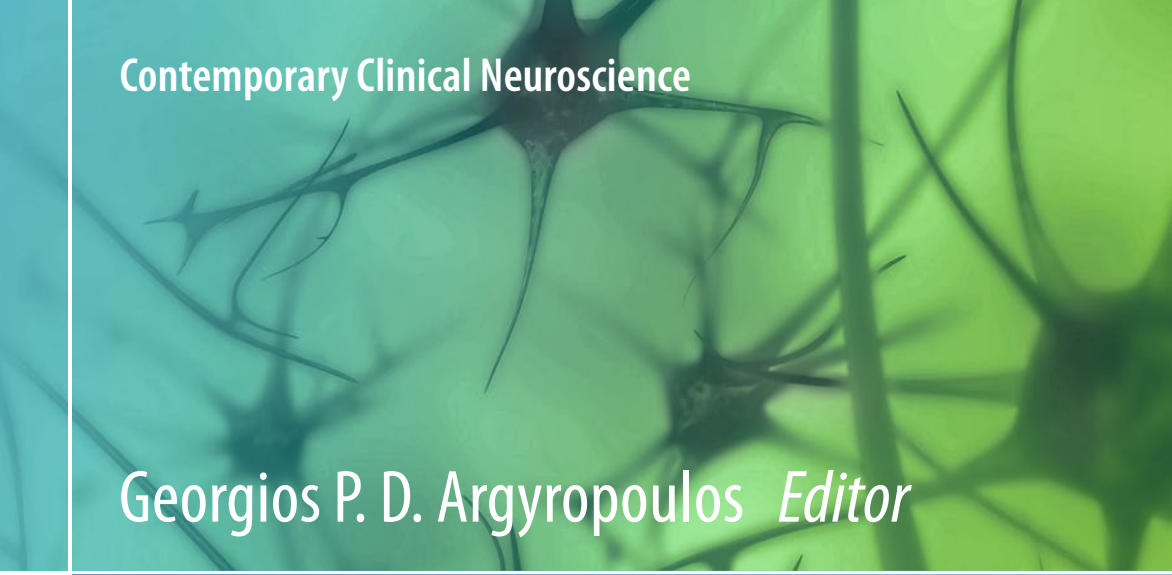

Contemporary Clinical Neuroscience

Georgios P. D. Argyropoulos *Editor*

Translational Neuroscience of Speech and Language Disorders

Springer

Contemporary Clinical Neuroscience

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Editor

Translational Neuroscience of Speech and Language Disorders

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Contemporary Clinical Neuroscience
ISBN 978-3-030-35686-6 ISBN 978-3-030-35687-3 (eBook)
https://doi.org/10.1007/978-3-030-35687-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

In memoriam Peter Mariën (1962–2017)

Preface

Advances over the past few decades in the neuroscience of speech and language underscore the potential for efficiently preventing the impairment, predicting and impeding the deterioration, or enhancing the recovery of speech and language function. Nevertheless, the translation of such advances into clinical applications remains strikingly slow. Virtually in their entirety, the large number of contemporary volumes that combine insight from neuroscience and speech–language pathology includes very little discussion of the translational insight that the relevant fields provide on prevention, prediction, and rehabilitation of speech and language disorders. While international scientific journals on the neuroscience of speech and language have been occasionally hosting special issues and reviews dedicated to translational neuroscience over the last decade, such papers have almost exclusively considered stroke-induced aphasia as the disorder of interest. Importantly, such work has not so far been represented in the form of a volume.

Instead of providing yet another volume dedicated to the Neuropsychology of speech and language disorders, or to the Cognitive Neuroscience of speech and language, this edited volume provides the first presentation of the state-of-the-art in the application of modern Neuroscience research in predicting, preventing, and alleviating the negative sequelae of neurodevelopmental, acquired, or neurodegenerative brain abnormalities on speech and language.

To this aim, this volume brings together contributions from several leading experts in a markedly broad range of disciplines, comprising Neurology, Neurosurgery, Genetics, Engineering, Neuroimaging and Neurostimulation, Neuropsychology, and Speech and Language Therapy. Likewise, the primary audience of this work comprises frontline clinicians, clinical and cognitive neuroscientists, neuropsychologists and neurologists, speech and language pathologists/therapists, health researchers, and assistive technologists.

This volume is evidently far from exhaustive with respect to either the vast range of speech and language disorders or the different theoretical frameworks and techniques that can afford us translational insight. However, we do hope to provide a framework for discussion, enabling scientists in academia or industry, or, alternatively, from preclinical or clinical backgrounds, to establish a more common

language, methodology, and motivation for conducting translational research in speech and language disorders. The reader will find not only state-of-the-art contributions, but also novel venues that are being investigated in a growing number of laboratories worldwide.

I would like to thank all of the contributors to this volume who have found time to prepare their chapters despite a busy schedule, as well as the anonymous reviewers for their valuable feedback. Additionally, I am very grateful to the Editor of the Series, Mario Manto, as well as the staff of Springer for their support and encouragement in making this volume possible.

Finally, this edited volume is dedicated to the memory of Prof. Peter Mariën, whose pioneering work continues to inspire us.

Oxford, UK
September 2019

Georgios P. D. Argyropoulos

Abbreviations

μV	Microvolt(s)
A1	Primary auditory cortex
AD	Alzheimer's disease
AF	Arcuate fasciculus
AFNI	Analysis of functional neuroimages (software)
AoS	Apraxia of speech
ASD	Autism spectrum disorder(s)
atDCS	Anodal transcranial direct current stimulation
BA	Brodmann area
BOLD	Blood oxygen level-dependent
C	Consonant
CBI	Cerebellar brain inhibition
CCT	Computerized cognitive training
CIT	Constraint-induced therapy
cm	Centimeter(s)
cTBS	Continuous theta-burst stimulation
ctDCS	Cathodal transcranial direct current stimulation
DCS	Direct cortical stimulation
DD	Developmental dyslexia
DLD	Developmental language disorder
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
DYS	Dyslexia
EEG	Electroencephalography
EF	Executive function(s)
EMG	Electromyography
F	Female
FA	Fractional anisotropy
FC	Functional connectivity
fMRI	Functional magnetic resonance imaging

FSL	FMRIB software library (software)
FTD	Fronto-temporal dementia
GM	Gray matter
h	Hour(s)
HD tDCS	High-density transcranial direct current stimulation
HRF	Hemodynamic response function
Hz	Hertz
IFG	Inferior frontal gyrus
IFOF	Inferior-fronto-occipital fasciculus
iTBS	Intermittent theta-burst stimulation
ITG	Inferior temporal gyrus
LH	Left hemisphere
LSM	Lesion-symptom mapping
LTD	Long-term depression
LTP	Long-term potentiation
M	Male
M1	Primary motor cortex
mA	MilliAmpère(s)
MCI	Mild cognitive impairment
MEG	Magnetoencephalography
MEP	Motor evoked potential
min	Minute(s)
mm	Millimeter(s)
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
NMDA	N-Methyl-D-Aspartate
nrTMS	Navigated repetitive transcranial magnetic stimulation
nTMS	Navigated transcranial magnetic stimulation
PA	Phonological awareness
PASAT	Paced auditory serial addition task
PASST	Paced auditory serial subtraction task
PDH	Procedural deficit hypothesis
PET	Positron emission tomography
PFC	Prefrontal cortex
PML	Principles of motor learning
PPA	Primary progressive aphasia
PPA-G	Agrammatic (variant of) primary progressive aphasia
PPA-L	Logopenic (variant of) primary progressive aphasia
PPA-S	Semantic (variant of) primary progressive aphasia
PSP	Progressive supranuclear palsy
(p)STG	(Posterior) superior temporal gyrus
RAN	Rapid automatized naming
RH	Right hemisphere
rs-fMRI	Resting-state functional magnetic resonance imaging

rTMS	Repetitive transcranial magnetic stimulation
s	Second(s)
SCA	Spino-cerebellar ataxia
SES	Socioeconomic status
SLF	Superior longitudinal fasciculus
SLI	Specific language impairment
SNP	Single nucleotide polymorphism
SPM	Statistical parametric mapping (software)
TBS	Theta-burst stimulation
TD	Typical development
tDCS	Transcranial direct current stimulation
TE	Echo time
tfEmC	Temporo-frontal extreme capsule
TLE	Temporal lobe epilepsy
TMS	Transcranial magnetic stimulation
TR	Repetition time
UF	Incinate fascicle
V	Vowel
VLBM	Voxel-based lesion-behavior mapping
VLSM	Voxel-based lesion-symptom mapping (software)
VWM	Verbal working memory

Contents

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Chapter 1
Translational Neuroscience of Speech and Language Disorders: State of the Art

Georgios P. D. Argyropoulos

Abbreviations

fMRI	Functional magnetic resonance imaging
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation

Translational neuroscience applies research findings on brain structure and function to the development of clinical applications for a broad range of neurodevelopmental, acquired, and neurodegenerative disorders. This rapidly advancing research area displays considerable therapeutic and commercial potential, especially given the global need to alleviate the economic burden to society and the suffering to patients and carers inflicted by these disorders.

In the case of speech and language disorders, translational approaches remain in their early infancy. Nevertheless, these can benefit from advances in several fields. Findings from basic research on animal models can help us gain a better understanding of the mechanisms of neuroplasticity and functional reorganization and the ways in which these can be enhanced, in order to maximize functional gains in recovering speech and language. Advances in noninvasive brain stimulation research highlight the potential of using repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS) to enhance the effects of speech-and-language treatment. Moreover, both rTMS and functional magnetic resonance imaging (fMRI) can be used for the detection of brain areas that support speech and language and that need to be spared during tumor resection or epilepsy surgery for each individual patient. In genetically determined neurodevelopmental disorders of language, such as developmental dyslexia and developmental language disorder, manipulating individual genes in animal models can help us disentangle the

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_1

gene-brain-behavior relationships and ultimately develop interventions customized to the needs of each child. Furthermore, identifying the learning and memory systems that remain unaffected by these neurodevelopmental disorders may help us develop behavioral interventions that maximize the compensatory contribution of these systems in acquiring language. Information accumulated on the brain lesions and speech/language deficits of several hundreds of patients can also be used to generate individualized predictions on the likelihood and time course of speech/language recovery for new patients, as well as to help select the interventions associated with the best rehabilitation outcomes.

These are some of the topics that this edited volume focuses on. In more detail, Chaps. 2 and 3 are dedicated to the translational neuroscience of language disorders in acquired and neurodegenerative brain damage. In Chap. 2, Kasselimis and colleagues discuss the challenges in research on post-stroke aphasia rehabilitation and recovery, as well as the difficulties in integrating the insights from basic neuroscience and studies with clinical populations. The chapter starts with an outline of key concepts and core topics involving prognostic factors, neuroplasticity, functional reorganization, and the role of the right hemisphere in aphasia recovery and rehabilitation. The authors then turn to issues related to post-stroke rehabilitation focusing on aphasia, as informed by basic neuroscience and clinical research studies. The chapter concludes with a number of reflections on future endeavors in research related to aphasia rehabilitation, and on how intervention programs implemented in aphasic patients could be improved, by translating findings from animal studies to human models of treatment.

In Chap. 3, Manouilidou and Nerantzini discuss the current state of intervention approaches to language impairments resulting from neurodegenerative conditions, a topic that is often overlooked, given the traditional focus of research on improving language performance following stroke. Focusing on Alzheimer's disease, mild cognitive impairment, and primary progressive aphasia, the authors highlight the evidence supporting the potential for neuroplasticity and responsiveness to therapy, even in neurodegeneration. The authors then turn to behavioral intervention methods targeting the word—as well as sentence-level impairment, and they also focus on neuromodulatory techniques and their applicability. Neuromodulatory techniques may have longer-lasting effects relative to behavioral treatment, while combined interventions (behavioral and neuromodulatory) have produced more promising results, maximizing the efficacy of the intervention.

Chapters 4 and 5 are dedicated to translational insights on neurodevelopmental language disorders. In Chap. 4, Centanni focuses on developmental dyslexia and discusses how differences in genetics entail challenges for researchers in determining the neurobiological mechanisms underlying dyslexia and optimizing customized interventions. The author argues that animal models are appealing for this type of research, as individual genes can be manipulated and the results can be studied in an ethical manner. This approach can help disentangle the gene-brain-behavior relationships and genetic interactions, providing translatable predictions that can then better inform studies in dyslexia. A better understanding of the gene-brain-behavior relationships underlying dyslexia may ultimately offer clinicians a set of guidelines

that may increase early diagnostic success rates in children with dyslexia. Importantly, this approach may help develop customized interventions for each child on the basis of their specific biological and behavioral needs.

