transferred to an instrumental task. This initial pavlovian learning improves transfer to the instrumental task. The authors stated that dopamine error signal is involved in PIT and likely acts on the nucleus accumbens shell and maybe the core (Dayan and Balleine 2002). This model was important because it acknowledged that in some cases, such as PIT, instrumental responding can have a goal-directed component.

Daw and colleagues (Daw et al. 2005) expanded on the ideas presented in previous models by providing a truly flexible model-based controller and outlining how it might interact with a model-free controller. While both models were striving to achieve the same goal, there was no cross talk between systems as the animal literature suggests that disparate neural circuits in rodents subserve habit- and goal-directed learning. Their model-free algorithm was along the same vein as Barto, with the calculation of scalar values that represent the worth of future rewards for each available action (Daw et al. 2005; Kosaki and Dickinson 2010).

They also provided a model-based algorithm, which utilized a tree-search system (Daw et al. 2005). All of the response–outcome contingencies are given an estimated value and all of these values are then taken into consideration (searched) before making a decision (Daw et al. 2005; Kosaki and Dickinson 2010). Importantly, unlike the model-free system, this model-based system is not blind to sudden changes in the value of an outcome (Daw et al. 2005; Kosaki and Dickinson 2010). The authors also provided an arbitrator that assessed the degree of uncertainty that an action would produce in each system and then chose the strategy that was most likely to produce a reward (Daw et al. 2005). This competition between strategies and selection of a strategy was truly novel, as most previous models that used multiple learning strategies created a hybrid model (Daw et al. 2005; Sutton and Barto 1998).

18.5.6 Other Variants

A caveat that has been raised for Daw and colleagues (Daw et al. 2005) model is that, in contrast to behavioral data, there was not a decrease in response latency throughout training (Keramati et al. 2011). This occurred because even in instances where the model-free controller won control, the model-based controller was still calculating an uncertainty value and the time associated with this process remained for the entirety of training (Keramati et al. 2011).

There are alternative variants of these models that incorporate response time computations. Several algorithms have attempted to model how dopamine is involved in response vigor. McClure and Colleagues (2003) created a model involving incentive salience that suggests that phasic dopamine activity mediates response vigor. Alternatively, in another model responses with a high reward rate were selected faster than responses with a decreased reward rate and the authors hypothesized that tonic dopamine activity represents average reward rate (Niv et al. 2007). While the authors did not provide model-based computations in this model, they acknowledged that average reward rates such as those calculated in their model could be involved in goal-directed and Pavlovian learning. The differing interpretations from McClure and colleagues (2003) was attributed to the implementation of a cost–benefit analysis between response effort and reward.

Shah and Barto (2009) also incorporated response time into an algorithm and proposed a similar model to Daw and Colleagues (Daw et al. 2005), except that the arbitrator was sensitive to computation time for each system. In their iteration, the model-based (referred to as planning strategy in their model) controller was only selected when all possible goals had been analyzed. These computations are time-consuming and their model-free controller was able to make decisions with incomplete sensory information, as there are instances when a decision needs to be made rapidly in the face of uncertainty. As in Daw and colleagues (Daw et al. 2005) simulations, the model-based controller dominated early, until the model-free controller dominated responding as training progressed. During the beginning of training, the model-free controller is slow to compute the values associated with different responses because of limited trial and error experience, which allows the model-based controller to complete its calculations.

Finally, Keramati and colleagues (Keramati et al. 2011) proposed a similar model to Shah and Barto (Shah and Barto 2009) that also pitted response speed against response accuracy. An arbitrator that relies on uncertainty to select a controller deviates from some of the reinforcement learning dogma. As mentioned previously, Daw and colleagues (Daw et al. 2005) treated these controllers as separate entities that have the same rational goal. Alternatively, in Keramati and colleagues (Keramati et al. 2011) model, controller selection depends on the trade-off between the faster model-free controller and the more accurate model-based controller. In contrast to Daw et al. (2005), the arbitrator in this model was tuned to the fact that model-free and model-based controllers have different strengths and weaknesses. Notably, the model-free approach is less accurate in novel and changing environments, but faster

and computationally cheaper than the model-based approach (Keramati et al. 2011). The cost of each computation is considered with the cost of making a poor decision.

Daw and colleagues (Daw et al. 2005) indirectly represented this conundrum, as model-based uncertainty did not improve with training because it was not feasible to engage the computational rich process of searching through the entire decision tree. While the present model also considers computational cost, the difference is that they have explicitly included one constraint (deliberation time) that is analyzed in a cost–benefit manner (Keramati et al. 2011). In contrast to the model presented by Shah and Barto (2009), in the present model response time was not contingent on how long the planned controller needed to calculate outcome values, but rather was dependent on how long it took to deliberate the consequences associated with each particular controller.

18.5.7 How Well Do These Models Fit with the Data?

18.5.7.1 Behavior and Neural Correlates

The models above have captured some of the key behavioral phenomena. First, as with human (Glascher et al. 2009; Tricomi et al. 2009) and animal data (Holland et al. 2004; Killcross and Coutureau 2003; Yin et al. 2004), early on in training the model-based system controlled responding, with the model-free controller assuming control as training progressed (Daw et al. 2005; Keramati et al. 2011; Shah and Barto 2009). Second, as in the human and animal data, outcome devaluation sensitivity occurred only in instances where the model-based system assumed control, and this outcome devaluation sensitivity decreased with extended training (Adams 1982; Adams and Dickinson 1981a, b; Daw et al. 2005; Dickinson et al. 1995a, b; Keramati et al. 2011; Killcross and Coutureau 2003; Shah and Barto 2009; Yin et al. 2004; Holland et al. 2004). Thirdly, in accordance with the prediction posited by the models regarding responding time (Keramati et al. 2011; McClure et al. 2003; Niv et al. 2007; Shah and Barto 2009), in humans, choice reaction time was shorter for situations in which model-free responding occurred compared to model-based responding (Lee et al. 2014; Otto et al. 2013a).

In addition to the behavioral phenomena, recent studies in humans and animals are continuing to add to our understanding of the neural circuits substrates of these controllers. Similar, to the rat electrophysiology data, a switch from model-based to model-free control or overtraining was associated with increased activity in the posterior putamen (DLS in rodents) (Tricomi et al. 2009; Wunderlich et al. 2012a; Yin et al. 2009). Similarly, in a task specifically designed to involve both model-free and model-based responding, the striatum was associated with a model-free reward prediction error signal, whereas the lateral prefrontal cortex was required for updating information in model-based situations (Beierholm et al. 2011). Fitting, with animal data, Gläscher and colleagues (Glascher et al. 2010) found a reward prediction error in the VS, and amazingly a model-based state error signal that evaluates states associated with outcomes that appeared to be mediated by the intraparietal sulcus and lateral prefrontal cortex.

Building off of their simulations, Daw and colleagues (2006) suggested that the anterior frontal cortex in humans might be involved in switching between what they called explorative (akin to model-based) and exploitative (akin to model-free) responding in a gambling task. In corroboration of the notion that uncertainty is driving strategy selection (Daw et al. 2005, 2006), there is further fMRI evidence for an arbitrator based on the uncertainty associated with each strategy, rather than an arbitrator that pits the two strategies against each other (Beierholm et al. 2011). The comparison of these error values might reside in the ventromedial prefrontal cortex (Tricomi et al. 2009; Wunderlich et al. 2012a). Similar to Glascher and colleagues (2010), in rats, the orbitofrontal cortex has been suggested to mediate a state error signal that is involved in model-based learning (Takahashi et al. 2011). This hypothesized function fits with the finding that the orbitofrontal cortex along with the ventral striatum is required for detecting changes in reward identity that are characteristic of a model-based controller (McDannald et al. 2011).

18.5.7.2 Strategy Selection

From the behavioral and computational data, it is apparent that instrumental learning involves different types of learning that have specific neural correlates. Importantly, during normal instrumental learning, both of these types of learning are involved (Daw et al. 2011; Glascher et al. 2010). As suggested by the computational models, it is likely that there is an arbitrator that selects a controller based on something like the uncertainty associated with each controller. Changes in brain function, task demands, or current state can favor the use of one strategy over the other. This section will review instances in which a certain strategy dominates behavioral control.

18.5.7.3 Changes in Task Parameters

As described above, training promotes a shift from goal-directed to habit-based responding; however, the rodent literature suggests that slight changes in the instrumental training paradigm can prevent this transition. Random interval reinforcement schedules, in which a reward is delivered for the first response after an average amount of time since the last reinforcer, promote the transfer to habit responding (Dickinson et al. 1983; Hiláro et al. 2007). Conversely, when rewards are contingent on the average number of responses performed, performance favors a goal-directed approach (Dickinson et al. 1983; Hiláro et al. 2007).

In addition to reinforcement schedule, components of responses that occur further away from the outcome location are less sensitive to outcome devaluation. For example, while lever pressing was sensitive to manipulations that affect outcome devaluation, entry into the food magazine to obtain the reward remained sensitive to outcome devaluation despite overtraining and various lesions (Killcross and Coutureau 2003).

As suggested by Daw and colleagues (2005), task complexity can also affect learning strategy. When two responses are associated with two different outcomes and not the same outcome, rats are sensitive to outcome devaluation even after extended training (Holland et al. 2004). Kosaki and Dickinson (2010) confirmed that the additional response–outcome association is necessary for the perseveration of a goal directed controller, as rats that associated a response with one outcome and then received another outcome that was not contingent on a response were insensitive to outcome devaluation for either outcome.

Daw and colleagues' (2005) simulations produced the previous two phenomena, as magazine entry and increased task complexity (two responses and two different outcomes) were sensitive to outcome devaluation after extended training and thus were controlled by the model-based controller. Although unknown, it is possible that these manipulations are somehow affecting the interaction between the infralimbic and prelimbic cortices, in which the infralimic cortex might promote habit-based responding by inhibiting prelimbic goal-directed control (Killcross and Coutureau 2003).

18.5.7.4 External Factors

Several recent human studies have suggested that external factors can influence strategy selection. As indicated by the computational models, a model-based strategy is more costly in terms of computational load and time than a model-free strategy. Increased working memory load swayed responding to a model-free system in a task that involved both controllers (Smittenaar et al. 2013a). Interestingly, in a similar vein, in the rat, prospective memory for an upcoming event disrupts a cognitively taxing instrumental task that involves time discrimination (Wilson et al. 2013). Although it is unknown if model-based control is involved in this rat task, it suggests that ongoing computations can disrupt a computational complex learned task.

In addition to cognitive load, as in the animal behavior data, manipulations that affect brain functioning in humans dictate which controller dictates behavior. Transcranial magnetic stimulation of the right dorsolateral prefrontal cortex, which is thought to be involved in model-based behavior, resulted in more model-free responding (Smittenaar et al. 2013a). Alternatively, presumed elevation of dopamine in the brain by the systemic administration of L-DOPA promoted model-based behavior (Wunderlich et al. 2012b). This finding appears contradictory due to the association of dopamine with the reward-predicted error signal involved in model-free behavior; however, the authors hypothesized that elevated dopamine might have disrupted the function of this signal (Wunderlich et al. 2012b). Lastly, acute stress (submersion of arm in ice-water) resulted in a bias for model-free behavior (Otto et al. 2013b). Stress also affects responding in rats, as chronically stressed rats were insensitive to changes in outcome, and remarkably this shift towards habit based responding was associated with atrophy in DMS and prefrontal cortex, whereas DLS actually displayed hypertrophy (Dias-Ferreira et al. 2009).

18.5.7.5 Individual Differences

While external factors can influence strategy selection, individual differences can also affect behavioral control. Rat data indicates some animals naturally favor specific learning strategies. In a water maze variant that assesses whether animals are using an allocentric place strategy or cued strategy, there is a 50/50 split in strategy preference (McDonald and White 1994). Similarly, incentive stimuli have various properties and some rats are naturally more attuned to specific properties. Sign-trackers are enamored with the incentive cue and its location, whereas goal-trackers focus on the goal-location (Boakes 1977; Flagel et al. 2007).

In humans, across subjects, model-free responding is typically favored over model-based responding (61–39 % in Daw et al. 2011; Otto et al. 2015). Although largely unknown, there are several possibilities for individuality in respect to responding style. First, degree of executive function affects strategy selection, as individuals with poorer cognitive control as indicated by the Stroop task and a contextual processing task were more likely to engage in model-free responding in a task that enabled the use of both strategies (Otto et al. 2015). Similarly, increased processing speed in a variety of cognitive tasks was associated with model-based responding (Schad et al. 2015).

Another aspect of executive function, working memory capacity influences responding with increased working memory capacity associated with more model-based responding (Eppinger et al. 2013; Gershman et al. 2014). Amazingly, increased working memory capacity also promotes model-based behavior in situations (stress; transcranial stimulation) that are trying to push control to the model-free system (Otto et al. 2013b; Smittenaar et al. 2013a). In addition to executive functioning, astonishingly personality influences responding behavior, with extraversion being associated with poor performance in both types of responding (Skatova et al. 2013). However, extroverts that were more engaged in the task preferred a model-free approach, which fit with their hypothesis that extroverts are better at model-free reward learning (Skatova et al. 2013).

18.5.7.6 Pathologies

Disease states can bias behavioral control in one system's favor. Not surprisingly, diseases that involve repetitive behavior, such as addiction, binge eating, and obsessive-compulsive disorder, typically involve a bias for model-free behavior (Huys and Petzschner 2015; Lucantonio et al. 2014; Voon et al. 2015). Interestingly, there is a shift from model-free to model-based behavior with longer amounts of abstinence (Voon et al. 2015). As in humans, in rats, psychostimulants impair model-based responding (Nelson and Killcross 2006; Schoenbaum and Setlow 2005; Wied et al. 2013). As stress is thought to contribute to these pathologies that involve repetitive behavior, it might contribute to the dominance of a model-free strategy (Dias-Ferreira et al. 2009; Lucantonio et al. 2014).

In contrast to diseases that affect repetitive behaviors, aging also affects strategy selection. As aging is associated with a decline in executive function, based on the

data presented in the individual differences section, it is not surprising that model-based responding is impaired in aged individuals, especially in situations that increase demand on model-based behavior (Eppinger et al. 2013).

18.5.7.7 Are Model-Free and Model-Based Behaviors Dissociable?

As discussed, there is a huge animal and human literature base, suggesting these behaviors are separate entities; however, some recent data suggests that these systems might interact or influence each other to control ongoing behavior. Several recent papers assessing the contribution on these two types of learning in humans report that a combination of the two strategies fit the data better than purely model-free or model-based accounts (Daw et al. 2011; Gershman et al. 2014; Otto et al. 2013a). Sutton (1990) proposed the idea that a model-based controller can train or influence a model-free controller offline. He provided one algorithm (DYNA) that includes both model-based and model-free influences. Daw and colleagues (2011) theorized that model-based error signals might train a model-free actor in much the same way that its own error signal does. Future responding by the model-free controller would not need future planning if the model-based information is stored or cached like model-free error information (Daw et al. 2011). However, similar Daw's account differs from Sutton's in that the model-based information could be acquired through instruction rather than experience with the world (Daw et al. 2011). Lee and colleagues (2014) suggested that when there is a transition between controllers across trials, the reward prediction error could involve a combination of the model-free and model-based estimates.

Recent rat data is also suggesting that the DLS and DMS have roles outside of those defined by the habit- and goal-directed dichotomy. First, trained rats that received DMS lesions had impaired retention of a simple discrimination task that required S–R associations, but surprisingly were unimpaired in a conditioned place preference task that required S–O associations (Featherstone and McDonald 2005). These and other data suggest that the DMS might be involved in the expression of S–R learning (Adams et al. 2001; Featherstone and McDonald 2005; Kantak et al. 2001). Similarly, DMS or DLS lesions inhibited flexible switching behavior in a binary choice task (Skelin et al. 2014). In fact, when only unpredicted choices were rewarded, contrary to the notion that the DLS is solely an S-R system, DLS-lesioned animals were more model-free (lose-stay) like in their responding than DMS-lesioned animals, which displayed more flexible behavior (Skelin et al. 2014). These data do not fit with the perceived roles of these structures, but are consistent with the neuroanatomical, neurochemical, and single-unit electrophysiological data presented in this chapter. Recent human and rodent data is supporting broader roles for these structures. In rat electrophysiology, data suggests that rewards are represented similarly in rodent DLS and DMS (Kim et al. 2013; Thorn et al. 2010). In humans, the putamen along with the prefrontal cortex might mediate inhibition involved in stopping responding (Smittenaar et al. 2013b). As with Skelin and colleagues (2014), these data are unexpected as DLS was thought to drive responding in situation even when it is not advantageous to do so, rather than stopping current responding, and/or promoting alternative responding. As a whole, it appears that in

certain situations or tasks, contrary to reinforcement learning dogma, the DLS and DMS can also influence goal-directed and habit learning, respectively.

18.5.8 Summary

Bayesian computational approaches are now delving into the issue of different potential controllers, like subregions of the dorsal and ventral striatum during learning experiences. This should lead to fundamentally interesting work, but the narrow focus on the idea that the dorsomedial and dorsolateral striatum mediate goal-directed versus habit learning, respectively, is a serious limitation. Alternative views of the functions of these circuits should also be tested and the idea that they do not work in isolation in the intact animal needs to be appreciated.

18.6 Final Conclusions

Consistent with the multiple memory systems account, specific brain areas and circuits mediate different types of learning and memory and instrumental behavior, including cognitive (S-S) and habit (S-R) learning as well as a hybrid form of higher-order habit [(S-S)-R] and flexible cognitive control of behavior under different conditions (see also Devan et al. 2011). Neuroanatomical, neurochemical, single-unit electrophysiological, and computer modeling using Bayesian approaches have been used to discern how these models might operate and interact with each other. Individual differences and external variables can favor the selection of one of these strategies. While cognitive control of behavior and/or goal-directed and stimulus–response habit learning consist of different memory-based behaviors and neural circuits, recent data suggests that these structures might synergistically interact in decision-making. Furthermore, in certain situations DLS and DMS can have functions that are not predicted within this theoretical framework. We encourage that the walls that have been built around these systems have some windows installed, as these behaviors and the neural structures that mediate them can interact during decision making.

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Chapter 19
Neural Dynamics of the Basal Ganglia During Perceptual, Cognitive, and Motor Learning and Gating

Stephen Grossberg

19.1 Introduction

19.1.1 Linking Brain to Mind with Neural Models: Method of Minimal Anatomies

The rapid development of behavioral and cognitive neuroscience parallels the growing interest in mechanistically linking brain mechanisms to behavioral functions. Expressed in another way, this interest asks: How can a brain gives rise to a mind? How can the classical Mind/Body Problem be solved? The remarkable experimental and theoretical progress in understanding brain *or* mind in the fields of neuroscience and psychology has not often provided clear mechanistic links between them, if only because mind is an emergent property that arises from widespread interactions among multiple brain regions, and experimental methods can probe the detailed structure of such interactions only partially. Yet establishing such a linkage between brain and mind is crucial in any mature theory of how a brain or mind works. Without such a link, the mechanisms of the brain have no functional significance, and the functions of behavior have no mechanistic explanation.

In order to establish such a link with sufficient clarity for it to be scientifically predictive, rigorous mathematical models are needed that can simultaneously describe multiple levels of brain and behavioral organization. A rapidly growing number of such models can now quantitatively simulate the neurophysiologically recorded dynamics of identified nerve cells in known anatomies *and* the behaviors that they control. Many predictions of these models have also been supported by

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subsequent experiments over the years. In this restricted sense, the Mind/Body Problem is at last starting to be understood.

A particularly successful approach uses a theoretical method that has been systematically developed and applied during the past 50 years (Grossberg 1999). One begins with scores or even hundreds of parametrically structured *behavioral* experiments in a particular problem domain because the brain has evolved to achieve *behavioral* success. Starting with behavioral data makes sense if one wants to derive a model whose brain mechanisms have been shaped during evolution by behavioral success. Large number of behavioral experiments are needed to rule out many otherwise seemingly plausible answers.

The method uses a large behavioral database to discover novel design principles and mechanisms to explain how an individual, behaving in real time, can generate these data as emergent properties. The minimal mathematical model that can realize these design principles has always looked like part of a brain. Fifty years of modeling have consistently led to the empirical conclusion that brains look the way that they do because they embody the natural computational designs to control an individual's autonomous adaptation to a changing environment in real time. Moreover, this kind of behavior-to-principle-to-model-to-brain theoretical derivation has often disclosed unexpected functional roles of the neural mechanisms that are not clear from neural data alone.

Having made a connection top-down from behavior to brain, one can now use mathematical and computational analysis to disclose what the minimal model, and its variations, can and cannot explain. Using this information, one can exert upon the model both top-down constraints from behavior, and bottom-up constraints from brain, to point to one or more additional design principles that are needed to explain even more data. These new design principles and their mechanistic realizations are then consistently assimilated into the model. This process is repeated cyclically, thereby leading by a process of "conceptual evolution" to a series of progressively unlumped models, each consistent with the others, and with an increasing broad explanatory and predictive range, including more neural mechanistic detail. At the present time, although one cannot "derive the entire brain" in one step, an increasing number of these models can individually explain behavioral, neurophysiological, neuroanatomical, biophysical, and even biochemical data.

19.1.2 Modeling the Basal Ganglia

The earlier perspective helps to clarify the challenge facing any theorist who wishes to model the basal ganglia. This is true because the basal ganglia, in addition to comprising multiple subcortical nuclei, are widely interconnected with multiple other brain regions, including the cerebral cortex, thalamus, amygdala, and hippocampus (http://en.wikipedia.org/wiki/Basal_ganglia, http://www.scholarpedia.org/article/Basal_ganglia). Numerous experimental studies have proposed roles for the basal ganglia in processes such as reinforcement learning and action selection, or gating. Figure 19.1 schematizes how these functions are organized in parallel

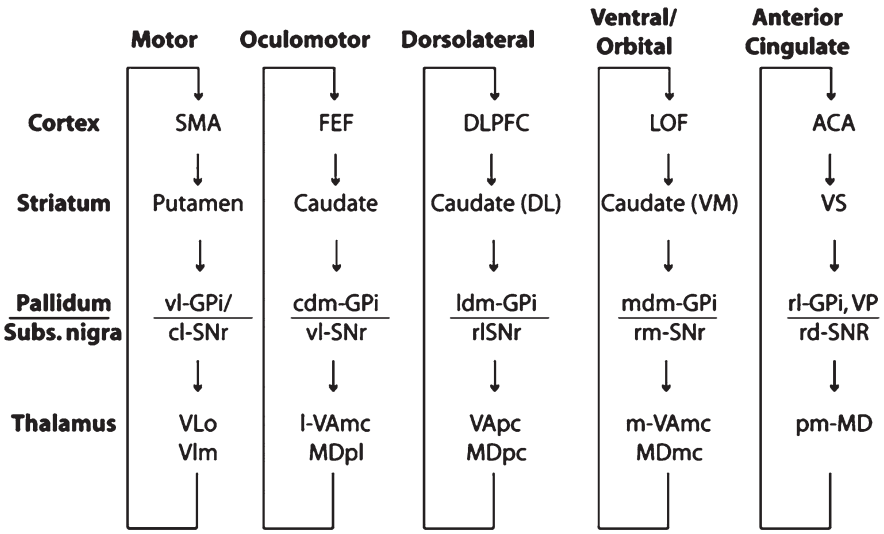


Fig. 19.1 Basal ganglia parallel loops. The dorsal and ventral striatum are differentially connected to discrete prefrontal cortical regions in segregated cortico-striatal circuits, as summarized by Alexander et al. (1996). The putamen plays a critical role within the motor circuit, while the caudate forms part of the oculomotor, dorsolateral, and ventral/orbital circuits. *SMA* supplementary motor area, *vl-GPi* ventrolateral globus pallidus (internal segment), *cl-SNr* caudolateral substantia nigra pars reticulata, *VLo* ventrolateral nucleus of thalamus pars oralis, *Vlm* ventrolateral nucleus of thalamus pars medialis, *FEF* frontal eye fields, *cdm-GPi* caudodorsomedial globus pallidus (internal segment), *vl-SNr* ventrolateral substantia nigra pars reticulata, *l-VAmc* lateral ventral anterior nucleus of thalamus pars magnocellularis, *MDpl* parvocellular subnucleus of mediodorsal nucleus of the thalamus, *DLPFC* dorsolateral prefrontal cortex, *Caudate (DL)* dorsolateral caudate, *Caudate (VM)* ventromedial caudate, *mdm-GPi* dorsomedial globus pallidus (internal segment), *rm-SNr* rostromedial substantia nigra pars reticulata, *m-VAmc* medial ventral anterior nucleus of thalamus pars magnocellularis, *MDmc* magnocellular subnucleus of mediodorsal nucleus of the thalamus, *ACA* anterior cingulate area, *VS* ventral striatum, *rl-GPi* rostrolateral globus pallidus (internal segment), *VP* ventral posterior nucleus of the thalamus, *rd-SNr* rostrodorsal substantia nigra pars reticulata, *pm-MD* posteromedial mediodorsal nucleus of the thalamus [Reprinted with permission from Grahn et al. (2009)]

thalamo-cortical motor, spatial, visual, and affective loops. To understand how these processes work, and what kinds of events are reinforced or selected, one needs models of how all the relevant brain regions interact and how these interactions give rise to the behaviors that they control.

19.1.3 Complementary Computing and Laminar Computing

What form do neural models of such processes take? This answer is constrained by the discovery of novel computational paradigms whereby advanced brains are organized.

Complementary Computing: Complementary Computing addresses the question: What is the nature of brain specialization? The brain's organization into distinct

anatomical areas and processing streams shows that brain processing is specialized. However, much data shows that these streams interact strongly and do not compute their respective functions in the manner of independent modules. *Complementary Computing* (Grossberg 2000b, 2012) concerns the discovery that pairs of parallel cortical processing streams compute complementary properties in the brain. Each stream has complementary computational strengths and weaknesses, much as in physical principles like the Heisenberg Uncertainty Principle. Each cortical stream can also possess multiple processing stages. These stages realize a *hierarchical resolution of uncertainty*. "Uncertainty" here means that computing one set of properties at a given stage prevents computation of a complementary set of properties at that stage. Complementary Computing proposes that the computational unit of brain processing that has behavioral significance consists of parallel interactions between complementary cortical processing streams with multiple processing stages to compute complete information about a particular type of biological intelligence. For example, it will be reviewed later how the basal ganglia and amygdala compute complementary properties of reinforcement learning, with the basal ganglia helping to control learning in response to unfamiliar and unexpected events and the amygdala helping to control conditioned reinforcement and incentive motivational support for familiar and expected events.

Laminar Computing: Laminar Computing concerns the fact that the cerebral cortex, the seat of higher intelligence in all modalities, is organized into layered circuits (often six main layers) that undergo characteristic bottom-up, top-down, and horizontal interactions. Laminar Computing proposes how variations and specializations of this shared laminar design embody different types of biological intelligence, including vision, speech and language, and cognition (Grossberg 1999, 2012). Laminar Computing explains how the laminar design of neocortex may realize the best properties of feedforward and feedback processing, digital and analog processing, and bottom-up data-driven processing and top-down attentive hypothesis-driven processing. For example, it will be reviewed later how the basal ganglia interact with prescribed layers of the frontal eye fields and prefrontal cortex to control the learning and performance of individual eye movements and sequences of eye movements.

19.2 Neural Models for Reinforcement Learning and Action Selection and Planning

Each of the subsequent sections summarizes a model that explains different aspects of how the basal ganglia contribute to associative and reinforcement learning, and to movement gating, in multiple brain systems.

The model in Sect. 3 proposes how the substantia nigra pars compacta (SNc) generates widespread dopaminergic learning signals in response to unexpected rewarding cues, including a circuit for adaptively timed learning using metabotropic glutamate receptor (mGluR)-mediated Ca2+ spikes that occur with different delays in striosomal cells. This section also notes that similar circuits for such adaptively timed learning,

which is called spectral timing, seem to occur at the parallel fiber-Purkinje cell synapses of the cerebellum, where they control adaptively timed movements, and the dentate-CA3 circuits of the hippocampus, where they control adaptively timed motivated attention. The hippocampal adaptive timing circuits go through lateral entorhinal cortex and its hippocampal projections, and include "time cells." These circuits seem to be computationally homologous to circuits for spatial navigation in medial entorhinal cortex and its hippocampal projections, and include grid and place cells.

The TELOS model that is reviewed in Sect. 4 shows how the substantia nigra pars reticulata (SNr) learns to selectively gate saccadic eye movements or cognitive plans. It also clarifies how spatially invariant object categories in the What cortical stream can learn to control spatially selective movement representations in the Where cortical stream.

The VITE model that is reviewed in Sect. 5 proposes how basal ganglia gating controls selection and variable speeds of arm movement trajectories that are planned in cortical circuits, including trajectories that can cope with obstacles and unexpected perturbations. The FLETE model complements VITE by simulating the spinal cord and cerebellar circuits that enable VITE to generate accurate trajectories that take into account muscle forces and tensions of a multijoint arm.

The cARTWORD model that is reviewed in Sect. 6 explains how prefrontally controlled basal ganglia gates contribute to an explanation of phonemic restoration, notably how future context can influence how past sounds are consciously heard. cARTWORD describes a hierarchy of laminar cortical circuits that are variations of laminar cortical circuits which have also been used to model 3D vision and figure-ground perception, as well as cognitive working memory and list chunking processes. These list chunks represent the most predictive sequences of items that are stored in the working memory at any time. In cARTWORD, the cognitive working memory activates list chunks that represent the most predictive sequences of stored sounds at any given moment. When such a list chunk gets sufficiently active, it opens a basal ganglia gate that enables the entire cortical hierarchy to generate a resonance that represents the consciously heard sequence as it unfolds through time.

The MOTIVATOR model that is reviewed in Sect. 7 clarifies how the basal ganglia and amygdala coordinate their complementary functions during learning and performance of motivated acts. In particular, whereas the basal ganglia generate Now Print dopaminergic signals to drive new learning in response to unexpected rewards, the amygdala is activated by already learned conditioned reinforcers and generates incentive motivational outputs that control motivated attention and performance to acquire valued and familiar goal objects. Of particular importance in MOTIVATOR is the role of inferotemporal-amygdala-orbitofrontal resonances that focus attention upon motivationally salient objects while supporting conscious awareness of emotions.

The lisTELOS model that is reviewed in Sect. 8 proposes how sequences of saccades can be learned and performed from an Item-Order-Rank spatial working memory under the control of three parallel basal ganglia loops. Such an Item-Order-Rank working memory model can store sequences of items with multiple repeats in working memory and is supported both by psychological and neurophysiological data. This Item-Order-Rank working memory is defined by a laminar cortical circuit

that is a variant of the cARTWORD cognitive working memory. Variations of the same working memory design have been predicted to represent spatial, linguistic, and motor sequences, thereby providing another example of the conceptual and mechanistic unification that Laminar Computing has begun to provide.

Section 9 summarizes how basal ganglia gating may also control working memory storage, visual imagery, useful field of view in spatial attention, thinking, planning, and Where's Waldo searching, as well as how its breakdown can lead to hallucinations.

Section 10 notes how complementary processes of spatially invariant object category learning and motivated attention interact with spatially variant control of actions. These complementary systems enable the brain to rapidly learn to recognize a changing world without experiencing catastrophic forgetting, yet to also be able to adapt its spatial and motor representations to efficiently control our changing bodies. The basal ganglia bridge this complementary divide to support learning and gating across the entire brain.

19.3 Adaptively Timed Reinforcement Learning in Response to Unexpected Rewards

19.3.1 Balancing Fast Excitatory Conditioning Against Adaptively Timed Inhibitory Conditioning

This overview begins by reviewing a neural model that proposes how the basal ganglia may use parallel excitatory and inhibitory learning pathways to selectively respond to unexpected rewarding cues, and to thereby trigger widespread dopaminergic Now Print, or reinforcement learning, signals to multiple brain regions (Fig. 19.2a; Brown et al. 1999). In particular, humans and animals can learn to predict both the intensities and the times of expected rewards. Correspondingly, the firing patterns of dopaminergic cells within the substantia nigra pars compacta (SNc) are sensitive to both the predicted and the actual times of reward (Ljungberg et al. 1992; Schultz et al. 1993, 1995; Mirenowicz and Schultz 1994; Hollerman and Schultz 1998; Schultz 1998).

Figures 19.2 and 19.3 summarize some of the main neurophysiological properties of these cells along with model simulations of them. Notable among them (Fig. 19.2b, c) is the fact that reinforcement learning enables SNc cells to respond selectively to unexpected cues, such as conditioned stimuli (CS), during classical conditioning, but to omit responses to expected rewards, such as unconditioned stimuli (US). The model also simulates related anatomical and neurophysiological data about the pedunculo-pontine tegmental nucleus (PPTN), lateral hypothalamus, ventral striatum, and striosomes (Fig. 19.3a). Thus, the responses of SNc cells are themselves altered by the conditioning process, even as they alter how other brain regions process associative learning signals.