In Chap. 5, Vogindroukas and colleagues focus on developmental dyslexia and developmental language disorder and discuss the translational insight afforded by research on the cognitive neuroscience of learning and memory in relation to language processing. The authors outline the evidence for impaired procedural learning in the face of preserved or even enhanced declarative learning in the non-linguistic domain, as well as findings of structural and functional brain abnormalities in the circuitry underlying procedural learning in these developmental disorders. The chapter concludes with an outline of testable, translatable predictions on maximizing the compensatory capacity of declarative learning and memory in acquiring language in these disorders within the context of planned interventions.

Chapters 6–11 investigate the contributions of specific neuroimaging and neuromodulatory methods in enhancing the prediction, treatment, and rehabilitation of speech and language disorders, as well as in presurgical language mapping and the maintenance of the integrity of language-critical areas on an individual basis.

In particular, Chaps. 6–8 are dedicated to the potential of noninvasive brain stimulation in enhancing the outcomes of speech and language therapy. In Chap. 6, Vandenborre and colleagues discuss the benefits of combining speech and language therapy with tDCS. The authors provide an elaborate, critical discussion of several parameters pertaining to tDCS protocols, the behavioral tasks of interest, the profile of the study groups involved, and the outcome measures employed. The authors present these variables within the context of a patient-centered virtuous circle, whereby speech and language therapy combined with tDCS is iteratively adjusted by the clinician in constant dialogue with each patient.

In Chap. 7, Nerantzini and colleagues provide an up-to-date narrative literature review of the findings from the relatively recent studies applying rTMS in aphasia therapy. The authors focus on issues pertaining to the effectiveness of rTMS, including the stimulation parameters as well as the combined use of rTMS with speech and language therapy. They also discuss the evidence for improvements in specific language domains following intervention with rTMS and critically assess the methodological limitations of the current rTMS studies on aphasia rehabilitation. Crucially, the authors argue that the combination of rTMS with traditional behavioral intervention methods may result in an additive improvement of patients' linguistic abilities.

In Chap. 8, Leggio and colleagues highlight the potential of targeting the cerebellum with noninvasive brain stimulation within the context of the neurorehabilitation of speech and language disorders. While the cerebellum has been traditionally viewed as a structure confined to motor control, this view has been revised over the past few decades, with several neuroanatomical, neuroimaging, and clinical studies providing evidence for cerebellar involvement in non-motor function, crucially involving language. After briefly reviewing the speech and language impairments associated with cerebellar damage and broader cerebro-cerebellar network

abnormalities, the authors provide an overview of the studies that have used noninvasive brain stimulation to investigate the cerebellar role in speech and language domains. The authors then turn to the translational potential of cerebellar neuromodulation to improve speech and language functions after cortical and subcortical damage. Leggio and colleagues conclude that cerebellar neuromodulation may have substantial potential as a treatment tool in speech and language disorders, not only for patients affected by cerebellar pathology but also for patient populations with supra-tentorial damage.

Chapters 9 and 10 cover the use of advanced methods in mapping the language network in preoperative settings for the accurate identification and sparing of language-critical cortex. In Chap. 9, Tsitlakidis and colleagues discuss the utility of neuronavigated rTMS for language network mapping in preoperative settings of brain tumors and epileptic disorders. The authors highlight the benefits in decision-making, surgical planning, patient counseling, and awake mapping optimization in resective brain surgery that is informed by preoperative rTMS as compared with language mapping with other techniques.

In Chap. 10, Benjamin and colleagues discuss the translation of fMRI from a technique developed to identify the brain correlates of cognition to a clinical tool for mapping the language network in preoperative settings. Since the use of clinical fMRI requires extensive multidisciplinary theoretical knowledge and technical training, the authors provide an accessible overview of key topics, including epilepsy, cognitive assessment, fMRI physics, statistical analysis, the language system, and the interpretation and communication of fMRI findings in a clinically meaningful manner.

Finally, in Chap. 11, I discuss the promising role of advanced lesion-symptom mapping methods in improving patient care for speech and language disorders. After a brief historical account of the development of lesion-symptom mapping in patients with speech and/or language deficits, I highlight the recent emergence of data-led systems, which combine information from brain lesions and impairment on speech and language. In the near future, these systems can provide clinicians, carers, and patients with individualized predictions on the possibility, extent, and time course of language recovery following brain damage. The chapter concludes with a discussion of a series of well-recognized issues in lesion-symptom mapping, along with an account of ways to address such limitations.

Overall, it is my hope that this volume will raise awareness of both the translational potential and the limitations of these approaches among the scientific community and stimulate further research in the translational neuroscience of speech and language disorders.

Chapter 2
Translational Neuroscience of Aphasia and Adult Language Rehabilitation

Dimitrios S. Kasselimis, Georgios Papageorgiou, Georgia Angelopoulou, Dimitrios Tsolakopoulos, and Constantin Potagas

Abbreviations

AF	Arcuate fasciculus
BA	Brodmann area
CIT	Constraint-induced therapy
(f)MRI	(Functional) magnetic resonance imaging
IFG	Inferior frontal gyrus
IFOF	Inferior-fronto-occipital fasciculus
PET	Positron-emission tomography
SLF (I,II,III)	Superior longitudinal fasciculi (segments I, II, III)
tfEmC	Temporo-frontal extreme capsule
UF	Uncinate fascicle

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_2

2.1 Perspectives and Challenges in Contemporary Aphasia Rehabilitation

Stroke is one of the most devastating neurological conditions, leading to deaths and, for stroke survivors, to motor and cognitive deficits, including aphasia. It is without doubt that the study of brain anatomy and pathophysiology, at the macroscopic as well as the neuronal level, has been of great value in the attempt to understand compensatory mechanisms after stroke and recovery processes in aphasia.

Subsequent to brain injury or disease, different molecular, biochemical, and anatomical changes occur that lead to motor, sensory, and/or cognitive deficits (Whishaw & Kolb, 1988). In the last 15 years, neuroscience research has focused on the relationship between molecular/cellular changes and cognition, in order to classify neural circuits amenable to rehabilitation strategies (Pal, Alves, Larsen, & Møller, 2014; Vallon, Chang, Zhang, & Kuo, 2014). However, the specific cortical mechanisms which could result in recovery from and rehabilitation of neurocognitive disorders, such as aphasia, are yet to be elucidated.

Even though lesion studies in acute and chronic post-stroke phases have been quite popular and have made great progress during the two last decades (Eaton et al., 2008; Fridriksson et al., 2018; Price & Crinion, 2005), it still remains difficult to clarify the exact mechanisms of the brain's structural and functional reorganization and how this is related with the observed behavior, in terms of linguistic ability (Saur et al., 2006). This is due to several reasons, including the huge individual variability concerning both brain anatomy (Ojemann, 1979; Steinmetz & Seitz, 1991) and post-stroke language deficits (Alexander, Naeser & Palumbo, 1987; Kasselimis, Simos, Peppas, Evdokimidis, & Potagas, 2017) that affect recovery (Lazar & Antoniello, 2008; Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). On the other hand, despite the long history of neuroanatomical research, there are still many questions to be answered regarding the "localization" of distinct language processes in the healthy brain and the role of specific brain areas and/or networks in language function (Campbell & Tyler, 2018; Fedorenko & Thompson-Schill, 2014; Friederici, 2011; Skeide & Friederici, 2016a, 2016b).

Ever since the first postmortem findings of Broca (1865) and Wernicke (1874), there is a long history of advanced neuroimaging studies in healthy brain structure and function, incorporating data from architectonical investigation of cortex (see for a review Amunts & Zilles, 2012) and comparative studies with primates such as the macaque monkey (e.g., Petrides & Pandya, 2009) but also studies of structural and functional neuroanatomy in relation to specific language functions (see for a review Price, 2012). It is worth mentioning that studies on nonhuman primates using autoradiographic methods provide more accurate results regarding white matter tracts connecting cortical regions, as current neuroimaging methods do not suffice to trace the exact nature of anatomical structure (Vernooij et al., 2007). However, that even if such methods are more accurate compared to noninvasive neuroimaging methods, these studies cannot provide direct evidence for brain-language relationships, given that language is unique to humans.

Beyond the importance of investigating the neural underpinnings of language and the phylogenetic history of the brain regions supporting it, along with the pathophysiological mechanisms underlying its breakdown, the thorny question of the efficacy of intervention strategies implemented in neurological patients remains. While aphasia rehabilitation began to gain major popularity after World War II (Basso, 2003), one of the most intriguing questions in contemporary clinical practice is whether individuals with acquired language disorders can improve their language abilities over the course of time (Mazzoni et al., 1995; Pickersgill & Lincoln, 1983; Sarno & Levita 1979a, 1979b). Recent meta-analytic studies on the efficacy of stroke-induced aphasia rehabilitation demonstrate that aphasia treatment is more effective compared to spontaneous recovery. It is however noteworthy that, despite the fact that a large number of studies have focused on different types of treatment for specific language deficits, such as word retrieval (Hicken, Best, Herbert, Howard, & Osborne, 2002; Martin & Laine, 2000), verbal fluency (Belin et al., 1996), and auditory verbal comprehension (Davidoff & Katz, 1985), very little is known about the neural basis of rehabilitation. In order to understand these effects, a shift of focus is required from the value of aphasia treatment to the optimization of rehabilitation strategies, based on the neurobiological phenomena that occur in the brain in response to neural injury or disease. In the following sections, we will present the contemporary view on the brain networks supporting language and then elaborate on the basic mechanisms of post-stroke recovery. Finally, we will discuss issues related to treatment and reflect on future endeavors for research in this field.

2.2 A Dual Model for Language Processing: Evidence from Humans and Nonhuman Primates

It could be argued that the genesis of aphasiology can be traced back to the nineteenth century. Postmortem studies during that era indicated that lesions affecting either one of the two traditional *language centers* (Broca's and Wernicke's areas), or the underlying fibers interconnecting them, would cause a specific language impairment, the characteristics of which would depend on the topology of the cortical lesion and/or subcortical disconnection (Lichtheim, 1885). For more than a century, the Wernicke-Lichtheim model dominated the field of aphasiology, despite the ongoing debate on the specifics of the structure and function of the perisylvian language network (for a historical review and critical discussion, see: Rijntjes, Weiller, Bormann, & Musso, 2012; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011).

At the dawn of the twenty-first century, a dual stream model was introduced in an attempt to interpret the neuroanatomical processing of auditory language (Hickok & Poeppel, 2004, 2007). The newly proposed language network consisted of two major pathways: a dorsal stream connecting prefrontal areas (with stronger connections in BA 44 and premotor areas, i.e., BA 6) with the inferior parietal and posterior temporal cortices, which supported sound-to-articulation mapping, and a ventral

stream, linking prefrontal areas (mostly BA 45 and BA 47) with ventral temporal regions involved in sound-to-meaning mapping (Saur et al., 2008).

Collectively, neuroimaging studies using diffusion tensor imaging and functional connectivity methods have provided insight to the properties of these two major streams, as well as to the way in which language-related information is integrated. The superior longitudinal fasciculi segments (SLF I, II, III; Makris et al., 2004; Petrides, 2014; Petrides & Pandya, 2009) and the arcuate fasciculus (AF) (Catani, Jones, & Ffytche, 2005; Frey, Campbell, Pike, & Petrides, 2008) are considered to be dorsal pathways, while the temporo-frontal extreme capsule (tfEmC) (Makris & Pandya, 2009; Petrides & Pandya, 2009), the uncinate fascicle (UF) (Duffau, Gatignol, Moritz-Gasser & Mandonnet, 2009), and the inferior-fronto-occipital fasciculus (IFOF) (Sarubbo, De Benedictis, Maldonado, Basso & Duffau, 2013) constitute the ventral system (Saur et al., 2008; Weiller et al., 2011). Diffusion data of probabilistic tractography in humans are comparable with task-based functional imaging results (Saur et al., 2008, 2010), thus allowing to assess the expected language-related function of the two streams and further strengthening the validity of the dual-path model (for a review in human and monkey brains, see Axer, Klingner, & Prescher, 2013; for an extensive discussion, see Rijntjes, Weiller, Bormann, & Musso, 2012; but see also Catani, Jones, & Ffytche, 2005). Structural and functional connectivity studies associate dorsal stream tracts with mapping sound onto articulation processes, as required for word- and nonword-repetition tasks (Saur et al., 2008), but also with hierarchical structure manipulation, as required in syntax (Friederici, 2012b, 2018). Similarly, task-based fMRI (Saur et al., 2008, 2010) and electrical stimulation studies (see Duffau, 2012 for a critical review) provide evidence for the role of the ventral stream and more specifically tfEmC in mapping sound onto meaning in healthy individuals (for a discussion, see Friederici, 2012a).

The aforementioned findings are in accordance with evidence derived from different patient cohorts, including tumors (Duffau, Herbet, & Moritz-Gasser, 2013), post-stroke aphasia (Fridriksson et al., 2018; Kümmerer et al., 2013; Holland, Johns, & Woollams, 2018), primary progressive aphasia (Agosta et al., 2013), and central alexia (Aguilar et al., 2018).

Moreover, there is a close correspondence between neuroimaging findings in humans and autoradiographic tracing studies in nonhuman primates. Macaque monkeys seem to have similar ventral tracts, and especially the tfEmC, connecting ventrolateral frontal and temporal and inferior parietal regions (Petrides & Pandya 2006, 2007, 2009; Schmahmann & Pandya 2006). It is noteworthy that in studies implementing autoradiographic tracing, the tfEmC has been delineated as a separate tract from the UF, which is considered to be a limbic pathway (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Schmahmann & Pandya 2006). Regarding the dorsal tract, AF and SLF have been delineated in the macaque monkey brain as distinct association fiber pathways (Schmahmann et al. 2007), while the middle and inferior longitudinal fasciculi contribute to the formation of both the AF/SLF and the tfEmC (Petrides & Pandya, 2007). It can be argued that comparative studies in human and nonhuman primates lend support to this dual stream language network,

yet differences arise concerning tract delineation and cortical representation. There is some evidence that connectivity patterns in the AF (Eichert et al., 2019; Rilling et al., 2008) and IFOF (Eichert et al., 2019) are different between humans and macaque monkeys. More specifically, Eichert et al. (2019) showed that the left frontal cortex is connected via the AF with the ipsilateral middle and inferior temporal gyri in the human brain, but not in the brain of chimpanzees or macaque monkeys, a finding also supported by Rilling et al. (2008).

In sum, most structural and functional brain connectivity studies confirm the existence of and illuminate the properties of an extensive language network that incorporates two major pathways connecting different cortical areas. Future research will benefit from further development in comparative anatomical and neuroimaging techniques to shed light on the mechanisms supporting language processes in the healthy brain and to expand findings in aspects of post-lesion brain reorganization. Along these lines, understanding the underlying mechanisms of stroke and, most importantly, post-stroke recovery is crucial, in order to integrate the available data derived from several fields of neuroscience and eventually formulate a multidisciplinary framework for aphasia recovery and treatment. In the following section, we attempt to describe the mechanisms of recovery after stroke.

2.3 Mechanisms of Post-stroke Recovery

Ischemic episodes are by far the most common types of stroke. Several events occur during an ischemic episode: mitochondria failure, breakdown of potassium and sodium pump, oxitoxicity following the release of glutamate and other neurotransmitters, and oxidative stress after the production of free radicals, ending with cell death (for a review, see Brouns & De Deyn 2009; Deb, Sharma, & Hassan, 2010). Hemorrhagic strokes cause more deaths compared to ischemic ones and often result in comparatively more severe motor and cognitive deficits. The hemorrhage leads to the death of cells and possible damage can also occur from secondary injuries. In general, hemorrhagic strokes have worse prognosis with regard to survival and cognitive outcome (Lezak, 2012).

Although full neural tissue regeneration cannot take place after a stroke (or any other event causing brain damage), mammalian brains have a specific mechanism which allows them to adapt and change based on external stimuli. This unique mechanism is usually referred to as "neuroplasticity." The design of the human brain may facilitate brain reorganization, given that it has a rather high number of neurons/body mass ratio and its cognitive processes are supported by diffuse functional connectivity (Turkstra, Holland, & Bays, 2003).

Over the last decades, advances in basic neuroscience have improved our knowledge in neural plasticity, a core principle in the field of neurorehabilitation. The unique ability of neurons to alter their structure and function in order to change behavior has been demonstrated even in the simplest animals, such as the nematode *C. elegans* (Bozorgmehr et al., 2013). The existing data suggest that neuroplasticity

is a prerequisite for learning new behaviors or relearning the lost ones. This is confirmed by a growing body of neuroimaging studies that demonstrate the plastic potential of the brain in healthy subjects (Raichle et al., 1994; Sowell, Thompson, Tessner, & Toga, 2001; van Turennout, Ellmore, & Martin, 2000) and in brain-damaged individuals as well (Belin et al., 1996; Musso et al., 1999; Small, Flores, & Noll, 1998).

In general, there are three ways in which an injured brain could compensate for lost tissue: (1) reorganization of all neuronal networks, (2) formation of new networks, and (3) regeneration of the lost tissue (Kolb, 1995). It is thus essential to understand that the "old" brain is developing into a "new" one, resulting into functional reorganization, even in the absence of rehabilitation (Kleim & Jones, 2008). In animal studies, rehabilitation training after unilateral cortical damage seems to improve motor function and to enhance neural plasticity in the remaining brain regions (Biernaskie & Corbett, 2001; Jones, Chu, Grande, & Gregory, 1999). However, there is evidence that plastic changes are not always beneficial (Mark & Taub, 2004). As a result, one key aspect of neurorehabilitation is to increase or induce neuroplasticity in order to maximize functional gains (Keefe, 1995). In the aphasia literature, there are studies indicating a relationship between neuroplastic changes and aphasia recovery, which indicates functional reorganization of the brain (for a review, see Thompson, 2000). There are sparse studies indicating that rehabilitation can induce neuroplasticity as well, leading to and possibly resulting in functional gains (Marcotte et al., 2012, Marcotte, Perlbarg, Marrelec, Benali, & Ansaldo, 2013; Meinzer et al., 2004). Importantly, the type of treatment appears to play a role in the reorganization of language networks (Musso et al. 1999; Wierenga et al., 2006). However, further evidence for neuroplasticity is needed in order to enhance the translation of this area into aphasia research and rehabilitation.

The main factors affecting neuroplasticity are the diffuse functional connectivity (which allows the brain to remap the neural connections), along with the location and size of brain damage. In cases of smaller lesions, the adjacent, intact regions may undertake the recovery of the lost function. In massive strokes resulting in extensive lesions, this capacity is associated with more distant areas of the lateral and contralateral hemisphere (Murphy & Corbett, 2009). Several events occur during this process, such as changes in synaptic strength, axonal remodeling, and contribution of the healthy areas of the brain (for further review, see Green, 2003). The process may be modulated by the Hebbian rule, according to which repeated activity and stimulation of the presynaptic cell is expected to strengthen the synapses that a particular neuron forms with other neurons (Hebb, 1949). In other words, neurons that fire together wire together. This could result in the alternation of the representation areas on the cortex. In addition, homeostatic mechanisms may be triggered by a cerebrovascular accident, in order to preserve adequate synaptic input, and thus Hebbian plasticity may redistribute synaptic strength (Marsh & Hills, 2006). Following this general pattern, a brain-damaged individual may regain, at least partially, a lost function. Indeed, many studies show how neuroplasticity works in a cortical and subcortical level (for a review, see Green, 2003), facilitating brain remapping, as well as how ipsilateral and/or contralateral unaffected regions may

play a compensatory role, as an alternative neural substrate of the lost function. An example regarding the role of the left hemisphere in aphasia is provided by a study conducted by Fridriksson, Bonilha, Baker, Moser, and Rorden (2010), who showed that improved naming performance was accompanied by increased cortical activation in the left hemisphere in a sample of aphasic patients with naming deficits. Apart from the processes taking place within the hemisphere ipsilateral to the lesion, there is accumulating evidence highlighting the role of contralateral (usually the right in the case of post-stroke aphasia) regions in language recovery. There is substantial evidence suggesting that language recovery relies on increased activation in the homologous right hemisphere areas ("theory of right hemisphere compensation"), in the residual undamaged left hemispheric areas ("map extension"), or in both (Thompson, 2000). For example, Rosen et al. (2000), in their PET/fMRI study, found that patients with aphasia due to lesions centered at the left inferior frontal gyrus (IFG) showed increased activation in the right IFG and left perilesional areas during language tasks; activation of the right IFG did not however correlate with verbal performance. The authors therefore attributed the activation of the contralesional IFG to either a recruitment of a healthy network via compensating behavioral strategies or a possible anomalous response to verbal stimuli in the absence of an intact left-lateralized IFG. A similar fMRI study (Staud et al., 2002) revealed that left-stroke survivors showed right-lateralized activation similar to the activation of the left hemispheric regions in healthy right-handed individuals during a silent word-generation task, thus indicating the recruitment of the homologous areas of the right hemisphere after brain damage. Similarly, in an attempt to explain the involvement of the contralateral hemisphere in recovery, Hamilton, Chrysikou, and Coslett (2011) have suggested that right-lateralized cortices homologous to the left perisylvian region may be activated during processing of linguistic stimuli due to a preexisting language network which was inhibited by the dominant hemisphere before brain damage occurred.

It should be however noted that, although some studies acknowledge the contribution of the right hemisphere in reorganization, the majority of studies suggest that the most crucial lesion-related prognostic factors are dependent on the integrity of the (left) affected hemisphere (Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Lazar et al., 2008; for a review, see Kasselimis & Potagas, 2015). Moreover, other studies have highlighted that right hemisphere changes could be maladaptive and that increased activation in those areas is associated with worse performance (Martin et al., 2009; Price & Crinion, 2005). As a means of preventing right hemisphere excitability, recent studies have applied transcranial magnetic stimulation (TMS) to individuals with aphasia and have shown improved language abilities after stimulating right homologues of the language network, such as pars triangularis (Naeser et al., 2005; for a review on TMS and aphasia recovery, see Hamilton et al., 2011). Taking into consideration the evidence highlighting the importance of the integrity of the left-lateralized perisylvian region, as well as the indications of the detrimental effects of right hemisphere functionality during post-stroke aphasia recovery, Hamilton et al. (2011) suggest a hierarchical model for the recovery of language functions in such patients. Hamilton et al. (2011) summarize a hierarchical

model to illustrate the recovery of patients with aphasia: (1) best recovery can be achieved when brain regions originally involved in the language network regain their normal function; (2) good recovery can be achieved when the functionality of perilesional areas is restored to counterbalance the function of the damaged areas originally involved in language; (3) limited recovery can be achieved when language recovery is based primarily on the right hemisphere.

In summary, the contribution of the left and right hemisphere changes in aphasia is not fully understood. Undoubtedly, in order to maximize treatment effects, other stroke factors need to be taken into account, such as the site and size of the lesion (Raymer et al., 2007), as well as individual differences in relation to brain remapping and the contribution of the right hemisphere to language recovery (Gainotti, 1993).

Post-stroke reorganization/recovery follows a specific process, comprising three phases (Marsh & Hills, 2006): (1) the acute phase, which involves tissue restoration and lasts for a few hours to days, in which some patients might see rapid improvement, due to restoration of the blood flow in the areas surrounding ischemia (i.e., the penumbra), where the damage is reversible, because the energy-dependent metabolic processes are still active (Hossmann, 1994); (2) the subacute phase, which involves recovery from diaschisis and reorganization, during which new synapses may form; and (3) the chronic phase, which is reflected in the development of new strategies with regard to cognitive skills in general, among which are language functions. This process could last for months, or even years in some cases (Marsh & Hills, 2006). Duration and degree of recovery depends on several factors, such as lesion type and extent, severity of cognitive and language deficits, as well as age and health status (Kasselimis & Potagas, 2015; Pedersen, Stig-Jørgensen, Nakayama, Raaschou, & Olsen, 1995). With regard to aphasia recovery in particular, Saur et al. (2006) have suggested that there are three phases of post-stroke language recovery, involving different brain areas: (1) in the acute phase, activation of the remaining left perisylvian areas is reduced; (2) in the subacute phase, activation of homologous right hemisphere regions is increased; (3) in the chronic phase, activation patterns tend to approach normalization.