The neural model depicted in Fig. 19.2a proposes how two parallel learning pathways from limbic cortex to the SNc work together to control adaptively timed SNc

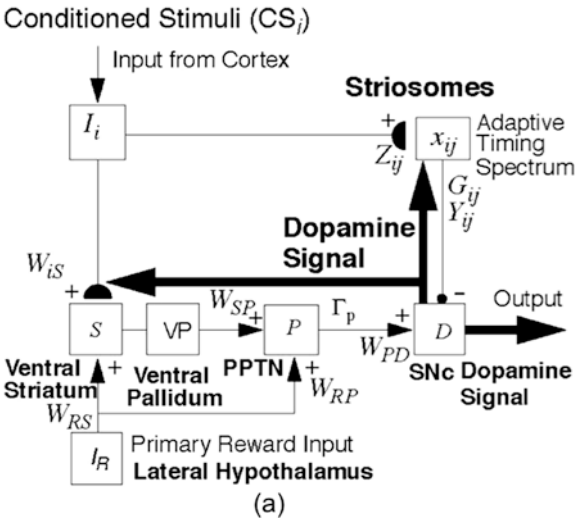
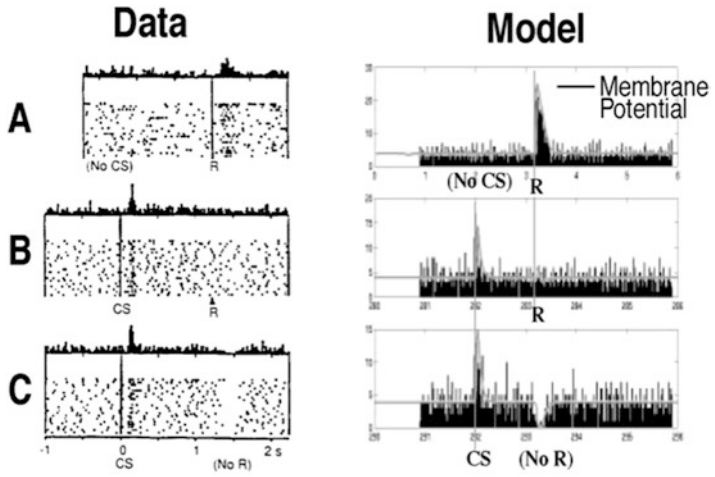


Fig. 19.2 (**a**) Model circuit for the control of dopaminergic Now Print signals in response to unexpected rewards. Cortical inputs (I_i), activated by conditioned stimuli, learn to excite the SNc via a multistage pathway from the ventral striatum (S) to the ventral pallidum, and then on to the PPTN (P) and the SNc (D). The inputs I_i excite the ventral striatum via adaptive weights W_{iS}, and the ventral striatum excites the PPTN via double inhibition through the ventral pallidum, with strength W_{SP}. When the PPTN activity exceeds a threshold GP, it excites the SNc with strength W_{PD}. The striosomes, which contain an adaptive spectral timing mechanism (x_{ij}, G_{ij}, Y_{ij}, Z_{ij}), learn to generate adaptively timed signals that inhibit reward-related activation of the SNc. Primary reward signals (I_R) from the lateral hypothalamus both excite the PPTN directly (with strength W_{RP}) and act as training signals to the ventral striatum S (with strength W_{RS}) that trains the weights W_{iS}. *Arrowheads* denote excitatory pathways, *circles* denote inhibitory pathways, and *hemidisks* denote synapses at which learning occurs. *Thick pathways* denote dopaminergic signals. [Reprinted with permission from Brown et al. (1999).] (**b**) Dopamine cell firing patterns: *Left*: Data. *Right*: Model simulation, showing model spikes and underlying membrane potential. *A*. In naive monkeys, the dopamine cells fire a phasic burst when unpredicted primary reward *R* occurs, such as if the monkey unexpectedly receives a burst of apple juice. *B*. As the animal learns to expect the apple juice that reliably follows a sensory cue (conditioned stimulus, CS) that precedes it by a fixed time interval, then the phasic dopamine burst disappears at the expected time of reward, and a new burst appears at the time of the reward-predicting CS. *C*. After learning, if the animal fails to receive reward at the expected time, a phasic depression, or dip, in dopamine cell firing occurs. Thus, these cells reflect an adaptively timed expectation of reward that cancels the expected reward at the expected time. [The data are reprinted with permission from Schultz et al. (1997). The model simulations are reprinted with permission from Brown et al. (1999).] (**c**) Dopamine cell firing patterns: *Left*: Data. *Right*: Model simulation, showing model spikes and underlying membrane potential. *A*. The dopamine cells learn to fire in response to the earliest consistent predictor of reward. When CS2 (instruction) consistently precedes the original CS (trigger) by a fixed interval, the dopamine cells learn to fire only in response to CS2. [Data reprinted with permission from Schultz et al. (1993).] *B*. During training, the cell fires weakly in response to both the CS and reward. [Data reprinted with permission from Ljungberg et al. (1992).] *C*. Temporal variability in reward occurrence: When reward is received later than predicted, a depression occurs at the time of predicted reward, followed by a phasic burst at the time of actual reward. *D*. If reward occurs earlier than predicted, a phasic burst occurs at the time of actual reward. No depression follows since the CS is released from working memory. [Data in *C* and *D* reprinted with permission from Hollerman and Schultz (1998)]. *E*. When there is random variability in the timing of primary reward across trials (e.g., when the reward depends on an operant response to the CS), the striosomal cells produce a Mexican Hat depression on either side of the dopamine spike. [Data reprinted with permission from Schultz et al. (1993).] [Model simulation reprinted with permission from Brown et al. (1999).]



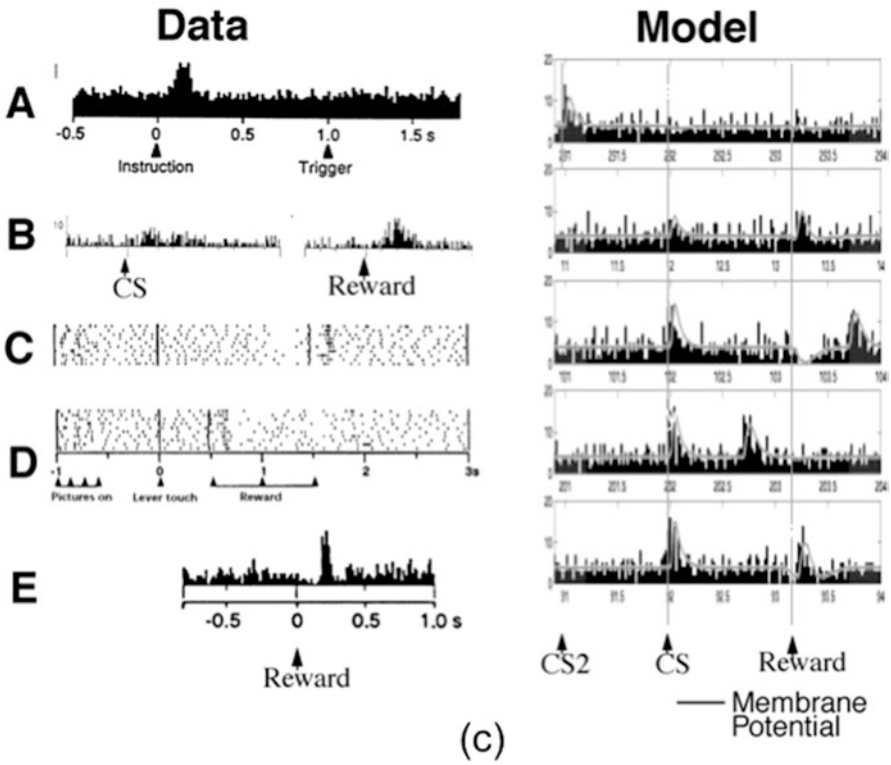


Fig. 19.2 (continued)

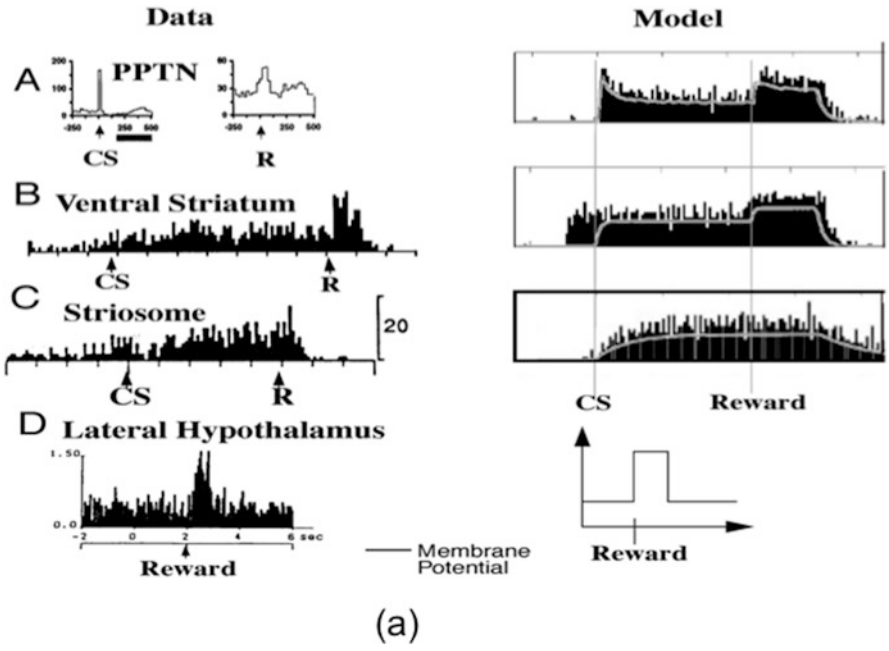


Fig. 19.3 (**a**) Trained firing patterns in PPTN, ventral striatum, striosomes, and lateral hypothalamus. *Left*: Data. *Right*: Model simulations, showing model spikes and underlying membrane potential. *A*. PPTN cell (cat), showing phasic responses to both CS and primary reward. [Data reprinted with permission from Dormont et al. (1998).] In the model, phasic signaling is due to accommodation or habituation (Takakusaki et al. 1997), which causes the cell to fire in response to the earliest reward-predicting CS and US reward, but not to subsequent CSs prior to reward. *B*. Ventral striatal cells show sustained working memory-like response between trigger and a US reward, and a phasic response to the US reward. [Data reprinted with permission from (Schultz et al. 1992).] *C*. A ventral striatal cell, predicted here to be a striosomal cell, shows buildup to phasic primary reward response. For the model cell, $j = 39$. [Data reprinted with permission from (Schultz et al. 1992).] *D*. A lateral hypothalamic neuron with a strong, phasic response to glucose reward. [Data reprinted with permission from Nakamura and Ono (1986).] The majority of these neurons fired in response to primary reward but not to a reward-predicting CS. The model lateral hypothalamic input is a rectangular pulse. [Model simulation reprinted with permission from Brown et al. (1999).] (**b**) Striosomal spectral timing model and close-up (inset), showing individual timing pulses. Each *curve* represents the suprathreshold intracellular Ca^{2+} concentration of one striosomal cell. The peaks are spread out in time so that reward can be predicted at various times after CS onset. Learning does this by strengthening the inhibitory effect of the striosomal cell with the appropriate delays. The model uses 40 peaks, spanning approximately 2 s and beginning 100 ms. after the CSs (cf., Grossberg and Schmajuk 1989). Model properties are robust when different numbers of peaks are used. It is important that the peaks be sufficiently narrow and tightly spaced to permit fine temporal resolution in the reward-cancelling signal. However, a trade-off ensues in that more timed signals must be used as the time between peaks is reduced. The timed signals must not begin too early after the CS, or they will erroneously cancel the CS-induced dopamine burst. The 100 ms post-CS onset delay prevents this from happening. [Reprinted with permission from Brown et al. (1999).]

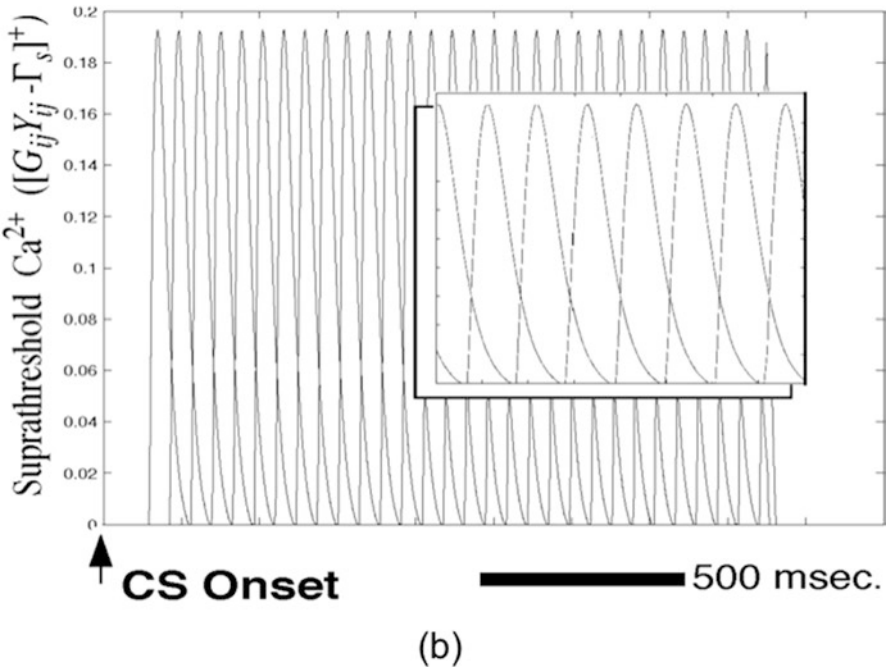


Fig. 19.3 (continued)

conditioning. One pathway controls excitatory conditioning through the ventral striatum, ventral pallidum, and PPTN. This pathway learns to generate CS-activated excitatory SNc dopamine bursts as conditioning proceeds (Fig. 19.2bA). The other pathways control adaptively timed inhibitory conditioning through the striosomes, thereby learning to prevent dopamine bursts in response to predictable reward-related signals. The net effect on SNc output bursting depends upon the balance of excitatory and inhibitory signals that converge upon these cells. When expected rewards are received, the excitatory and inhibitory signals are balanced, so that SNc cells do not fire (Fig. 19.2bB). On the other hand, if an expected reward is not received, then striosomal inhibition of SNc that is unopposed by excitation results in a phasic drop in dopamine cell activity (Fig. 19.2bC).

19.3.2 Spectral Adaptively Timed Inhibitory Conditioning by Ca^{2+} and mGluR

The adaptively timed inhibitory learning is proposed to arise from the population response of an intracellular spectrum of differently timed responses (Fig. 19.3b). The differently timed responses are proposed to arise from metabotropic glutamate receptor (mGluR)-mediated Ca^{2+} spikes that occur with different delays in

striosomal cells. A dopaminergic burst that co-occurs with a Ca^{2+} spike is proposed to potentiate inhibitory learning at that delay.

The model's mechanism for realizing adaptively timed inhibitory conditioning is proposed to be a variation of a mechanism of adaptively timed learning that is found in several brain regions. This mechanism is called *spectral timing* because it relies upon the population response of a spectrum of differently timed cells or cell sites. The Spectral Timing model proposes an answer to a perplexing problem: How do brains generate responses that are adaptively timed over hundreds of milliseconds or even seconds, when individual neuronal cell potentials respond on a time scale that is orders of magnitude faster? The model proposes that a gradient of Ca^{2+} responses within the mGluR system accomplishes this feat (Fiala et al. 1996), and that this is an ancient discovery by evolution that has been utilized in cellular tissues outside the brain as well.

19.3.3 Spectrally Timed Learning in Basal Ganglia, Hippocampus, and Cerebellum

Accordingly, the Spectral Timing model has been used to explain and simulate several different types of data that exhibit adaptively timed learning, including both normal and abnormal adaptively timed behaviors. The normal behaviors include reinforcement learning, motivated attention, and action, via circuits involving basal ganglia, hippocampus (Grossberg and Merrill 1992, 1996; Grossberg and Schmajuk 1989), and cerebellum (Fiala et al. 1996). In particular, a spectrally timed circuit through dentate-CA3 hippocampal circuits is proposed to control adaptively timed motivated attention via incentive motivational signals that are proposed to subserve the Contingent Negative Variation (CNV) event-related potential. A spectrally timed circuit through cerebellar (parallel fiber)-(Purkinje cell) synapses is proposed to control adaptively timed responding via mechanism of learned long-term depression (LTD). Abnormal adaptive timing due to cerebellar lesions, or in autistic individuals, may cause actions to be prematurely released in a context-inappropriate manner that can prevent them from receiving normal social rewards (Grossberg and Seidman 2006; Grossberg and Vladusich 2010; Sears et al. 1994).

It should also be emphasized that spectral timing is not the only mechanism whereby the brain can cause responses to be delayed over significant time intervals. Cognitive working memories also have this property and have been modeled by laminar prefrontal cortical circuits (Grossberg and Pearson 2008); see Sect. 8. One signature of spectral timing is a Weber Law property, also called scalar timing (Gibbon et al. 1984), whereby longer delays coexist with greater variance in the response distribution through time. A spectrum of adaptively timed "time cells" have been discovered using neurophysiological recordings in the hippocampus (MacDonald et al. 2011). These cells exhibit the predicted Weber law property.

19.3.4 Neural Relativity: Space and Time in the Entorhinal-Hippocampal System

Another interesting feature of the spectral timing story concerns the fact that the hippocampus processes spatial as well as temporal information. This observation raises the question: Why are both space and time both processed in the hippocampus? The fact of this convergence is consistent with data and hypotheses about a possible role of hippocampus in episodic learning and memory, since episodic memories typically combine both spatial and temporal information about particular autobiographical events; e.g., Eichenbaum and Lipton 2008. Grid cells in the medial entorhinal cortex (Hafting et al. 2005) and place cells in the hippocampal cortex (O'Keefe and Dostrovsky 1971) together play a key role in the representation of space in the entorhinal–hippocampal system and how it controls both spatial navigation and episodic memory. Multiple scales of entorhinal grid cells can develop in a self-organizing map and cooperate in a second self-organizing map to learn place cell receptive fields (Grossberg and Pilly 2014; Pilly and Grossberg 2013). These multiple scales form along a dorsoventral spatial gradient in the entorhinal cortex such that grid cells have increasingly large spatial scales (i.e., larger spatial intervals between activations in a hexagonal grid) in the ventral direction. Grid cells with several different spatial scales along the dorsoventral gradient can cooperate to form place cells that can represent spaces much larger than those represented by individual grid cells, indeed place cells capable of representing the lowest common multiple of the grid cell scales that activate them (Gorchetchnikov and Grossberg 2007; Pilly and Grossberg 2012).

This background indicates the similarity in how the entorhinal–hippocampal system deals with both time and space. In the case of temporal representation by Spectral Timing, a spectrum of small time scales can be combined to represent much longer and behaviorally relevant temporal delays. In the case of spatial representation by grid cells, a spectrum of small grid cell spatial scales can be combined to represent much larger and behaviorally relevant spaces through place cells. This homology has led to the name Spectral Spacing for the mechanism whereby grid cells give rise to place cells.

The Spectral Timing model reflects the part of entorhinal–hippocampal dynamics that is devoted to representing objects and events, and includes lateral entorhinal cortex. The Spectral Spacing model reflects a complementary part of entorhinal–hippocampal dynamics that is devoted to representing spatial representations, and includes medial entorhinal cortex. Both of these processing streams are joined in the hippocampus to support spatial navigation as well as episodic learning and memory (Eichenbaum and Lipton 2008).

This proposed homology between spatial and temporal representations is supported by rigorous mathematical modeling and data simulations. Grossberg and Pilly (2012, 2014) have developed the Spectral Spacing model to show that neural mechanisms which allow a dorsoventral gradient of grid cell spatial scales to be

learned are formally the same as mechanisms that enable a gradient of temporal scales to control adaptive timing in the Spectral Timing model (Grossberg and Merrill 1992, 1996; Grossberg and Schmajuk 1989). Grossberg and Pilly (2012, 2014) were forced into this mechanistic homology in order to be able to quantitatively simulate challenging data about parametric properties of grid cells along the dorsoventral gradient. Thus, it may be that space and time are both in the hippocampus because they both exploit a shared set of computational mechanisms. The phrase "neural relativity" tries to celebrate this predicted homology of spatial and temporal properties of the entorhinal–hippocampal system.

In summary, spectrally timed learning seems to play multiple roles in learning to control motivated attention and action. Its role in the basal ganglia thus seems to illustrate a brain design that has been exploited to control multiple types of adaptively timed behaviors.

19.4 Associative and Reinforcement Learning of Eye Movements

19.4.1 Eye Movements as a Model System for Understanding Movement and Cognition

The circuit in Fig. 19.2a generates Now Print reinforcement learning signals that regulate associative learning in multiple brain regions. The TELOS model (Fig. 19.4a; Brown et al. 2004) was developed to illustrate how this widespread Now Print signal can be used to learn several different types of saccadic eye movement behaviors. Eye movements were chosen as a good explanatory target for this modeling task because, first, behavioral and neurophysiological data are abundant for this kind of behavior and, second, eye movements are an excellent brain system for understanding how sensory modalities, like vision and audition, control motor actions. In addition, it is known that the parietal attention circuits that are used to command eye movement target positions are also used to command arm movement target positions (Andersen et al. 1997; Deubel and Schneider 1996). Thus, such a model can be adapted to control the targeting of arm movements as well.

This task is facilitated by the availability of detailed neural models both of eye movement control (e.g., Gancarz and Grossberg 1998, 1999; Grossberg and Kuperstein 1989; Grossberg et al. 1997a, b, 2012; Srihasam et al. 2009) and arm movement control (e.g., Bullock et al. 1998; Bullock and Grossberg 1988, 1991; Contreras-Vidal et al. 1997; Grossberg and Paine 2000). Finally, some eye movements can be made to remembered positions in space, and sequences of planned eye movements can be learned; see Sect. 8. Thus, this system also provides a useful window into higher order cognitive brain processes, and how they interact with sensory and motor processes.

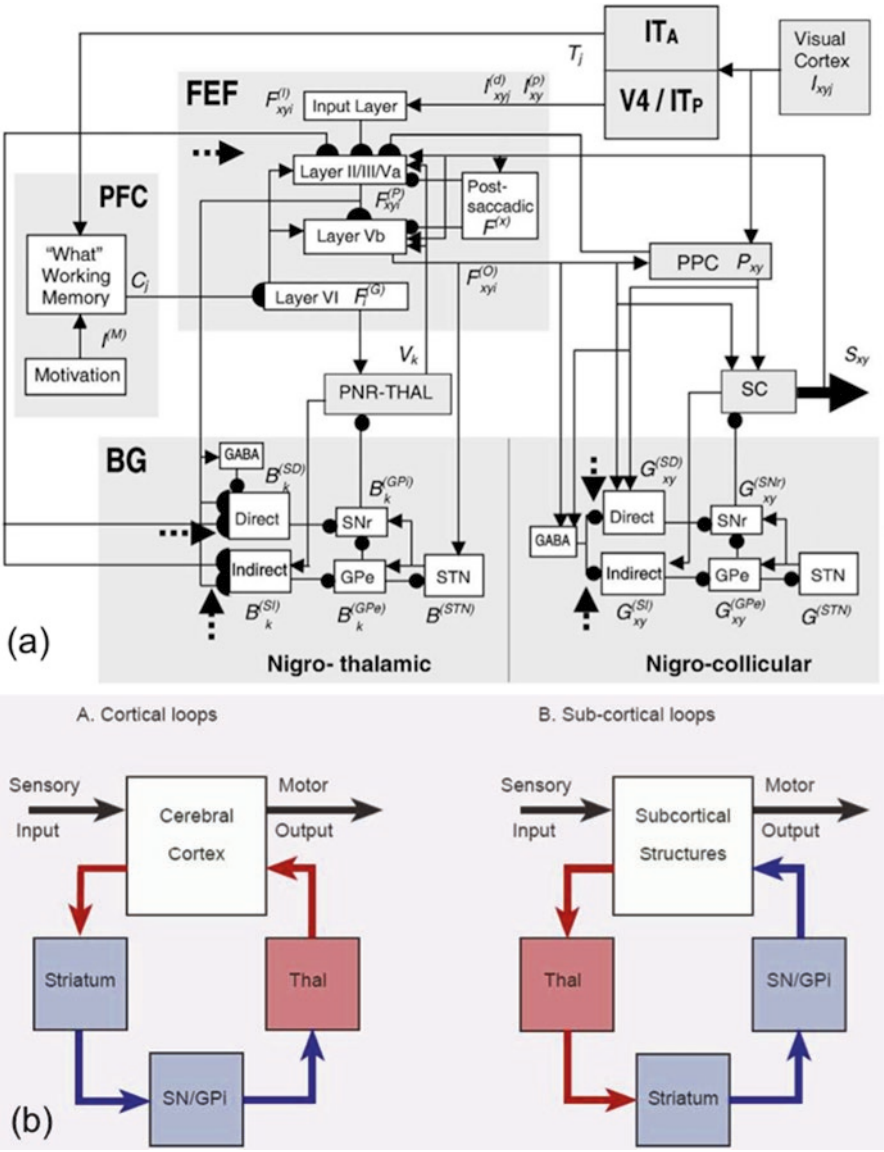


Fig. 19.4 (**a**) TELOS model macrocircuit showing how layers of the frontal eye fields (FEF) interact with several brain regions, including the basal ganglia (BG), superior colliculus (SC), GABA-ergic striatal interneurons (GABA-SI), external (lateral) segment of the globus pallidus (GPe), internal (medial) segment of the globus pallidus (GPi), anterior inferotemporal cortex (ITa), posterior inferotemporal cortex (ITp), prestriate cortical area V4 (V4), posterior parietal cortex (PPC), prefrontal cortex (PFC), substantia nigra pars reticulata (SNr), subthalamic nucleus (STN), pallidal-(GPi) or nigral-(SNr) receiving zone of the thalamus (e.g., mediodorsal, ventral anterior, and ventral lateral pars oralis nuclei) (PNR-THAL). Separate *gray-shaded blocks* highlight the major anatomical regions whose roles in planned and reactive saccade generation are treated in the model.

19.4.2 How Does the Brain "Know Before It Knows"? Gating Reactive and Planned Behaviors

The TELOS model proposes detailed mechanistic solutions to several basic problems in movement control: How does the brain learn to balance between reactive and planned movements? How do recognition and action representations in the brain cooperate to launch movements toward valued goal objects: How does the brain learn to switch among different movement plans as it is exposed to different combinations of scenic cues and timing constraints?

Fig. 19.4 (continued) Excitatory connections are shown as *arrowheads*, inhibitory connections as *ballheads. Filled semicircles* denote cortico-striatal and cortico-cortical pathways whose connection weights can be changed by learning. Such learning is modulated by reinforcement-related dopaminergic signals (*dashed arrows*) that are generated from SNc, as described in Fig. 19.2a and the surrounding text. In the FEF block, Roman numerals I–VI label cortical layers; Va and Vb, respectively, are superficial and deep layer V. Further symbols are variable names in the mathematical model. Subscripts *xy* index retinotopic coordinates, whereas subscript *i* denotes an FEF zone wherein a plan is learned and that is gated by an associated BG channel. All variables for FEF activities use the symbol F. Processed visual inputs $I_{xy}^{(p)}$ and $I_{xyj}^{(d)}$ emerging from visual areas including V4 and ITp feed into the model FEF input cells and affect activations $F_{xyi}^{(\mathrm{I})}$. Connections that carry such inputs are predicted to synapse on cells in layer III (and possibly layers II and IV). Visual input also excites the PPC, P_{xy}; and ITa, T_j. A PFC motivational signal $I^{(\mathrm{M})}$ arouses PFC working memory activity C_i, which in turn provides a top-down arousal signal to model FEF layer VI cells, with activities $F_i^{(\mathrm{G})}$. The FEF input cell activities $F_{xyi}^{(\mathrm{I})}$ excite FEF planning cells $F_{xyi}^{(\mathrm{P})}$, which are predicted to reside in layers III/Va (and possibly layer II). Distinct plan layer activities represent alternative potential motor responses to input signals, e.g., a saccade to an eccentric target or to a central fixation point. FEF layer VI activities $F_i^{(\mathrm{G})}$ excite the groups/categories of plans associated with gated cortical zones *i* and associated thalamic zones *k*. The BG decide which plan to execute and send a disinhibitory gating signal that allows thalamic activation *Vk*, which excites FEF layer Vb output cell activities $F_{xyi}^{(\mathrm{O})}$ to execute the plan. The model distinguishes a thalamus-controlling BG pathway (Kemel et al. 1988), whose variables are symbolized by *B*, and a colliculus-controlling pathway, whose variables are symbolized by *G*. Thus, the striatal direct (SD) pathway activities B_k^{SD} and $G_{xy}^{(\mathrm{SD})}$, respectively, inhibit GP_i activities $G_k^{(\mathrm{BP}_i)}$ and *SNr* activities $G_{xy}^{(\mathrm{SN}_r)}$ which, respectively, inhibit thalamic activities V_k and collicular activities S_{xy}. As further specified in Fig. 19.3a, if the FEF saccade plan matches the most salient sensory input to the PPC, then the BG disinhibit the SC to open the gate and generate the saccade. However, if there is conflict between the bottom-up input to PPC and the top-down planned saccade from FEF, then the BG-SC gate is held shut by feedforward striatal inhibition (note BG blocks labeled GABA) until the cortical competition resolves. When a plan is chosen, the resulting saccade-related FEF output signal $F_{xyi}^{(\mathrm{O})}$ activates PPC, the STN and the SC (S_{xy}). The SC excites FEF postsaccadic cell activities $F_{xyi}^{(\mathrm{X})}$, which delete the executed FEF plan activity. The STN activation helps prevent premature interruption of plan execution by a subsequent plan or by stimuli engendered by the early part of movement. [Reprinted with permission from Brown et al. (2004).] (**b**) Cortical and subcortical sensorimotor loops through the basal ganglia. *A*. For cortico-basal ganglia loops, the position of the thalamic relay is on the return arm of the loop. *B*. In the case of all subcortical loops, the position of the thalamic relay is on the input side of the loop. Predominantly excitatory regions and connections are shown in *red* while inhibitory regions and connections are *blue*. Tonic basal ganglia inhibition gates shut the activation of targeted cells. *Thal* thalamus, *SN/GP* substantia nigra/globus pallidus. [Reprinted with permission from P. Redgrave, Basal ganglia, Scholarpedia, 2(6):1825]

Rapid reactive movements are needed to ensure survival in response to unexpected dangers. Planned movements, that involve focused attention, often take longer to select and release. How does the brain prevent reactive movements from being triggered prematurely in situations where a more slowly occurring planned movement would be more adaptive? If this could not be achieved, then reactive movements could always preempt the occurrence of more appropriate context-selective planned movements, and indeed could prevent them from ever being learned.

This requirement leads to a second critical role of the basal ganglia, in addition to its role in selectively responding to unexpected rewards in SNc and broadcasting Now Print signals across the brain to learn the contingencies that have caused the unexpected event. This critical role concerns how the basal ganglia select context-appropriate movement plans and actions using *movement gates*. Such a movement gate can, for example, prevent a reactive movement from being launched until the planned movement can effectively compete with it.

All movement gates that are controlled by the basal ganglia tonically inhibit movement commands (Fig. 19.4b). When a specific gate is inhibited, the cells that control the corresponding movement command can be activated. Thus, the brain needs to keep each movement gate active until it can be inhibited to release the corresponding plan or action. The successive inhibitory connections illustrated in Fig. 19.4b accomplish this. The substantia nigra pars reticulata (SNr) regulates this sort of gating process. In particular, outputs from the basal ganglia provide GABA-ergic inhibitory gating of their target structures. In the primate saccadic circuit, cells in the SNr tonically inhibit the superior colliculus (SC), but pause briefly to allow the SC to generate a saccade to a selected target location (Hikosaka and Wurtz 1983, 1989). Lesions in this system can release a 'visual grasp reflex' (Guitton et al. 1985); namely, impulsive orienting to any visually salient object. Ancient vertebrate species, such as frogs, already had basal ganglia (Marin et al. 1998). Indeed, lesions of the basal ganglia projection to the optic tectum, the SC homolog in frogs, impair the frog's ability to orient selectively (Ewert et al. 1996).

These gates solve the following challenging problem: When a sensory cue occurs, such as an extrafoveal flashing light on the retina, the fastest response would be an orienting response to look at it. For this to happen, the cue needs to open the appropriate basal ganglia gate to enable the reactive movement to occur. If the cue is a discriminative cue to do a different action, especially an action that requires rapid execution, then the reactive response is not adaptive. However, it may take longer to fully process the cue to determine its adaptive conditional response than it would to activate the reactive response. How does the brain know that a plan is being elaborated, even before it is chosen, so that the reactive gate can be kept shut? How does the brain "know before it knows"? In particular, how does the brain prevent a reactive movement command from opening its gate before a planned movement command is ready to open a different gate, yet also allow a reactive movement command to open its gate as rapidly as possible when no planned movement command is being selected?

The TELOS model (Fig. 19.4a) was developed to explain and simulate how the brain may achieve this sort of balance between reactive and planned movements as it controls the learning and performance of saccadic eye movements. The acronym TELOS (TElencephalic Laminar Objective Selector) is inspired by the ancient Greek word telos for goal, end, or completion of a plan.

19.4.3 Frontal–Parietal Resonance Codes Plan Choice and Leads to Planned Gate Opening

According to TELOS, the brain "knows before it knows" in the following way: The model predicts how the distribution of excitation and inhibition that converges on the basal ganglia when a plan is being elaborated keeps the reactive gate closed (Fig. 19.5a). Before the appropriate movement plan is selected, there can be multiple bids converging on the basal ganglia to open one or another movement gate. It is this competition between different reactive and planned representations that keeps the reactive movement gate closed. When a movement plan is finally chosen, there is agreement between cells in the frontal eye fields (FEF) and the parietal cortex representations of target position (Fig. 19.5aD). This agreement changes the excitatory–inhibitory balance and enables excitatory feedback to become activated between FEF and the parietal cortex.

This mutually reinforcing excitatory feedback develops into a synchronous resonance (Grossberg 2012) that is predicted to signal consistency between a finally selected movement plan and the parietal representation of the corresponding attended target location. When this happens, the balance of excitation and inhibition enables the appropriate basal ganglia movement gate to open and release the context-appropriate action. Buschman and Miller (2007) have reported such prefrontal–parietal resonances during movement control, and Pasupathy and Miller (2004) have reported different time courses of activity in the prefrontal cortex and basal ganglia that are consistent with the TELOS model prediction of how basal ganglia-mediated gating of prefrontal cortical plans may be learned.

19.4.4 Spatially Invariant Object Categories Control Spatially Directed Actions

In further support of this proposal, TELOS model simulations emulate how SNc dopaminergic reward and nonreward signals guide monkeys to learn and perform saccadic eye movements in fixation, single saccade, overlap, gap, and delay (memory-guided) saccade tasks (Fig. 19.5b). After learning occurs, model cell activation dynamics quantitatively simulate, and predict functional roles for, the dynamics of 17 types of identified neurons during performance of these tasks.