2.4 Timing and Intensity of Treatment

Studies investigating the optimal conditions under which neural repair and consequent remediation of sensorimotor and/or cognitive deficits can be achieved have shown that timing of intervention is a key element in neurorehabilitation. Recent findings suggest that training is more effective when applied shorty after injury (Kleim, Jones, & Schallert 2003; Woodlee & Schallert, 2004). Biernaskie, Chernenko, and Corbett (2004) observed that a 5-week rehabilitation program in rats initiated 30 days after brain injury was far less efficacious in improving motor function compared to the same treatment program starting 5 days post-infarct. A meta-analysis carried out by Robey (1998) concluded that treatment which initiates

early in the acute/subacute phase (less than 3 months post-onset) is more effective compared with rehabilitation sessions starting at 3 or 12 months post-onset. It should be also noted that delays in treatment delivery may even induce the development of compensatory behavioral strategies that may conflict with future rehabilitation efforts (Kleim & Jones, 2008). In sum, timing of treatment seems to be a crucial factor severely affecting the outcome. However, further research is needed in order to clarify the specifics of rehabilitation gains in relation to the onset of treatment and the different improvement patterns that may emerge in the acute, subacute, and chronic stages after brain injury in humans and other animals (Raymer et al., 2007).

Another critical aspect which is shown to have a significant effect on rehabilitation course and outcome is the intensity of treatment. Kleim (2003) found that intense training on a skilled reaching task changes the synapse formation within the motor cortex in rats, eventually resulting in reorganization of motor mapping in the brain. Taub, Uswatte, and Elbert (2002) suggest that motor rehabilitation programs implemented in the chronic stage in humans may be most effective if they are delivered with high intensity over a relatively short period. However, one potential drawback of training intensity after brain damage is that the possible overuse of an impaired function may inhibit overall plasticity and worsen overall function (Molteni, Zheng, Ying, Gomez-Pinilla, & Twiss, 2004). Despite such possible shortcomings, the general consensus is that intense treatment programs are beneficial in aphasia. A recent review of ten studies showed that the optimal duration for significant rehabilitation effects is 8.8 h of treatment per week for an overall period of 11.2 weeks (Bhogal, Teasell, & Speechley, 2003). Results showed that intensity in general is beneficial in aphasia rehabilitation (Basso, 2005; Baumgaertner et al., 2013).

2.5 "Use It or Lose It"

In addition to a number of physiological changes after brain injury, individuals develop behavioral compensatory strategies in order to perform daily activities, such as the constant use of the unaffected limb by stroke survivors with hemiparesis (Kwakkel, Kollen, & Lindeman, 2004). Research from basic neuroscience indicates that these strategies lead to a significant restructuring and neuronal growth in the contralesional hemisphere (Adkins, Voorhies, & Jones, 2004; Jones & Schallert, 1994). However, avoidance of using the injured limb ("learned nonuse") may lead to further degradation of structure or function and may inhibit improvement, even after treatment (Taub et al., 2002). Based on this notion, constraint-induced therapy (CIT) has shown promising results with regard to recovery of motor abilities in patients with post-stroke chronic hemiplegia (Kunkel et al., 1999). In motor rehabilitation, the key principles of CIT are massed practice, constraint of the unaffected limb with forced use of the affected limb, and behavioral shaping of the response. Pulvermüller et al. (2001) implemented CIT in an attempt to treat individuals with chronic aphasia. In their study, nonverbal communication was constrained, and 17

patients were forced to interact exclusively by talking, practicing their language skills for 3 hours on each weekday over a 2-week period. In comparison with patients that received the standard treatment of the institution, CIT-treated patients improved in tests both of language ability and in ecological verbal competence, under everyday living conditions. It should be however noted that the amount of training patients were given in conventional therapy was significantly smaller than that in CIT.

2.6 Future Endeavors for Aphasia Rehabilitation

Language is a rather complex behavior that can be broken down to several subfunctions and is supported by a widely distributed network, while its associations with other aspects of cognition are not yet fully understood. In addition, the phenomenology and underlying pathological mechanisms of acquired language disturbances remain, at large, elusive. Despite the different approaches adopted with regard to testing, intervention strategies, as well as measuring alterations in activation patterns through brain imaging and post-injury cortical remapping, in both humans and animal models, the exact mechanisms behind the restoration of language functions after brain damage have yet to be identified. Findings from basic neuroscience have revealed principles that are crucial to human studies and remain a major influence on the development of rehabilitation research in patients with aphasia. Undoubtedly, there are limitations in the translation of findings from animal studies to aphasia rehabilitation. In order to bridge that gap, computational models of cognition and language could translate basic neuroscience to human models of treatment (Nadeau, 2000). It should be emphasized that further evidence is needed about how intensity and timing can interact efficiently in individuals with aphasia, thus avoiding the negative effects of plasticity (Raymer et al., 2007). Finally, using human in vivo imaging, identification of changes in brain organization in individuals with aphasia under treatment could aid in the attempt to customize intervention programs for specific aspects of language, taking into consideration possible individual differences (Turkstra et al., 2003).

Acknowledgments Dr. Kasselimis is supported by the IKY Scholarships Programme, cofinanced by the European Union (European Social Fund [ESF]) and Greek national funds through the action entitled "Reinforcement of Postdoctoral Researchers," in the framework of the Operational Programme "Human Resources Development Program, Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) 2014–2020. Mr. Tsolakopoulos is supported by Greece and the European Union (European Social Fund (ESF)) through the Operational Programme "Human Resources Development, Education and Lifelong Learning" in the context of the project "Strengthening Human Resources Research Potential via Doctorate Research" (MIS-5000432), implemented by the State Scholarships Foundation (ΙΚΥ); Georgia Angelopoulou, doctoral student, was supported by the Fulbright Foundation under its 2017–2018 Doctoral Dissertation Visiting Research Students program in the United States.

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Chapter 3
Treatment and Intervention Approaches for the Improvement of Language Abilities in Neurodegenerative Diseases

Christina Manouilidou and Michaela Nerantzini

Abbreviations

(r)TMS	(Repetitive) transcranial magnetic stimulation
AD	Alzheimer's disease
CCT	Computerized cognitive training
DLPFC	Dorsolateral prefrontal cortex
EF	Executive functions
FTD	Frontotemporal dementia
LH	Left hemisphere
MCI	Mild cognitive impairment
PPA	Primary progressive aphasia
PPA-G	Agrammatic PPA
PPA-L	Logopenic PPA
PPA-S	Semantic PPA
RH	Right hemisphere
tDCS	Transcranial direct current stimulation

3.1 Introduction

The aim of this chapter is to provide an overview of the current treatment and intervention methods for improving language abilities in aging, especially when it is accompanied by neurodegenerative disorders.

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https://doi.org/10.1007/978-3-030-35687-3_3

Recent advances in our understanding of the neurobiology of language have helped revise some early ideas about language recovery. For instance, focal damage in stroke-induced aphasia nowadays is mainly investigated with respect to deficits in broader language networks and less so with problems in isolated brain areas (for a review see Kiran & Thompson, 2019). Evidence for neuroplasticity in aphasia research has been confirmed in several studies, showing that therapeutic techniques can effectively be used to modulate the brain's capacity for functional reorganization, by engaging regions that had previously been uninvolved in language processing to undertake new compensatory roles (Abel, Weiller, Huber, Willmes, & Specht, 2015; Berthier & Pulvermüller, 2011; Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013; Sarasso et al., 2010; Saur et al., 2006; Taub, Uswatte, & Elbert, 2002). Specifically, the recruitment of the left hemisphere (LH) and nearby perilesional tissue is essential for therapy-induced reorganization (Fridriksson, 2010; Fridriksson et al., 2012; Heiss, Thiel, Kessler, & Herholz, 2003; Martin et al., 2009; Meinzer & Breitenstein, 2008; Saur et al., 2006; Winhuisen et al., 2007), although studies of language recovery in chronic stroke have also shown right hemisphere (RH) recruitment post-treatment (Kiran, Meier, Kapse, & Glynn, 2015; Menke et al., 2009; Musso et al., 1999). However, in most cases, RH activation is often ineffective or even maladaptive, and typically, the best aphasia outcome (improvement of language functions) is yielded when inhibiting the right inferior frontal gyrus (Barwood et al., 2011; Hamilton, Chrysikou, & Coslett, 2011; Martin et al., 2009; Naeser et al., 2005).

Language intervention has traditionally been focused on improving communication abilities of individuals after stroke. Nonetheless, as our knowledge about language problems in dementia and in neurodegenerative diseases advances, intervention studies are gradually planned and implemented in aging populations as well. This field, however, remains in its early infancy, but it is quickly gaining grounds. Given that the underlying cause of these two major types of disorders (focal vs. neurodegenerative) appears to be more or less the same, i.e., a processing slowdown, it is unclear why language intervention should only be administered in one but not the other. This becomes particularly relevant given that although post-stroke aphasia and neurodegenerative diseases (e.g., primary progressive aphasia (PPA)) overlap in terms of their phenomenology (Grossman, 2018; Thompson et al., 2013), they are essentially different with respect to injury type and recovery processes. For instance, PPAs are characterized by the slow, diffused degeneration of cellular units within the language system with a *graceful degradation* of the affected systems (Norise & Hamilton, 2017). That is why in neurodegenerative dementias like Alzheimer's disease (AD) and frontotemporal dementia (FTD), neural degeneration occurs for years before patients become symptomatic (Grossman, 2010). Despite the progressive/ongoing nature of these conditions, several studies have shown that language impairment in PPA can be responsive to treatment, demonstrating the potential for neuroplasticity in PPA (e.g., Jokel, Graham, Rochon, & Leonard, 2014). However, early detection of the neuropathological changes in dementia is crucial (Snyder et al., 2014), as early intervention can serve as a protective mechanism against the decline of the functional level at the very early stages of the disease.

In addition to behavioral treatments, an important development in language intervention both for focal and for neurodegenerative diseases is the use of noninvasive brain stimulation. In general, the pharmacological treatment methods used to manage the symptoms of dementia have a limited degree of efficacy and sometimes cause serious side-effects. Thus, researchers focus on finding and developing supplementary or alternative therapies which will benefit dementia patients. Recently, non-invasive brain stimulation approaches such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have attracted considerable clinical and research interest, since they facilitate language recovery by modulating the excitability of the cortex and enhancing neuronal plasticity at the level of synaptic communication (Hattori, Moriwaki, & Hori, 1990; Liebetanz, Nitsche, Tergau, & Paulus, 2002; Moriwaki, 1991), possibly strengthening the connectivity within language networks.

rTMS produces an electromagnetic field, which is delivered to the brain, and affects cortical plasticity and neuronal activity (Elder & Taylor, 2014). In a similar vein, tDCS alters[1] cortical excitability and functional connectivity leading to behavioral changes, including improvements in motor, cognitive, and speech abilities. These techniques do not normally entail risks to the participants and have been used worldwide as treatment tools for disorders associated with stroke-induced aphasia, neurodegenerative diseases such as PPA, or AD, depression, epilepsy, and developmental deficits (for rTMS: Dadgar, Alaghband Rad, Khorrami, & Soleymani, 2016; Ren et al., 2014; Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; van den Noort, Struys, & Bosch, 2015; Wilkinson & Murphy, 2016; for tDCS: Baker, Rorden, & Fridriksson, 2010; Cotelli et al., 2014; Gervits et al., 2015; Hupfeld & Ketcham, 2016; Kuo, Paulus, & Nitsche, 2014; Tippett, Hillis, & Tsapkini, 2015; Wassermann & Grafman, 2005).

Neuromodulation techniques hold the potential of alleviating neuropsychiatric symptoms and improving cognition, with effects lasting for weeks or months (Elder & Taylor, 2014). Due to its ability to modulate cortical excitability, TMS was initially used in normal-healthy participants in order to explore its effectiveness in language processing and cognitive performance. Results of different studies suggest that TMS might successfully improve language performance (e.g., naming ability) and cognition (memory, attention, learning) in healthy populations (Elder & Taylor, 2014). Previous studies examined also whether the application of non-invasive neuromodulatory techniques can have similar effects on patients diagnosed with dementia.