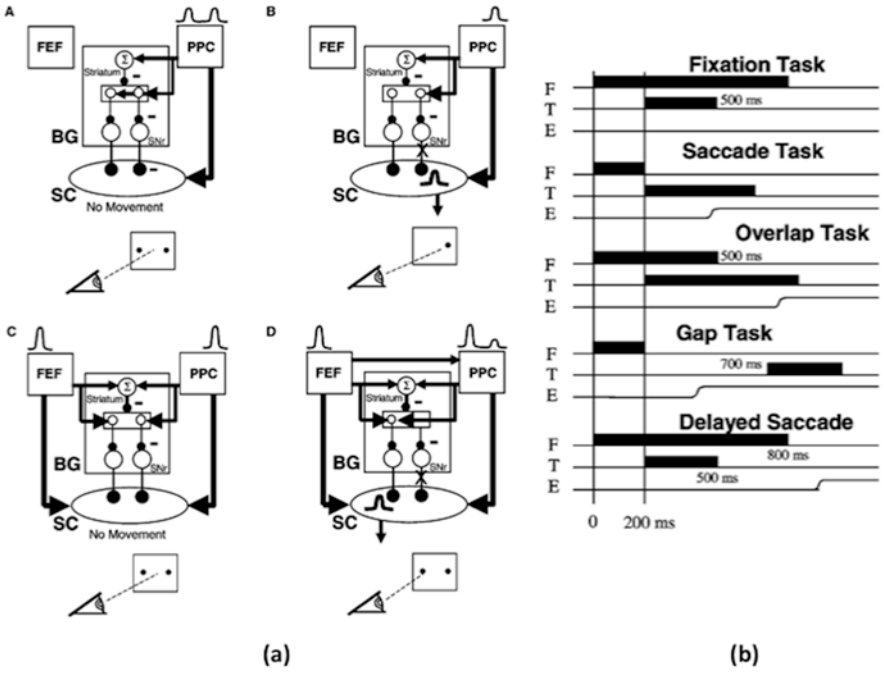


Fig. 19.5 (**a**) Cortical and striatal processes in location-specific gating of the superior colliculus (SC) by the basal ganglia (BG), leading to a resonance between the frontal eye fields (FEF) and the posterior parietal cortex (PPC) when a target location is selected. *A*. When multiple stimuli exist as potential saccade goals, the corresponding PPC representations specifically excite striatal spiny projection neurons (SPNs; shown in the *rectangle* within the BG rectangle) and nonspecifically excite feedforward inhibitory interneurons (labeled with a capital sigma) via corticostriatal projections. If more than one saccade plan is active, then striatal feedforward inhibition from all active plans prevents any one plan from activating its corresponding striatal SPNs to open the BG gate. This is because the pooled inhibitory input to each SPN can overwhelm the specific excitatory input. Therefore, the SC is not released from inhibition from the SNr, and movement is prevented while conflicting cortical plan activities remain unresolved. *B*. Targets compete in the PPC via inhibitory interactions. When competition resolves so that the movement plan is unambiguous, the PPC's excitatory input to striatal SPNs eventually exceeds striatal feedforward inhibition, which wanes as competing plans lose activation and stop convergent excitation of striatal inhibitory interneurons. The output signals from the winning SPN inhibit the SNr, thereby opening its normally closed gate, which disinhibits part of the SC map. *C*. If the FEF plans a saccade goal that differs from the location of a strong visual stimulus, the competing frontal and parietal activities collectively drive striatal feedforward inhibition to keep the BG gate shut until the conflict resolves. *D*. As the frontal cortex imposes its saccade goal on the parietal cortex, the competition between saccade goals resolves, enabling a FEF-PPC resonance to develop, and allowing the selected BG gate to open, thereby enabling the chosen saccadic command to be released. *Note*: The absence of an icon for FEF activity in *B*. indicates not that FEF would be inactive in case *B*., but only that FEF contains no plan contrary to PPC in case *B*. [Reprinted with permission from Brown et al. (2004).] (**b**) Oculomotor tasks of Hikosaka et al. (1989a, b). *Black bars* indicate intervals of visual stimulus presentations and the trace labeled E gives the horizontal component of eye position (line of gaze). In the *fixation task*, the subject must maintain gaze on the fixation point, F, despite a brief display of a distracter target, T, at a different locus. In the *saccade task*, the subject must make a pro-saccade from the fixation point to the target, which appears at a different locus, just as the fixation

Movements toward valued goal objects cannot be made until the goal objects are recognized and movement directions specified. To achieve efficient object recognition, the What cortical processing stream builds object representations that become increasingly invariant under changes in object views, sizes, and positions at higher cortical areas. In particular, these representations become significantly 'positionally invariant,' or independent of the retinotopic position or size of the object (Bar et al. 2001; Sigala and Logothetis 2002; Tanaka et al. 1991). Indeed, recent neural models have clarified how such invariant object categories may be learned and recognized in the anterior regions of the inferotemporal cortex (ITa) as a result of suitable interactions between the What and Where cortical streams (Cao et al. 2011; Fazl et al. 2009; Foley et al. 2012; Grossberg 2009; Grossberg et al. 2011).

In addition to overcoming the crippling combinatorial explosion of memory and search requirements that would have occurred if every variation in an object's appearance forced learning of a different recognition code, such invariant representations are sufficiently compact to facilitate their learned association with reinforcement and motivational mechanisms, such as those supported by the amygdala (Aggleton 1993; Barbas 1995; Baxter et al. 2000; LeDoux 1993; Schoenbaum et al. 2003). Positive feedback between the invariant representations and the amygdala, as part of an inferotemporal-amygdala-orbitofrontal resonance (see Sect. 7), enables the brain to focus motivated attention upon the representations of valued goal objects (Chang et al. 2014; Grossberg 1972a, b, 1975, 1982); see Sect. 7.

Notwithstanding the possible pleasures of Platonically contemplating a valued goal object, such contemplation is insufficient to ensure survival in the forest primeval, let alone in a modern society. Indeed, even to discover and learn what objects may have value, it is also necessary to also be able to physically engage them by moving and reaching toward them. Given that the recognition codes that are attentively amplified by motivational signals are often independent of position, the brain then faces the challenging problem of computing how to move to the position of an object after it is attended and recognized. The invariant object categories are learned within the What cortical stream. The Where cortical processing stream elaborates the representations of object spatial position and direction that are needed to compute motor commands.

The TELOS model proposes how interactions across the What and Where processing streams overcome their computationally complementary informational deficiencies (Grossberg 2000a, b, c) to generate movements toward recognized objects.

Fig. 19.5 (continued) point shuts off. In the *overlap task* (similar to a GO/NOGO task), the target and the fixation point are displayed in overlapping intervals. A pro-saccade to the target is rewarded only if generated after the fixation point shuts off. The *gap task* imposes a delay between the offset of the fixation point and the onset of the target. The gap task target appears at a consistent location across trials, and the subject learns to make an anticipatory pro-saccade to the target location during the gap between fixation light offset and target onset. The *delay task* requires the subject to remember the location of a briefly flashed target and later foveate it. [Adapted with permission from Hikosaka et al. 1989a, b, p. 781.] The TELOS model in Fig. 19.4a learned and performed all these tasks

In the model, the pathways from ITa and ITp to FEF (Fig. 19.4a) mediate the associative linkage between invariant object categories and positionally sensitive motor representations. Indeed, cells in ITp are sensitive to simple features falling within particular retinotopic loci (Kobatake and Tanaka 1994; Tanaka et al. 1991; Komatsu and Ideura 1993), whereas the position-invariant cells in ITa are sensitive to objects regardless of their specific retinotopic locus (Gross et al. 1985; Tanaka et al. 1991). This linkage, combined with the inferotemporal-amygdala-orbitofrontal resonance that focuses attention upon valued goal objects, has been used to propose a solution to the Where's Waldo problem, or how to search for a valued goal object in a cluttered scene (Chang et al. 2014).

Data about the anatomical projections from feature-sensitive areas such as ITp, when combined with physiological evidence on the emergence of feature selectivity in FEF neurons when features are consistently rewarded (Bichot et al. 1996), support this anatomical linkage, as well as the model hypothesis that dopaminergic Now Print signals from SNc (Figs. 19.2a and 19.4a) regulate reward-guided learning mediated by weight changes in the IT to FEF pathways. In particular, reward-related dopaminergic signals modulate learning in both the striatum of the basal ganglia and the frontal cortex (Gaspar et al. 1995; Schultz 1998).

The trained system allows or prevents movements, according to their appropriateness (Bullock and Grossberg 1991; Crosson 1985; Hikosaka and Wurtz 1983; Mink 1996; Mink and Thach 1993; Redgrave et al. 1999). Indeed, it is not enough to recognize and move toward an object. An animal or human needs to know when to move toward or away from an object and when not to do so, depending on reward contingencies. In addition, when confronted with the same scene, an animal may respond differently depending on its changing needs, such as eating food if hungry, or drinking water if thirsty. The model explains how the brain learns and remembers many plans that involve different sets of discriminative and scheduling constraints, and how it switches among them as needed. These design and circuit details go beyond the scope of the current review.

19.5 Basal Ganglia Gating of Variable-Speed Arm Movements: Synergy, Synchrony, and Speed

19.5.1 VITE Model of Arm Trajectory Formation

The basal ganglia control the gating of all phasic movements, including both eye movements and arm movements. Arm movements, unlike eye movements, can be made at variable speeds that are under volitional basal ganglia control. Arm movements realize the Three S's of Movement Control; namely, Synergy, Synchrony, and Speed: Specific combinations of muscle groups can be combined into a movement *synergy*, whereby the bound muscles can move *synchronously*, in equal time, to a target position at variable *speed*s. The simplest model of arm movement trajectory

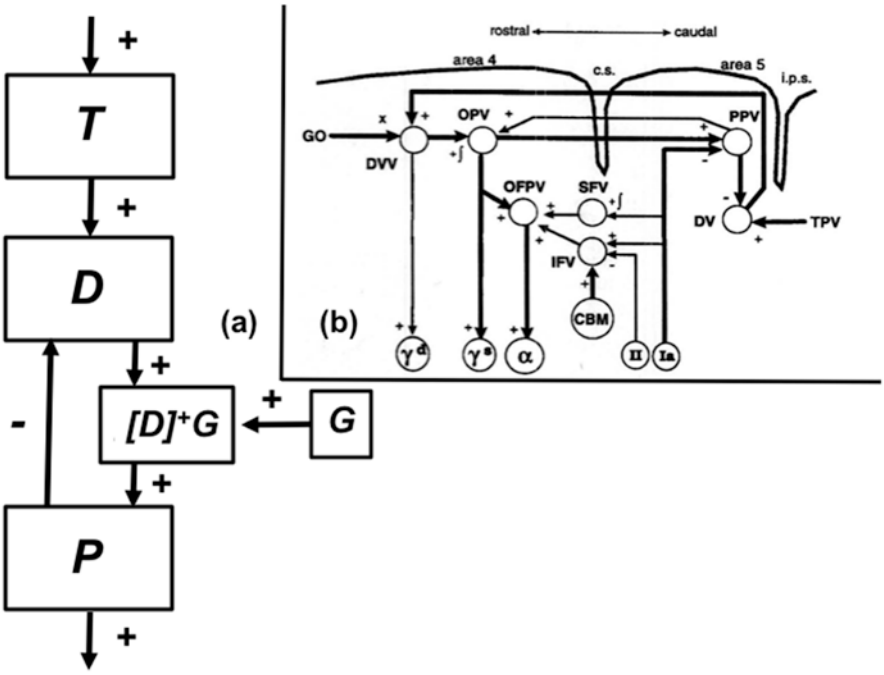


Fig. 19.6 (**a**) Vector Integration to Endpoint circuit (Bullock and Grossberg 1988) for control of movement trajectories. *T* is the target position vector, *P* the outflow present position vector, *D* the difference vector, and *G* the volitional GO signal that multiplies, or gates, *D*. See text for details. (**b**) Cortical circuit mode of VITE interactions that can compensate for obstacles and variable loads on the arm during trajectory formation. *Thick connections* represent the kinematic feedback control aspect of the model, with thin connections representing additional compensatory circuitry. *GO* scalable basal ganglia gating signal, *DVV* desired velocity vector, *OPV* outflow position vector, *OFPV* outflow force-plus-position vector, *SFV* static force vector, *IN* inertial force vector, *CBM* assumed cerebello-cortical input to the IFVstage, *PPV* perceived position vector, *DV* difference vector, *TPV* target position vector, γ^d dynamic gamma motoneuron, γ^s static gamma motoneuron, α alpha motoneuron, *la* type la afferent fiber, *II* type II afferent fiber (position error feedback), *c.s.* central sulcus, *i.p.s.* intraparietal sulcus. The symbol + represents excitation, − represents inhibition, *x* represents multiplicative basal ganglia gating, and $+\int$ represents integration. See Bullock et al. (1998) for details. [Reprinted with permission from Bullock et al. (1998).]

formation with these properties is the Vector Integration to Endpoint, or VITE, model (Fig. 19.6a; Bullock and Grossberg 1988). To make such a movement, a representation of where the arm is now (its *present position vector*) is subtracted from a representation of where we want the arm to move (its *target position vector*), thereby computing a *difference vector* that represents the direction and distance of movement needed to attain the target. After moving to the target, the target and present positions agree, so the difference vector is zero. In other words, this sort of matching is inhibitory.

19.5.2 Variable-Speed Arm Movements Due to Variable-Size GO Signals

To better understand how this works, note that the difference vector is volitionally gated, or multiplied, by a basal ganglia GO signal (Fig. 19.6a) that determines when and how fast the movement will occur (Bullock and Grossberg 1988; Bullock et al. 1998). When both the GO signal and the difference vector are positive, their product is integrated by the present position vector, causing the present position vector to approach the target position vector. When both vectors are the same, the movement stops.

The cells with nonzero activities in the target position vector control the muscle groups that are included in the currently active synergy. A zero GO signal does not move the arm at all, whereas a progressively larger GO signal enables it to move at increasingly fast speeds. It is because the GO signal multiplies the difference vector that all muscles within the synergy contract synchronously and reach the position represented by the target position vector at the same time.

19.5.3 Motor-Equivalent Reaching and Arm Movements Given Perturbations and Obstacles

The VITE model has been extended in several directions. One extension is to the Direction-to-Rotation Effector Control Transform, or DIRECT, model of motor-equivalent reaching (Bullock et al. 1993), which clarifies how accurate, single-synergy, reaches can be made on the first try, under visual guidance, with a tool or with clamped joints. DIRECT suggests how learning a spatial representation of reaching coordinates using a Piagetian circular reaction automatically enables the ability, or affordance, to touch a target in space with a tool. A variant of DIRECT, called the Directions-Into-Velocities-of-Articulators, or DIVA, model, has been used to simulate data about motor-equivalent speech articulator movements during speech production (Guenther 1995; Guenther et al. 2006). Another VITE extension (Fig. 19.6b) describes the cortical circuits that enable arm movements to be made in the presence of unexpected perturbations and obstacles (Bullock et al. 1998). This elaboration enables the quantitative simulation of neurophysiological data about the dynamics of multiple identified cell types in cortical areas 4 and 5.

Models such as VITE focus primarily on Platonic aspects of movement planning and trajectory formation, although for VITE to cope with unexpected perturbations and obstacles, feedback to the cortex from subcortical processes, such as alpha and gamma motoneurons, is also modeled (Fig. 19.6b). The Factorization of Length and Tension, or FLETE, model (Fig. 19.7) complements VITE by using cerebellar and spinal circuits to compensate for the forces and tensions that are needed to accurately move real arms along commanded trajectories. These cerebellar and spinal circuits of FLETE interact with the thalamo-cortico-basal ganglia circuits of VITE,

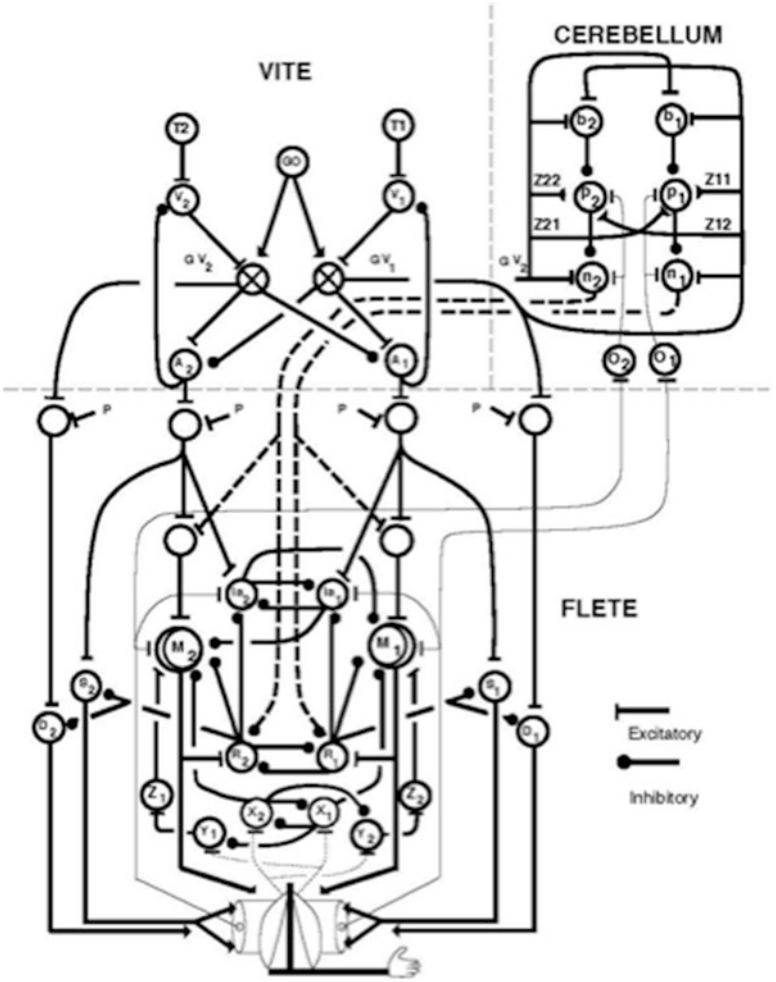


Fig. 19.7 Model circuit for neuromuscular control system. *Upper-left part*: The VITE model for variable-speech synergy formation and trajectory generation. *Lower part*: The FLETE model of the opponently organized spino-muscular system. *Dotted lines* show feedback pathways from sensors embedded in muscles. The two lateral feedback pathways arise in spindle organs sensitive to muscle stretch and its first derivative. The two medial feedback pathways arise in Golgi tendon organs sensitive to muscle force. Signals T_1 and T_2 specify the target position vector; signals A_1 and A_2 specify the desired position vector; signals V_1 and V_2 specify the difference vector; signal $GO = G$ is the basal ganglia GO signal that controls movement selection and speed; signals GV_1 and GV_2 specify the desired velocity vector; and signal P scales the level of coactivation. *Upper-right part*: Feedforward cerebellar model computes transient inverse-dynamic signals that excite motoneurons and modulate the gain in spinal circuits. *Key*: *b* basket cells, *p* Purkinje cells, *n* nucleus interpositus cells, *O* inferior olive, *CF* climbing fibers from inferior olive to Purkinje cells, and *z* long-term memory weights. Paths ending in *filled dots* are inhibitory; all others are excitatory. [Reprinted with permission from Contreras-Vidal et al. (1997).]

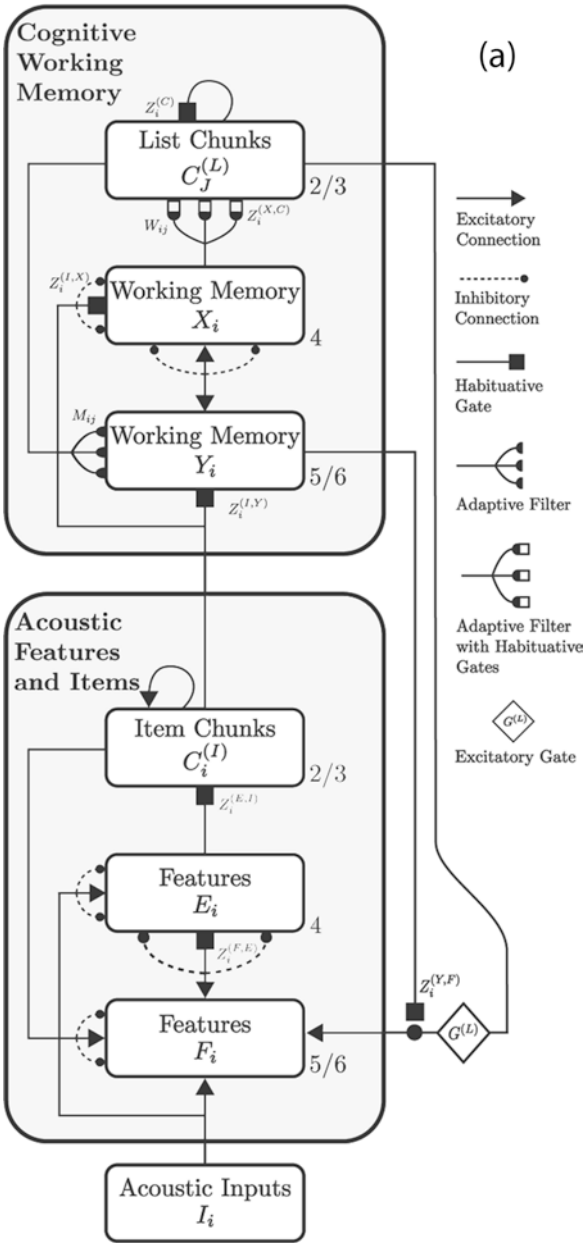


Fig. 19.8 (**a**) Macrocircuit of the cARTWORD model. This macrocircuit shows a hierarchy of cortical levels that help to explain several of the processes that enable speech and language perception. Each level is organized into laminar cortical circuits, wherein deep layers (6 and 4) are responsible for processing and storing inputs, and superficial layers (2/3) are proposed to group distributed patterns across these deeper layers into unitized, or chunked, representations. The lowest level is responsible for processing acoustic features (cell activities F_i and E_i) and items (cell activities $C_i^{(I)}$), whereas the higher level is responsible for storing of sequences of acoustic items in working memory (activities Y_i and X_i), and representing these stored sequences of these items as unitized, context-sensitive representations by list chunks (activities $C_J^{(L)}$). The list chunks are

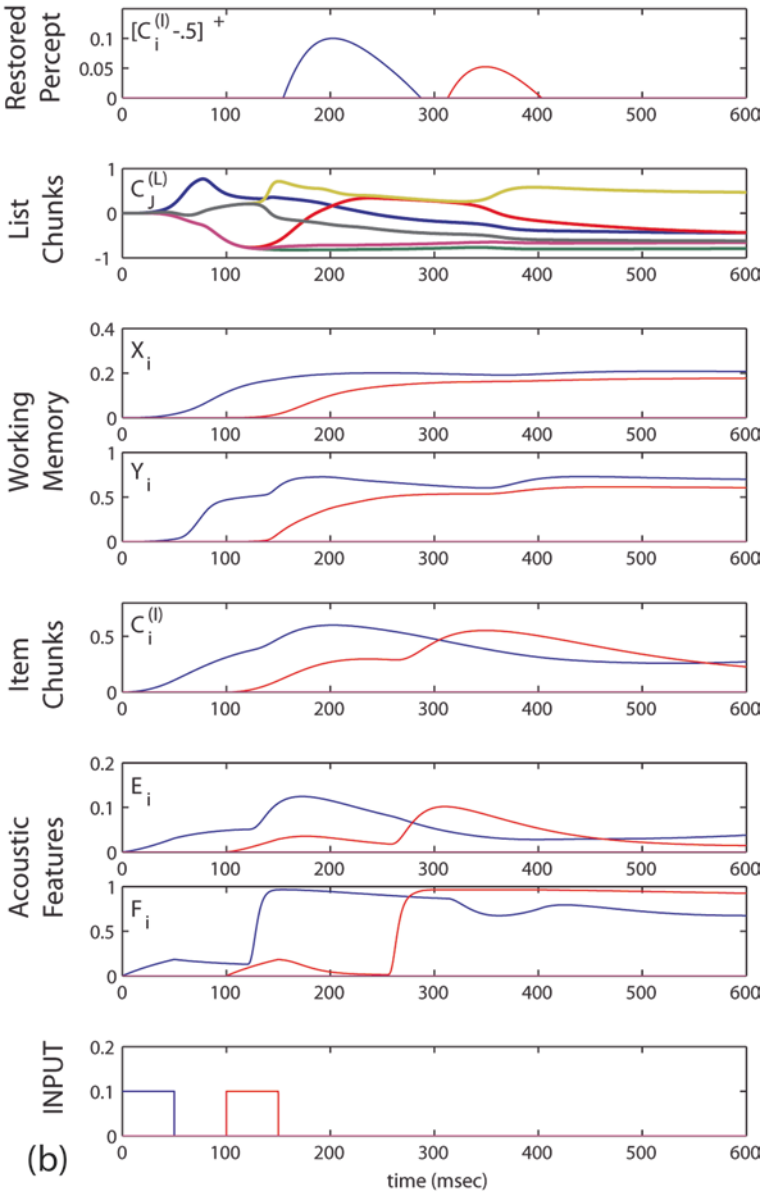


Fig. 19.8 (continued) selected and stored in short-term memory by a masking field, which is a multiple-scale, self-similar, recurrent on-center off-surround network. The top-town pathway from the list chunks in cognitive working memory to the acoustic feature level schematizes the role of the basal ganglia. When a list chunk or chunks gets sufficiently active (and is thus most predictive of the current working memory context), it generates an output signal that acts like an excitatory gating signal $G^{(L)}$, which enables the top-down modulatory feedback from the cognitive working memory to amplify the attended featural patterns and thereby trigger a system-wide resonance between all the processing levels. This excitatory gating signal is a simplified representation of the kind of disinhibitory process whereby the basal ganglia enable cortico-cortical processing loops to resonate, as in Fig. 19.4a. (**b**) Network dynamics in response to a sequence of three inputs presented "1- -3" (*bottom row*, with '1' shown in *blue* and '3' in *red*), with a 50 ms silence duration interval. See text for details. [Reprinted with permission from Grossberg and Kazerounian (2011)]

and with opponent muscle groups in the arm, in order to plan and execute arm movement trajectories using multijoint arms (Bullock and Grossberg 1991; Contreras-Vidal et al. 1997).

In all these arm control models, the gating effects of the basal ganglia on movement are represented with a simple GO signal. A similar simplification has been sufficient to explain an important gating role of the basal ganglia on speech perception.

19.6 Basal Ganglia Gating of Speech Perception

19.6.1 cARTWORD Model, Resonant Wave, Conscious Speech, and Phonemic Restoration

Interactions between the frontal cortices and the basal ganglia arise across several different modalities of intelligence, including cognitive processes such as the control of consciously heard speech and language. The conscious ARTWORD (cARTWORD) model of Grossberg and Kazerounian (2011) illustrates how such gating helps to control the consciously heard temporal order of noisy speech that is disambiguated by contextual cues that may occur after the heard formant inputs (Fig. 19.8a). cARTWORD describes how the laminar circuits within a hierarchy of cortical processing stages may interact to generate such a disambiguated conscious speech percept. Earlier modeling work showed how variations of this circuit design may be used to explain and predict challenging psychophysical and neurobiological data about 3D vision, figure-ground perception, and visual object recognition (e.g., Cao and Grossberg 2005; Fang and Grossberg 2009; Grossberg and Versace 2008; Grossberg and Yazdanbakhsh 2005), and about cognitive working memory and list chunking (Grossberg and Pearson 2008; Silver et al. 2011); see Sect. 8. This unity of processing clarifies how variations of a shared laminar neocortical design across modalities enable the brain to compute multiple types of biological intelligence and thereby illustrate the paradigm of Laminar Computing.

cARTWORD further develops the hypothesis that conscious speech percepts are emergent properties that arise from resonant states of the brain (Grossberg 1978a, b, c, 1986, 2003; Grossberg et al. 1997a; Grossberg and Myers 2000). Such a resonance develops when bottom-up signals that are activated by environmental events interact with top-down expectations, or prototypes, that have been learned from prior experiences. The top-down expectations carry out a matching process that selects those combinations of bottom-up features that are consistent with the learned prototype while inhibiting those that are not. In this way, an attentional focus concentrates processing on those feature clusters that are deemed important on the basis of past experience. The attended feature clusters, in turn, reactivate the cycle of bottom-up and top-down signal exchange. This reciprocal exchange of signals equilibrates in a resonant state that binds the attended features together into a coherent brain state.

Such resonant states, rather than the activations that are due to bottom-up processing alone, are proposed to be the brain events that regulate fast and stable learning of speech and language, and that give rise to conscious speech and language percepts. Indeed, I have predicted that "conscious speech is a resonant wave" and that "silence is a temporal discontinuity in the rate at which the resonance develops" (Grossberg 2003).

The feedback dynamics of these resonances enable the brain to incorporate both past and future contextual information, often acting over hundreds of milliseconds, into the processing of speech and language, without destroying the correct temporal order of consciously heard words. Such contextual disambiguation is necessary to understand speech and language during the multispeaker noisy environments that are characteristic of real-life speech and language experiences. The fact that conscious speech percepts are influenced by cues that sometimes occur up to one hundred milliseconds before or after the heard formants challenges classical concepts about the functional units of speech perception and recognition. In order for such contextual influences to have an effect on speech perception, sequences of speech items are temporarily stored in a working memory.

A classical example of a percept in which future context disambiguates consciously heard speech is *phonemic restoration* (Samuel 1981a, b; Warren 1970, 1984; Warren and Obusek 1971; Warren and Sherman 1974; Warren and Warren 1970). cARTWORD explains and computationally simulates how a hierarchy of laminar cortical processing stages, gated by the basal ganglia, can explain this and related speech percepts wherein conscious percepts depend upon contextual information (Fig. 19.8a).

The following example of phonemic restoration illustrates the conceptual issues. Suppose broadband noise replaces the phonemes /v/ and /b/ in the words delivery and deliberation, respectively. Despite the initially ambiguous initial portion of these words ('deli-'), if the broadband noise is immediately followed by 'ery' or 'eration,' listeners hear the /v/ or /b/ as being fully intact and present in the signal. Such experiences show that top-down lexical influences contribute to the formation of conscious speech percepts.

Several challenging conceptual issues are raised by this and related examples. First, why is the noise in "deli-noise-[ery/eration]" not heard before the last portion of the word is even presented? This may be explained by the fact that, if the resonance has not developed fully before the last portion of the word is presented, then this portion can influence the top-down expectations that determine the conscious percept.

Second, how does the expectation convert the noise in "deli-noise-[ery/eration]" into a percept of [/v/-/b/]? This occurs due to the top-down matching process that selects expected feature clusters for attentive processing while suppressing unexpected ones. In the "deli-noise-[ery/eration]" example, spectral components of the noise are suppressed that are not part of the expected consonant sound.

Attentive selection during phonemic restoration and other speech and language percepts is not merely a process of symbolic inference. Indeed, it directly influences

phonetic percepts. For example, if a reduced set of spectral components is used in the noise, then a correspondingly degraded consonant sound is heard (Samuel 1981a, b).

Third, how do future events influence past events without smearing over all the events that intervene? In particular, if the /v/ or /b/ in "delivery/deliberation" is replaced by silence, how is the silence perceived as silence despite the fact the disambiguating cue would have influenced the percept were these phonemes to be replaced by noise? Here again the nature of the top-down matching process is paramount. Top-down attentive matching process is *modulatory*; it can prime, sensitize, and select feature components that are consistent with its prototype, but it cannot create something out of nothing.

Fourth, how can sharp word boundaries be perceived even if the sound spectrum that represents the words exhibits no silent intervals between them? cARTWORD illustrates the hypothesis (see the review in Grossberg 2003) that silence will be heard between words whenever there is a temporal break between the resonances that represent the individual words. In other words, just as conscious speech is a resonant wave, silence is a discontinuity in the rate at which this resonant wave evolves.

The top-down attentive matching that selects context-appropriate sounds is controlled by recognition categories that are sensitive to particular combinations of sequences of speech items through time. These categories are also called *list chunks* (see Grossberg and Pearson (2008) for a review). List chunks are selected and stored in short-term memory by a multiple-scale, self-similar, on-center off-surround network that is called a *masking field* (Cohen and Grossberg 1986, 1987; Grossberg 1978a). A masking field can select the list chunks that are mostly strongly supported by the sequence of items currently stored in the working memory. The multiple spatial scales that are represented in a masking field enable list chunks to be selected that are sensitive to item sequences of different length. The self-similar property of the masking field enables list chunks that represent longer sequences to inhibit list chunks that represent shorter sequences. This property also helps to explain data such as the word superiority effect and the Magical Number Seven of George Miller (Cohen and Grossberg 1986; Grossberg 1986; Grossberg and Pearson 2008).

These facts lead to the fifth issue: How does the brain know how to wait until the most active, and thus predictive, combination of list chunks is chosen to release the top-down attentive signals that will select and resonate with the syllable, word, or sentence sounds that will be consciously heard? Here is where the basal ganglia play a critical role in the model. In particular, basal ganglia gating enables future phonetic contexts to have enough time to help choose the list chunks that will become sufficiently active to open a basal ganglia gate. Gate opening, as illustrated in Fig. 19.8a, then enables the entire hierarchy of processing stages—acoustic features, acoustic items, stored sequences of these items in working memory, and list chunks—to resonate during a conscious speech percept.

19.6.2 Adaptive Resonance Theory, Language Learning, and the Stability-Plasticity Dilemma

The name cARTWORD derives from the fact that this model is an example of Adaptive Resonance Theory, or ART. ART has predicted that the attentive resonance and matching processes that support phonemic restoration are necessary ones to enable speech and language to be learned quickly without forcing the nonselective, or catastrophic, forgetting of previously learned memories (Grossberg 1978a, b, c, 1986, 2003). Indeed, the need to solve this *stability-plasticity dilemma* occurs in many perceptual and cognitive processes.

It has elsewhere been mathematically proved that the properties of this top-down attentive matching process, called the ART Matching Rule, are necessary to enable fast learning without catastrophic forgetting (Carpenter and Grossberg 1987). The ART Matching Rule proposes how a top-down, modulatory on-center, off-surround network controls the read-out of learned top-down expectations and attentional focusing, as well as the dynamical stabilization of both bottom-up and top-down learned memories (see Sect. 9). Because of the role of the off-surround, or competition, in attentional focusing, this process is sometimes described as "biased competition" (e.g., Desimone 1998; Kastner and Ungerleider 2001).

Due to the need to solve the stability-plasticity dilemma in all perceptual and cognitive processes, the ART Matching Rule for top-down attentional matching seems to occur in other perceptual modalities, notably vision (Bhatt et al. 2007; Carpenter and Grossberg 1987; Gove et al. 1995). Reviews of supportive perceptual and neurobiological data, ART models that describe the mathematical form of the ART Matching Rule, and the predicted link between attentive matching, resonance, and learning, can be found in Grossberg (2013), Grossberg and Versace (2008), and Raizada and Grossberg (2003).

19.6.3 Simulations of Phonemic Restoration

Figures 19.8b and 19.9 illustrate how cARTWORD simulates percepts of phonemic restoration in the consciously heard temporal order, even when the sound that disambiguates the utterance occurs after the noise. Figure 19.8b depicts the model's dynamics in response to a sequence of three inputs presented "1- -3" (bottom row, with '1' shown in blue and '3' in red), with a 50 ms silence duration interval between '1' and '3.' The plots in rows 2 and 3 from the bottom show the response of the acoustic feature layers F_i and E_i. The fourth plot from the bottom shows the activities $C_i^{(I)}$ of the acoustic item category cells. The activities Y_i and X_i of cells in the cognitive working memory layers (shown in the fifth and sixth plots from the bottom) respond to the incoming activity from the acoustic item layer. The seventh plot from the bottom shows the response of list chunk activities $C_J^{(L)}$ in the masking field in response to the evolving pattern of activity in working memory. When one or more list chunks gets sufficiently active, it opens the basal ganglia gate that will

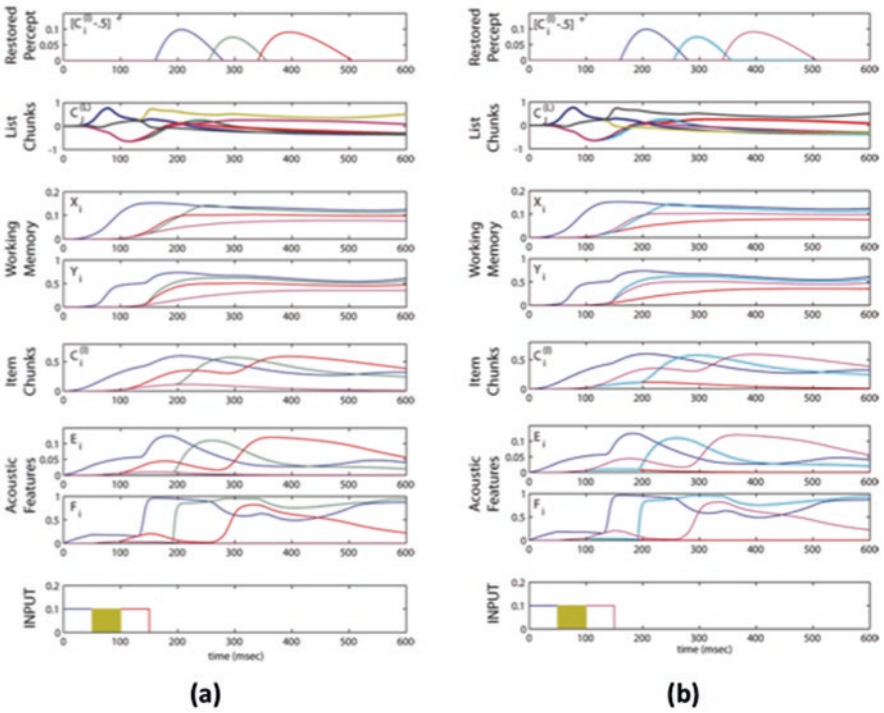


Fig. 19.9 (**a**) Network dynamics in response to a sequence of three inputs presented "1- * -3" where '*' denotes noise as presented for 50 ms in place of any phoneme ('1' is shown in *blue*, '*' is shown as a *filled yellow pulse*, and '3' is shown in *red*). See text for details of how the excised item '2' is restored. (**b**) Network dynamics in response to the sequence "1- * -5," where * again denotes noise ('1' is shown in *blue*, '*' is shown in *yellow*, and '5' is shown in *purple*). See text for details of how the excised item '4' is restored. [Reprinted with permission from Grossberg and Kazerounian (2011)]

enable the resonance to unfold throughout the network. The singleton list chunks coding for "1," "2," and "3" are shown in blue, green, and red, respectively, and the list chunks coding for "1-2-3" and "1-4-5" are shown in yellow and black, respectively. The top plot shows the resonant activity across the acoustic item layer and exhibits a temporal break between the superthreshold activity of item cells '1' (blue trace) and '3' (red trace), corresponding to the silence perceived by listeners under these presentation conditions.

Figure 19.9a depicts model dynamics in response to a sequence of three inputs presented "1- * -3" where '*' denotes noise that is presented for 50 ms in place of any phoneme ('1' is shown in blue, '*' is shown as a filled yellow pulse, and '3' is shown in red). The bottom row shows presentation of the inputs, and the next two rows again show the response of the acoustic feature layers F_i and E_i. The fourth plot from the bottom shows the activities $C_i^{(I)}$ of the acoustic item category cell activities. The activities Y_i and X_i in the cognitive working memory layers, in

response to the inputs from the acoustic item cells, are shown in the fifth and sixth plots from the bottom. The seventh plot from the bottom shows the response of list chunk activities $C_J^{(L)}$ in the masking field in response to the evolving pattern of activity in working memory. The singleton list chunks coding for "1," "2," and "3" are shown in blue, green, and red, respectively, and the list chunks coding for "1-2-3" and "1-4-5" are shown in yellow and black, respectively. Once the list chunk coding for "1-2-3" (the yellow trace) wins the competition with the "1-4-5" chunk (the black trace) upon unambiguous presentation of the acoustic item '3' at 100 ms, feedback from the chunk cells allows for the selection of and amplification of the components of noise consistent with its learned expectations, namely, the excised acoustic item '2' in working memory. Basal ganglia gated feedback from the selected list chunk then drives acoustic features and items in such a way that the resonant wave across these items (shown in the top plot) continuously progresses across '1,' '2,' and then '3' (blue, green, and red traces, respectively), indicating that the excised item '2' has been restored.

Figure 19.9b shows that the backward-in-time restoration is specific to the item that disambiguates the utterance. In particular, this simulation shows the network dynamics in response to the sequence "1- * -5," where * again denotes noise ('1' is shown in blue, '*' is shown in yellow, and '5' is shown in purple). The only difference between this simulation and that of Fig. 19.9a is the final item of the sequence, '5,' which serves as future contextual information with respect to the excised phoneme, '4,' which is to be restored. Rather than selection of the "1-2-3" list chunk (shown in yellow in the seventh plot from the bottom), presentation of the acoustic item '5' allows the "1-4-5" list chunk (shown in black) to win the competition across the masking field layer. Feedback from this chunk allows the selection and amplification of the components of noise consistent with its learned expectations, namely '4,' whose activity is shown in cyan in the working memory activities of Y_i and X_i. The feedback from working memory to acoustic features again causes the superthreshold activity in the acoustic item layer (shown in the top plot) to exhibit a resonant wave from '1,' to '4,' and then to '5' (blue, cyan, and magenta traces, respectively), indicating that the excised item '4' has indeed been restored.

These simulations illustrate how that the restoration occurs in response to inputs arriving after the noise and, just as the restoration examples with 'delivery' and 'deliberation,' completes the intervening sound in a context-appropriate way.

19.7 Complementary Roles of Basal Ganglia and Amygdala in Reinforcement Learning

19.7.1 MOTIVATOR Model

The TELOS model (Sects. 3 and 4) illustrates how the basal ganglia, notably SNc, may generate dopaminergic Now Print signals in response to unexpected rewarding events. This proposal does not explain how previously rewarded, and currently

valued, behaviors can be carried out under familiar and expected circumstances. The amygdala works together with the basal ganglia to support the complementary roles of new learning in response to unexpected reinforcing events and motivated performance in response to already conditioned cues, respectively. The MOTIVATOR model (Fig. 19.10; Dranias et al. 2008; Grossberg et al. 2008) proposes how key aspects of this interaction take place. MOTIVATOR is an acronym for Matching Objects To Internal VAlues Triggers Option Revaluations.

MOTIVATOR describes cognitive-emotional interactions between higher order sensory cortices and an evaluative neuraxis composed of the hypothalamus, amygdala, orbitofrontal cortex, and basal ganglia. Given a conditioned stimulus (CS), the model amygdala and lateral hypothalamus interact to calculate the expected current value of the subjective outcome that the CS predicts, constrained by the current state of deprivation or satiation. The amygdala codes value categories (Aggleton 1993; LeDoux 1993) that relay the expected value information to object-value categories in the orbitofrontal cortex (Barbas 1995; Baxter et al. 2000; Schoenbaum et al. 2003). These object-value categories also receive inputs from object categories in the anterior inferotemporal cortex, while medial orbitofrontal cells receive gustatory inputs from rhinal cortex. Both object and value information are needed to vigorously activate orbitofrontal cells. The activations of these orbitofrontal cells code the subjective values of objects. These values guide behavioral choices.

The model basal ganglia detect errors in CS-specific predictions of the value and timing of rewards. As in TELOS, excitatory inputs from the pedunculopontine nucleus interact with timed inhibitory inputs from model striosomes in the ventral striatum to regulate dopamine burst and dip responses from cells in the SNc and ventral tegmental areas. Learning throughout the brain is strongly modulated by these dopaminergic signals. Once conditioned, the amygdala can receive learned conditioned reinforcer signals from sensory cortices, such as the inferotemporal and rhinal cortices, and convey learned incentive motivational signals to the orbitofrontal cortex (Fig. 19.10).

Using these mechanisms, MOTIVATOR proposes mechanistic answers to the following kinds of questions: What brain processes allow an animal to use cues to quickly assess the options in its environment and estimate their values relative to the animal's current needs? How are strong needs ignored when the environment affords no opportunity for their satisfaction? How are normally attractive and highly available options ignored for a time after the needs that they consummate have been satisfied? In particular, MOTIVATOR simulates data about the conditioning of cues that predict specific outcomes in a task setting, the automatic revaluation of conditioned reinforcers following food-specific satiety, and motivational and emotive influences on decision processes, reaction time, response vigor, and blood pressure. Revaluation refers to the observation that motivational shifts can alter the vigor of conditioned responses (Dickinson and Balleine 2001; Corbit and Balleine 2005).

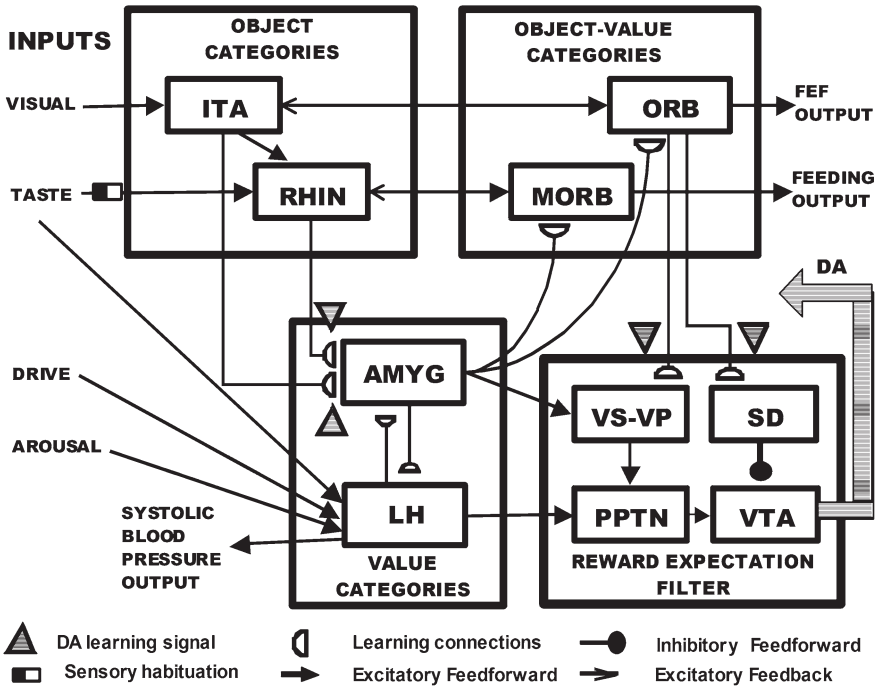


Fig. 19.10 Overview of MOTIVATOR model: Brain areas in the MOTIVATOR circuit can be divided into four regions that process information about conditioned stimuli (CSs) and unconditioned stimuli (USs). (**a**) Object Categories represent visual or gustatory inputs, in anterior inferotemporal (ITA) and rhinal (RHIN) cortices; (**b**) Value Categories represent the value of anticipated outcomes on the basis of hunger and satiety inputs, in amygdala (AMYG) and lateral hypothalamus (LH); (**c**) Object-Value Categories resolve the value of competing perceptual stimuli in medial (MORB) and lateral (ORB) orbitofrontal cortex; and (**d**) the Reward Expectation Filter in the basal ganglia detects the omission or delivery of rewards using a circuit that spans ventral striatum (VS), ventral pallidum (VP), striosomes of the striatum, the pedunculopontine nucleus (PPTN) and midbrain dopaminergic neurons of the SNc/VTA (substantia nigra pars compacta/ventral tegmental area). The circuit that processes CS-related visual information (ITA, AMYG, ORB) operates in parallel with a circuit that processes US-related visual and gustatory information (RHIN, AMYG, MORB). The model captures systematic changes in processing of the same stimuli at different times, due to processes of learned category formation, sensory habituation, satiation or deprivation of particular rewarding outcomes, CS-US associative learning, and violations of expectations based on learned regularities. Model outputs modulate saccadic choice and reaction time, and blood pressure changes. [Reprinted with permission from Dranias et al. (2008)]

19.7.2 Basal Ganglia Learning Affects Sensory-Amygdala-Orbitofrontal Motivated Performance

MOTIVATOR unifies and further develops the Cognitive-Emotional-Motor, or CogEM, model of cognitive-emotional learning and performance (Grossberg 1971, 1972a, b, 1975, 1982, 1984, 2000c; Grossberg and Gutowski 1987; Grossberg and Levine 1987; Grossberg et al. 1997b Grossberg and Merrill 1992; Grossberg and Schmajuk 1987) and the TELOS model of how an animal learns to balance reactive vs. planned behaviors through learning based on reward expectation and its disconfirmation (Brown et al. 1999, 2004). The CogEM model focused on how affective brain regions, such as the lateral hypothalamus and amygdala, interact with sensory and cognitive areas, such as inferotemporal cortex and orbitofrontal cortex. In particular, an inferotemporal-amygdala-orbitofrontal resonance focuses motivated attention upon currently valued objects, as it also supports core consciousness and "the feeling of what happens" (Damasio 1999). Indeed, the heuristic model that Damasio (1999) derives from his clinical data has the same form as the CogEM model, but uses different terminology for its processing stages. As reviewed in Sects. 3 and 4, the TELOS model focused on how the basal ganglia regulate attention and reinforcement-based learning in thalamocortical systems. MOTIVATOR clarifies how both amygdala and basal ganglia processes interact to control reward-based processes.

Here is a more detailed summary of how MOTIVATOR proposes that these brain regions interact: Visual inputs activate view-invariant representations of visual objects in the anterior inferotemporal cortex (ITA). Gustatory cortex relays the taste properties salty, sweet, umami, and fatty to rhinal cortex (RHIN) and to gustatory-responsive lateral hypothalamic cells (LH_gus). RHIN cells also receive ITA inputs, and can thereby code gustatory-visual properties of food rewards. Endogenous drive and arousal inputs project to lateral hypothalamic input cells (LH_in). LH_in cells represent the homeostatic state of the animal by reporting fat, salt, amino acid, and sugar levels. LH_gus cells correlate gustatory tastes with corresponding homeostatic features and excite lateral hypothalamic output cells (LH_out), which project to amygdala (AMYG) cells that categorize distributed patterns of activity across LH_out states, and thus represent value categories. The LH-AMYG network computes the net subjective outcome associated with a consummatory act. It thereby defines a neural representation of US (unconditioned stimulus) reward value. Because the AMYG also receives conditionable CS-activated signals from ITA and RHIN, it can mediate CS-US learning. Given a CS, the AMYG and LH interact to calculate the expected current value of the subjective outcome that the CS predicts, given the current state of deprivation or satiation for that outcome. The AMYG relays the expected value information via incentive motivational signals to ITA-recipient orbitofrontal (ORB) and RHIN-recipient medial orbitofrontal (MORB) cells, whose activations code the relative subjective values of objects. These values guide behavioral choices.

The model basal ganglia (BG) detect errors in CS-specific predictions of the value and timing of rewards. Striosomes (SD) of the ventral striatum (VS) prevent

predicted rewards from generating SNc/VTA responses by inhibiting dopamine cells in the SNc/VTA with adaptively timed signals. Inputs from the LH_gus and the ventral striatum (VS) excite the pedunculopontine nucleus (PPTN/LDT) whenever a conditioned (CS) or unconditioned (US) rewarding cue occurs. Cells in the PPTN/LDT, in turn, excite dopamine cells in the SNc/VTA.

When inhibitory signals from the SD and excitatory signals from the PPTN/LDT mismatch, a dopamine dip or dopamine burst may occur. A dopamine burst occurs in the SNc/VTA when an unexpected rewarding CS or US is presented. When an unexpected rewarding cue is presented, SD cells are unable to relay anticipatory inhibitory signals to the SNc/VTA and reward-related excitation is relayed from the PPTN/LDT to dopaminergic cells in the SNc/VTA, eliciting a dopamine burst. When an expected reward is omitted, a dopamine dip occurs. In this case, a rewarding CS is presented and SD cells send an adaptively timed inhibitory input to the SNc/VTA at the expected time of reward. When US presentation is omitted, dopaminergic SNc/VTA cells never receive a reward-related excitatory signal from the PPTN/LDT and are instead transiently suppressed by inhibitory signals from the SD (Fig. 19.2b).

Model simulations reproduce discharge dynamics of known cell types, including signals that predict saccadic reaction times and CS-dependent changes in systolic blood pressure. Learning in cortical and striatal regions is strongly modulated by dopamine, whereas learning between the AMYG and LH_out cells is not.

19.7.3 Influences of Amygdala and Orbitofrontal Lesions on Learning and Behavior

In addition, interactions of the BG and AMYG with sensory and ORB cortices enable the model to replicate the complex pattern of spared and impaired behavioral and emotional capacities seen following lesions of the amygdala and orbitofrontal cortex (Grossberg et al. 2008). For example, experimental data show that the ability of a conditioned stimulus to act as a conditioned reinforcer is impaired following amygdala lesions (Hatfield et al. 1996; Setlow et al. 2002a). Experiments also reveal that, if the CS is trained prior to the amygdala lesion being made, the ability of the CS to function as a conditioned reinforcer and to induce secondary conditioning is intact. This preserved function relies on pathways through the ventral striatum (Setlow et al. 2002b). In the model, US-specific drive-value category cells in the amygdala project to the ventral striatum, providing teaching signals for inputs from the ORB. When the model is trained prior to amygdala lesions, connections between the orbitofrontal cortex and US-specific ventral striatal cells learn to reflect US value and compensate for the loss of the amygdala. Recovery of second-order conditioning occurs because this pretraining establishes a learned pathway from the ORB to the ventral striatum that enables the CS to trigger a dopamine burst.

19.8 Item-Order-Rank Working Memory and Basal Ganglia Gating of Behavioral Sequences

19.8.1 Basal Ganglia Control of Sequential Learning and Performance of Saccades

Although the TELOS model included some properties of the prefrontal cortex (PFC, Fig. 19.4a), including its ability to store salient plan representations in short-term memory using recurrent shunting on-center off-surround networks (Grossberg 1973), its model PFC did not include a sequential working memory; namely, a network capable of temporarily storing in short-term memory a sequence of items and their temporal order. However, intelligent behavior depends upon the capacity to think about, plan, execute, and evaluate sequences of events. Whether we learn to understand and speak a language, solve a mathematics problem, cook an elaborate meal, or merely dial a phone number, multiple events in a specific temporal order must somehow be stored temporarily in working memory. As event sequences are temporarily stored, they are grouped, or chunked, through learning into unitized plans, or list chunks, and can later be performed at variable rates under basal ganglia volitional control either via imitation or from a previously learned plan. See Grossberg and Pearson (2008) for simulations of how such variable-speech sequential performance can be controlled.

The cARTWORD model does include a sequential working memory that temporarily stores a sequence of acoustic items in working memory as they are unitized through learning into list chunks. However, the effects of basal ganglia gating in cARTWORD were expressed in the simplest way, and did not attempt to explain how different parts of the basal ganglia gate the release of different components of sequentially organized behaviors. The lisTELOS model (Silver et al. 2011) does offer this kind of detailed explanation of basal ganglia dynamics during the learning and performance of sequences of saccadic eye movements.

19.8.2 Item-Order-Rank Working Memories Store Sequences Using Activity Gradients

Lashley (1951) suggested that items are temporarily stored in working memory (WM) within spatially separable neural populations, thus transforming the temporal problem of serial order into a spatial problem. Grossberg (1978a, b) developed a neural model of WM through which a temporal stream of inputs could be stored as an evolving spatial pattern before being performed sequentially during rehearsal. In such an Item-and-Order WM, individual nodes, which represent cells or cell populations, represent *list items*, and the order in which the items were presented is stored by an *activity gradient* across these nodes. A *primacy gradient* achieves performance in the correct temporal order. In a primacy gradient, the first item in the sequence is represented by the cell(s) with the highest activity, and subsequent items

are stored with progressively less activity. A rehearsal wave, that is volitionally controlled by the basal ganglia, opens gates that enable readout of these stored activities when it is time to reproduce the sequence. The cell with the highest activity is read out first and self-inhibits its WM representation, an example of an *inhibition of return*, thereby preventing perseverative performance of this item. This process is repeated until the entire sequence is reproduced and there are no active nodes in the WM.

Such an Item-and-Order WM is also sometimes called *competitive queuing* (CQ; Houghton 1990), and many models have adapted this scheme. Both psychophysical and neurophysiological data have confirmed its predicted properties. For example, psychophysical experiments have shown that latency data from error trials can be best explained by models that use a primacy gradient and self-inhibition; e.g., Farrell and Lewandowsky (2004). Electrophysiological recordings from PFC have, moreover, shown that the temporal order of items in a sequence of stored motor commands is stored using their relative activity levels, and that these activities are reset by self-inhibition as each motor command is executed; e.g., Averbeck et al. (2002, 2003).

In addition to these Item-and-Order properties, the activity of PFC neurons for a given list item is sometimes modulated by the rank, or position, of that item within the sequence, and error data imply utilization of rank information in serial recall (see Silver et al. (2011) for a review).

The LIST PARSE model of working memory and list chunking (Grossberg and Pearson 2008) proposed how laminar circuits in PFC represent these two types of processes. Grossberg and Pearson (2008) also suggested how rank-order coding may be incorporated into the activity gradients within an Item-and-Order WM to represent item repeats at arbitrary list positions. They suggested, in particular, that the PFC rank information is derived from representations of numerosity in posterior parietal cortex (PPC; Grossberg and Repin 2003). Silver et al. (2011) built upon this heuristic proposal to rigorously model a prefrontal *Item-Order-Rank* model of WM storage and performance. This WM was used to quantitatively simulate neurobiological data about rank-order coding in a spatial WM in PFC as it interacts with multiple brain regions, including SC, PPC, PFC, FEF, and the supplementary eye fields (SEF), all regulated by the basal ganglia, in order to learn and perform sequences of saccadic eye movements. This neural architecture is called the lisTELOS model (Fig. 19.11a) to acknowledge that it unifies and extends properties of both the LIST PARSE and TELOS models.

19.8.3 All Working Memories Are Variations of the Same Circuit Design

Grossberg (1978a, b) derived Item and Order working memories from two postulates: the LTM Invariance Principle and the Normalization Rule. The LTM Invariance Principle makes precise the idea that there is no point in storing novel sequences of events in working memory if the brain cannot learn to unitize the

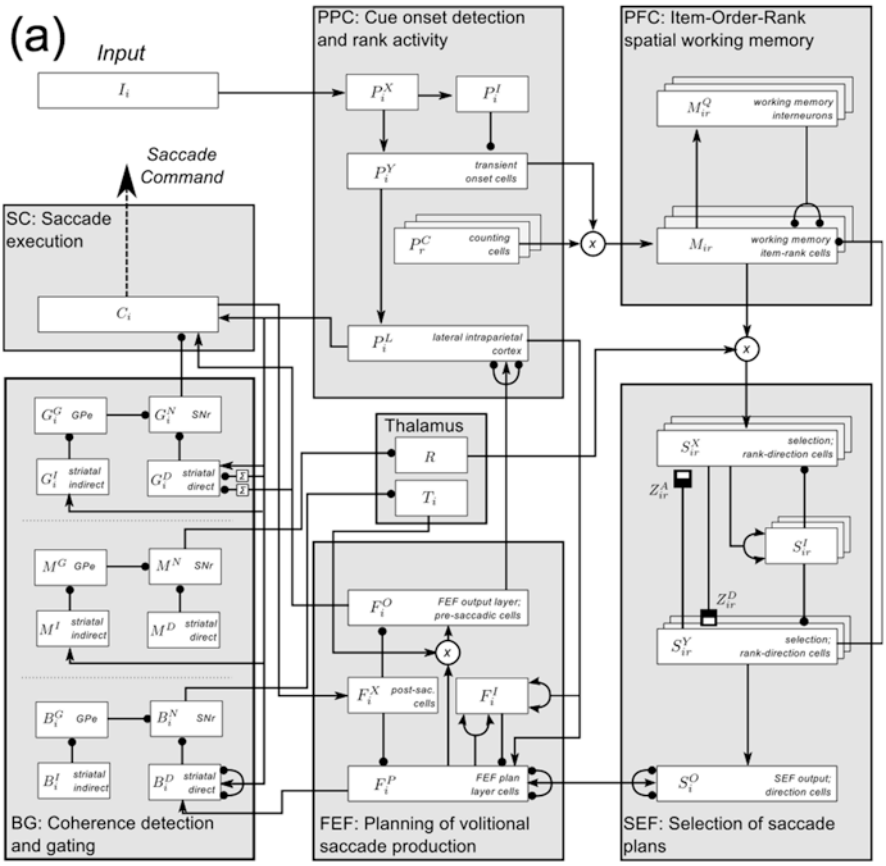


Fig. 19.11 (**a**) The lisTELOS Item-Order-Rank spatial working memory and performance model. Each *gray box* represents a brain region within which fields of cells, represented by *white inset boxes*, share similar functional roles. *Arrowheads* denote excitatory connections between cells, and *filled circles* represent inhibitory connections. *Curved branches* at the ends of connections represent one-to-many fan-out connections that impact all other cells in the field. *Half-filled boxes* at the ends of connections represent habituative gates which exhibit activity-dependent changes in synaptic efficacy. White *circles* containing a multiplication sign (×) represent multiplicative interaction between two signals. *Boxes* containing a sigma (Σ) represent the sum of outputs from all cells in the field that gave rise to the projection. Stacked field representations denote populations of rank-sensitive cells. See Fig. 19.12 for more details about how three basal ganglia loops contribute to the learning and performance of saccadic eye movement sequences by the model. [Reprinted with permission from Silver et al. (2011).] (**b**) Evidence that prefrontal cortex and SEF embody spatial representations of saccadic target locations. *A*. Microstimulation causes saccade trajectories to converge. The bias observed for each of the six pairs of adjacent cues (insets) can be used to identify the saccade trajectory rendered more likely by microstimulation (*arrows*). Note that the saccadic trajectories converge toward the upper left target. *B*. Model simulations reproduce the convergence effect. *C*. In model simulations, microstimulation habituates synapses according to a two-dimensional Gaussian function centered over the microstimulation site. Saccade trajectories following microstimulation tend to climb this gradient. [Data adapted with permission from Histed and Miller (2006). Simulation reprinted with permission from Silver et al. (2011)]

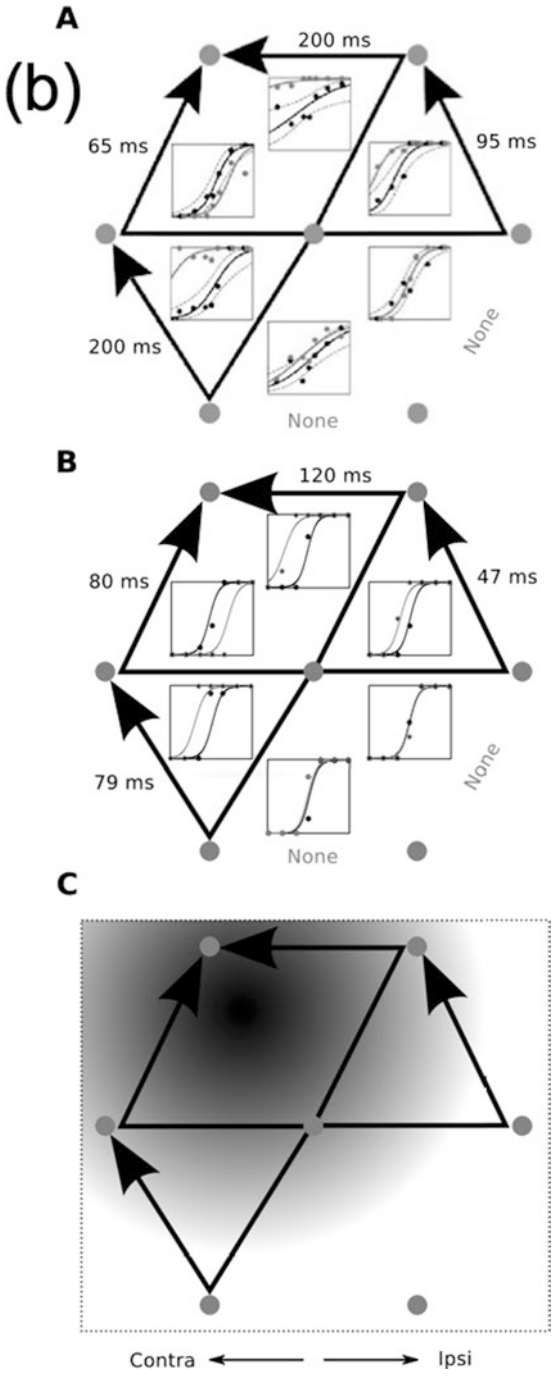


Fig. 19.11 (continued)

sequences for future skillful performance. This Principle claims that working memories are *designed* to enable such stable list chunking to occur. In particular, it demands that all working memories enable a novel superset list chunk (up to a certain maximal length) to be learned without forcing catastrophic forgetting of familiar subset chunks. For example, the LTM Invariance Principle ensures that a novel superset word like MYSELF can be learned without forcing forgetting of the familiar subwords MY, SELF, and ELF. As a result, as new items are stored through time in working memory, subset list chunks can continue to activate their familiar list chunks until they are inhibited by contextually more predictive superset list chunks; e.g., until MY is supplanted by competition from MYSELF through time. The *learning* of chunk MY within its bottom-up filter is not undermined, but the *current activation* of the chunk MY can be inhibited by MYSELF.

The Normalization Rule assumes that the *total activity* of the working memory network has a maximum that is (approximately) independent of the total number of actively stored items. In other words, working memory has a *limited capacity* and activity is redistributed, not just added, when new items are stored.

Two properties are needed for these postulates to hold:

1. In order not to force recoding of sublists (like MY) as superlists of them (like MYSELF) are stored in working memory, activities of items in working memory tend to preserve their *relative* activations, or *ratios*, throughout the time that they are stored in working memory, even if the storage of new items through time might change the absolute amount of activity with which each item is stored. This property enables the adaptive filter that converts the distributed pattern of stored items into list chunks (see Fig. 19.8a) to activate already learned list chunks in response to their sublists in working memory.
2. Novel superlists (like MYSELF) must be able to activate the chunking network despite the salience of already learned sublists (like MY), so that learning of a new list chunk with which to represent the novel superlist can occur. This is accomplished by using a masking field at the list chunk level, as in the cART-WORD model.

How can brain evolution be smart enough to discover the laws of something so seemingly sophisticated as a working memory? Remarkably, Item-and-Order and Item-Order-Rank working memories that satisfies the LTM Invariance Principle and Normalization Rule can be realized by a ubiquitous kind of neural network: an on-center off-surround network whose cells obey the shunting, or membrane, equations of neurophysiology and which interact via *recurrent* on-center off-surround connections. Recurrent shunting on-center off-surround networks are ubiquitous in the brain (Grossberg 1973). Recurrence is needed because the positive feedback from a cell population to itself in the recurrent on-center stores the evolving input pattern, while the recurrent competition contrast-normalizes the stored activities across the network. The shunting, or multiplicative, properties of the membrane equations, combined with the on-center off-surround interactions, enable the network to compute *ratios* of cell activities across the network, as is required by the LTM Invariance Principle, even as they normalize the total activity across the network, as required by the Normalization Rule.

Because all working memories need to obey the LTM Invariance Principle and the Normalization Rule, similar working memory circuits were predicted to store spatial, linguistic, and motor sequences (Grossberg 1978a). The cARTWORD and lisTELOS models and their data explanations provide supportive evidence for this prediction for the cases of linguistic and spatial working memories. See Grossberg (1978a, b) for a review of additional supportive experimental evidence.

19.8.4 Supplementary Eye Fields Select Saccadic Targets from Sequences Stored in Spatial Working Memory

LisTELOS proposes how item representations may be chosen from WM by the SEF, an oculomotor area in dorsomedial frontal cortex (Schlag and Schlag-Rey 1987) which is heavily interconnected with the PFC (Barbas and Pandya 1987; Huerta and Kaas 1990) and which also exhibits rank-related activity (Berdyyeva and Olson 2009; Isoda and Tanji 2002, 2003). SEF is thus anatomically and physiologically well suited to interact with a rank-selective WM. Its role in the selection of saccadic targets is consistent with many data, reviewed in Silver et al. (2011). For example, patients with lesions in what was at the time called the supplementary motor area (Gaymard et al. 1990, 1993) have mostly intact performance for visually guided saccades, antisaccades, and single memory-guided saccades, but greatly degraded performance for *sequences* of memory-guided saccades. In addition, activation of SEF during sequential saccade tasks has been observed with positron emission tomography (Petit et al. 1996) and during a functional magnetic resonance imaging study (Heide et al. 2001) whose authors concluded that "the supplementary eye field essentially controls the triggering of memorized saccade sequences."