Finally, one of the most recent advancements in language intervention is the option of treating general cognitive abilities, e.g., executive functions (EF), in order to improve language as well. Successful language processing is the result of close "collaboration" between language knowledge and cognitive resources. Individuals

[1] Low-frequency (1–4 Hz) rTMS has inhibitory effects, while high-frequency stimulation (>5 Hz) causes excitatory effects; similarly, cathodal tDCS induces neural hyperpolarization reducing the responsiveness of the neurons leading to inhibition of performance, while anodal induces neural depolarization, increasing neurons' excitability (Pini et al., 2019).

with neurodegenerative conditions are predicted to be unable to use these cognitive resources, thus leading to language failures as well. Driven by that, researchers have suggested that training EF (e.g., working memory or conflict resolution) may also demonstrate positive transfer effects in the linguistic domain, given that similar processing mechanisms are taking place in both domains. In other words, training focused on the shared processes between EF and language skills might facilitate performance in particular language tasks. Given that conflict resolution processes contribute to a range of linguistic skills, EF training targeting such processes could theoretically yield wider performance gains in the domain of language. Up to now, studies have shown that EF enhancement can cause positive transfer effects in healthy participants as well as in individuals with damage to the left ventrolateral prefrontal cortex (which has been directly associated with EF) in comprehension tasks (Hoffman, Jefferies, & Lambon Ralph, 2010), in verbal fluency (Kan & Thompson-Schill, 2004; Novick, Kan, & Thompson-Schill, 2009; Schnur et al., 2009), as well as in resolution of lexical (Bilenko, Grindrod, Myers, & Blumstein, 2009; Copland, Sefe, Ashley, Hudson, & Chenery, 2009; Khanna & Boland, 2010), syntactic (Hussey & Novick, 2012; Hussey, Teubner-Rhodes, Dougherty, Bunting, & Novick, 2010; Novick, Trueswell, & Thompson-Schill, 2005), and referential ambiguities (Brown-Schmidt, 2009). In these studies, generalization of the positive transfer effects of the training is not predicted only for the untrained items but also for all other tasks that share similar underlying processes, common to the processes enhanced. For instance, training of conflict resolution might facilitate memory, e.g., in the *n-back* memory task which requires conflict resolution (D'Esposito & Postle, 1999; Kane & Engle, 2000), while transfer is also predicted to occur in language processing. Although such outcomes have substantial implications for language processing, these findings have been largely neglected in psycho~/neurolinguistic research, theoretical or clinical approaches.

In the remaining of the paper, we will be tackling these issues and presenting some key studies and findings related to language intervention in neurodegenerative diseases. The paper is organized as follows: in Sect. 3.2, we briefly present the neurodegenerative conditions we will be discussing (mild cognitive impairment (MCI), AD, PPA) with a focus on the language deficits these populations exhibit. Section 3.3 is dedicated in presenting the various behavioral and neuromodulatory interventions on populations with dementia (AD and MCI), while Sect. 3.4 describes intervention approaches in PPA. Section 3.5 summarizes the findings and concludes the chapter.

3.2 Language Profiles of Individuals with MCI, AD, and PPA

3.2.1 MCI

MCI is defined as the transition stage between normal aging and dementia and is characterized by loss of cognitive and functional abilities, without, however, meeting the dementia criteria (Petersen et al., 2001). Patients who demonstrate impair-

ment in domains other than memory, including language, are more likely to develop dementia (ibid.). With respect to language impairment in MCI, there exists plentiful evidence from standardized tests (for a review, see Taler & Philips, 2008) and not much from psycholinguistic studies. Concerning word finding abilities and verbal fluency, results are controversial. Some studies report no impairment (e.g., Albert, Moss, Blacker, Tanzi, & McArdle, 2007), while others found word generation and retrieval process to be compromised in both phonemic and category verbal fluency tasks (Demetriou & Holtzer, 2017). MCI patients were, also, found to have difficulties in recalling and producing verbs in a verb fluency task (Alegret et al., 2018). Difficulties in processing ambiguous words (Taler & Jarema, 2006) and impaired naming and semantic knowledge of objects (Joubert et al., 2010) were also reported. In a lexical decision task, Manouilidou et al. (2014) reported difficulties in processing concrete and abstract words and impaired semantic priming in MCI. Concerning morphological knowledge and syntactic structure, studies have disclosed controversial findings in MCI individuals showing either impaired (Lambon Ralph, Patterson, Graham, Dawson, & Hodges, 2003) or spared performance (e.g., De Jager, Hogervorst, Combrinck, & Budge, 2003). In a recent study, Manouilidou, Dolenc, Marvin, and Pirtošek (2016a) examined MCI individuals' abilities to detect morphological violations in an off-line grammaticality judgment task and an online lexical decision task. Results revealed that patients' structural knowledge was not affected, but processing morphological structure was impaired, especially in the lexical decision task due to time pressure.

MCI individuals' language difficulties have been attributed to impairments in episodic, working (Summers & Saunders, 2012), and semantic memory (Wilson, Leurgans, Boyle, & Bennett, 2011), processing speed limitations, impaired attention, and executive dysfunction (Summers & Saunders, 2012). Duong, Whitehead, Hanratty, and Chertkow (2006), by employing a Stroop picture-naming task, suggested that MCI patients' performance might be affected by the type of task they are asked to perform and not only by their language abilities. Increased task complexity might lead MCI patients to low performance levels, indicating that impaired EF can also interfere with language processing. Similarly, Manouilidou et al. (2016a) point out that impaired EF, which helps patients evaluate the necessary information according to the requirements of the specific task, might affect MCI individuals' language performance.

3.2.2 AD

AD is a chronic neurodegenerative disease and the most common type of dementia (Visser, Verhey, Knol, Scheltens, et al., 1999), characterized by progressive cognitive dysfunction. Diagnosing dementia based on neuropsychological assessment requires the presence of impairment in the domain of memory and in one of the other cognitive domains (Lindenboom & Weinstein, 2004). At the initial stages of AD, working memory is impaired (Braaten, Parsons, McCue, Sellers, & Burns, 2006), leading to difficulties in learning new things related either to semantic or

episodic memory. As the disease progresses, dysfunction in other cognitive domains, such as EF, attention, and visuospatial skills, is observed. Language abilities are also affected during all stages of the disease with patients having difficulties in both production and comprehension of discourse, reading, and writing (Taler & Philips, 2008). Generally, AD patients' speech displays word-finding difficulties, empty phrases, lack of coherence, and impairment in both grammatical and semantic aspects of language (Altmann, Kempler, & Andersen, 2001; Kavé & Dassa, 2018; Kavé & Goral, 2018).

An early symptom of AD is difficulties in producing and recalling single words. Previous studies have already revealed noun and verb naming disorders in AD patients due to impairment at different levels of language processing. Recent studies report noun naming deficits in AD patients in a revised version of Boston Naming Test and a picture-naming task (Salehi, Reisi, & Ghasisin, 2017; Silagi, Bertolucci, & Ortiz, 2015). More specifically, regarding patients' naming abilities, these studies (Salehi et al., 2017; Silagi et al., 2015) revealed that naming errors are different in terms of quantity and quality among the different stages of the disease (mild and moderate), with patients at the initial stage producing more semantic errors and patients with moderate symptoms producing fewer correct responses and mainly no responses at all. While nouns were found to be more impaired than verbs (Whatmough & Chertkow, 2002), verb naming is also affected in AD. Robinson, Grossman, White-Devine, and D'Esposito (1996) have reported category-specific impairments in AD patients, with nouns being better preserved than verbs in a picture-naming task where homophonic and homographic nouns and verbs (e.g., "fish," "paint") were tested. Moreover, Masterson et al. (2007) observed more errors and slower reaction times to verbs compared to nouns in a picture-naming task and a word-picture verification task in an AD population. The above findings are in line with studies suggesting that verb production and comprehension abilities are more impaired than noun naming abilities in AD (Drucks et al., 2006; Kim & Thompson, 2004). Finally, impaired processing of verbs in AD has also been observed through verb fluency tasks, where patients presented with recalling and producing difficulties (Alegret et al., 2018).

Morphosyntactic abilities in AD have been found to be intact in previous studies. For instance, Kavé and Levy (2003) found AD patients' speech less informative with more semantic errors compared to controls, but their language remained structurally rich. More specifically, patients produced the same syntactic (e.g., independent, declarative clauses) and morphological (e.g., inflected words, verb forms) structures as the cognitively intact participants did. Contrary to these findings, Fyndanis et al. (2013) found Greek-speaking mild-to-moderate AD individuals to be impaired in tense, agreement, and especially aspect production in a sentence completion task. Other studies also reveal general morphosyntactic impairment in AD, such as impaired verb morphology (Walenski, Sosta, Cappa, & Ullman, 2009), morphosyntactic errors (e.g., incorrect inflections, word order errors, and missing matrix or subordinate clauses) in AD individuals' spontaneous speech and oral production (Altmann et al., 2001), and difficulties in interpreting thematic roles of

verbs (e.g., Manouilidou & de Almeida, 2009; Manouilidou, de Almeida, Schwartz, & Nair, 2009).

It has been argued that language impairment in AD is associated with memory limitations and cognitive impairment. Naming deficits, for example, might be attributed to degraded semantic memory, the part of long-term memory which includes language and mental lexicon information (Braaten et al., 2006; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005). Problems with lexical retrieval might indicate either deficit in accessing semantic knowledge-information of a word or difficulties in recalling its phonological form (Salehi et al., 2017; Silagi et al., 2015). Working memory limitations may also be the source of deficits in some language aspects. Specifically, the central executive component of working memory has been found to be impaired in AD individuals (Baddeley, 1996; Kensinger, Shearer, Locascio, Growdon, & Corkin, 2003).

3.2.3 PPA

PPA is a clinical syndrome caused by a neurodegenerative disease, in which language is the main domain of dysfunction for at least the initial stages of the disease, while other cognitive functions such as memory, behavior, and visuospatial abilities deteriorate as the disease progresses (Mesulam, 1982, 2013). Based on language impairments and neuropathological criteria, three major PPA variants have been reported (Gorno-Tempini et al., 2004, 2011; Maruta, Pereira, Madeira, De Mendonça, & Guerreiro, 2015; Mesulam et al., 2009; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012): *semantic PPA* (PPA-S), which is linked with deficits in semantic knowledge and object naming; *logopenic PPA* (PPA-L), which is characterized by impaired word retrieval and sentence repetition; and *agrammatic PPA* (PPA-G), which is associated with grammatical impairments that are evident across linguistic domains in both production and comprehension.

While there are striking similarities between these three variants, given that they all affect word-level knowledge, we also find distinct language profiles. Specifically, although anomia is a common feature in all variants, several studies that have examined the performance of PPA patients in various aspects of word knowledge, such as functional category (i.e., content vs. function words), grammatical category (i.e., nouns, verbs, adjectives), and morphological status of a word (i.e., inflected, derived, or compound words), suggest different word knowledge deficits in each PPA subtype. In particular, PPA-G patients have shown greater difficulty in production (but not in comprehension) of verbs compared to nouns (Ash et al., 2010; Hillis et al., 2006; Thompson, Lukic, King, Mesulam, & Weintraub, 2012) and a trend towards higher ratios of content compared to function words in connected speech production (Thompson et al., 2012, 2013; Wilson et al., 2010). Moreover, PPA-L patients did not significantly differ from controls in the production of content versus function words. Concerning the effect of grammatical category, they did not exhibit differences in nouns and verbs in either production or comprehension, albeit there is a

tendency for impaired noun production (Thompson, Cho, et al., 2012; Wilson et al., 2010). Finally, PPA-S patients exhibited lower content to function word ratios than controls (Thompson, Cho, et al., 2012). Furthermore, they present with impairments in noun processing (Hillis et al., 2006; Thompson, Lukic, et al., 2012), while production and comprehension of verbs is relatively maintained. The noun-verb dissociation indicates that objects are more impaired than actions in both comprehension and production domains, which is thought to result from semantic memory impairment in object recognition and knowledge (Adlam et al., 2006).