The competence of the lisTELOS model was tested by simulating data collected from several different paradigms, including visually guided and memory-guided saccade tasks and several sequential saccade tasks, notably the immediate serial recall (ISR) task. The model is also compatible with known anatomical data and reproduces behavioral and electrophysiological data under a variety of conditions, including those in which SEF activity is perturbed by microstimulation (Histed and Miller 2006; Yang et al. 2008). These last data provide particularly strong support for the concept of a spatial Item-Order-Rank working memory due to the manner in which microstimulation may alter the temporal order, but not the target positions, that are acquired by the sequential saccadic eye movements (Fig. 19.11b).

19.8.5 Basal Ganglia Regulation of Saccade Sequence Learning and Performance

To explain learning and performance of eye movement sequences, and by extension other kinds of movement sequences, the lisTELOS model simulates in considerable cellular detail how three loops through the basal ganglia (BG; Middleton

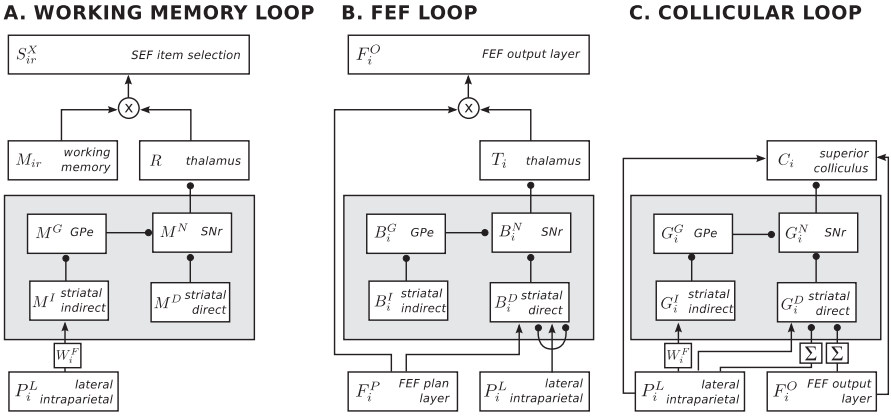


Fig. 19.12 The lisTELOS model explains how three loops through the basal ganglia contribute to saccadic performance. Each loop projects to a separate thalamic or collicular population (cf., Fig. 19.1), modulating the population's excitability and thereby controlling the flow of information from one model stage to another. *A*. The *left panel* represents the working memory loop through the BG, which is responsible for controlling the flow of information from working memory cell activities M_{ir}, to the SEF selection cell activities S_{ir}^{X}. *B*. The FEF loop controls the flow of plan signals from FEF plan layer cell activities F_i^{P} to FEF output layer cell activities F_i^{O}. *C*. The collicular loop controls excitation of SC cell activities C_i, by FEF output cell activities F_i^{O}, and LIP cell activities P_i^{L}. See text for details. [Reprinted with permission from Silver et al. (2011)]

and Strick 2000) control the flow of information between model areas (Fig. 19.12). Each of these loops is based on the BG implementation used in the TELOS model (Fig. 19.4a). As reviewed in Sect. 4, in TELOS, consistent with hypotheses of other researchers (Alexander and Crutcher 1990; Bullock and Grossberg 1988, 1991; Gancarz and Grossberg 1999; Grossberg et al. 1997b; Hikosaka and Wurtz 1983; Mink 1996), the BG are responsible for controlling the selective release of a movement through a gating process. Eye movements are initiated when consistent saccade plans in FEF and PPC occur, thereby changing the balance of excitation and inhibition impinging on the BG in favor of selective gate opening, and triggering a frontal–parietal resonance that embodies a system consensus about a chosen saccadic command (Fig. 19.9d). By ensuring that these areas reach consensus before allowing saccade generation, the BG avoid various problems such as premature execution of reactive saccades when a planned saccade is appropriate, or simultaneous execution of multiple saccade plans, as sometimes occurs in the form of saccadic averaging (Lee et al. 1988; Ottes et al. 1984). Thus, in addition to unifying processes of numerosity in PPC, spatial WM storage in PFC, and saccade selection in SEF, the model elaborates how the BG selectively gate the release of a saccadic movement when frontal–parietal resonance occurs.

BG gate opening in the model relies on opposing forces between the direct and indirect pathways (Figs. 19.4a and 19.11a; Brown et al. 2004; Frank 2005; Frank et al. 2001; Mink 1996). The direct and indirect pathways begin with two distinct populations of γ-aminobutyric acid (GABA) releasing medium spiny projection

neurons (MSPNs) in the striatum, the input nucleus of the BG. These pathways differentially express D1 and D2 receptors (Gerfen et al. 1990; Surmeier et al. 2007). In particular, MSPNs in the direct pathway send projections directly to the globus pallidus internal segment (GPi) and the substantia nigra pars reticulata (SNr), which serve as output nuclei of the BG. Cells in GPi/SNr are GABAergic and tonically inhibit cells in the thalamus or SC (Bullock and Grossberg 1991; Hikosaka and Wurtz 1983; Horak and Anderson 1984). Activation of direct pathway MSPNs inhibits GPi/SNr cells, and thereby disinhibits cells downstream from the tonic GPi/SNr signal.

Indirect pathway MSPNs inhibit cells in the nearby globus pallidus external segment (GPe) which, in turn, inhibit the GPi/SNr output nuclei. Thus, exciting indirect pathway MSPNs disinhibits GPi/SNr cells. The resulting increased activity of GPi/SNr inhibits SC or thalamic cells. As a result, the indirect pathway acts in opposition to the direct pathway: Direct pathway activation excites cells in thalamus or SC, whereas indirect pathway activation inhibits them. These opposing processes of disinhibition and inhibition realize BG gating.

Working memory loop and gate: Each of the three parallel BG loops gate a separate process. The BG WM loop (Fig. 19.12a) controls signaling from PFC WM cell activities M_{ir} to SEF selection cell activities S_{ir}^{X} through a thalamic rehearsal gate R (see Sect. 7.2). LIP cell activities P_i^{L} activate MSPN activities M^{I} of the indirect pathway using hard-coded connection weights W_i^{F}. The model hereby responds selectively to the presence of a fixation cue by inhibiting indirect pathway GPe cell activities M^{G} and thereby disinhibiting SNr cell activities M^{N}. The resulting increased SNr activity keeps the WM rehearsal gate R closed, thereby restricting the flow of information into SEF.

When the fixation point is removed, LIP cell activities P_i^{L} no longer excite MSPNs, and the rehearsal gate R opens, thereby allowing SEF cell activities S_{ir}^{X} to be activated by WM cell activities M_{ir}. In the absence of any additional fixation cues, this gate remains open, enabling each saccadic plan to be successively selected and to activate downstream areas, such as FEF and SC, to generate the corresponding saccade. Direct pathway MSPN activities M^{D} maintain constant activity so that, in the absence of indirect pathway activity, the WM rehearsal gate R is open.

Frontal eye fields loop and gate: The second BG loop, the FEF loop (Fig. 19.12b), controls the flow of information between the FEF plan layer cell activities F_i^{P} and the FEF output layer cell activities F_i^{O}. The thalamic gate T_i controlled by this loop remains closed until FEF plan layer cell activities F_i^{P} and LIP cell activities P_i^{L} represent a consistent plan as part of a frontal–parietal resonance. Once the regions contain consistent saccade plans, they excite direct pathway cell activities B_i^{D} which inhibit SNr cell activities B_i^{N}, thereby disinhibiting the thalamic cell activities T_i. Once disinhibited, thalamic cell activity, combined with FEF plan layer activity, activates FEF output layer cell activities F_i^{O}. The FEF output layer then is ready to excite a corresponding saccade plan in further stages of the model, but cannot do so until a second BG gate is opened. Indirect pathway MSPN activities B_i^{I} and GPe cell activities B_i^{G} provide a constant source of inhibition to SNr cell activities B_i^{N} to ensure that only consistent FEF and LIP activity, resulting in strong direct pathway activity, is able to release thalamic activity T_i from inhibition.

Superior colliculus loop and gate: The third gate controls outputs from the SC (Fig. 19.12c) and receives inputs from both FEF output layer cell activities F_i^{O} and LIP cell activities P_i^{L}, with special emphasis placed on the central region of the visual field where fixation cues are present, as in the WM loop. A fixation cue at the center of the visual field selectively activates the collicular loop indirect pathway MSPN activities G_i^{I}, which inhibit GPe cell activities G_i^{G}, then disinhibit SNr cell activities G_i^{N}, which in turn inhibit colliculus cells with activities C_i. While a fixation cue is on, it is difficult for FEF or LIP to excite the activities G_i^{D} of direct pathway MSPNs enough to overcome activity in the indirect pathway. If no fixation cue is on, and the saccadic plans in FEF and LIP are consistent, this third gate opens, which allows FEF and LIP to excite SC cell activities C_i, thereby leading to a saccadic movement that is consistent with the selected plan.

The three BG loops are critical for holding the model in a state of preparedness as information important for guiding its future responses is being presented, and detecting the task conditions which signal that it is time to utilize the stored information to drive behavior. This process depends largely on the presence and absence of the fixation point. When a fixation cue is present, the rehearsal and collicular gates are held shut and task-relevant cues are simply stored in memory. Once the fixation point is removed, SEF can select saccade targets from WM and excite corresponding representations in FEF. Provided the selected saccade plan is not inconsistent with any external cues represented in LIP, the FEF and collicular BG loops open their gates and allow plan signals to flow to SC, which generates the response.

The earlier mechanisms propose how an Item-Order-Rank spatial working memory can be used to represent arbitrary spatial sequences, and suggests how three distinct BG gates enable SEF to select spatial targets from WM and excite corresponding representations in downstream oculomotor areas such as SC that are responsible for saccade production.

19.9 Basal Ganglia Gating of Perceptual and Cognitive Processes

19.9.1 From Top-Down Attentional Priming to Suprathreshold Activation

Many other brain processes can also be gated by the basal ganglia, whether automatically or through conscious volition. Several of these gating processes seem to regulate whether a top-down process subliminally primes or fully activates its target cells. As noted in Sect. 5.1, the ART Matching Rule enables the brain to dynamically stabilize learned memories using top-down attentional matching. Such attentional matching is realized by variants of a top-down, modulatory on-center, off-surround network (Fig. 19.13a) that enables a top-down expectation to prime, or sensitize, the target cells in its on-center without fully activating them. It seems, however, that

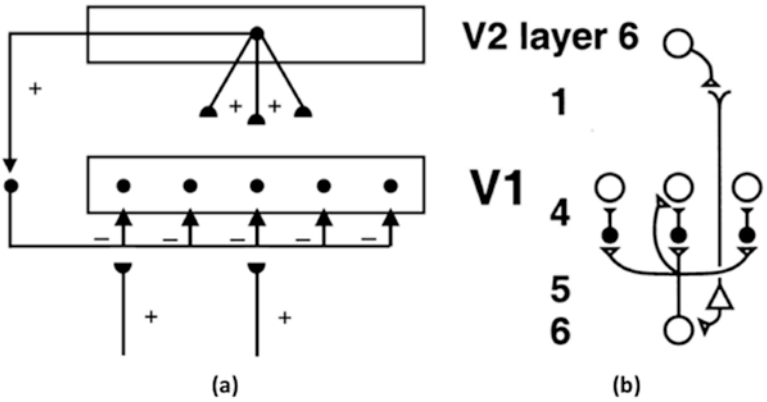


Fig. 19.13 (**a**) The ART Matching Rule is achieved by a top-down, modulatory on-center, off-surround network. The excitatory on-center (*plus signs*) encodes a learned prototype in its adaptive weights, or long-term memory traces (*hemidisks*). This prototype learns from bottom-up inputs, which can fully activate targets cells when top-down signals are off. The inhibitory off-surround (minus signs) is balanced against the on-center so that top-down signals, by themselves, are modulatory, and cannot fully activate their target cells. When both bottom-up and top-down signals are active, only the cells in the top-down on-center that are also receiving bottom-up inputs can fire. Other cell activities are inhibited. A volitional signal from the basal ganglia can disrupt the top-down excitatory-inhibitory balance to enable top-down signals, by themselves, to cause suprathreshold activation. (**b**) Model circuit for how the ART Matching Rule is realized within the laminar circuits of visual cortical areas V1 and V2. Similar circuits are proposed to occur in other sensory and cognitive cortical areas. *Open circles* and *triangles* denote excitatory cells and pathways, respectively; *closed black circles* and *triangles* denote inhibitory cells and pathways, respectively. A *folded feedback* circuit carries top-down attentional signals from layer 6 of V2 to layer 4 of V1 via an on-center off-surround pathway from layer 6 to 4 of V1. Corticocortical feedback axons from layer 6 in V2 tend to terminate in layer 1 of V1 (Salin and Bullier 1995, p. 110) where they can, for example, excite apical dendrites of layer 5 pyramidal cells whose axons send collaterals into layer 6. From layer 6, the feedback is then "folded" back into the feedforward flow of information from layer 6 to 4 of V1 via an on-center off-surround pathway (Bullier et al. 1996). See Grossberg (2012) and Raizada and Grossberg (2003) for a more complete model of how this circuit is embedded within the bottom-up, horizontal, and top-down (both intracortical and intercortical) interactions within visual cortex

many of these attentional processes may be gated by the basal ganglia to enable the top-down priming to be converted into suprathreshold activation.

Phasic volitional signals can shift the balance between excitation and inhibition to convert the top-down modulatory on-center into a driving excitatory input that can cause suprathreshold activation. In the ART Matching Rule laminar circuit in Fig. 19.13b, this gating action can either weaken the inhibitory effect of the off-surround, say by inhibiting the inhibitory interneurons in layer 4, or by further disinhibiting the excitatory on-center, say via cells in layer 5; cf. the gating of FEF laminar circuits in the TELOS model (Fig. 19.4a).

19.9.2 Visual Imagery, Thinking, Planning, and Searching

Such a volitionally mediated shift enables top-down expectations, even in the absence of supportive bottom-up inputs, to cause conscious experiences of imagery and inner speech, and thereby to enable visual imagery, thinking, and planning activities to occur. Thus, the ability of volitional signals to convert the modulatory top-down priming signals into suprathreshold activations provides a great evolutionary advantage to those who possess it.

Such a competence is also important when the brain tries to search for a valued goal object in a cluttered scene; that is, to solve the Where's Waldo problem. As noted in Sect. 4.4, the reciprocal ART-learned connections between spatially variant recognition categories in cortical area ITp and spatially invariant categories in ITa, combined with the inferotemporal-amygdala-orbitofrontal resonance that focuses motivated attention upon valued goal objects, have been used to propose a solution to the Where's Waldo problem, or how to search for a valued goal object in a cluttered scene (Chang et al. 2014). This solution uses the top-down attentional priming by the ART Matching Rule from orbitofrontal cortex to ITa. By itself, such a prime cannot drive its ITa category to suprathreshold activity levels. Volitionally opening the corresponding basal ganglia gate, just as in the triggering of visual imagery, allows the motivationally amplified orbitofrontal object-value categories to fully activate their target invariant ITa object categories, which in turn can subliminally prime consistent ITp categories, again by the ART Matching Rule. When a bottom-up input from Waldo combines with such a prime at the ITp category that represents Waldo's location, this ITp category can become supraliminally activated, and inhibit less activated ITp categories. It can also activate the corresponding position in parietal cortex, which in turn can drive an eye movement toward Waldo's location. Thus, basal ganglia gating can also enable motivated searches to occur.

19.9.3 From Phasic to Tonic Gate Opening: Hallucinations

What happens, however, if volitional control of such priming signals is lost? During a mental disorder like schizophrenia, it is proposed that the phasic volitional signal may become tonically hyperactive. As a result, top-down sensory expectations can generate conscious experiences that are not under the volitional control of the individual who is experiencing them. The net effect is a hallucination. Since the top-down expectations learn prototypes that incorporate the critical feature patterns that are used to bind sensory features into conscious experiences, these hallucinations, just like the imagery and inner speech that are generated under normal conditions, are sufficient to generate conscious experiences with vivid personal content. Such hallucinations derive from the critically important ability to learn quickly throughout life without experiencing catastrophic forgetting, along with the consequent ability to learn expectations that focus attention upon important objects. These abilities provide the computational context in which basal ganglia gating can control

imagination, thinking, and planning. The fact that these circuits may occasionally get out of balance and cause hallucinations may be viewed as one of the evolutionary costs of our ability to be human. See Grossberg (2000a) for additional discussion of such hallucinations and supportive data.

19.9.4 Working Memory Storage and the Useful Field of View of Spatial Attention

The LIST PARSE model of working memory (Sect. 8.2) is realized by an on-center off-surround recurrent network whose on-center is modulatory except when sequential lists of items are being stored in working memory. LIST PARSE proposes, moreover, that this on-center off-surround network occurs in the deeper layers of ventrolateral prefrontal cortex, a location where basal ganglia volitional signals can convert the modulatory on-center into a driving on-center that enables list items to be stored in working memory. A termination of this gating signal then allows the list to be cleared from working memory. This proposal needs to be further tested experimentally.

Another example where basal ganglia gating may influence performance concerns the span of spatial attention, also called the useful field of view. In particular, the distributed ARTSCAN (dARTSCAN) model (Foley et al. 2012) suggests how the span of spatial attention may be varied in a task-sensitive manner via learned or volitional signals that are mediated by the basal ganglia. Spatial attention may be focused on one object (unifocal) to control invariant object category learning, or spread across multiple objects (multifocal) to regulate useful field of view, thereby raising the question of how the span of spatial attention is regulated. Individual differences in detection rate of peripheral targets in useful field of view tasks are instructive and are illustrated by the improved performance of experienced video game players over nonvideo game players (Green and Bavelier 2003, 2007). These differences have been explained by dARTSCAN model (Foley et al. 2012) as being due to the way in which volitional basal ganglia signals, or learned prefrontal-to-basal ganglia signals, may control the gain for gating the balance between excitation and inhibition in parietal and prefrontal cortex that helps to control the span of spatial attention in these cortical areas. The computer simulations of Foley et al. (2012) simulated the video game player advantage by assuming that they experienced a lower inhibitory gain.

19.10 Concluding Remarks

The earlier examples illustrate how the basal ganglia can influence learning and performance across brain systems in the What and Where cortical streams that obey computationally complementary laws (Sect. 1.3; Fig. 19.14). For example,

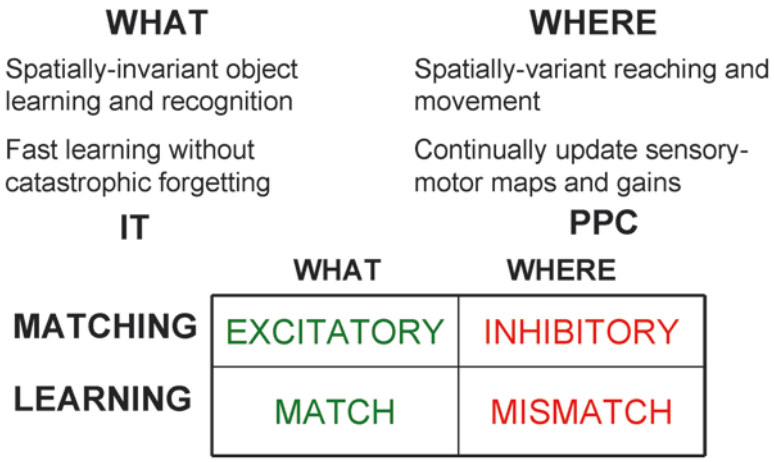


Fig. 19.14 Complementary What and Where cortical processing streams for spatially invariant object recognition and spatially variant spatial representation and action, respectively. Perceptual and recognition learning use top-down excitatory matching and match-based learning that achieves fast learning without catastrophic forgetting. Spatial and motor learning use inhibitory matching and mismatch-based learning that enable rapid adaptation to changing bodily parameters. *IT* inferotemporal cortex, *PPC* posterior parietal cortex. See text for details. [Reprinted with permission from Grossberg (2009)]

volitional GO signals control the selection of motor synergies and the speeds with which they execute arm movement trajectories in the VITE model and its variants (Figs. 19.6 and 19.7). The VITE model simulates *inhibitory matching* between a present position vector, or where the arm is now, and its target position vector, or where the arm wants to move. When the difference vector between the present and target position vectors equals zero, the movement stops. Corresponding to such inhibitory matching, motor systems that obey VITE-like dynamics also experience *mismatch learning* that calibrates the gains of the vectors that are matched so that the difference vector equals zero when the target and present position vectors represent the same position in space.

Models that experience such vector-based mismatch learning are called Vector Associative Map, or VAM, models or adaptive VITE, or aVITE, models (Gaudiano and Grossberg 1991, 1992). Such mismatch learning is susceptible to catastrophic forgetting. However, catastrophic forgetting is a good property for learning the spatial maps and sensory-motor gains that control movements in the Where cortical stream. In particular, it would be maladaptive to remember for life the maps and gains whereby our brains controlled our infant limbs. Continual recalibration of maps and gains enables us to efficiently control our changing bodies.

In contrast, perceptual and cognitive systems that obey the ART Matching Rule (Carpenter and Grossberg 1987, 1991; Grossberg 2013) experience *excitatory matching* (Fig. 19.13) that can gain-amplify and synchronize cell responses that are

part of a bottom-up and top-down matching event. Corresponding to such excitatory matching, ART systems undergo *match-based learning* that helps to solve the stability-plasticity dilemma, so that perceptual and cognitive systems can cumulatively learn more about the world, notably invariant object recognition categories within the What cortical stream, without undergoing catastrophic forgetting.

These differences between What and Where stream processing also clarify key properties of conscious experience. For example, the ART prediction that "all conscious states are resonant states" has been elaborated into a classification of the resonances that support different conscious experiences (Grossberg, 2013, 2016), including those supporting declarative memory. This prediction also clarifies why spatial and motor, also called procedural, processes are unconscious: the inhibitory matching process that supports spatial and motor processes cannot lead to resonance.

In summary, perceptual/cognitive processes often use ART-like excitatory matching and match-based learning to create self-stabilizing memories of objects and events that enable us to achieve increasing expertise as we learn more about the world. Complementary spatial/motor processes often use VAM-like inhibitory matching and mismatch-based learning to continually update spatial maps and sensory–motor gains to compensate for bodily changes throughout life. Together these complementary predictive and learning mechanisms create a self-stabilizing perceptual/cognitive front end for intelligently manipulating the more labile spatial/motor processes that enable our changing bodies to act effectively upon a changing world. How the basal ganglia evolved to bridge across, and help to coordinate, these computationally complementary competences to support multiple learning and movement gating processes is an intriguing question for future research.

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Chapter 20
The Basal Ganglia and Hierarchical Control in Voluntary Behavior

Henry H. Yin

20.1 Introduction

Although the importance of the basal ganglia (BG) has long been recognized, how these nuclei function remains a matter of dispute. Over a century ago, in his review on the striatum, the input nucleus of the BG, Kinnier Wilson wrote: "the question of its function became an enigma, and, as a consequence, there was eventually assigned to it a varied assortment of motor, sensory, vasomotor, psychical and reflex functions . . ." (Wilson 1914). This state of affairs remains true today.

Here I present a new theory of BG function, based on recent findings and the principles of hierarchical perceptual control. I shall first review recent findings that question traditional assumptions. I shall then endeavor to show that these findings, as well as a wealth of experimental and clinical observations, can be explained by a hierarchical control model, according to which the BG function to control perceptual transitions.

20.1.1 Basic Facts

There is no consensus on exactly what the BG comprise. Here I adopt Swanson's classification, which draws attention away from conventional anatomical terminology (Swanson 2000). Conventional terminology is a source of persistent confusion,

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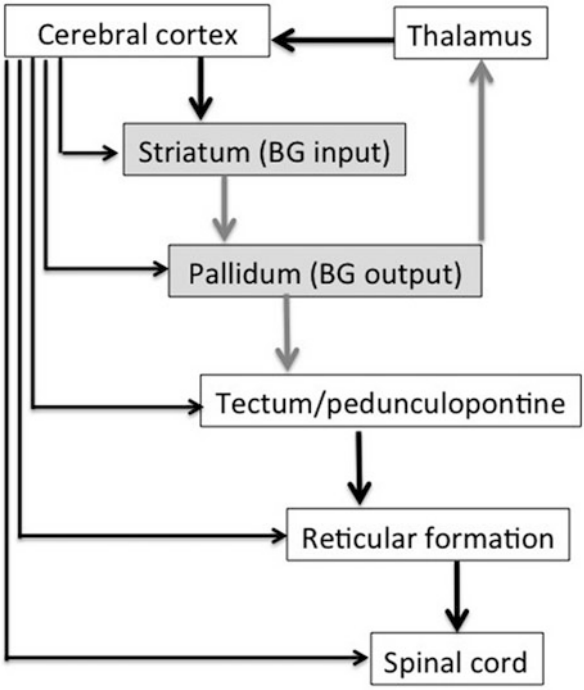

Fig. 20.1 This figure illustrates the place of the basal ganglia in the hierarchy of the nervous system. A major feature of this hierarchy is that the pallidal/cortical projections reach all lower levels, including the BG, the midbrain, brainstem, and finally the spinal cord

because it is largely based on visual appearance to the naked eye, with names of brain structures proposed before the availability of facts about physiology and functional connectivity. Instead, Swanson divides the cerebrum (brain) proper into two parts—cortex and basal ganglia. This classification is based on the transmitter used by the projection neurons in each area, and on their overall connectivity patterns. Cortical regions are defined as those with glutamatergic projection neurons and BG as those with GABAergic projection neurons. The striatum is the input nucleus that receives cortical and thalamic inputs (Gerfen and Wilson 1996). Because these are excitatory, the striatal projection neurons are spiny (medium spiny neuron, MSN), dendritic spines being sites of glutamatergic synapses. On the other hand, the pallidum is the output nucleus, also with GABAergic projection neurons, which are less spiny because they lack dense glutamatergic inputs. The striatum primarily projects to the substantia nigra pars reticulata (SNr), external globus pallidus (GPe), internal globus pallidus (GPi) in primates or entopeduncular nucleus (ENP) in rodents, and ventral pallidum.

The standard BG circuit is illustrated in Fig. 20.1. In addition to the areas shown, Swanson also includes areas such as the medial amygdala nuclei and lateral septal nuclei as parts of the striatum. These areas also have their corresponding pallidal output nuclei such as the bed nucleus of stria terminalis and medial septum. In each case, we can discern a basic motif: excitatory cortical inputs from pyramidal projection

neurons and inhibitory outputs from BG nuclei. But the "limbic" BG outputs do not reach the skeletomotor effector system, as do the conventional BG circuits; rather they influence mostly visceral effectors, including those that produce neuroendocrine outputs. Finally, just like the classic BG circuit, in the amydaloid and septal circuits there is also an output to the thalamus. For further discussions on the anatomical organization of the basal ganglia, the reader is also referred to Chaps. 1–5 in this volume.

According to Swanson's proposal, the cortico-BG networks comprise the entirety of the cerebrum proper and some of its downstream targets. By focusing on a single organizational motif, this proposal is in fact an ambitious step towards a theory of the brain, suggesting that there is a single computational function performed by the BG circuits. As we shall see, the model described here is in accord with this suggestion.

20.1.2 Conservation of BG Circuitry

A key fact, often neglected, is that the organization of the nervous system is conserved in all vertebrates (Grillner and Robertson 2015; Stephenson-Jones et al. 2011; Swanson 2012). This basic plan has been conserved for some 560 Ma, similar between lampreys and humans (Ocaña Francisco et al. 2015).

Which functions are shared by lampreys and humans? In order to survive, both must be capable of homeostatic control of the essential variables for survival, such as oxygen and body temperature. Yet the cerebrum (cortex and BG) is not necessary for maintaining homeostasis in this sense. Decerebrate animals can be kept alive because autonomic homeostatic functions remain despite the loss of descending signals from the cerebrum. But they cannot survive on their own in any natural environment, mainly because they cannot initiate movements. The inability to initiate movements is due to the loss of the BG. Most voluntary movements are intact in animals with complete removal of the cortex, but abolished after very extensive lesions of the BG. Animals without BG must remain entirely passive despite intact reflexes. Consequently, they cannot feed or drink, or produce any type of adaptive behavior (Bjursten et al. 1976; Palmiter 2008; Sorenson and Ellison 1970; Ungerstedt 1971). Thus, in trying to explain BG function a convenient starting point is to consider how they contribute to movements. This is a key question that must be addressed by any theory of BG function.

20.2 Basal Ganglia Activity During Behavior

Since the BG output neurons are GABAergic with high tonic firing rates, they are assumed to inhibit their target neurons in the midbrain, brainstem, and thalamus (Beckstead et al. 1979; Hikosaka 2007). According to the standard model, the BG function as a gatekeeper that normally suppresses behavior; by transiently pausing the output neurons, the gate is opened and behavior is somehow allowed to occur

(Chevalier and Deniau 1990; Chevalier et al. 1985; Hikosaka 2007). The assumption, then, is that an increase in BG output inhibits behavior, whereas a decrease in BG output enables behavior. But recent results challenge this basic assumption: an increase in BG output does not necessarily suppress behavior, nor does a decrease in BG output generate more behavior.

In one study, we trained mice to hold down a lever for a short period (e.g., 800 ms), during which there is little movement until the lever release (Fan et al. 2012). We found two types of putative projection neurons in the SNr. The first type increases firing at the onset of pressing, and maintains the higher firing rates for the entire duration of the holding period. The second type showed the exact opposite pattern, reducing firing rates during the same period (Fig. 20.2). At the onset and offset of the lever press, the firing rates of these two types of neurons changed in opposite directions (Fig. 20.2d). Given the sustained decrease in firing observed during the holding period, the standard model would predict a release of "action," but there is in fact little movement during this period.

Why should there be opponent activity in the SNr at the onset or offset of the lever press? Opponent activity has been found in studies using very different behavioral measures, suggesting that it is a common feature of the BG output (Barter et al. 2014; Basso et al. 2005; Fan et al. 2012; Rossi et al. 2013; Sato and Hikosaka 2002). For example, opponent signals were found while mice maintained their posture during a postural disturbance task (Barter et al. 2014). When the mouse was tilted to the left, one set of neurons increased firing, and another set of neurons decreased firing. When tilted to the right, the opposite was observed: the left tilt-activated neurons decrease firing and the right tilt-activated neurons increase firing. Not only are there both increases and decreases in BG output during any behavior, these signals also appear to be symmetric and roughly 180° out of phase.

20.2.1 SNr Outputs Map Instantaneous Position of the Animal

The key question, which previous work failed to address, is exactly which aspects of behavior the BG outputs represent. Our results from the lever holding task suggest that a *fixed* position of the animal is associated with *fixed* firing rates of SNr neurons (Fig. 20.2). When this position changes, the associated firing rate also changes. The firing rate, then, appears to be a readout of the body position. This possibility is examined in another study, in which we used wireless multielectrode recording and continuous video tracking to study the relationship between movement and neural activity in the BG (Barter et al. 2015b).

The firing rates of SNr neurons are correlated with the instantaneous position coordinates during movement. Their firing rates represent the 2D position vector in Cartesian coordinates. We found two major classes of neurons, one for *x*-axis motion and the other for *y*-axis motion. Moreover, each class contains two types of neurons according to the direction of motion. For example, among x-related neurons, one population increases firing rate during leftward movement and decreases during rightward movement, and vice versa for the opposite type. There is thus a linear

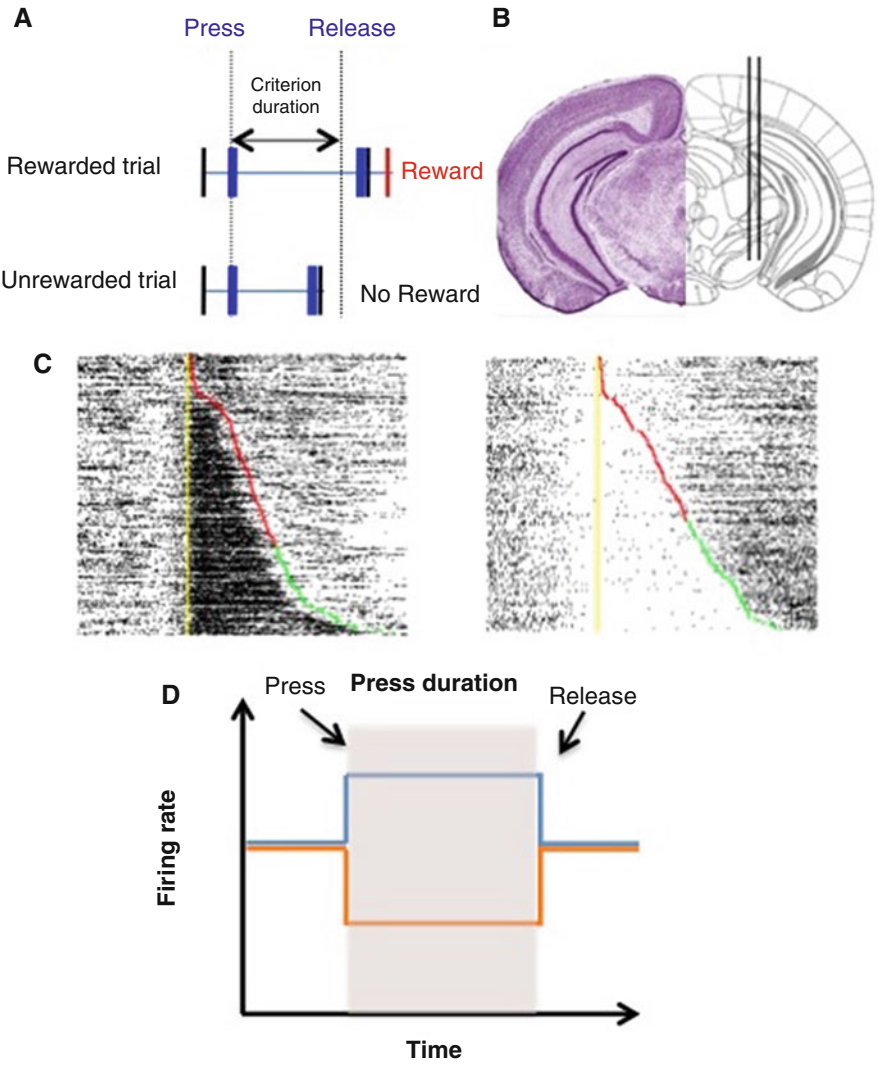

Fig. 20.2 Substantia nigra, pars reticulata (SNr) output during the operant lever holding task (Fan et al. 2012). (**a**) Illustration of the lever holding task. (**b**) Illustration of the electrode location in the SNr. (**c**) Representative examples of neurons that increase or decrease firing during the holding period. Each row shows data from a single trial. *Yellow markers* indicate "Lever Start." *Red markers* indicate "Lever End Unrewarded"; unrewarded trials on which the press duration did not exceed the criterion duration (800 ms). *Green markers* indicate "Lever End Rewarded." The trials are sorted according to the duration of the lever press, starting with trials with the shortest action durations on top. (**d**) Schematic illustration of SNr neural activity during lever holding. Opponent signals appear to be a common feature of the BG output

relationship between neural activity and position coordinates, with at least four types of neurons corresponding to motion in four different directions (up, down, left, right). All these neurons change their firing rates systematically during movement.

For example, during a diagonal movement to the upper left corner, two of these four types (leftward and upward) will increase firing, whereas the rightward neuron as well as the downward neurons will reduce firing (Fig. 20.3). A constant firing rate in the BG output neurons represents a fixed posture and no overt movement. A *change* in firing rate, therefore, reflects a change in body configuration, i.e., movement. It follows that the rate of change in the SNr firing rate reflects the rate of change in body configuration, i.e., movement velocity.

20.2.2 Striatal Activity and Movement Velocity

The major projections to SNr neurons come from the striatum (striatonigral pathway). Early studies reported that striatal activity was correlated with movement speed (Alexander et al. 1986; Turner et al. 1998), but these studies did not examine the different axes of motion, or treat movement kinematics as a continuous variable. Using the same video tracking technique, we recorded from MSNs in the dorsolateral (sensorimotor) striatum (Kim et al. 2014). The MSNs are normally quiet, firing only with extensive glutamatergic drive from the cerebral cortex or thalamus (Wilson 2004). Bursts of activity are commonly observed during behavior (Alexander 1987; Costa et al. 2004; Cui et al. 2013; Romo and Schultz 1992). We found that, just like the SNr neurons, the striatal neurons are highly correlated with movement kinematics. They are not correlated with position coordinates, but with vector components of velocity (Fig. 20.4). Firing in a given striatal neuron is positively correlated with movement velocity in one direction and negatively correlated with movement velocity in the opposite direction. Their firing rates reflect either horizontal velocity or vertical velocity but not both.

On some trials, an aversive air puff was delivered from the same location as the sucrose reward. When we examined the relationship between kinematics and the firing rates of MSNs on both rewarding and aversive trials, we found the same correlation between vector components of velocity and neural activity. The relationship between kinematics and firing rate is therefore independent of the goal of the behavior.

20.2.3 DA Neurons Represent Movement Velocity and Acceleration

The striatum receives direct dopaminergic (DA) projections from the pars compacta of the substantia nigra (SNc). DA is a major neuromodulator of striatal activity, and DA depletion is known to abolish behavior in animal models and in severe cases of Parkinson's disease (Palmiter 2008; Ungerstedt 1971).

We found that DA neurons are similar to striatal neurons in their correlation with kinematics (Barter et al. 2015a). Most DA neurons showed activity correlated with vector components of either velocity or acceleration (Fig. 20.5). Like striatal

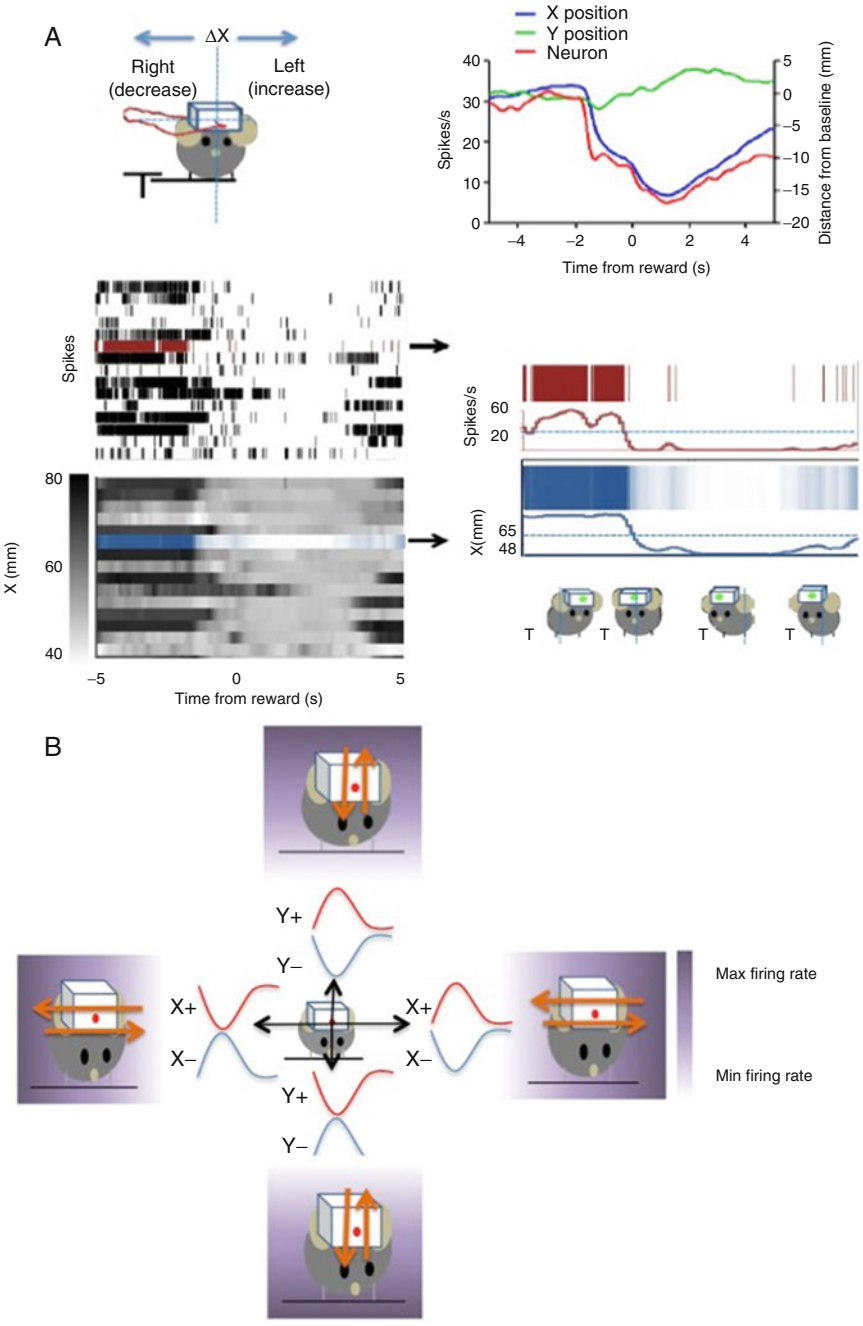

Fig. 20.3 BG output maps the instantaneous Cartesian coordinates of the body during behavior. (**a**) An example of leftward selective neuron, which increases firing during leftward movement and decreases firing during rightward movement. Neural activity and x-coordinates from ten consecutive trials are shown. Each row represents a single trial. Neural and position data from a single trial are selected and compared. *x*-axis position changes during each movement are reflected in the firing rate of this neuron. The activity of the neuron decreased during rightward movement and then increased when the mouse moved left to recover its initial starting position. (**b**) Schematic illustration of different types of SNr neurons responding to different coordinate changes. Opponent neurons are identified for both *x* and *y* axes

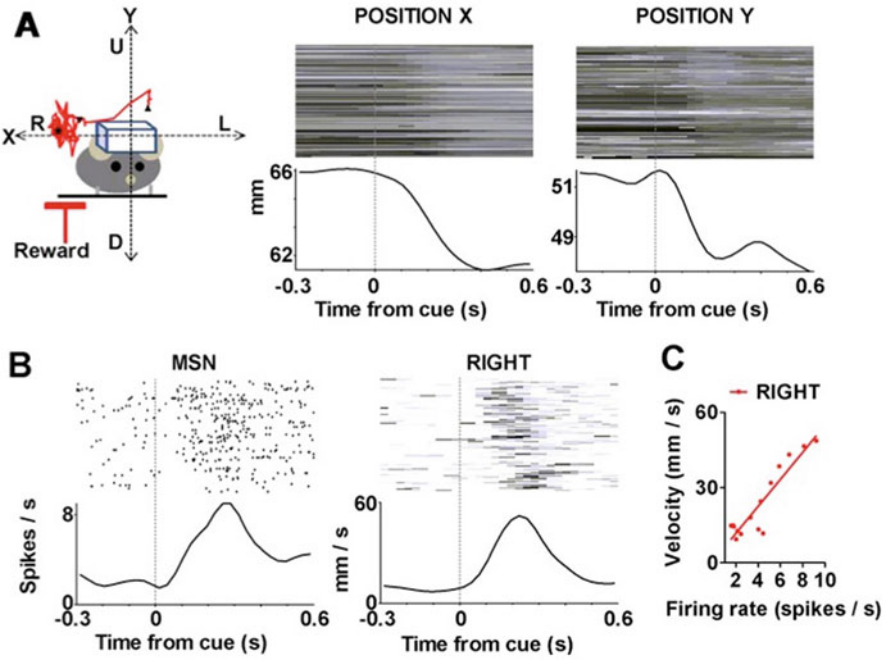

Fig. 20.4 Striatal neurons show correlations with movement velocity. (**a**) Activity of putative medium spiny projection neurons is correlated with movement velocity (Kim et al. 2014). *Left*, illustration of the behavioral task. The mouse stands on an elevated platform. *R* right, *L* left, *U* up, *D* down. (**b**) A representative MSN showing high correlation with velocity in the right direction (relative to the animal). Correlation is much weaker for movement in other directions (not shown). (**c**) High correlation ($r=0.83$) between the firing rate of this neuron and velocity vector component corresponding to rightward movement

neurons, they also show direction preference. It is well known that striatal stimulation can generate movements (Ferrier 1876; Kravitz et al. 2010). Mimicking phasic DA activity with selective optogenetic stimulation, we were also able to elicit movements, though not as readily as stimulation of striatal neurons (Bartholomew et al. 2016; Rossi et al. 2015).

These results seem contrary to the influential reward prediction error (RPE) hypothesis of DA function (Schultz 1998). The firing rates of DA neurons represent movement kinematics whether the movement is performed to acquire sucrose or to avoid air puff. DA signaling thus appears to be independent of the hedonic aspects of motivated behavior (but see below). Moreover, our results suggest that, in previous studies supporting the RPE hypothesis, there is an important movement confound. Such a confound is introduced by experimental manipulations commonly used in such studies, such as reward probability or magnitude (Cohen et al. 2012; Fiorillo et al. 2003). Previous studies did not measure detailed movement kinematics and the continuous relationship between DA and movement kinematics. Our results suggest alternative explanations for these findings.

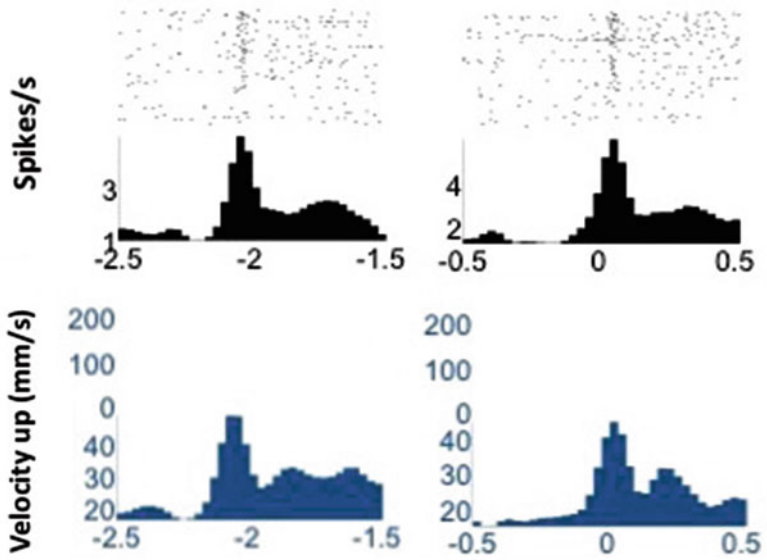

Fig. 20.5 Dopamine neurons represent movement kinematics. Firing rate of a representative neuron showing a positive correlation with vector components of velocity and acceleration. There were two major movements, one in response to the cue and the other in response to reward delivery (Barter et al. 2015a, b). It is worth noting that the same correlation between neural activity and kinematics is present on aversive trials, when an air puff is presented instead of a reward

20.2.4 Departures from Previous Models

According to the standard model of the BG, high firing rate of BG output neurons should inhibit movement, and a reduction or pause in BG output should initiate movement (DeLong 1990). But this model cannot explain why the same neuron can have opposite responses depending on the direction of motion (i.e., increase during leftward motion but decrease during rightward motion), or why there are neurons with opposite preferences (i.e., decrease during leftward and increase during rightward motion).

Contrary to the standard model, our studies show that a change in body configuration is not achieved by a pause in SNr nuclei, or by either increasing or decreasing the BG output. Rather a movement is associated with coordinated changes in at least four different types of neurons: each increase in firing rate during movement in a particular direction (up, down, left, right). One does not simply observe a pause in the output neurons when a behavior is produced. Just as often, neurons can increase firing at the onset of movement. Movement speed is correlated with the rate of change in the SNr output.

One attempt to explain opponent signals from the BG is the action selection model, according to which the appropriate action is selected by pausing of the SNr/

GPi neurons, while the inappropriate action is prevented by increasing their outputs (Mink 1996). But this model fails to explain what is being selected and prevented, because it lacks a meaningful definition of actions. The example given by Mink is that of a reaching movement: at rest, one maintains arm position via postural control, but to perform a reaching movement, it is necessary to turn off postural control and selectively activate the neurons responsible for reaching. The antagonism is thought to be between some system that keeps the animal still and a different system that moves the animal. Yet our results suggest that there is no antagonism between posture and movement. Rather the antagonism is between units that move the body in opposite directions along a particular axis.

There has been much confusion regarding the role of the BG in movement. On the one hand, the extensive clinical symptoms strongly implicate the BG. On the other hand, previous studies on the relationship between BG activity and arm movements in monkeys concluded that BG activity occurs too late to be critical for movement initiation (DeLong et al. 1984a; Delong et al. 1984b; Georgopoulos et al. 1983). Consequently, it is often claimed that the BG may facilitate, rather than initiate, actions. But this conclusion is based on a number of unwarranted assumptions. It is often assumed, for example, that the corticospinal pathway, in particular direct projections from the primary motor cortex to the spinal cord, is responsible for movement. Consequently, there has been almost exclusive focus on the BG projections to the thalamus, which projects back to the frontal cortex, where the corticospinal neurons are found (Alexander et al. 1986). But the corticospinal pathway is certainly not the only route by which the BG can generate movements. Movements of the arm and distal digits, which rely on direct corticospinal projections, may be different from other types of movements, especially axial movements that rely on the reticulospinal pathway. Whereas many movements are intact following lesions of the corticospinal pathway, lesions of the reticulospinal pathway produced much more devastating effects on axial movements (Lawrence and Kuypers 1968), which are usually neglected in primate studies on the BG.

There are direct projections from the SNr to the mesencephalic locomotor region and to the reticular formation (Grillner et al. 2008; Krosigk and Smith 1991; Perciavalle 1987). The BG output is in a position to contribute to axial and locomotor movements via direct and indirect projections to the reticulospinal pathway. This is supported by recent optogenetic stimulation studies, which showed short latency movements following selective stimulation of striatal neurons (Bartholomew et al. 2016; Rossi et al. 2015). The BG contribution to movement therefore appears to be far more important than is acknowledged by primate electrophysiological studies.

Our results raise several questions. Why should descending signals from the SNr match actual position coordinates achieved by the animal? What should velocity-related signals be integrated to produce position-related signals? How are the descending signals from the BG ultimately transformed into activity in the final common path from motor neurons to muscles? To answer such questions, I recently proposed a

new model of BG function, which explains the role of the BG in movement kinematics as well as a wealth of observations (Yin 2014a, c). Before this model can be described in detail, however, it will be necessary to introduce some concepts from control theory, upon which this model is based.

20.3 Negative Feedback and Closed Loop Control

Although the word "control" is widely used, the sense in which it is used here differs from its various conventional senses in cybernetics, engineering, and psychology (Craik 1947; Merton 1953; Rosenblueth et al. 1943). In fact, I shall argue that a crucial misunderstanding in these fields is responsible for the failure to apply control theory correctly to the study of the brain.

20.3.1 Control of Input

Control is always associated with a controlled variable. When a disturbance pushes the controlled variable in one direction, the control system generates an action that specifically opposes the effect of the disturbance on the controlled variable. This will serve as a scientific definition, even if other usages remain, like "power" or "work" in physics. Control thus defined characterizes many engineered systems that employ negative feedback, and control theory explains how such systems work. Although the process of control appears to be simple, it has in fact counterintuitive properties that are rarely appreciated by life scientists. Above all, a closed loop negative feedback control defies the traditional paradigm of linear causation, according to which some cause precedes its effect (Powers 1973b). Applied to the study of behavior, the linear causation paradigm interprets all behavior as outputs from the organism. As a result of transformations taking place within the nervous system, inputs to the organism are transformed into outputs. A closer examination of how control systems work shows that this assumption is wrong.

That control theory failed to challenge the dominant paradigm of linear causation is, paradoxically, due to a crucial conceptual confusion introduced by the same engineers who first understood the process of control. Contrary to the conventional view, what is controlled is *not* behavioral output, but perceptual inputs. While not all inputs are controlled, the only variables that can be controlled are perceptual inputs (Powers et al. 1960).

The confusion stems from conventional terminology in engineering. The goal of the engineer is to build machines that can perform some function that a human performs. Hence a "servo" is designed to replace a human operator: It receives a command and produces exactly the output that the user wants, *or so it seems to the*

observer. Consequently, in engineering the reference signal (or desired value of the controlled variable) is injected into the system, usually by the user. The diagram for this type of organization is shown in Fig. 20.6a.

For example, we can walk into a room with a thermostat, change the temperature setting to 25 °C, and the temperature controller will take care of the rest. What the engineer wants, or the reference signal, is by convention labeled "input," and compared with the output, which is really some measure of the output (sometimes called the "process variable") fed back to the controller. The measured output is a source of input to the controller. Thus for the engineered controller, there are two inputs: the feedback or output reading comes from some sensor measuring the relevant effect or feature of the output, and the input is the reference, or desired value. The fact that the household thermostat allows the user to adjust its temperature setting (reference) is a feature designed by the engineer. But reference signals in living organisms are intrinsic; there is no user, and all "command" signals come from inside the organism, and serve intrinsic biological purposes. Moreover, the only way organisms can detect the effects of their behavior is through their sensors and neuronal machinery for perception. There is no engineer to measure the effect. The measures are "taken" by the living organism itself.

With the engineering convention, one gets a distorted view of how the organism contributes to the process of control (Robinson 1981; Wiener 1948). With reference signal as "input," and measured input as "output," one obtains a picture of the control system that is inside out (Fig. 20.6). What should be considered a part of the organism—the internal reference—is considered a part of the environment, and what should be the part of the environment, the feedback function that relates how behavior affects perceptual inputs, is viewed as the system output. For decades, this mistake has prevented progress in applying control theory correctly to the study of the brain.

Control theory raises new questions that are not considered by traditional studies: what is the perceptual variable that is being controlled? Where is the internal reference found? Which effectors are needed to change the value of this particular variable? How does the output affect the input? Conventional studies do not address such questions, because they follow the linear causation paradigm, in which behavioral output is a function of inputs to the organism. Paradoxically, it is precisely the idea that one thing can cause another that represents the greatest obstacle to scientific progress on the mechanisms of behavior.

Traditional measures are also "event-based." The assumption, evident in current models of the BG, is that behaviors are discrete events that either occur or do not occur (Alexander et al. 1986; Hikosaka et al. 2000; Mink 1996). When behavior is coded as a series of time stamps, the only information recorded is that it did occur. Control theory, on the other hand, assumes continuous reciprocal relationships between the organism and its environment. By dividing these into discrete time stamps, event-based measures mask the underlying processes.

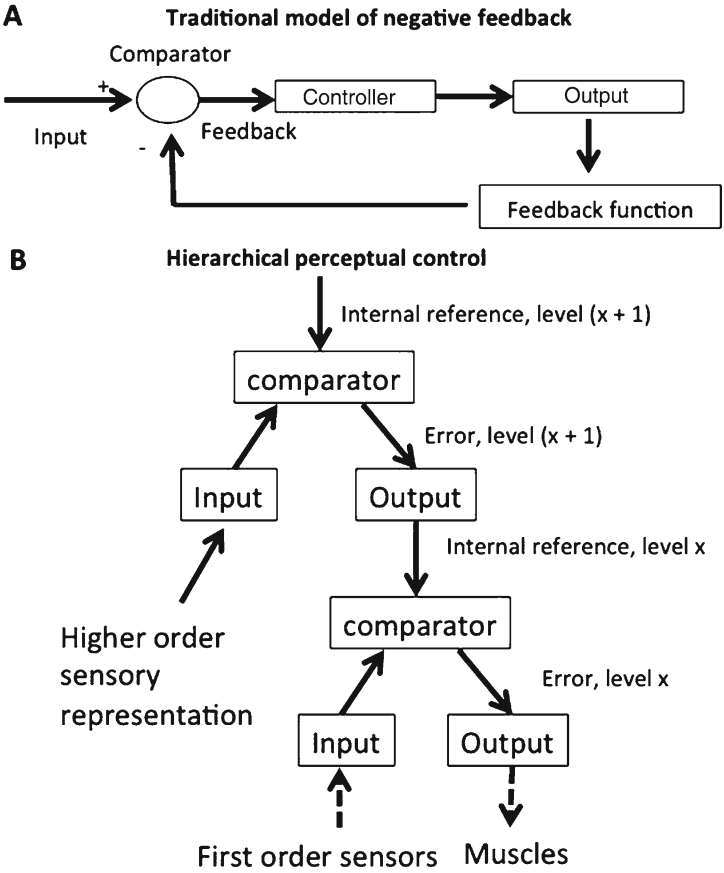

Fig. 20.6 (**a**) Conventional illustration of the control loop. The crucial mistake made by Cybernetics and engineering control theory is in the assignment of the input and output of the system, as shown in the basic control diagram (Wiener 1948). This way of illustrating the relationship between the controller and the environment creates the appearance that the controller is some device that transforms error into output. It has led to the misunderstanding that the output is controlled, and the system input is the command from the user. (**b**) Illustration of the control loop discussed in this chapter, in which the controlled variable is the perceptual input derived from sensory receptors. So long as there is effective control, the input signals will resemble the reference signal. The reference signal has to specify a magnitude only, not what kind of perception is to be obtained. The kind of perception, its relationship with the external world, is determined by the connectivity of the input function—i.e., whether it comes from auditory sensors or visual sensors, etc. The perceptual signal represents its current magnitude; a separate reference signal specifies how much of the perceptual signal is to be reached. Because the system produces an output that, via sensory feedback, reduces the discrepancy between what the input variable should be and what it is, it is capable of reaching the desired or referenced perception. Negative feedback does not mean that the sign of the feedback is negative. It means that the feedback reduces the error. By contrast, positive feedback amplifies error by increasing the discrepancy between reference and input. Here two levels are illustrated showing the principle of hierarchical organization. The error signal from the comparator in the higher level ($x+1$) is turned into the reference signal of the lower level (x). The lowest level in the hierarchy is the final common path from motor neurons to muscles. The correct illustration of the control loop is shown in Fig. 20.6b. Because output is produced by a comparison between some perception and some reference, a complete knowledge of the input will not allow one to predict the behavioral output of a closed loop system. In a closed loop, because the input is affecting the output at the same time that the output is affecting the input, the concept of cause or effect is simply not applicable

20.4 Neural Implementation of the Control Hierarchy

Control is here assumed to be the primary function of the nervous system. The development of neural signaling, which provides rapid and long-range signaling as well as analog computing using firing rates, is critical for the implementation of highly effective control systems for important biological variables. As a given controller can only control a single one-dimensional variable, to control multiple variables multiple controllers are needed. The nervous system can thus be viewed as a collection of distinct controllers. The question is how these controllers are connected to each other. To answer this question, Powers proposed the hierarchical control model, according to which each controller is a basic building block in a control hierarchy (Powers et al. 1960). Each level in this hierarchy can have multiple controllers of the same type. The higher level in a hierarchy uses inputs that are re-representations of lower level inputs. Their outputs do not directly affect effectors, but change the reference signal of the lower levels. The error signal from a higher level can be transformed into a reference signal for the lower level, allowing direct command of the lower levels. The higher level does not dictate how much output the lower level should produce, but only how much input it is to obtain. To the lower level controller itself, this amount of requested input has no particular significance. It is only significant via some environmental feedback function that links the ultimate effect of the output on the input of the higher order controller. The order given to the lower controller has the effect of changing the value of the higher level controlled variable in the right direction, reducing its error.

The hierarchical organization of the nervous system has long been recognized (Fuster 1995; Hayek 1952), but the crucial error in previous models is the assumption of linear causation, rather than closed loop control (Yin 2013). For example, it is often assumed that higher levels have cognitive functions, e.g., cognitive control modifies existing stimulus–response paths (Miller and Cohen 2001). By contrast, here it is postulated that the higher levels send projections to the comparator function of lower controllers to alter their reference signals, thus specifying how much input the lower level should obtain. If this basic postulate is correct, it follows that all neurons can be classified according to their functional role in a control system—namely input function, comparator, and output function, and that different brain regions would correspond to different levels of the control hierarchy.

20.4.1 Muscle Tension Control and the Final Common Path

The cerebral cortex and the BG are situated at the top of the neural hierarchy. Outputs from the BG do not reach the lower motor neurons directly, but they can set the reference signals of lower levels, which ultimately result in muscle contraction. To understand BG function, we must start from the lower levels, which interact with the external environment. There are many types of effectors, including cells that

secrete hormones and transport fluids. For our purposes, by far the most important effectors are the skeletal muscles. The final common path, the projection from alpha motor neurons to muscles (Sherrington 1906), is shared by virtually all behaviors. The force generated by muscle contraction is proportional to alpha motor neuron output. The resulting tension is sensed by Golgi tendon organs, which are in series with the extrafusal muscle fibers and produce a net inhibitory input to the alpha motor neuron that is proportional to the amount of contraction (Houk and Henneman 1967; Houk and Rymer 2011). This control system therefore uses muscles as its output function and tension sensors as its input function (Powers 1973a; Yin 2014c). The comparison function is implemented by the alpha motor neuron. The error signal is the difference between tension reference dictated by the signals arriving at the alpha motor neuron and sensed tension. Normally this control system maintains the muscle tone specified by the sum of the descending tension reference signals. An unexpected contraction elicits muscle relaxation, i.e., the inverse myotatic reflex.

Variability in output is the key feature of all control systems. There is no consistent one-to-one mapping between muscle activity and behavior. That is, from a measure of muscle activity (e.g. EMG) we cannot tell exactly what the animal is "doing." Repeating output will not repeat the behavior, because the output is not the only force responsible for observable behavior (Bernstein 1967). For example, because the environmental disturbances change (e.g., wind), the muscle force needed to raise one's arm can be different every time. The output varies according to disturbances, as defined by deviations from internal references.

There is therefore a fundamental ambiguity if we only measure the output from the nervous system. Based on output, blinking and winking might be similar, but they differ in the variables being controlled. Behaviors can only be classified according to their purpose or reference signals, not by their outputs. The same outputs can be used to serve different purposes, yet different outputs can be used to serve the same purpose. Muscle tension only reflects the reference setting of the tension controller. It varies in order to reach the reference value of some other variable. With the exception of the inverse myotatic reflex, tension control usually serves higher purposes.

20.4.2 Muscle Length Control

The level just above the tension controller is a muscle length controller. Muscle length and muscle tension are independently controlled variables. Both can vary at the same time, but there is an intrinsic hierarchical relationship between these two variables: tension regulation is the means by which muscle length control can be achieved (Yin 2014c).

The length error signal is conveyed by the Ia primary afferent from the muscle spindle. This signal is traditionally viewed as a sensory signal conveying information about muscle length, because the muscle spindle, being in parallel with the extrafusal fiber, is activated whenever the extrafusal muscle is elongated. In fact, the Ia afferent signal is independent of actual muscle length. It can be produced either

as a result of the extrafusal muscle fibers in parallel with the spindle, or as a result of the contraction of intrafusal muscles due to gamma neuron activity. It reflects the difference between desired muscle length and actual length—the error signal in the length controller. The spindle acts as a mechanical comparator, as a stretch detected by muscle spindle is compared with the net reference signal for muscle length. The discrepancy or error is then sent to the alpha motor neuron to produce muscle contraction. At the same time, however, the alpha motor neurons can also be commanded directly by corticospinal projections. Such direct adjustment of force reference seems particularly important for the movement of distal digits.

The descending signals for length reference come from the gamma motor neurons, which in turn receive inputs from the brainstem and the cerebral hemispheres. When gamma motor neurons are activated, the contractile parts of the spindle (intrafusal fibers) attempt to shorten. A pull is generated at the equatorial region of the spindle that results in Ia afferent activity, even though the spindle length does not change significantly because it is anchored at both ends. Consequently, alpha motor neurons are activated.

20.4.3 Position Control: Joint Angle and Body Configuration

To change a joint angle, the lengths of multiple muscles must be changed simultaneously. In turn, a body configuration consists of a set of joint angles. In each case, the relevant perceptual input is represented as a one-dimensional signal. The controlled variable is a configuration of lower order proprioceptive inputs, and the output function can reach a group of muscles that work together to produce the appropriate net effect.

The control of body configurations is a type of position control. In position control, the controlled variable represents some position coordinate, and output is generated by computing the difference between the reference or desired position coordinate and the input signal reporting the actual position. For motion with multiple degrees of freedom, the actual position vector is determined by the action of multiple orthogonal controllers. In the brainstem, for example, there is evidence for distinct position controllers for vertical and horizontal movements (Deliagina et al. 2012; King et al. 1981; Luschei and Fuchs 1972; Masino 1992; Masino and Knudsen 1990).

The key neural substrates for posture control are the reticulospinal, vestibulospinal, and rubrospinal pathways (Deliagina et al. 2008; Foreman and Eaton 1993; Peterson et al. 1979). For example, stimulation of the reticulospinal pathway can produce coordinated changes in joint angles: depending on stimulation location, ipsilateral flexion and contralateral extension or the opposite pattern of ipsilateral extension and contralateral flexion can be produced (Sprague and Chambers 1954). The reticulospinal pathway receives direct and indirect projections from the SNr. These descending projections are assumed to alter the reference signals for body configuration control.

20.4.4 Locomotion and Gait

Although the reticulospinal pathway receives direct projections from the BG, more is known about the indirect projections via the mesencephalic locomotor region (MLR) and the pedunculopontine nucleus (PPN) (Garcia-Rill 1986; Sherman et al. 2015; Shik and Orlovsky 1976). In addition, another area critical for locomotion, the diencephalic locomotor region (DLR), is found in the ventral thalamus in the lamprey and thought to be analogous to the zona incerta in mammals (Menard and Grillner 2008). DLR appears to be functionally similar to MLR but their respective roles remain unclear (Mogenson and Nielsen 1983). In rodents, the substantia innominata or ventral pallidum projects to the zona incerta as well as the pedunculopontine nucleus. One possibility is that the DLR is primarily concerned with head movements, whereas the MLR is important for axial and limb movements. This is supported by studies showing rotational movements of the head and eyes produced by zona incerta stimulation (Hyde and Toczek 1962) and deviation and torsion of the eyes as well as tilting of the head following damage to this region (Hedges and Hoyt 1982).

The MLR is a primary target of BG outputs (Grillner et al. 2008). Recent work showed that the core of the MLR is not in the PPN, but the lateral pontine tegmentum, which sends direct glutamatergic projections to the ventral horn of the spinal cord. The SNr output reaches the midbrain extrapyramidal area, which in turn projects to the lateral pontine tegmentum (Sherman et al. 2015). The firing rates of many MLR neurons are correlated with speed of running (Lee et al. 2014). Lesions of this area produce cataplexy and episodic immobility. There appears to be a limb extensor circuit in the ventral MLR that is critical for the standing posture, receiving an inhibitory projection from the SNc (GABAergic and dopaminergic neurons); the dorsal MLR contains a flexor-dominant circuit necessary for locomotion, receiving a projection from the SNr (Sherman et al. 2015).

The PPN and MLR send projections to the reticulospinal pathway, where they alter the activity of locomotor oscillators (Garcia-Rill et al. 2014; Lee et al. 2014; Moruzzi and Magoun 1949). But the same region is also part of the reticular activating system that can enhance overall arousal in the forebrain (Garcia-Rill et al. 2014; Lee et al. 2014; Moruzzi and Magoun 1949). Autonomic functions as well as perceptual functions are adjusted at the same time to accommodate the needs of locomotion.

In addition to the SNr output, the ventral tegmental area (VTA) also appears to provide a critical BG output to locomotion-related body configuration controllers (Swanson and Kalivas 2000; Wang and Tsien 2011). Common to all forms of locomotion is the alternating swing of the body. Locomotion involves not only alternating rhythms in limb movements (e.g., extensor/flexor alternation), but also left right alternation in the spine configuration in locomotion. Whereas the MLR appears to be more important for regulation of limb joint angle, the PPN and other related regions could be critical for controlling torso joint angles, e.g., bending the spine.

The BG are not responsible for generating locomotor rhythm per se, which depend on lower levels of the hierarchy. But the BG output can determine the rate

of change in body configurations. In locomotion, the rate of propulsion is proportional to the rate of change in the configuration reference signal.