When it comes to morphological processes, a few studies have reported that PPA-G is linked to impaired production of English inflected words (Schneider, Thompson, & Luring, 1996; Thompson, Cho, et al., 2012; Thompson & Mack, 2014), albeit there is evidence for better performance in regular words (Wilson et al., 2014). Regarding derivation, Manouilidou, Nerantzini, Dougherty, and Thompson (2016b) have examined PPA-G patients' ability to detect different types of pseudo-words violating various constraints of deverbal word formation[2] and reported that they appeared to be not very sensitive to the violations of the combinatorial properties of stems and affixes. Moreover, while derivational morphology has not been examined in PPA-L, evidence from inflectional morphology indicated that patients did not exhibit difficulties in production of verb morphology (Thompson et al., 2013; Thompson & Mack, 2014). On the other hand, research in inflection and derivation is more fruitful in PPA-S (Auclair-Ouellet, Fossard, Houde, Laforce, & Macoir, 2016). In particular, as in PPA-L, production of verb morphology is also preserved in PPA-S (Thompson & Mack, 2014). Additionally, several studies have reported more difficulties with the formation of irregular verbs than regular ones, suggesting a preservation of rule knowledge despite the shortcomings in lexical retrieval procedures (Benedet, Patterson, Gomez-Pastor, & Luisa-Garcia de la Rocha, 2006; Jefferies, Rogers, Hopper, & Lambon Ralph, 2010; Wilson et al., 2014). Given that irregular verbs (e.g., "go"-"went") are more idiosyncratic and rely more on semantic features, this pattern could be attributed to semantic decline which dominates in PPA-S (Patterson et al., 2006). Additional evidence for retained rule knowledge in PPA-S comes from recent studies on derivational morphology which indicated that derivational rules are relatively preserved in this variant (Kavé, Heinik, & Biran, 2012; Meteyard & Patterson, 2009). Specifically, Auclair-Ouellet et al. (2016) reported findings from a PPA-S patient who retained the ability to produce derived verbs semantically related to nouns in a transparent way, while when the morphological relationship was opaque (e.g., due to root allomorphy), the patient made errors by adding the more frequent productive ending to the noun bases. Finally, Kordouli, Manouilidou, Stavrakaki, Mamouli, and Ioannidis (2018) report major difficulties with the production of compound words with prominent errors being descriptions of the compound targets and single-word errors, suggesting unawareness of the compound status and morphological structure in PPA-G.

[2] The process of creating a lexical item from a verbal basis. For instance, *teach* > *teacher*, *play* > *playing*, *understand* > *understandable*.

Evidently, a wide spectrum of disorders and language problems appear in each of the aforementioned conditions. With this in mind, in the following sections we will be discussing intervention approaches in populations with MCI, AD, and PPA.

3.3 Intervention Approaches in MCI and AD

Different types of interventions have been used in neurodegenerative diseases aiming to either alleviate some symptoms or reduce the rate of decline in the disease progression. Notably, the beneficial effects of pharmacological treatments [e.g., dextroamphetamine (McNeil, Small, Masterson, & Fossett, 1995); bromocriptine (Farrajota et al., 2012; Reed, Johnson, Thompson, Weintraub, & Mesulam, 2004); galantamine (Kertesz et al., 2008); oral steroids (Decker & Heilman, 2008); and memantine (Johnson et al., 2010)], have not been proven scientifically, since there is no compelling evidence that medications can successfully be used as cognitive enhancers in dementia by slowing or eliminating language decline. Instead, Boxer et al. (2013) showed that the use of memantine treatment in PPA-S and PPA-G can even have a negative effect, with participants performing significantly worse on the Boston Naming Test after receiving memantine treatment, compared to the control group who received a placebo. However, other treatment types such as behavioral treatments, neuromodulatory rehabilitation (e.g., rTMS and tDCS), or combined interventions (e.g., neuromodulatory and linguistic intervention) have shown more promising results, maximizing the efficacy of the intervention while producing more sustained improvements.

Specifically, when it comes to MCI and AD behavioral intervention techniques, Zhao and Li (2017) report that there are three main types: a) rehearsal-based approaches, (b) compensatory techniques, and (c) mnemonic strategies. As the name suggests, rehearsal-based approaches require patients to repeat information over time. Techniques employing compensatory aids, on the other hand, aim to change or augment memory processes, hence altering the manner of learning, retention, and information retrieval of patients. Finally, cognitive "instruments" that help organize and connect new messages through internal compensatory aids fall under the category of mnemonic strategies.

A common characteristic of most intervention studies related to MCI is their low success rate in both receptive and expressive communication (for a review, see Johnson & Lin, 2014), a fact that can be attributed either to the small sample size of these studies or to their treatment focus, which has not always been directly related to communication. Their success rate is considerably higher in AD though. The most common language domains of intervention in both MCI and AD are *verbal fluency*, *semantic memory*, *speech*, and *discourse*, although the majority of existing studies target multiple cognitive domains, such as memory, EF and visuospatial skills, as well as language. Computerized cognitive training (CCT) appears to be an intervention method favored by a significant number of studies. Specifically, Wenisch et al. (2007) targeted memory, EF, and visuospatial skills by teaching cog-

nitive strategies and demonstrated no significant change in the measure of verbal fluency in either the 12 subjects with MCI or the 12 healthy counterparts following the intervention. Barnes et al. (2009) targeted auditory processing speed and accuracy by using CCT; no significant differences were found between treatment (22 subjects with MCI) and control (25 subjects without MCI) groups on measures of semantic memory and verbal fluency in the post-intervention phase. Similarly, Cipriani, Bianchetti, and Trabucchi (2006) failed to elicit improvement on verbal fluency after CCT for attention, memory, perception, visuospatial cognition, and language skills in MCI, but the ten AD patients who participated in this study did improve on the phonemic fluency task. Finally, Talassi et al. (2007), by combining CCT with occupational therapy and behavioral training, also found no significant difference in the intervention groups (30 with MCI, 24 with mild dementia) on verbal fluency or discourse (story recall). In contrast, Rozzini et al. (2007) examined the effects of CCT (addressing attention, memory, abstract reasoning, visuospatial skills, and language) alone, as well as in combination with cholinesterase inhibitors, to a no treatment group (n = 22) and demonstrated significant improvement for the group receiving the combined intervention on story recall (receptive and expressive discourse), but not on verbal fluency measures. The CCT-only group and the control group did not show any significant improvements on either language measure.

While behavioral treatments do not appear to be particularly successful, high-frequency rTMS has typically been used successfully in studies of neurodegenerative diseases, given that the LH language network is broadly downregulated (Norise & Hamilton, 2017; Pini et al., 2019). Trebbastoni et al. (2016) have recently investigated cortical excitability and synaptic plasticity in 40 patients with amnestic MCI which have the highest risk of conversion to AD. The authors applied trains of 5 Hz rTMS stimulation, and participants were followed up annually up to a period of 48 months. MCI participants displayed cortical hyperexcitability and altered synaptic plasticity to 5 Hz-rTMS when compared with healthy controls, suggesting that these alterations, which have previously been observed in AD, are thus present in the early stages of disease and may be considered as potential neurophysiological markers of conversion from MCI to AD.

In a series of studies, Cotelli and colleagues have reported significant long-lasting effects of high-frequency rTMS in AD patients. For instance, in Cotelli et al. (2011), rTMS was applied to AD patients to assess the duration of its effects on language performance. It was found that a 4-week daily real rTMS treatment was able to induce at least an 8-week lasting effect on the improved performance when it comes to cognitive abilities (memory, language, executive functions). Similarly, rTMS was found to improve *naming* at all stages of AD (Cotelli, Manenti, Cappa, Zanetti, & Miniussi, 2008), to improve specific *action naming* (Cotelli et al., 2006) and also *auditory sentence comprehension* (Cotelli, Calabria, Manenti, et al., 2012). In Cotelli et al. (2012), a significant difference was found between groups (TMS vs. placebo) over sessions in terms of the percentage of correct responses of auditory sentence comprehension. Only real treatment induced an improvement in performance with respect to baseline or placebo. Moreover, both groups showed a lasting effect on the improved performance 8 weeks after the end of treatment.

Similarly, Ahmed, Darwish, Khedr, El Serogy, and Ali (2012) have reported long-lasting effects in mild-to-moderate AD patients who received high-frequency rTMS for 5 consecutive days. More specifically, in the follow-up evaluation (after each session and after 1 and 3 months since the end of the treatment), 15 mild-to-moderate AD patients who had received high-frequency rTMS were found to be improved in the Mini Mental State Examination scale compared to the 15 who had received low-frequency stimulation and the 15 ones who had received sham treatment. Moreover, both Cotelli et al. (2011) and Ahmed et al. (2012) have reported behavioral improvement and enhanced performance in the Instrumental Activities of Daily Living Scale and Geriatric Depression Scale.

In healthy populations, the effect of rTMS was limited to the left DLPFC (Cotelli et al., 2008). However, in AD participants, the stimulation of both right and left DLPFC seems to lead to more effective results, supporting the idea of functional plasticity. It is possible for AD individuals to recruit the RH in order to balance the impairment of the LH.

3.4 Intervention Approaches in PPA

Most of the behavioral intervention studies in PPA have either focused on *fluency* and *word finding* difficulties, as anomia is the most pervasive symptom in all PPA variants (e.g., Carthery-Goulart, Silveira, Machado, et al., 2013; Croot et al., 2015; Croot, Nickels, Laurence, & Manning, 2009; Dressel et al., 2010; Frattali, 2004; Harciarek, Sitek, & Kertesz, 2014; Jokel et al., 2014; Krajenbrink, Croot, Taylor, & Nickels, 2016; Meyer, Tippett, Turner, & Friedman, 2018; Newhart et al., 2009; for computer-based treatment applications, see Evans, Quimby, Dickey, & Dickerson, 2016; Jokel, Cupit, Rochon, & Leonard, 2009; Jokel, Rochon, & Leonard, 2006), or on *spelling impairments* (dysgraphia), which also arise early in all three types of PPA (Faria et al., 2013; Graham, 2014; Rapp & Glucroft, 2009; Tsapkini & Hillis, 2013). A combination of treatments focusing on both oral and written difficulties (Krajenbrink et al., 2016) has recently been applied in PPA to investigate the facilitatory effect of written components to lexical retrieval. Other behavioral treatments target grammatical deficits and verb production (Hameister, Nickels, Abel, & Croot, 2017; Henry et al., 2018; Machado, Campanha, Caramelli, & Carthery-Goulart, 2014; Schneider et al., 1996), semantic processes (Bier et al., 2009), phonological processes (Jefferies, Bott, Ehsan, & Lambon Ralph, 2011; Louis et al., 2001), discourse (Cartwright & Elliott, 2009; Whitworth et al., 2018), speech intelligibility (Henry et al., 2013, 2018), or reading (Heredia, Sage, Lambon Ralph, & Berthier, 2009).

These studies have shown that behavioral treatment can be substantially beneficial for PPA patients if early intervention takes place, since these patients have proven adequate (a) to change and relearn/or regain their lost abilities by adopting new strategies and (b) to impede further loss of a particular function by retaining the gained abilities and generalizing therapy gains over time. Nonetheless, varying out-

comes have been observed across studies, possibly due to the fact that their vast majority are either single-case studies or have a small sample size, mainly involving PPA-S patients, but markedly fewer PPA-L or PPA-G patients.

Generalization of therapy gains seems to vary substantially across the different subtypes of PPA, with higher prevalence reported for PPA-G or PPA-L, compared with PPA-S (Cadorio, Lousada, Martins, & Figueiredo, 2017), although treatment studies for PPA-L are far fewer than those for PPA-G or PPA-S. Specifically, although immediate treatment gains have been documented in almost all published studies of lexical retrieval in PPA (Cadorio et al., 2017; Croot et al., 2009, 2019; Jokel et al., 2014; Savage, Piguet, & Hodges, 2014), PPA-S participants are less amenable to treatment in terms of generalization to untreated items (Graham, Patterson, Pratt, & Hodges, 2001; Bier et al., 2009, 2011, Bier et al., 2015, Dressel et al., 2010; Senaha, Brucki, & Nitrini, 2010; Newhart et al., 2009; Frattali, 2004; but see Savage et al., 2014; for generalization in contexts closely resembling the training concepts), possibly due to impairment in the semantic network and its concomitant deterioration. Interestingly, Mayberry, Sage, Ehsan, and Lambon Ralph (2011) reported overgeneralization in two participants with PPA-S patients, who tended to overgeneralize the relearned trained items to concepts that were semantically and superficially similar, but not to distantly related or unrelated items, suggesting that the degraded semantic system is still involved.