20.4.5 Orientation Control and the Tectum

Neural position controllers differ in how they sense position. Proprioceptive sensors from muscles and joints report the state of the body. Senses such as vision and hearing are used to report distal changes in the environment, and the relevant receptors must be moved toward the relevant part of the environment. This type of signal acquisition is equivalent to orientation control. Orientation is not a property of the organism only, but of the relationship between the organism and its external environment. The levels below orientation control cannot act on the environment in any directed way. Devoid of any distal senses, one cannot move towards some distal target.

The key neural structure for orientation control is the tectum, a large region in the midbrain that receives visual, auditory, and somatosensory inputs. Indeed, in some organisms the primary visual analysis occurs at the level of the tectum (superior colliculus), which enables adaptive behaviors such as striking at prey (Lettvin et al. 1959). Signals from each tectal sensory map converge on the comparator. The error signal from the comparator, in turn, has access to a number of body configuration controllers. The error signal is transformed into the position reference signals that ultimately specify the movements. For example, to foveate on a moving target, one can move the eyes, the head, or the whole body. Any of these can acquire the visual input needed, thus achieving the orientation of "straight ahead," and normally all can be engaged at the same time. The head will turn if the body is restrained, and the eyes will move if the head is restrained.

Foveation is just another example of the control of input. The photoreceptors are organized retinotopically, and moving up the neural hierarchy this organization is retained at multiple levels, including the superficial layer of the superior colliculus (Drager and Hubel 1976; Robinson 1972). Activity of each unit on this map can have a certain range of values. To orient the sensory receptors towards the distal stimulus, the value of the relevant units on the map can be matched with a reference value. Thus the sensory signal acquired at each map location is dictated by the reference. This is effective not only for foveation, which keeps a high level of activation roughly in the "center" of the visual field, but for other types of behaviors, e.g., grasping or whisking, that rely on different sensory receptors.

The high firing rates on a map of low firing rates represent the reference location, the default setting which allows the eyes to be "centered" at rest. Movements will be produced to reduce the error until each unit returns to the baseline level specified by the reference for peripheral units. But as soon as the position changes to the receptive field of the neighboring unit, that unit too will generate a direction-specific movement to reduce its error, and so forth until the foveation units are reached. These units have different reference signals, so that the high perceptual input no longer creates an error signal.

The tectal orientation controller can function in two modes. In the bottom-up mode, any salient stimulus can trigger an orienting movement. Pavlov called this the "what is it reflex," whose primary function is to orient one towards changes in the environment, in preparation for possible behavioral engagement, whether to approach, avoid, or ignore (Konorski 1967). In the top-down mode, the animal can select any part of its perceptual field and orient towards it, regardless of its salience.

20.4.6 Nigrotectal Projections Send Descending Reference Signals

On the tectal map, activation of any unit above its reference level will generate an error signal from the comparator, resulting in movement. In foveating animals, it appears that high level of activation is allowed only in the rostral fovea representation, as a result of topographical differences in the reference signals received. To break foveation, the higher level must reset the reference for the periphery. For "voluntary" saccades, neurons are activated in a region that represents the location to which the saccade will be directed. Just prior to a saccade, activity rapidly builds up at the target location, reflecting the reference signal sent to the chosen location in the peripheral visual space that is not currently foveated. Descending projections to the tectum select which part of the map is to be activated.

A major source of descending reference signals is the BG, via the massive nigrotectal projections. The SNr sends direct GABAergic projections to the tectum (Beckstead 1983; Redgrave et al. 1992; Rinvik et al. 1976). The nigrotectal projection is critical for self-initiated or memory-guided saccades (Hikosaka et al. 2000). When the monkey must move its eyes towards some arbitrary target, SNr neurons pause transiently, whereas their target neurons in the intermediate layers of the superior colliculus burst. The intermediate layer receives two sets of inputs, glutamatergic inputs from the superficial layers, where the visual inputs arrive, and GABAergic inputs from the SNr, which represent descending reference signals from the BG (Isa and Hall 2009). Thus these neurons can implement a comparator function to generate the difference between reference and input.

20.4.7 Turning and Steering

Orientation control is critical for steering during locomotion. Unilateral striatal stimulation produces muscle contraction on the contralateral side of the body. Unilateral striatal (caudate) lesions produce a posture in which neck and body are curved towards the side of the lesion. The laterally curved posture results from an imbalance of the activities of the two striata, and the animal turns away from the side of the greater activity, presumably due to contralateral contraction and ipsilateral relaxation of different muscle groups along the spine (Ferrier 1876; Jung and Hassler 1960).

We assume that leftward modules are mainly located in the right striatum, and rightward modules in the left striatum. Balanced outputs from both striata are needed for moving straight ahead. Thus, the net effect of stimulation on the right side will be leftward turning and vice versa. Unilateral muscimol injections into the SNr, by activating GABA-A receptors, can mimic the effects of unilateral striatonigral transmission (Cools 1985). Cools found that the animal repeatedly attempted to bridge the gap between the current position and some egocentrically defined point. The fully symmetric posture is the point of departure, or neutral position, for the drug-induced movements. While the initial turning movements are restricted to that of the head, with time there is progressively more movements with different points of departure moves from the ears to the eyes, to the midline of the head, and then more caudally, from the head to the tail (oculus, auriculum, cranium, scapula, and pelvis). The point of departure lies on the vertical axis of the egocentric coordinate system. These are the locations where the descending reference signals can alter the body configuration.

20.5 Transition Control

According to the present model, the BG implement transition control. By sending reference signals to position controllers, the BG can reach some desired rate of change (transition) in different perceptual variables. This insight was anticipated by Cools, who speculated that the inhibitory output from the SNr represents reference signals, which contain a "proprioceptive code," and that the BG circuit could implement transition control (Cools 1985). But lacking knowledge of the computational roles of striatal and nigral neurons and the neural integrator needed to convert velocity error into position reference, Cools could not provide a model of how transition control is implemented.

The results discussed earlier, which reveal representation of movement kinematics by BG neurons, suggest a control system for movement velocity, in which the rate of change in body configurations is a controlled variable (Yin 2014a). In a velocity controller, the actual velocity will match the desired velocity.

If we only cared about start and end positions, then position control would be adequate, and the speed with which the position is altered is determined largely by loop gain. Given a specific amount of position error, the speed cannot be varied and the movements may appear jerky. But if we wish to vary how quickly this transition occurs, it is important to control the rate of change itself.

Velocity control is critical for smooth motion. To achieve it, it is necessary to sense the rate of change in body configurations. For example, in an engineered speed controller, the rotation speed of the motor can be sensed, and this sensed value is compared with the reference to calculate the error signal. Any deviation is used to generate the output. In a biological organism, there are proprioceptive inputs that sense the rate of transitions (Yin 2014a). Movement velocity in this sense is independent

of movement in space. On the other hand, rate of change in exteroceptive inputs, such as optic flow, is detected and controlled by a different system (see below).

20.5.1 Cascade Organization and Velocity Control

Engineered velocity controllers and position controllers are similar in design, with the key difference being how the output is measured or transduced. For example, a potentiometer changes its voltage output proportional to the position moved, whereas a tachometer generates a voltage proportional to the rotational speed of the motor. In a biological organism, these are achieved by the perceptual inputs at different levels of the hierarchy. New properties emerge when a velocity controller is placed just above a position controller, i.e., arranged hierarchically. This arrangement is similar to a common engineering design called cascade control, with the higher controller called the inner or master loop and the lower controller the outer or slave loop.

Suppose we have a position controller with three positions: 1, 2, and 3. A reference signal of 3 is a command to sense the position 3. If the reference signal is fixed at 3, this position controller will maintain position 3, producing variable outputs as needed to resist the effect of environmental disturbance. To the casual observer, however, there is no movement whatsoever. If we plot position (a string of 3 s) over time, we would see a flat line. If we change the reference to 2—this command tells the position controller to bring the reading of its position transducer to the new reference value. But to control how *quickly* the value changes from 3 to 2, velocity is needed. In the cascade organization, the velocity loop is placed just above the position loop, so that the error in the velocity controller becomes the reference for the position controller (Fig. 20.7). For this to be possible, the error of the velocity controller must be converted to the rate of change in the position reference. That is to say, integration is needed.

The neural implementation of movement velocity control is the sensorimotor cortico-BG network. As reviewed earlier, striatal activity is related to velocity whereas nigral activity is related to position. The present hypothesis is that striatal output reflects the velocity error signal, which is integrated by the SNr. Thus the velocity error is converted to a rate of change for the position reference, regardless of the start or end position.

Integrators are common in negative feedback systems. When “integral gain” is used in the output function, the output is proportional to the time integral of the error signal. Output can be produced even when the current error is zero, maintaining a steady reference command to downstream systems. With no leak or discharging, the amount of output at any given time reflects total error accumulated in the past. In principle, the steady state error of this system can be zero and the loop gain infinite.

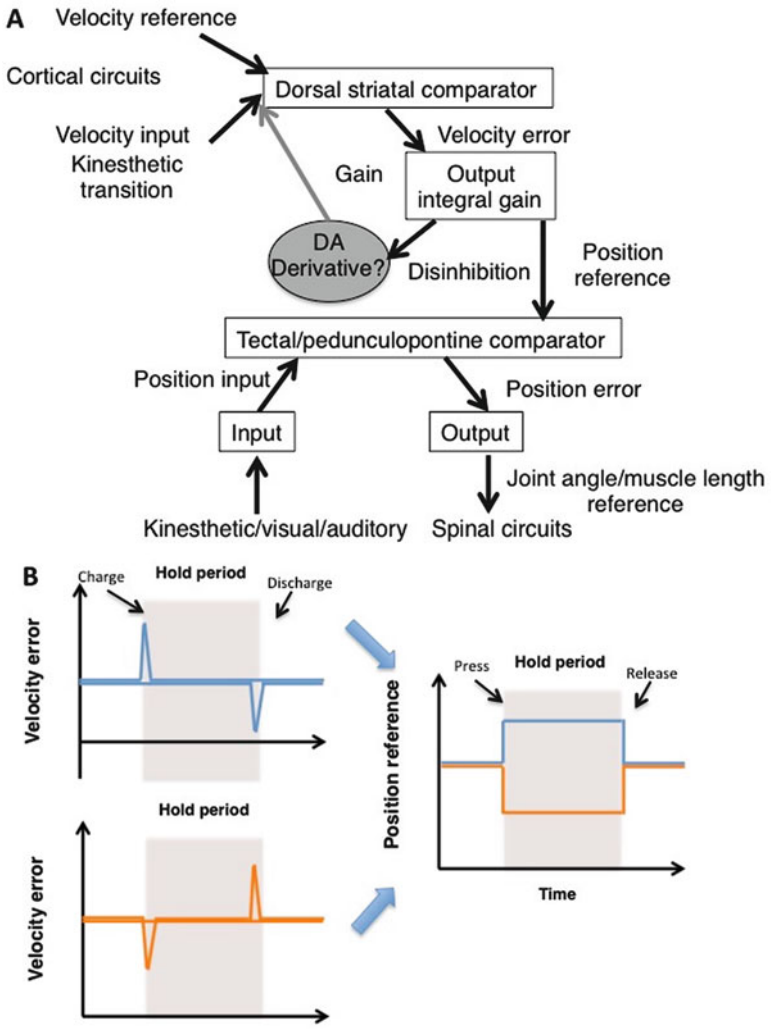

Fig. 20.7 Relationship between velocity control and position control. (**a**) An illustration of the hierarchical relationship between a velocity (transition) controller and a position controller. The velocity error is integrated to yield position reference. The rate of change in the BG output therefore reflects movement velocity, while the firing rate itself represents position. (**b**) Illustration of charging and discharging the integrator. The lever holding task (Fig. 20.2) is used as an example. On the *left* are the velocity errors from the striatum that are assumed to enter the integrator, and on the *right* is the position reference from the SNr

When integral gain is used in the transition controller, the latest position achieved is maintained. The BG output nuclei, e.g., the SNr, are characterized by high tonic firing rate, which can be explained by membrane properties of the GABAergic projection neurons (Zhou and Lee 2011). But functionally the significance of such high

firing rates has never been clear. According to the present model, this is because SNr output represents a position vector. To maintain position, the SNr output neurons continue to fire at the *same* rates (Fig. 20.2). When the firing rates change, a new position is achieved. The dynamic range of the neural signaling reflects the range of egocentric position coordinates, and maximum movement amplitude.

20.5.2 Direct and Indirect Pathways

An important feature of the BG is the parallel direct (striatonigral) and indirect (striatopallidal) pathways (Gerfen 1992; Parent and Hazrati 1995). Although this anatomical feature remains controversial, there is general consensus that these two pathways have opponent effects on the SNr output neurons, via direct inhibition and indirect disinhibition.

One possibility is that the direct/indirect organization implements a phase splitter. In a phase splitter, a common signal enters the circuit, and two opposite signals are generated. One increases as the other decreases, creating antiphase signals. Because the direct and indirect neurons share largely overlapping inputs, they are expected to be activated simultaneously by cortical and thalamic input, as supported by recent results (Cui et al. 2013; Isomura et al. 2013; Tecuapetla et al. 2014). There must be concurrent activation in order to generate opponent effects on the BG output, i.e., the inhibitory effect of the direct pathway and the disinhibitory effect of the indirect pathway on the SNr output can create antiphase signals. Because the nigral neurons influenced by these two pathways typically show tonically high firing rates, both increases and decreases from the baseline are possible.

Opponent or antiphase signals are needed for the control of opponent downstream controllers. The reciprocal inhibition organization in the spinal cord, for example, acts as a phase splitter of the length error signal (McDougall 1903; Sherrington 1906). For example, to lift a dumbbell (reduce the joint angle at the elbow) one can contract the biceps while relaxing the triceps. On the other hand, opponent BG outputs are required to command distinct position controllers that move parts of the body in different directions along a particular axis of motion. The antagonism is not between antagonistic muscles, but between directions of movement.

The question is whether these two pathways act on the same SNr output neurons. If they reach distinct SNr populations, then the two populations of SNr neurons with antiphase signals can be explained by the opponent inputs (inhibition and disinhibition) from the direct and indirect pathways. Another possibility is that the opponent SNr neurons are mutually inhibitory via collaterals from their axons. This arrangement can also produce antiphase signals, without relying on a phase splitter upstream of the SNr. These possibilities are not mutually exclusive. In addition, the "hyperdirect pathway" can also increase the output of the SNr, via glutamatergic inputs from the subthalamic nucleus (Nambu et al. 2002), and the net effect is the opposite of that of the direct pathway.

According to the traditional model, direct pathway activation promotes movement, whereas indirect pathway activation inhibits movement (Freeze et al. 2013; Hikosaka et al. 2000; Kravitz et al. 2010). This interpretation, however, is inadequate in view of the relationship between neural activity and kinematics discussed earlier. Let us consider the direct pathway first. Striatonigral neurons are not identical. Different classes, belonging to distinct velocity controllers, are involved in movements in different directions. For antagonistic directions (e.g., up and down) one population must increase firing as the antagonistic population stops firing. Therefore it is simplistic to conclude that the direct pathway neurons uniformly promote movement. Some of them promote movement in some direction, but if the antagonistic units are activated, then the movements will be stopped.

The role of the striatopallidal neurons is more difficult to understand. One important clue comes from observations on turning behavior after unilateral striatal manipulations. Increasing striatal output on one side produces contraversive turning, largely due to activation of the direct pathway, because unilateral optogenetic direct pathway stimulation mimics the effect of nonselective unilateral striatal stimulation. By contrast, indirect pathway stimulation produces the opposite effect of ipsiversive turning, though this effect is usually weaker (Kravitz et al. 2010; Tecuapetla et al. 2014). This observation suggests that the effect of striatopallidal activation is indeed the opposite of striatonigral activation, but the opposition is between two *directions* of movement.

As described above, a given velocity controller is responsible for motion in one direction only and contains an integrator in its output function. The accumulation of signals in this integrator will therefore produce motion in one direction. To get motion in the opposite direction, the integrator must be "discharged," and another antagonistic velocity controller must be activated. The discharging of the integrator requires an error signal with the opposite sign (e.g., a leak in the bucket), which is exactly what a phase splitter can provide. Thus, one possibility is that the direct pathway initiates the action and the indirect pathway serves as a brake by introducing a leak in the integrator. The amount of leak can be independently controlled. The more leak there is, the more damped the system will be. More "ballistic" actions will involve less leak. The presence of highly plastic striatonigral axonal collaterals that target the external globus pallidus suggests a mechanism for adjusting the damping of the system (Cazorla et al. 2014).

There are only a few neutral postures that are specified by innate reference settings. These neutral positions often involve body symmetry, whereas movement requires a transient break in symmetry. Most movements are transient and cyclical, involving a return to the resting neutral position. The return back to the original position also requires a discharging of the integrator with the opposite error. Both the indirect and hyperdirect pathways are capable of introducing the opposite error (or leak) to the integrator.

In the sensorimotor striatum, a given striatal module generates a set of signals that will move some body part in a specific direction with a specific speed. Such a module could include a set of striatonigral units and striatopallidal units that are also activated by the same reference signal for leftward motion. As pointed out above,

this module is found in the right striatum. In this module, the firing rates of both striatonigral and striatopallidal neurons are both correlated with leftward velocity, yet their ultimate effects on the BG output, and on behavior, are different. The direct pathway moves the body to the left, accumulating signals in the leftward integrator, whereas the indirect pathway discharges the integrator and brings this movement to a stop. It was proposed long ago that these pathways can scale movement amplitude and speed (DeLong 1990), but the original proposal confounded two very different variables and failed to take into account the key property of direction specificity.

Why should unilateral stimulation of the indirect pathway produce ipsiversive movement? According to the present model, to turn left, the leftward module must be turned on, and the rightward module suppressed. There is therefore antagonism between these modules. At the same time, within the same module there is antagonism between direct and indirect pathway neurons, because the striatonigral neurons accelerates contraversive movement whereas the striatopallidal neurons decelerates it, i.e., introduces acceleration in the ipsiversive direction. The deceleration, however, is usually dependent on the same reference command for contraversive motion, used to damp the movement as needed, and to return to the original position. Normally the striatopallidal unit in this module cannot be activated in isolation, but selective optogenetic stimulation can reveal the acceleration in the opposite direction.

20.5.3 Role of Dopamine

Midbrain DA neurons project to most striatal regions. There are two major DA pathways: the nigrostriatal pathway targets the dorsal striatum and the mesolimbic pathway targets the ventral striatum and the prefrontal cortex. DA has the same computational function in both pathways: it is hypothesized to adjust the gain of striatal neurons. But the impact on behavior will differ depending on the neural circuit affected and the types of variables being controlled. We will start by considering the nigrostriatal pathway, by far the dominant DA pathway.

DA modulates synaptic transmission. "Modulation" here does not simply mean "change," as used loosely in the physiological literature, but a multiplicative operation in the engineering sense. Nigrostriatal DA alters the responsiveness of dorsal striatal neurons (Cepeda et al. 1993; Gerfen and Surmeier 2011; Hjelmstad 2004; Yin and Lovinger 2006). It has opposite effects on striatonigral pathway neurons, which express D1-type receptors, and striatopallidal neurons, which express D2 receptors (Gerfen and Surmeier 2011; Zhou and Lee 2011). By activating D1-like receptors, DA increases the responsiveness of striatonigral neurons to glutamatergic input, as well as its release of GABA at the axon terminal. By contrast, in the striatopallidal pathway, DA reduces the responsiveness of striatopallidal neurons to glutamatergic input, and reduces GABA release.

The known properties of BG synapses are in accord with the present model. Striatonigral synapses are facilitating. Each additional presynaptic spike in a train

produces a greater response postsynaptically. This pattern suggests nigral integration of the inhibitory input. On the other hand, pallidonigral synapses are depressing, suggesting integration of the excitatory (disinhibitory) input is possible (Connelly et al. 2010; Zhou and Lee 2011). The nigrotectal synapse appears to be neither facilitating nor depressing (Kaneda et al. 2008), so there does not appear to be a neural integrator in the tectum. This arrangement avoids having two integrators in the overall control loop, which can create undesirable oscillations.

SNr GABA neurons directly inhibit DA neurons in the SNc (Tepper and Lee 2007). Tonic firing of SNc DA neurons at a low rate is mediated by calcium entry through voltage-gated calcium channels, while burst firing requires glutamatergic inputs and the activation of NMDA glutamate receptors. In addition, reduced GABA release can also generate burst firing, so that disinhibition can produce burst firing in DA neurons (Kang and Kitai 1993; Paladini et al. 1999; Tepper et al. 1995). The DA neurons are therefore in a position to take the derivative of the GABA outputs from the BG. This is supported by the finding that, whereas most DA neurons are correlated with velocity and acceleration, GABA neurons are correlated with instantaneous position coordinates (Barter et al. 2015b). Due to GABAergic inhibition of DA neurons, the derivative of the GABA output is subtracted from the output of the DA neurons. This organization suggests a mechanism for adaptive gain control, in which the gain can vary according to the movement velocity. Anatomical studies have shown that nigral output can disinhibit SNc DA neurons that projection back to the striatum, thus forming a striatonigrostriatal loop (Haber et al. 2000). It could allow the rate of change in one controlled transition to adjust the gain for the same controller as well as a different controller.

20.5.4 Dopamine Depletion and Symptoms of Parkinson's Disease

The hypothesis that DA serves as a gain in the velocity controller sheds light on common symptoms in movement disorders. PD is associated with degeneration of the nigrostriatal DA pathway. A major consequence of DA depletion is bradykinesia or slowness in movement. Indeed, 6-OHDA, a toxin that kills DA neurons, dose-dependently slows down movement (Yin 2014a). Recent work also showed that DA depletion resulted in bradykinesia and abolished striatal representation of velocity (Panigrahi et al. 2015).

An important property of control system is that even a large reduction in gain will not necessarily result in system failure. To estimate the value of the controlled variable at steady state, we can use the equation:

$$p = r * g / \left(g + 1\right))$$

where p is the input variable controlled (e.g., movement velocity), g is the loop gain, and r is the reference. Assuming a loop gain of 100, then the controlled input

variable will reach about 99 % of the reference value. If the gain is reduced to 50, then controlled variable can still reach ~98 % of the reference. With half the gain, the steady state error increases from 1 to 2 %. The system still functions well. For the behavioral symptoms of DA cell loss to become apparent, there must be a large loss of DA signaling, even without taking into account compensatory changes in the postsynaptic neurons (e.g., receptor supersensitivity). Not surprisingly, the PD symptoms usually become obvious only after the loss of the majority of DA neurons.

Another prediction of the present model is that both amplitude and speed of movements will be reduced. For the sake of simplicity, let us assume a single input signal—a cortical command of 10 Hz for one second—entering the striatal unit. This signal generates ten spikes in output in 1 second. As a result of DA depletion, however, the striatal responsiveness to input is reduced. Consequently the striatal output, in the absence of DA, is 5 Hz. The total amplitude achieved by this specific command is reduced, as well as speed. The reduction in the total number of spikes leaving the striatal units corresponds to the reduction in amplitude, whereas the reduction in firing rate corresponds to the reduction in velocity. This is attributed to a reduced striatal output in response to cortical inputs. Alternatively, it is possible that some striatal neurons still fire as before, but the number of responsive striatal units is reduced.

The standard model predicts increased activity in BG output nuclei after DA depletion, which results in excessive inhibition of movement (DeLong 1990). Deep brain stimulation (DBS) treatment is supposed to reduce the excessive output from the DA-depleted BG, but there is little evidence supporting these claims (Vitek 2008). By contrast, the present model does not predict hyperactivity in the BG output nuclei, because the output firing rates represent position coordinates, not "actions." High firing rates in BG output neurons do not indicate that behavior is being inhibited, since what generates movements is a change in their firing rates. Average firing rates in any part of the BG are not meaningful measures. When the firing rates reflect position coordinates, which vary tremendously over time in a behaving animal, the mean rate over time is not at all informative. More informative is the variance in firing rate, which is a rough measure of movement (changes in position reference), but even a variance measure tells us little about the actual behavior. As already mentioned, coordinated changes (both increases and decreases) in multiple classes of neurons are needed. As the gain, DA can determine the rate of change in these signals.

20.6 How Can the BG be Commanded?

So far I have described how the BG circuit can implement transition control, using movement velocity as an example. Any reference signal entering the comparator function of the transition controller can command it to bring its perceptual input to the level specified by the reference. This is a key property of voluntary behavior.

In principle, there is no limit to the number of "purposes" or reference signals that any action can serve. The current model differs from traditional ideas on purposive behavior such as the ideomotor theory or purposive behaviorism (James 1890; Tolman 1932). Purpose, in this sense, is not a "cause" of action. A comparison between current input and reference is needed, so neither can be considered to be the cause of the behavioral output.

Where do higher reference signals come from? Anatomically, the major source of inputs to the striatum is the cerebral cortex. We can assume that the corticostriatal projections (and possibly the thalamostriatal projections) carry signals that reflect the purpose or reference signals for the transition controllers.

The purpose or higher reference normally follows "in order to," e.g., one walks in order to buy coffee. The corticostriatal projection can be seen as the anatomical substrate for where, in folk psychological terms, the will is translated into action. Thus the goal of behavior, whether to seek rewards and avoid harm, can be understood in the framework of control theory.

The corticostriatal projections come from virtually all areas of the cortex, including primitive cortical regions such as the basolateral amygdala and hippocampal formation (McGeorge and Faull 1989; Swanson 2000). To a large extent, they are organized topographically, so that the type of cortical signals that reach the striatum depends largely on the cortical location whence the projections arise. To understand these descending reference signals to the transition controllers, we must first examine the organization of the cerebral cortex.

20.6.1 Cortical Organization

The literature on the cerebral cortex is even more daunting than that on the BG. Only the most relevant features are considered here. As shown in Fig. 20.1, cortical projections from pyramidal projection neurons reach all levels of the control hierarchy (Shepherd 2013; Swanson 2000). This suggests that the cortex is in a position to command any level of the hierarchy by sending reference signals appropriate to that level, be it velocity, position, or force. Through learning, the connections between these projections and their targets can be strengthened, allowing recruitment of the appropriate set of controllers by higher levels.

The cerebral cortex can be divided along the central sulcus into an anterior part and a posterior part. Following the Bell/Magendie law that separates the sensory and motor components of the spinal cord, it has been argued that these two major divisions serve sensory and motor functions: the frontal areas serving motor or executive functions and the posterior areas serving perceptual functions (Fuster 1995). Such a distinction is based on stimulation experiments that reliably generate movements (Ferrier 1876). This is obviously true of the primary motor cortex, the major primary cortical area in the executive division of the cortex, but stimulation

of the primary somatosensory cortex is also known to generate movements (Matyas et al. 2010). The fact that stimulation of a particular brain area can generate movements is not particularly informative, because signals generated at any level of the control hierarchy, whether in the input, comparator, or output functions, can produce movements, so long as error signals are generated. Labels like sensory and motor are therefore not useful in describing components of control systems.

Nevertheless, the division between executive and perceptual function is still a useful starting point, because a different interpretation of this division can be given in view of the types of signals that can reach the striatum, where the comparator functions are found. In general, the posterior perceptual division contains projection fields of most sensory inputs, while the executive division contains the motor cortical areas with the strongest descending projections to the brainstem and spinal cord premotor and motor neurons. When we consider the striatal targets of these corticostriatal projections, an interesting pattern emerges. Both perceptual and executive divisions of the cortex project extensively to the striatum (McGeorge and Faull 1987, 1989). For example, the sensorimotor striatum (putamen in primates) receives massive inputs from both primary motor (executive) and primary somatosensory (perceptual) cortices. In fact, there is no striatal region that only receives perceptual or only executive inputs.

Moreover, the corticostriatal projections are not only topographically organized, especially those to the sensorimotor striatum, but can be divided according to the general type of cortical area whence they originate (i.e., primary or higher order neocortex or limbic cortex). Thus sensorimotor striatum receives inputs mainly from the primary executive and perceptual regions for the kinesthetic (proprioceptive and somatosensory) senses, whereas the associative striatum receives inputs from the higher order or association cortices.

If the striatum contains comparator functions for the transition controller, then clearly these two cortical divisions are in a position to provide the input function and reference signals for the comparator function in the transition control system (Fig. 20.8). The frontal executive division appears a major source of reference signals, whereas the perceptual division can supply the perceptual inputs.

For example, stimulation of the prefrontal region traditionally called the frontal eye field can produce eye movements and turning towards the opposite side. In addition to the striatum, where the transition comparator is located, this area projects to the intermediate layers of the visual tectum, where the visual position (orientation) comparator is located (Helminski and Segraves 2003; Schiller et al. 1980). The comparable area in rodents also appears to be critical for producing the reference signal for action (Erlich et al. 2015; Hanks et al. 2015). Posterior perceptual cortices can also send projections to lower levels, but they generally enhance the gain of perceptual functions, in a top-down manner. For example, visual cortical projections to the tectum can alter gain of tectal input units (Zhao et al. 2014). In cases when they evoke movements, they probably do so by introducing an error in the control system through the perceptual input (Colby and Goldberg 1999).

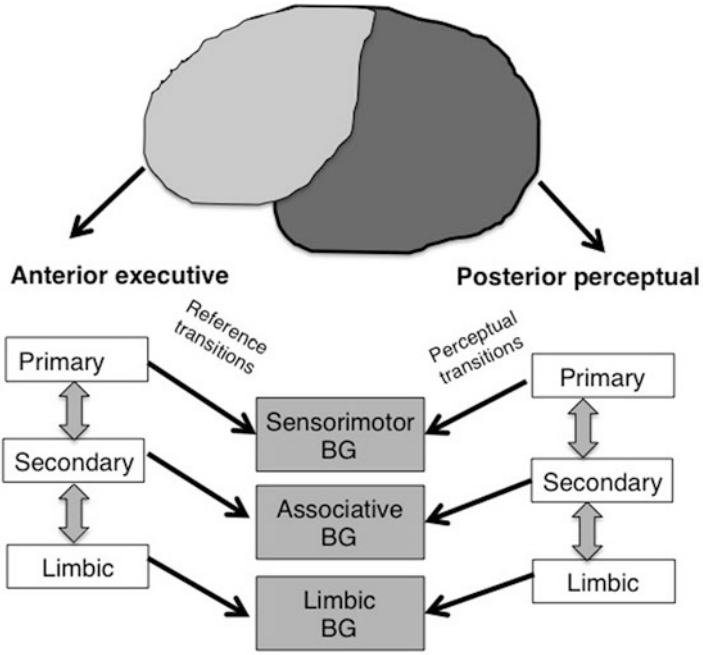

Fig. 20.8 Organization of corticostriatal projections. The anterior executive division is the source of the reference signals to the transition comparators in the striatum, whereas the posterior perceptual division is the source of perceptual inputs. There may be some exceptions, e. g., when arbitrary stimuli are predictors or discriminative stimuli (e.g., red light), so that their cortical representation can also serve as reference signals to the velocity controller after learning has occurred. *BG* basal ganglia

20.6.2 Goals and Perceptual Representations

Although all negative feedback controllers can be considered teleological and purposive, the lower level reference signals for variables such as muscle tension, length, or body temperature are not readily available to conscious awareness. They are not the same as the folk psychological notion of purpose. At the transition level, however, the signals usually represent the goal or purpose of behavior.

It is important to emphasize that goal representations are perceptual representations, however abstract they may be. At any time, only a few perceptual representations at the cortical level serve as reference signals, but any perceptual representation can in principle become a goal of behavior. Goals which change reference signals to transition controllers are acquired through experience. For example, animals are born with certain crude taste preferences, determined by innate but modifiable reference settings of energy homeostasis, but their preference for specific foods is acquired rapidly through experience. Once incentive values are assigned to specific food memories, these become potential sources for reference signals given the

appropriate error signals (motivational states). Such reference signals may even become independent of the innate homeostatic errors, but only to a limited extent in most cases.

This raises the question of how a specific reference signal corresponding to a behavioral goal is retrieved. There are two related mechanisms for goal retrieval, which I will call intrinsic state selection and associative selection. In intrinsic state selection, a change in motivational state produces error in homeostatic controllers for variables essential for survival. What is commonly called hunger originates mainly from the error in energy homeostasis. Through reorganization, this error recruits the most effective controller for reducing its error. For example, when random variations in synaptic strength in the projection from the error resulted in a strong response in some comparator function, the error reduction can stop the variation and thus save the new setting. This reorganization process is responsible for linking various food and flavor representations, which predict error reduction in energy homeostasis, with satisfaction of hunger (error reduction). In addition, the overall activation of all executive and perceptual systems is regulated by the reticular activating system, which is also sensitive to the internal states of the animal. Note that all these variables are related to the homeostatic controllers for essential variables, which are genetically specified. Specific objects and places acquire incentive value that become independent of errors in the primary homeostatic controllers. The related processes of evaluative and incentive learning cannot be discussed in any detail here (Balleine 2001). For our purposes, it suffices to assume that, as a result of these processes, specific objects in the environment can be represented, and their representations act as reference signals, with the type of comparison process characteristic of all negative feedback control systems.

In associative selection, perceptual inputs that predict the outcome will activate the goal representation. A predictor of chocolate will activate the chocolate representation, which becomes a potential goal of behavior. This type of association formation has been studied mainly in the form of Pavlovian conditioning (Pavlov 1927), and it is commonly assumed that an association has been formed between the stimulus and outcome. Both are of course perceptual representations. As a result of learning, the control apparatus that controls the goal or outcome perception is activated by the predictor (Yin 2013, 2014b). This process of association formation allows any perceptual signal to activate the relevant controllers, even in the absence of the intrinsic error signals due to changes in motivational states.

20.6.3 Imagination

If the reference signal to the transition controller is itself some form of acquired perceptual representation, then why isn't it always manifested in actual behavior? What happens if two or more such representations are evoked and a decision must be made? How can we generate the perceptual experience of the goal (e.g., chocolate) when we desire it, in the absence of any chocolate in the immediate environment? To address

these questions, it is necessary to describe a key function of the control hierarchy, namely imagination.

Like control, imagination has a technical meaning. In the imagination mode, a control system sends a copy of its output signal back to its own perceptual input function (Powers 1973a). The ascending inputs to higher level input functions are transiently blocked; the reference signal is largely responsible for the error and output. The controller therefore receives a perception of its reference condition. Yet this does not result in overt behavior. Either the order is not sent or, in the more likely scenario, it is cancelled at lower levels. The imagination mode allows the organism to experience its own goals virtually, by replaying the perceptual memory of the feedback associated with the requisite actions, without generating the behaviors output. Only the higher levels are active in a simulation of action, while the lower levels are suppressed. According to the present model, the imagination mode characterizes the transition level of the control hierarchy. To imagine is to simulate change in perceptual representations. It is especially prominent in exteroceptive perceptions, which are time varying, usually available to consciousness, and capable of being retained as memories in the perceptual system.

In the absence of any actual perceptual input from the lower levels, i.e., without any sensory inputs related to chocolate, the perceptual units can be activated by desire alone. Even when there is no chocolate, the reference unit representing chocolate can become active. In addition to perceiving its own reference condition, the imagination mode can also retrieve all perceptual memories that are associated with the reference signal, because the relevant reference signal can be used as an associative address for memory, i.e., part of the memory serves as the address for the whole (Powers 1973a). When the address is activated, all relevant memories can in principle be simultaneously retrieved, which means that potentially all matching perceptual functions can be experienced. The vividness of the perceptual experience depends in part on the extent to which lower levels of perceptual processing can be engaged. This is the basis for common errors in memory and the phenomenon of false memory. The same higher order perceptual channels are activated by imaginative recall as by actual perception, which is why one cannot imagine and perceive the same object at the same time.

The imagination mode plays a key role in what is commonly called remembering, which reflects the action of the transition controllers in the imagination mode. The perceptual experience that results is primarily guided by some reference signal corresponding to a specific desire. This mechanism is used to recall past memory that has been stored, to plan a sequence of reference signals before action (Konorski 1967), and to maintain recent perceptual inputs online. This latter capacity is usually called working memory (Baddeley and Hitch 1974). Baddeley was right to emphasize, at least in humans, the phonological loop and the visuospatial sketchpad, as the means by which the perceptual signals are maintained online. The phonological loop relies on imaginative repetition of auditory feedback; the visuospatial sketchpad on imaginative repetition of visual feedback, active manipulation of visual perception being similar to imaginatively sketching a scene.

The imagination mode is responsible for generating an internal model of the environment. Curiously, in part due to earlier conceptual confusions, the idea of an

internal model is often associated with motor control, where it is not needed (Ashby 1958). The perceived need for calculating inverse kinematics and predicting consequences of actions, so commonly assumed in modern theories of motor control, is due to the mistaken reversal of the organism/environment relationship in the systems analysis mentioned earlier (Wolpert et al. 1995). Hierarchical negative feedback control does not require this type of internal model at all (Yin 2013).

The persistent failure of internal models in motor control, however, does not mean that such models do not exist. Internal models are critical not for control per se, but for evoking and selecting the desired outcome, for selection of the appropriate controller in decision-making, for maintaining the relevant information online to initiate control action at the appropriate time, and for determining the sequence of activation of different controllers (Craik 1947). For these functions, there is indeed a need to predict sensory consequences of actions at the transition level. But such internal models consist of imaginary perceptual inputs, generated by the transition controller addressing and by feeding back sequences of perceptual signals. The contents of such models are readily available to consciousness.

Clearly planning is important for adaptive behavior, but the key question is exactly what can be planned. According to the present model, the content of plans consists of reference signals specifying perceptual inputs. Detailed values reporting limb positions are not needed when we plan a stroll in the park. While imagined outcome is critical for any type of planning before the action, when it is engaged during the actual action it can only interfere with performance. The relevant perceptual channels, as noted above, can either be perceptually activated or imaginatively activated, but not both.

The imagined outcome is similar to outcome expectancy in the animal conditioning literature (Dickinson 1989; James 1890). Through learning, perceptual representations associated with the desire can also act as reference signals. In this case, another associative address (predictor) is created using the existing associative address (outcome). Any perceptual representation at the cortical level can initiate action of the appropriate transition controllers. For example, the behavior of stepping on the brakes can be produced either by the desire to stop the car or by the red light. Note, however, that these are not causes in the sense of linear causation, as they effectively activate specific reference signals, rather than the actual behavioral outputs.

To summarize, the imagination mode has three major functions: (1) recalling past memory for use, as potential reference signals; (2) simulating behavioral feedback, allowing one to plan actions ahead of time; (3) keeping relevant signals online simply by repetition of the imagination mode, which is usually transient.

20.6.4 Neural Implementation of the Imagination Mode

The imagination mode of transition control also requires the cortico-BG networks. The velocity controller described earlier is the highest level of the motor hierarchy. As we shall see, there are still higher levels, but the hierarchical relationship above the transition level is labile and flexible.

The frontal executive division is hypothesized to contain reference units, which can serve associative addresses for different goals. It is critical for selection of the appropriate reference signals in store (Badre and Wagner 2007; Fuster 2001). These can activate all relevant perceptual memories in a widely distributed network, especially in the posterior cortical division (association cortices).

Detailed perceptual representations are retrieved via the imagination mode. This is achieved either through the long-range projections between cortical areas or through the reentrant projections back to the cerebral cortex from the thalamus and the BG. Here it is assumed that the BG network is engaged whenever the perceptions depend on controlling or manipulating perceptions with self-initiated action. Thus, falling rain is a simple visual transition that may not engage the BG, but the perception of how the visual feedback changes as one walks down the hall will require the activation of the relevant controllers for orientation, body configuration, and locomotion. Considering how common the latter example is, it is safe to assume that the imagination mode usually relies on the BG circuits. For example, working memory tasks typically activate the prefrontal cortex as well as its striatal target regions (Levy et al. 1997). Planning and working memory can also be impaired in PD (Morris et al. 1988; Owen et al. 1997).

20.6.5 Action Observation and Simulation

There is an extensive literature on the neural basis of action observation, action simulation, and mental rotation. So-called mirror neurons, found in the premotor cortex, are activated during action performance and action observation (Rizzolatti and Craighero 2004). Human imaging work also showed that action observation activates premotor and parietal areas in a somatotopic manner (Buccino et al. 2001). According to the present model, this is not surprising because these cortical areas send reference signals to the striatal comparators, thereby commanding the transition controllers, whether in the performance mode or in the imagination mode.

The best illustration of the imagination mode comes from studies of mental rotation. In the classic task devised by Shepard: "all subjects claimed (1) that to make the required comparison they first had to imagine one object as rotated into the same orientation as the other and that they could carry out this 'mental rotation' at no greater than a certain limiting rate; and (2) that, since they perceived the two-dimensional pictures as objects in three-dimensional space, they could imagine the rotation around whichever axis was required with equal ease. The reaction time to determine whether two line drawings of objects are identical is a linearly increasing function of the angular difference in their orientations" (Shepard and Metzler 1971). Mental rotation of perceptual images requires manipulation of the corresponding cortical representations. For example, mental rotation of branching objects engendered activation in the parietal lobe and visual association cortex, whereas mental rotation of hands is associated with primary motor cortex activation (Kosslyn et al. 1998). These are examples of imagined visual image feedback and kinesthetic feedback.

There is evidence suggesting that mental and motor rotation use the same systems (Pellizzer and Georgopoulos 1993; Wexler et al. 1998). When subjects were tested on mental rotation while performing simultaneous motor rotation, motor rotation that is compatible with mental rotation results in faster times and fewer errors in the imagery task than when the two rotations are incompatible. A change in the speed of motor rotation can correspondingly slow down or speed up simultaneous mental rotation.

Human imaging studies of mental rotation reported activation of motor and premotor areas, parietal regions, as well as BG regions like the striatum (Alivisatos and Petrides 1997; Cohen et al. 1996). The critical role of the BG is also supported by the slowed mental rotation in PD patients (Amick et al. 2006; Lee et al. 1998). The rate of change in perceptual variables during mental rotation is comparable to that during physical location, because in both cases the same transition controllers are used. The key difference is that there is probably suppression of motor output at lower levels in the case of imagination. In short, the BG control perceptual transitions whether in actual performance or in imagination. The reentrant projections from BG outputs to the thalamocortical network are assumed to be critical for this process.

20.7 Cortico-BG Networks

Traditionally, three major striatal areas have been classified—limbic (ventral), associative (dorsomedial/dorsocentral), and sensorimotor (dorsolateral)—based on their anatomical connectivity. Behavioral tests have also revealed considerable functional heterogeneity in these regions (Rossi and Yin 2011; Yin et al. 2008, 2009). Each of these areas can be further subdivided. For example, the ventral striatum has the core, shell, as well as olfactory tubercle, each area characterized by distinct anatomical connectivity patterns. As more is learned about the organization of the cerebrum, additional areas are also classified as BG. For example, the ventral striatum, as well as related output nuclei such as the ventral pallidum, including the substantia innominata, was added to the BG circuits (Heimer et al. 1982). Swanson proposed to include several additional areas, which are often called the extended amygdala, to the BG circuit (Swanson 2000). The input nuclei of these BG circuits include the medial and central amygdala, the lateral septal nucleus, and olfactory tubercle, and the output nuclei include the bed nucleus of stria terminalis, and medial septum/diagonal band of Broca.

It is hypothesized that different cortico-BG networks control different types of transitions. They can be classified according to the content of the signals sent via the corticostriatal projections. Thus the brain proper can simply be viewed as a collection of transition controllers. This calls for a classification of perceptual transitions.

We can sort different perceptual transitions according to proximity of the relevant environmental stimuli, ranging from interoceptive inputs from inside the body,

to distal inputs with sources that are miles away. Different sensory receptors are required to detect these changes, and different effectors are often required to control these changes. For example, an increase in heart rate is the means by which the nervous system regulates blood flow to different parts of the body. At the other extreme, running is the means by which a visual image of the prey is controlled.

So far I have only discussed the role of the sensorimotor striatum and associated circuitry in velocity control. Movement velocity is tantamount to rate of change in proprioceptive configuration perception. The primary motor cortex, for example, sends projections that convey higher order proprioceptive signals. There are many different types of perceptual transitions. For example, "movies" are literally moving visual configurations. In addition, there are transitions in relationships, e.g., the distance between the self and target. Sequence, too, can be viewed as a higher order transition.

All negative feedback controllers are alike in the basic elements of the loop, but they differ in the types of signals they process. There are three key questions:

1. What is the controlled perceptual variable? This question is about the specific sensors used and their higher order perceptual representations.
2. What is the behavioral output that must ultimately be varied to control this variable? This question is about the nature of the feedback function, the relationship between output and input.
3. What types of reference signals must be generated to command the requisite lower level controllers?

Distinct cortico-BG networks are responsible for independent control of these variables. To give an exhaustive account of the functions of the different cortico-BG networks would require a comprehensive account of brain function, which is not feasible here. Nevertheless, it is instructive to consider the major types of transitions and how different transition controllers are implemented by different cortico-BG networks. Below I will briefly describe the three commonly classified networks: sensorimotor, associative, and limbic. I will not attempt to provide a definitive classification of the networks here, for too much remains unknown. Rather, the aim is to show how the present model can shed light on functional specialization in cortico-BG networks.

20.7.1 Sensorimotor (Somatic) Network

As described early, the sensorimotor striatum is a key part of the velocity control system. The controlled variable is the rate of change in body configurations. Its outputs represent velocity errors that can be transformed into position reference signals. Because the corticostriatal projections are topographical, different areas within the dorsolateral striatum correspond to different parts of the body (Alexander et al. 1986; Carelli and West 1991).

This network's primary function is the control of proprioceptive transitions, because the perceptual inputs largely represent movements produced by the skeletomotor system. It is in a position to be used by hierarchically higher systems. In addition,

this network may also control "relational variables," such as the distance between self and target, and the serial order of specific transitions (Rothwell et al. 2015; Yin 2009, 2010. Broadly speaking, this network is necessary for what is known as internally generated or self-initiated movements.

20.7.2 The Associative Cortico-Basal Ganglia Network

The associative striatum (roughly caudate in primates and dorsomedial striatum in rodents) receives massive inputs from association cortices such as prefrontal and posterior parietal areas (Divac et al. 1967; McGeorge and Faull 1989). Unlike the kinesthetic inputs to the sensorimotor striatum, these inputs are exteroceptive, representing physical changes that are farther away from the animal. The association cortices can represent exteroceptive sequences, whole field motion, and complex configurations of objects. This network plays a key role in orientation control (Hikosaka et al. 2000). Whereas the tectal orienting controller is capable of orienting towards salient stimulus, without descending reference signals it is incapable of selecting any arbitrary location detected by the exteroceptive senses and move the sensors toward that location (Mizumori et al. 2000). For example, rats with unilateral striatal lesions were impaired when approaching the side contralateral to the lesion. This explains the symptoms of neglect when parts of this network are damaged (Brasted et al. 1997).

The entorhinal inputs and posterior parietal projections to the associative striatum are responsible for the spatial inputs, whereas areas like the inferotemporal cortex can provide the relevant object representations. The key controlled variables in the associative network are exteroceptive transitions, and the outputs can reach any needed controllers for movement, including the sensorimotor network. Feedback from the distal senses and the locomotor pattern generators can independently or jointly activate the comparators in the associative network. For example, the type of feedback provided by a virtual reality setup or a video game will strongly engage this network. Finally, because the content of imagination is dominated by exteroceptive representations, the associative network is critical for the imaginative mode.

20.7.3 Differences Between Associative and Sensorimotor Network

The sensorimotor network uses an egocentrically based reference frame in changing the body configuration. But the associative network can be considered "allocentric," i.e., based on external features of the environment, e.g., landmarks. This difference can be illustrated with the "place/response" task. On this task, rats learned to find food at the end of either the left or right arm on a T-shaped maze. One probe trials, the maze is reversed, so that to reach the correct arm, the animal has to use the

spatial landmarks rather than the remembered direction of turning (Restle 1957). The use of the place strategy relies on exteroceptive cues in relation to one's body, whereas the response strategy uses egocentric coordinates (left turn or right turn). Hippocampal lesions impair place strategy (Packard 1999; Packard and McGaugh 1996). The associative striatum is also critical for the implementation of place strategy (Yin and Knowlton 2004). This distinction between allocentric and egocentric cues reflects the different perceptual input functions for the orientation controller commanded by the associative network and the body configuration controller commanded by the sensorimotor network (Yin and Knowlton 2004).

Running on a treadmill can have high movement velocity. Even though one is not going anywhere and the exteroceptive inputs do not change much, the proprioceptive transitions feedback indicates how quickly the body configurations change. However, sensed motion with respect to some external landmark usually relies on visual feedback, e.g., when one is riding in a train. The strength of visual motion signals will create the sense of how fast one is moving. These two types of feedback illustrate the key difference between the sensorimotor proprioceptive transition controller and the associative exteroceptive transition controller.

In addition, the associative network has been associated with the "goal-directed" action system, whereas the sensorimotor network with the "habitual" system (Yin and Knowlton 2006). This dissociation is primarily based on results from devaluation tests. Usually hungry animals are first trained to press a lever for food reward. Once trained, the incentive value of the food can be manipulated by pre-feeding, so that the animal no longer desires the food. But when tested on a probe test, conducted in the absence of reward feedback, the rate of lever pressing is not always reduced by the devaluation treatment, and such variations in sensitivity to devaluation vary depending on the amount and type of training (Adams 1982). According to the model proposed here, devaluation reduces the reference signal from a higher lever controller for the rate of reward, the key controlled variable in instrumental conditioning (Yin 2013).

In instrumental actions, it is necessary to use one type of feedback (rate of pressing) to control another type of feedback (rate of reward). To couple two independent transition controllers, the error in one rate of change changes the reference in another rate of change. As the animal gets sated, less reward is desired, and less reference signal is sent to the system controlling the rate of pressing. This account predicts reduced pressing following devaluation, which is usually found. With habit formation, however, there is increasing reliance on the feedback associated with the performance of the action, such as proprioceptive and somatosensory inputs associated with the movement and touch of the lever. In addition, representations of discriminative stimuli (e.g., sight of the lever) can alter the reference signals sent to action controllers. In other words, this type of control relies on a different type of perceptual feedback, so that the action sequences are more efficiently performed. Any change in the reference signal in the reward rate controller (i.e., reduced desire for the food reward) does not have a direct impact on the output from the sensorimotor network. For the same reason, in experienced drivers, the action of stepping on the brakes when seeing a red light cannot be easily reduced even if they are told that doing so will result in a penalty.

Thus the difference between actions and habits can be explained by the hierarchical relationship between the associative and sensorimotor networks. With habit formation, there is enhanced reliance on local action feedback rather than higher level reward rate feedback control systems. This account is supported by lesion experiments. Excitotoxic lesion or inactivation of the dorsomedial striatum results in lever pressing that is impervious to changes in outcome value or action–outcome contingency, in the absence of the reward feedback (Yin et al. 2005), even after training that generates devaluation-sensitive performance in control animals. In addition, the lesioned rats also failed to show sensitivity to degradation of the action–outcome contingency, which is really a feedback function relating rate of reward to rate of action (Baum 1973). By contrast, lesions of the dorsolateral or sensorimotor striatum can produce the opposite effect, rendering behavior sensitive to devaluation even when the training generates goal-directed performance in controls (Yin et al. 2004).

20.7.4 Limbic Network: Nucleus Accumbens

The associative network moves the organism toward any exteroceptive perceptual stimulation it desires, and the sensorimotor network achieves the actual movements by controlling for the appropriate perception of body configurations. In both cases, there is control of input, but they differ in the type of input variable controlled and thus in the behavior achieved. But there remains the question of what the animal wants, and how such wants can be satisfied.

We assume that there are genetically specified reference signals for essential variables (Ashby 1960). When the value of an essential variable deviates from the reference value, error signals are generated. Just like peripheral perceptual signals, these are represented at progressively higher levels of the hierarchy. The limbic cortical projections come from the basolateral amygdala, insula, orbitofrontal, and other areas and reach the ventral striatum (Nauta et al. 1978). These projections convey information about interoceptive states, including motivational states. Both cortical projections and brainstem projections (e.g., parabrachial nucleus) sending visceral inputs can reach the ventral striatum (Norgren et al. 2006a; Prinssen et al. 1994; Smith 2004). The outputs are directed at the ventral pallidum (substantia innominata) and areas like the hypothalamus (Swanson et al. 1984; Swerdlow et al. 1984).

The controlled variables of the limbic networks are related to internal and proximal perceptual inputs. In consummatory behavior, the controlled variables include food flavor, smell, and texture. Taste, for example, can be considered an interoceptive sense, associated with visceral reactions in the body. Compared to smell, large quantities of the same substance are required to produce the sensation of taste, i.e., when the substance in question has already reached the organism. The behavioral outputs are the sympathetic and parasympathetic responses, which bidirectionally adjust energy expenditure, as well ingestion-related movements that propel ingested

substances in either direction. The sense of smell, on the other hand, has an exteroceptive component, which contributes to sensing substances far away, and an interoceptive component, the retronasal component that contributes to the integrated sense of flavors.

The limbic networks can also control the rate of change in other interoceptive inputs related to reproductive, social, and defensive behaviors. For example, pheromone receptors in the accessory olfactory bulb (a cortical region) project to the medial amygdala (a striatal region), and this circuit could be important for social and reproductive behaviors (Swanson 2000).

Here I will only discuss two major types of controllers in the limbic network, namely proximity control based largely on the sense of smell, and flavor control using smell and taste. The output function for proximity control is mainly the locomotor system, and for flavor control orofacial movements including licking and chewing.

20.7.5 Proximity Control

The consummatory phase of behavior can be triggered by taste stimulation in the mouth. But unless the food is placed in the mouth, this is rarely the initial component of the behavioral sequence in any natural environment. In order to initiate the consummatory phase of behavior, it is necessary to bring food to the mouth. And in order to obtain food, it is necessary to find it, in most cases relying on smell and vision. In a primitive organism devoid of vision or hearing, the sense of smell is critical. Even the simplest organisms possess some chemical senses, and are capable of ascending and descending a chemical gradient. Thus the behavior varies to reach a specific proximity reference. This is proximity control.

The chief means by which proximity is controlled is progression or retreat. The chief sense required is smell, especially in animals with poor vision. Smell is an intensity signal that can be controlled by sensing more or less of it. One can increase the intensity by moving towards the source and decrease it by moving away. There is therefore bidirectional control of the concentration of odor molecules sensed.

Herrick called the ventral striatum the olfacto-striatum (Herrick 1948). While olfactory inputs are certainly not the only inputs to the ventral striatum, in most animals olfaction is a critical sense used for proximity control. There are strong inputs from the olfactory association cortex in the piriform area to the olfactory tubercle, a part of the ventral striatum that has been neglected, and less extensive to other parts including the accumbens core and shell (McGeorge and Faull 1989).

The output of the proximity controller must command the locomotor system, probably via the ventral tegmental area (Swanson and Kalivas 2000; Wang and Tsien 2011). The VTA sends both ascending DA projections to the ventral striatum and descending projections to the MLR (Rolland et al. 2009; Ryczko et al. 2013). The prefrontal cortex, part of the executive division that stores the relevant reference units, can directly activate the midbrain DA neurons to increase locomotion (Kim et al. 2015). This system is turned on by psychostimulants (Pierce and Kalivas

1997), which are known to increase locomotion dramatically as well as to generate sniffing and orofacial movements.

More advanced than the chemical gradient constructed from the sense of smell is the related representation of space. Spatial perception relies on visual and vestibular inputs, used in computations like path integration (Whishaw 1998). The dorsal hippocampal-subiculum complex and the retrosplenial and anterior cingulate cortical areas are critical for navigation and exploration (Fanselow and Dong 2010). These areas also project directly to the limbic striatum, especially the nucleus accumbens core. Exploration involves systematic variations in proximity control reference signals with respect to any novel aspects of the environment. These regions also project to parts of the dorsomedial striatum, where the associative network and limbic network overlap.

20.7.6 Consummatory Network

During food ingestion, taste is acquired by movements of the tongue, and retronasal stimulation, the interoceptive component of smell, is generated as volatile molecules from the food move from the back of the oral cavity to the olfactory epithelium (Shepherd 2006). A configuration of taste and smell combine to form a given flavor that is associated with specific foods. This is a high level perception that allows the animal to identify specific foods. The flavor of chocolate, for example, is a complex configuration. Such perceptual variables are controlled primarily through orofacial movements, e.g., movements of the tongue, the key sensor for taste. These movements can "center" the sensory stimuli by moving food and liquid to the right location, much like visual foveation or grasping.

The accumbens shell and surrounding regions are striatal components of a flavor controller. Perceptual variables controlled by the consummatory network are usually related to taste and smell. The outputs from the accumbens are implicated in a variety of orofacial behaviors, including licking and eating, as well as related behaviors like sniffing (Bassareo and Di Chiara 1999; Gutierrez et al. 2006; Tellez et al. 2012).

20.7.7 Reward and Aversion

A vast literature has implicated the limbic cortico-BG network in reward. The limbic network, more specifically the nucleus accumbens and its mesolimbic DA innervation, is thought to be a 'reward center,', based on two classes of observations: (1) lesions of these areas reduce seeking or consumption of rewards and (2) neurons in these areas are often activated during reward-guided behavior.

Recall that any controlled variable is assumed to be one-dimensional, which can be represented well by firing rate as an analog signal. For any controlled variable, two types of output functions are needed, one for increasing the value and the other

for decreasing it. For example, in temperature control, the heating unit and the cooling unit are separate. In the autonomic nervous system, the distinct functions are usually accomplished by the sympathetic and parasympathetic systems, e.g., increasing and decreasing heart rate. For the control of flavor, which is a form of chemical sense, there are two major outputs: either to acquire more of the flavor, e.g., by protruding the tongue, or to reject the food in question, e.g. to spit it out.

Sweet and salty solutions can elicit rhythmic mouth movements followed by tongue protrusions (Grill and Norgren 1978a, b). Bitter solutions with a high quinine concentration elicit gapes, chin rubbing, head shaking, face washing, forelimb flailing, and paw pushing. In response to orally injected taste stimuli, chronic decerebrate rats showed a similar pattern. In contrast, all taste stimuli elicited rejection sequence from chronic thalamic rats, and the ingestive sequence was absent.

The ingestive sequence is associated with the appetitive system and the rejection sequence with the disgust system. Thus, from an analysis of consummatory behavior we can see the operation of the dichotomy between liking and disgust, reflecting the underlying process of bidirectional control. From the present perspective, both reward and aversion are inadequate concepts, because they do not suggest any model that can generate the full range of behavioral phenomena. Operationally, reward is consistently used to refer to whatever the animal wants more of. Aversive stimuli are what the animal wants less of. Why should the mouse want sucrose but reject quinine? Why should the same food be rewarding when the animal is hungry but aversive when it is sated? Traditional models simply do not address these questions at all, because they do not contain internal reference states. The concept of reward is too vaguely defined to be useful (Schultz 2012). Only by comparison with the reference can something be "too much" or "not enough." These are the error signals that generate distinct behavioral outputs that change the variable in question in opposite directions.

There appears to be an innate preference for sucrose, as predicted by sweet taste. Bitter taste, which predicts toxic substances harmful to the body, is not tolerated. These innate preferences reflect genetically specified reference signals, but they are not absolute. They can be modified by learning, and the reference signals themselves change as the motivational states change (Berridge and Kringelbach 2015). A high concentration of NaCl, for example, generates rejection behaviors normally, but ingestive behaviors after sodium depletion ("hedonic alliesthesia shift"). Lesions of the ventral pallidum, part of the limbic circuit, can change the reaction from positive to disgust (Castro et al. 2015). On the other hand, high salt concentration can recruit aversive reactions, but such reactions can be abolished selectively via genetic manipulations, so that only appetitive reactions are elicited (Oka et al. 2013).

Appetitive reactions are outputs with feedback functions that increase the perceptual input, and disgust reactions do exactly the opposite. Satiety reduces the error signal, and the appetitive reaction that is driven by it. Deprivation will differentially activate the appetitive system and suppress the disgust system. This account can easily lead to a model that shows exactly the types of shifts in hedonic impact to sweet and salty foods as observed empirically.

Whenever an error signal increases in some essential variable controller, the reduction of that error is rewarding. More broadly, appetitive systems are seeking systems, whereas disgust systems are avoidance systems. These control systems may be found at every level of the hierarchy. But the difference is that at the cortico-BG level, there is representation of global variables such as food flavors and smells.

20.7.8 Mesolimbic Dopamine

The above account allows an extension of our hypothesis for DA function to the limbic domain. The DA projections adjust the gain of the transition controllers for gustatory as well as proximity inputs. The ventral striatum also receives major DA projections, but mainly from the VTA. For decades it has been widely accepted that dopaminergic signaling in the accumbens encodes reward. But no study ever monitored preparatory approach movements or orofacial movements in relation to DA firing.

Just because accumbens DA is correlated with sucrose concentration does not mean that DA is an index of reward value (Norgren et al. 2006b). Previous interpretations fail to take into consideration the obvious confounding contribution of movement. Instead, we hypothesize that it is not reward delivery per se, but the signals used to generate the actions to control the rewards, that are represented by DA. Thus DA can act as the gain for the ingestive control system, which controls variables such as flavor and determines the rate of ingestive behaviors (Roitman et al. 2004).

For example, DA antagonists can reduce lick force, duration, and tongue, as well as the number of licks in a bout and the number of bouts (Fowler and Mortell 1992). By contrast, DAT KO, which increases and prolongs DA signaling by abolishing reuptake mechanisms, resulted in the opposite pattern—increasing the number of licks within a bout, as well as prolonging the bouts and the individual contact duration (Rossi and Yin 2015). These results suggest that DA increases the gain of the controller for ingestive behavior through licking. Increasing DA signaling increases the gain of a control system for the rate of reward. The rate of reward is measured as the rate of gustatory inputs, including flavor and perhaps proprioceptive feedback from the orofacial musculature. Although the licking pattern is stereotyped and generated by brainstem nuclei, the signal that initiates the bout is prolonged. Retraction time is decreased as the contact time is increased, with a net increase in "duty cycle."

On the other hand, DA signaling is not restricted to appetitive behaviors (Horvitz 2000). Distinct populations of DA neurons can modulate the gain of distinct output functions that permit bidirectional control of the value of the same variable. The effect of DA on proximity control and flavor control is then analogous to its effect on movement velocity control (Kim et al. 2015). In velocity control, there are antagonistic systems that can generate movement in different directions. In flavor control, there are antagonistic output systems that move the tastant in different directions.

20.8 Integrative Action of the Cortico-Basal Ganglia Networks

The cortico-BG networks share a similar motif: excitatory inputs from cortical modules corresponding to acquired reference signals. Anatomically, there are multiple ways for these networks to interact (Haber and McFarland 2001; Haber et al. 2000; Joel and Weiner 1994). In addition to the motor hierarchy from tension control to velocity control, these parallel networks form an additional labile motivational hierarchy. To understand the difference between the relatively fixed motor hierarchy and the more labile motivational hierarchy, we must analyze the feedback functions involved.

The feedback function defines the effect of behavioral output on the perceptual inputs. It is neglected by traditional analysis, which assumes a passive organism that is merely acted upon, but exerts no effect on its own perception. Different effectors are typically associated with different feedback functions, on account of their physical effects in the environment. For example, the tension sensed by the Golgi tendon organ is a function of muscle contraction. The feedback function is usually fixed in polarity: more contraction, more tension. This is true of the lower levels of the motor hierarchy. Similarly, muscle stretching increases spindle output.

The polarity is fixed at the lower levels because the environment defined by their feedback functions is a very small part of the larger physical environment—proximal to, or simply a part of, the organism. The stability of the causal relationship and the polarity has resulted in phylogenetic development of innate settings for the relevant control systems. Experience-dependent modifications of the system parameters are possible, but they are minor (Weiss 1941). A key property of these lower systems is that, on account of their innately specified reference settings, they cannot adapt to a reversal in the polarity of the feedback function. For example, one cannot learn to sweat in order to stay warm, because sweating is a part of the output function for cooling or lowering the body temperature. Nor is choice or decision-making applicable at these levels.

Ascending the hierarchy, the relevant feedback functions begin to change. The environment defined by the feedback function becomes larger; between action and perception there are more intermediate steps. The feedback function can become complex and arbitrary, subject to change from moment to moment. Optic flow, for example, may be affected by locomotion in a predictable way in most environments, but the feedback function is not fixed in polarity. The opposite relationship could be arranged arbitrarily, or there could be the same feedback independent of locomotor output, as when one is on a train. For proximity control, it is usually the case that as objects remove away, to reduce the error the progression system is engaged to move one forward. The innate settings indeed show this, so that a reversal in polarity does not alter the behavioral output in the absence of new learning and adaptation (Hershberger 1986; Schwartz and Gamzu 1977). But in order to show adaptive behavior following a reversal in the feedback function polarity, e.g., retreat to get closer to goal, higher levels are needed to recruit and command the opponent output system, while suppressing the innately connected output function.

No phylogenetic setting suffices to produce adaptive behavior in the face of uncertainty in the environment. The feedback function between pressing a lever and food, for example, is arbitrary and unstable. Likewise, I can raise my hand to achieve any number of "results," e.g., to ask a question or to vote. To adapt to these feedback functions (new action–outcome contingencies), learning is needed.

On the other hand, there is a natural chain of command in the motivational hierarchy. In any natural environment, what is desired is not readily available to the organism. Hunger, for example, cannot be satisfied by chewing movements, if there is no food in the mouth. Hence the need for locomotion and exploration. There is thus a hierarchical relationship by which the limbic level can command the other levels in the motivational hierarchy. Unlike the motor hierarchy, however, the motivational hierarchy is more labile. Although one usually orient towards the food in order to approach it, and approach it in order to consume it, this type of dependency is not fixed. It is also possible, through learning, to learn to retreat or take a circuitous route to reach the goal.

In short, different cortico-BG networks can form a labile motivational hierarchy. Because the contingencies between specific perceptual inputs can depend on uncertain and arbitrary environmental properties, it is critical for the brain to select any one of the transition controllers to serve as the lead level in reaching some goal (Premack 1959).

At the highest levels of the control hierarchy, there is no specific relationship between a particular reference signal and the higher purpose it serves. If the higher purpose is to stay warm, one can move towards a fireplace, or put on a sweater. Both actions require the use of multiple transition controllers. The effect is to introduce a line of communication between two levels of the motivational hierarchy so that the reference of one level can be adjusted by the output of another level. Just as error reduction at the highest levels of the motivational hierarchy can be achieved in multiple ways, so the transition level can also serve multiple masters. In order to achieve any higher purpose, as acquired and represented by the cortical neurons, it would be necessary to use different types of transition controllers, e.g., for gustatory, proximity, and body configuration. Each is implemented by some BG circuit, which compares desired rates of change with actual rates in any perceptual variable. The dependency between one set of inputs and another is not determined by the organism, but by the environment. But within the brain, these dependencies are reflected in the associations formed between different transition controllers. It is the recruitment of other existing transition controllers that allows the formation of a labile motivational hierarchy. The internal chain of command mirrors the external environmental contingencies.

20.9 Conclusions

My cursory sketch of the model must remain qualitative and incomplete. Many important features of the BG have not been incorporated, e.g., striosome/matrix compartments in the striatum, the role of recurrent collaterals among striatal

projection neurons, the role of pallidostriatal projections, and the distinction between pyramidal tract and intratelencephalic corticostriatal projections.

The main objective of this chapter is to introduce a conceptual framework that can explain the major contributions of the BG to behavior. Although only movement velocity control is analyzed in detail, it is hoped that the concept of transition control will generate testable predictions about neural implementations and stimulate future research. According to the present framework, the brain is a control hierarchy, and behavior is merely the outward manifestation of the observable aspects of the more fundamental process of control. Control systems determine what and how much of something it should sense, and produce actions needed to create the preselected inputs. It makes it possible for some future, unrealized state to be reached. The output is both generated by error and also reduces the error through a link in the environment. In a control system, behavioral output is not an output of any antecedent state whatsoever, but always a result of a comparison at one or more levels of the control hierarchy. Consequently, we must abandon the traditional assumption that behavioral output is either a function of sensory input or of intrinsic states.

Although the basic unit of control is a negative feedback loop, there is enormous variation in the sensors used and perceptual variables represented, as well as in the effectors used to alter the readings of these variables. The hierarchical control organization, using the basic control loop as building blocks, can generate extremely complex behavior. But the complexity of the behavioral output belies the simplicity of the underlying computational mechanisms.

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