Similarly, lexical retrieval interventions in PPA-G revealed that although participants are able to relearn associations and improve in the trained items, training gains do not generalize to untrained items (Croot et al., 2015, 2019; Marcotte & Ansaldo, 2010) but only to different tasks (Jokel et al., 2009). Specifically, Jokel et al. (2009) documented no generalization to untreated items after administering a naming intervention, but they noticed an improvement outside the context of picture-naming, (i.e., in the accuracy of their syntactic production, as measured by a sentence production task). Given that anomia emerges later in this variant (Gorno-Tempini et al., 2004; Hillis, Oh, & Ken, 2004; Hillis, Tuffiash, & Caramazza, 2002), sentence-level behavioral treatments have also been applied in PPA-G. Schneider et al. (1996) demonstrated that verbal treatment [production of transitive verbs with different tense markers in simple sentences (e.g., *The Woman Kissed the Man*)] can yield treatment gains for verb tense markers, and generalization to untrained verbs within similar contexts (e.g., *The Man Pushed the Baby*), suggesting that other word classes apart from nouns are amenable to treatment in PPA. Similar results were obtained by Machado et al. (2014), who reported an improvement for trained and untrained sentences after applying a short-term treatment focusing on errorless learning targeting verb inflection and sentence production, and by Hameister et al. (2017), who demonstrated significant therapy benefits in the production of trained and untrained grammatical structures after applying a constraint-induced treatment approach (Pulvermüller et al., 2001). Recently, Henry et al. (2018) showed that script treatment targeting speech production and fluency can result in immediate gains in the production of correct, intelligible scripted words for trained topics, a reduction in grammatical errors for trained topics, and an overall increase in intelligibility for trained as well as untrained topics post-treatment.

In PPA-L, lexical retrieval interventions have proven beneficial, with training gains evident in both trained and untrained items (Beeson et al., 2011; Meyer, Snider, Eckmann, & Friedman, 2015; Newhart et al., 2009). Newhart et al. (2009) demonstrated significant improvements in naming accuracy both to trained and untrained categories in a participant with PPA-L, after administering a cueing hierarchy treatment for naming pictured objects. The authors associated this effect to his relatively spared semantic system and to the activation of the network involved in lexical retrieval, which led to improved access to the phonological lexicon. Similarly, Beeson et al. (2011) presented the beneficial results of semantic elaboration strategies in lexical retrieval in one participant with PPA-L that led to significant improvements in naming and broader generalization even to untreated items, compared to learning lists of items, a strategy that typically results in item-specific generalization. Meyer et al. (2015) applied an orthographic treatment in English in a Norwegian-English bilingual woman with PPA-L, which resulted in transfer of the therapy gains to her other language (Norwegian) in the same task (oral naming) and in a different task (name retrieval based on written definitions read aloud by the experimenter). The authors suggested that the English orthographic training reinforced the language-independent semantic representations of the treated items, thereby facilitating access to their Norwegian phonological representations.

Nonetheless, most studies to date have not followed patients for a substantial period of time post-treatment to determine the longer-term outcomes of intervention (but see Henry et al., 2013; Meyer et al., 2018). Thus, it is hard to ultimately assess the effectiveness of behavioral interventions in the different variants of neurodegenerative diseases since our current knowledge regarding the maintenance of improvement in the long-term perspective is rather limited or not systematically examined due to the absence of randomized clinical trials. Despite the progressive nature of the disorder, most of the studies have shown that therapy gains are maintained for the short term (1 week to 6 months post-therapy), irrespective of PPA subtype. Continuous rehearsal has proven beneficial to maintaining relearned knowledge (Jokel et al., 2006; Jokel, Rochon, & Anderson, 2010). Characteristically, in the absence of continuous rehearsal, performance tends to decline under baseline levels after a period of 6 months (Graham, Patterson, Pratt, & Hodges, 1999).

More recently, the use of TMS has proven to be a powerful tool for intervention in PPA. Several studies have shown that high-frequency rTMS in PPA patients can enhance the residual language function in atrophic cortical areas, improving participants' performance in a variety of language tasks, including action naming (Cotelli et al., 2012), verb production (Finocchiaro et al., 2006), and oral and written abilities (Trebbastoni, Raccah, de Lena, Zangen, & Inghilleri, 2013), as well as in cognitive tasks (Antczak et al., 2018). Similar results have been yielded with anodal tDCS, with improvements reported in naming (Cotelli et al., 2014; Hung et al., 2017), speech production and narration (Gervits et al., 2016), spelling (Tsapkini, Frangakis, Gomez, Davis, & Hillis, 2014), and subtests of the Psycholinguistic Assessment in Chinese Aphasia including auditory word-picture identification, picture-naming, oral word reading, and word repetition (Wang, Wu, Chen, Yuan, & Zhang, 2013). For a comprehensive review of noninvasive brain stimulation find-

ings in post-stroke and neurodegenerative aphasia, see Norise and Hamilton (2017) and Crinion (2016).

Specifically, Cotelli et al. (2012) applied bilateral high-frequency rTMS to the DLPFC during object and action naming in ten PPA-G and four PPA-S patients, showing action-naming enhancement only after/during real stimulation in PPA-G, while no facilitating effect was found on object naming. In PPA-S patients, no effect of stimulation was reported. Finocchiaro et al. (2006) applied 20 Hz rTMS over the left prefrontal cortex in one PPA participant and reported sustained significant and lasting improvement in verb production compared to both baseline and sham conditions. Trebbastoni et al. (2013) demonstrated that the application of high-frequency rTMS to the left DLPFC in a PPA-L patient led to improvements in accuracy of oral and written skills (with significant reduction in the number of semantic and syntactic errors in sentences) only after real stimulation. Recently, Antczak et al. (2018) applied bilateral rTMS (10 Hz) over the DLPFC in nine patients with the behavioral variant of FTD and one with PPA-G, showing cognitive improvements and significant reduction of errors in tasks such as the MoCa screening test, the Stroop color naming-word reading task, the verbal fluency test, and the letter and the digit cancellation test (which assesses sustained attention).

Regarding tDCS, Cotelli et al. (2014) investigated whether the application of anodal tDCS over the left DLPFC in combination with individualized speech therapy would benefit PPA-G patients in naming accuracy. Eight PPA-G patients were enrolled in the treatment group and eight others in the placebo group. Although both groups benefited from the individualized speech therapy, the group who received anodal tDCS benefited the most, since greater improvements in naming skills were reported compared to the placebo group. Wang et al. (2013) also applied anodal tDCS over the left posterior peri-Sylvian region in the morning and over the left inferior frontal gyrus in the afternoon, for 5 consecutive days, in a PPA-G patient. Performance improvements were reported in language-related tasks such as auditory word comprehension, picture-naming, oral word reading, and word repetition only after real stimulation, suggesting that anodal tDCS over the left posterior peri-Sylvian region and Broca's area can enhance language learning in PPA patients. Additionally, cortical excitability during language tasks was upregulated in the stimulated and non-stimulated areas, providing evidence for the modulatory effects of tDCS on the brain region directly underlying the stimulated areas, but also on a network of regions that are functionally interconnected with the stimulated area. Gervits et al. (2016) applied anodal tDCS paired with a speech elicitation task over the left frontotemporal region in four patients with PPA-L and two PPA-G participants. Improvements were observed in language-related tasks, including picture-naming, speech fluency (with increased speech rate and utterance length in a spontaneous picture narration task), grammatical comprehension, semantic processing, and sentence repetition. The authors suggested that the wide range of improvements observed in language abilities might be due to the increased distribution of the current flow to a broader network of LH peri-Sylvian areas supporting these abilities. Recently, Hung et al. (2017) applied anodal tDCS over the left temporoparietal cortex paired with behavioral therapy (semantic feature analysis) that

consisted of repeated naming and semantic feature generation, in three patients with PPA-S, one with PPA-L, and one with severe anomia associated with early-onset AD. All participants (with the exception of the AD patient) showed advantages in naming trained over untrained items after real stimulation, an effect that lasted for 6 months post-treatment, relative to untrained items that showed continued progressive decline.

Thus, it seems that although the application of those techniques as independent therapeutic tools has been effective, there is still room for improving their combination with behavioral training, given that their synergistic effects creat more persistent behavioral changes (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Gill, Shah-Basak, & Hamilton, 2015; Tippett et al., 2015; Tsagaris, Labar, & Edwards, 2016).

3.5 Conclusion

The vast majority of the reviewed studies has shown improvements on language skills in patients with different forms of dementia receiving behavioral or noninvasive neuromodulatory stimulation, suggesting that participants with neurodegenerative diseases are able to regain their lost abilities and retain the gained abilities over some time.

However, not all of those studies have shown generalization to other tasks/or untrained items and long-lasting effects, possibly due to methodological or individual factors. With respect to methodological caveats, the majority of the conducted studies in the field are small-sized studies or single-case studies, in which treatment duration and designs differ across studies. In that sense, the interpretation of the reported outcomes requires caution. Moreover, most studies to date have not followed patients for a substantial period of time post-treatment to determine the longer-term outcomes of intervention (but see Henry et al., 2013; Meyer et al., 2018). Determining the duration of therapeutic effects is critical, because it enables more effective planning as to when treatment should be repeated, if at all. Besides, individual factors also interfere, since there is huge heterogeneity of symptoms and pathologies within the different dementia types and PPA variants, different stages of disease progression at baseline, and variable disease resilience with different decline rates among participants (Wilson et al., 2013). In light of these methodological caveats, it remains difficult to ultimately assess the effectiveness of interventions in the different types of neurodegenerative diseases. Our current knowledge regarding the presence of generalization of therapy effects and the maintenance of improvement in the long-term perspective is, thus, rather limited or at least not systematically examined due to the absence of randomized clinical trials.

Nonetheless, neuroplasticity-based interventions remain highly promising with respect to delaying and even altering the trajectory of language decline in neurodegeneration. Strong collaborations between basic and clinical research can help address pivotal questions regarding plasticity mechanisms, better understand the

limitations of current approaches, and head toward improved models of intervention with coherent results for all populations involved.

Acknowledgments We would like to thank Georgios Argyropoulos and Ioannis Papakyritsis for thoroughly reading the manuscript. Writing of the chapter was partly supported by grant J6-1806 from ARRS (Slovenian Research Agency) awarded to Christina Manouilidou.

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Chapter 4
Neural and Genetic Mechanisms of Dyslexia

Tracy M. Centanni

Abbreviations

A1	Primary auditory cortex
DYS	Dyslexia
PA	Phonological awareness
RAN	Rapid automatized naming
SES	Socioeconomic status
SNP	Single nucleotide polymorphism
TD	Typically developing

4.1 Dyslexia Is a Heterogeneous Disorder: Behaviorally, Cortically, and Genetically

Dyslexia is a common neurodevelopmental disorder, affecting between 5 and 15% of children (Peterson & Pennington, 2012). Individuals with this diagnosis exhibit reading skills less than 1 standard deviation below their peers in spite of normal nonverbal intelligence and adequate instruction. In spite of this clear set of diagnostic criteria, the population of individuals with dyslexia is diverse, with various combinations of deficits [including difficulties in rhyming, spelling, phonological awareness, fluency, and/or comprehension (Zoubrinetzky, Bielle, & Valdois, 2014)]. For many decades, the field has debated (sometimes fiercely) the underlying core deficit(s) of dyslexia—which deficit is the causal one?

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_4

Two specific skills have received the most attention in this arena. The first, phonological awareness (PA), is defined as an individual's understanding of the individual sounds within a word and the ability to parse and manipulate these phonemes (Gillon, 2005). Difficulties in PA are highlighted in a number of tasks, including subtests of the Comprehensive Test of Phonological Processing (CTOPP; Wagner, Torgesen, & Pearson, 2013), Elision (the participant is asked to manipulate phonemes, e.g., say the word "brake" without the "r" sound), and Blending Words (two pseudowords are presented, e.g., "dade" and "mame," and the participant must blend them together to form a word, e.g., "dame" or "made"). Phoneme knowledge is especially important in early reading because knowledge of individual letter-sound relationships subserves the ability to sound out and read unfamiliar words. Across languages, phoneme awareness ability is an early predictor of reading difficulties in children up to age 12, but this skill loses its predictive value quickly in transparent orthographies where each letter is associated with only one sound (Furnes & Samuelsson, 2010; Landerl et al., 2013; Landerl, Wimmer, & Frith, 1997; Ziegler et al., 2010). In these cases, since the letter-sound relationships are simple, they are easier to master, and reading instruction shifts away from phonology earlier in schooling than in more difficult orthographies such as English. Therefore, PA deficits that persist are more prevalent in complex orthographies than in transparent ones.

The second dyslexia deficit that has been extensively studied is rapid automatized naming (RAN)—a skill related to the fluency with which an individual can name objects, digits, and letters (Denckla & Rudel, 1976; Norton & Wolf, 2012). In opaque orthographies, where there can be multiple sounds associated with a single letter or combination of letters, such as English, RAN skills early in life predict outcomes for children who will go on to be reading-impaired but not for children who go on to be typical readers (Lervåg & Hulme, 2009; Meyer, Wood, Hart, & Felton, 1998; Scarborough, 1998). Interestingly, this relationship exists across orthographies, with children in more transparent orthographies such as Spanish exhibiting RAN deficits more frequently than PA ones (Serrano & Defior, 2008). A study comparing children who spoke English, Greek, and Chinese demonstrated comparable relationships between rapid naming and reading across orthographies (Georgiou, Parrila, & Liao, 2008).

These two deficits, PA and RAN, are common in the population of individuals with dyslexia, and their prevalence in dyslexia is described by a theory known as the "double-deficit hypothesis" (Wolf & Bowers, 1999). This hypothesis posits that the population of those with developmental dyslexia is composed of individuals that fail to acquire reading through PA deficits, RAN deficits, or both. Under this model, there should be separable subgroups within dyslexia who share their reading struggles but differ in the biological mechanisms that cause the failure. The documentation of such subgroups is not a recent phenomenon—in the mid-1980s, researchers reported a group of children with dyslexia who exhibited automaticity deficits without the hallmark PA deficits typically attributed to dyslexia and a group of children with both RAN and PA deficits (Lovett, 1984). In order to begin addressing the different intervention needs of a child with dyslexia who struggled with speed

(as measured by RAN), Wolf, Miller, and Donnelly (2000) designed an intervention focused on automaticity and fluency to be used with or without more traditional PA interventions. After 70 h of intervention using the RAVE-O intervention program (Retrieval, Automaticity, Vocabulary Elaboration, Orthography) (Wolf et al., 2000), second and third graders with reading disabilities outperformed children with phoneme training only or math-tutored controls on a number of outcome measures, including decoding, word reading, and comprehension (Wolf et al., 2009). Though these behavioral subgroups have been documented, and customized interventions like RAVE-O exist, the focus on these subgroups has not yet reached the classroom, the clinic, or even many research labs. However, recently, researchers using neural imaging techniques have begun to study these subgroups in new ways.

In the sections that follow, I will discuss the history of mechanism research in humans with dyslexia, recent approaches to tackling these questions in animal models, and the relationship between these findings and those in humans. Finally, I will discuss potential applications for this approach into the future as well as the limitations of this method.

4.1.1 Heterogeneity in Dyslexia: Neural Differences

Since noninvasive neural imaging techniques are now well-established and often-used tools in studies of neurodevelopmental disorders in both children and adults, research on the double-deficit hypothesis has similarly branched out into this domain. Of course, research on the neural basis of dyslexia did not begin under a double-deficit framework, so many studies independently reported neural activation differences in response to auditory speech sounds and differences in the brain's response to rapid processing tasks. Two main hypotheses have arisen from this work, often referred to as the "Phonological Representations Hypothesis" and the "Access Hypothesis." The Phonological Representations Hypothesis states that the source of PA deficits in dyslexia is abnormal auditory cortex responses to speech sounds (Swan & Goswami, 1997). This hypothesis has been supported by a variety of imaging techniques, including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). Hypoactivation during phoneme-grapheme matching tasks resulted in reduced activation in ventral temporal cortex, suggesting deficits in matching auditory phoneme to visual graphemes (Cao, Bitan, Chou, Burman, & Booth, 2006). Studies using EEG (Hornickel & Kraus, 2013; Neef, Schaadt, & Friederici, 2016) and MEG (Centanni et al., 2018; Lehongre, Ramus, Villiermet, Schwartz, & Giraud, 2011) have similarly found that the auditory brainstem and primary auditory cortical areas in dyslexic participants respond inconsistently to speech sounds and amplitude-modulated noise, further supporting abnormal phonological representations.

In contrast, the Access Hypothesis states that dyslexia is caused not by abnormal phoneme representations but by deficits in retrieving those representations accurately and efficiently (for review, see Ramus & Szenkovits, 2008). A study using

positron-emission tomography (PET) replicated the reduced activation in language areas typically attributed to the Phonological Representations Hypothesis but theorized that these hypoactivations were due to deficits in connectivity between language regions and not due to abnormal auditory processing (Paulesu et al., 1996). Similarly, an fMRI study did not find differences in the auditory cortex responses to speech sounds between adults with and without dyslexia but did observe weaker connections between regions in the reading network (Boets, de Beeck, & Vandermosten, 2013).

In 2014, the first study to demonstrate separate neural activation patterns in children with each profile in the double-deficit hypothesis was conducted (Norton et al., 2014). First, the authors reported different patterns of activation during PA tasks (left frontal and parietal regions) compared to RAN tasks (right cerebellum), supporting that these skills are supported by separate neural networks. Children with deficits in both PA and RAN exhibited reduced activation in the frontal-parietal network during phoneme tasks compared to children with PA deficits alone and controls. Similarly, children with deficits in both skills exhibited reduced cerebellar activation on rapid naming tasks compared to children with RAN deficits alone and controls (Norton et al., 2014). Such heterogeneity in neural activation profiles among children with dyslexia supports the idea that children with different behavioral deficits require different intervention approaches. However, the cause of such heterogeneity is still relatively unknown.

4.1.2 Heterogeneity in Dyslexia: Genetic Differences

The variability in the dyslexia population, in terms of both behavior and neural correlates of the disorder, may be driven by the heterogeneity of the genes involved. Dyslexia is a heritable disorder, meaning that it has a strong genetic component and runs in families. Early studies on the genes implicated in dyslexia began by studying the postmortem brains of individuals who had dyslexia during their lifetimes. Galaburda and colleagues discovered common anatomical abnormalities among several individuals with dyslexia (Galaburda & Kemper, 1979; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Humphreys, Kaufmann, & Galaburda, 1990). Specifically, they observed two types of physical abnormalities: perisylvian polymicrogyria (an increased number of small folds in language areas of the brain) and ectopia (clusters of neurons in tissue where neurons were otherwise evenly distributed). The presence of ectopia was the more common of the two and was often observed in language-specific areas of the left temporal lobe. Given that these anatomical abnormalities involved neurons in unexpected locations and orientations, the authors concluded that genes involved in dyslexia were most likely to be genes involved in neural migration during in utero development. From this work, they identified four neural migration genes that remain the most well-studied dyslexia candidate genes: *DYX1C1*, *ROBO1*, *KIAA0319*, and *DCDC2* (Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006). Depending on the gene affected, some neurons

migrate too far, not far enough, or cluster together in ectopia (Burbridge et al., 2008; Galaburda et al., 2006; Szalkowski et al., 2012; but see Martinez-Garay et al., 2016). Follow-up work in rodent models has confirmed that suppressing the function of these genes leads to comparable anomalies, supporting the direct link between these genes and physical differences in the brain (Burbridge et al., 2008; Szalkowski, Fiondella, Truong, et al., 2012). Such physical abnormalities may interfere with the way in which neurons become specialized later in development or cause abnormal connections between neurons. Although these in utero functions are well known, it is possible that some or all of the deficits in dyslexia are due to postnatal gene dysfunction, though this hypothesis has not yet been tested.

Though these genes continue to be the target of most studies on the genetics of dyslexia, none of these genes has emerged as the single causal one, nor is there a consensus as to which of these is/are more influential on the disorder or how they interact to cause dyslexia. Like many communication disorders, dyslexia is likely a disorder caused by many genes and their interaction with the environment. Further, to date there is no single gene marker present across all cases of dyslexia, suggesting that there are multiple genetic pathways to the same disorder (Fisher & DeFries, 2002; Pennington et al., 1991; Scerri & Schulte-Körne, 2010). It has therefore been difficult to determine which genes are "dyslexia genes" and how each gene contributes to the disorder. Some researchers have therefore shifted their efforts towards understanding the role each of these genes plays in the context of dyslexia and the behavioral deficits that lead to failed reading acquisition.

4.2 The Use of Animal Models to Study the Genetics of Dyslexia

In humans, research attempting to link specific genes to behavioral deficits is correlational in nature by default—genetic expression cannot be altered in a human population for the purposes of a scientific inquiry. Therefore, research on the genetics of dyslexia has moved to an unlikely arena for reading research—animal models (most often rodents). When referring to gene names, common nomenclature is to italicize the gene name but not the protein. Human genes and proteins are written in all capital letters, while gene names and proteins in rat and mouse models have only the first letter capitalized. Although communication skills like language and reading are not present in the rodent, analogous versions of the genes controlling basic developmental functions, such as neural migration, are well conserved. Since, as described above, many of the dyslexia-associated genes are involved in neural migration processes, rodent models were initially used to replicate the structural abnormalities observed in postmortem study of humans with dyslexia (Burbridge et al., 2008; Currier, Etchegaray, Haight, Galaburda, & Rosen, 2011; Szalkowski, Fiondella, Truong, et al., 2012; Threlkeld et al., 2007). Of the four dyslexia-associated genes involved in regulating the process of neural migration, the two that

have been most extensively studied are *KIAA0319* and *DCDC2*. During neural migration, *KIAA0319*'s role is to ensure that a migrating neuron is well attached to the radial glia, a tightrope-like neuron that guides the neuron in the correct direction. Conversely, *DCDC2*'s role is to help propel the neuron farther along this tightrope-like radial glia (Galaburda et al., 2006).

Though the relationship between these genes and physical abnormalities in dyslexia was a necessary first step, the critical question is whether these genes are functionally related to the deficits in dyslexia and not just to physical abnormalities that may or may not lead to reading impairment. In fact, research in rodent models has now demonstrated that these two genes are associated with a variety of deficits, including abnormal speech sound processing (Centanni et al., 2016; Centanni, Booker, et al., 2013; Centanni et al., 2014), spatial reasoning (Szalkowski, Fiondella, Truong, et al., 2012), memory (Truong et al., 2014), and learning (Che, Truong, Fitch, & LoTurco, 2016).

4.2.1 Neural and Behavioral Deficits Linked to Dyslexia-Associated Genes: Rat Models

Humans with a single nucleotide polymorphism (SNP) in *KIAA0319* are significantly more likely to have reduced activation in left temporal cortex during a reading task, near brain areas important for reading and language (Pinel et al., 2012). This evidence suggested that this gene causes a reduction in the brain's activity during reading tasks. However, when the rodent homolog of this gene (*Kiaa0319*) was knocked down (the amount of protein created by this gene was reduced) in rats, there was no evidence of reduced neural activity, as expected. Instead, the auditory cortex of rats with reduced activity of this gene fired with increased *variability* compared to controls. In other words, their brains responded just as frequently but exhibited significantly more variability in the timing of their responses to stimuli (Centanni, et al., 2014; Fig. 4.1a). *Kiaa0319*-related abnormalities in auditory processing have since been replicated in a mouse model (Guidi et al., 2017), suggesting that this gene may influence dyslexia through cortical processing after birth rather than by disrupting in utero neural migration.

In the *Kiaa0319* knockdown rat, increased cortical variability was associated with poor performance on speech sound discrimination tasks, in which rats were trained to press a lever to a target speech sound and ignore distracter sounds using the initial consonant as a cue (e.g., press to /dad/ but not to /bad/, /sad/, /tad/, or /gad/). Rats are good at these tasks and exhibit thresholds similar to those seen in humans with respect to tolerance for background noise (Shetake et al., 2011), signal degradation (Ranasinghe, Vrana, Matney, & Kilgard, 2012), and presentation rate (Centanni et al., 2013). Therefore, they are excellent models of not only speech sound perception in the brain but also to allow researchers to investigate the behavioral consequences of these gene-brain relationships. In the case of rats with reduced

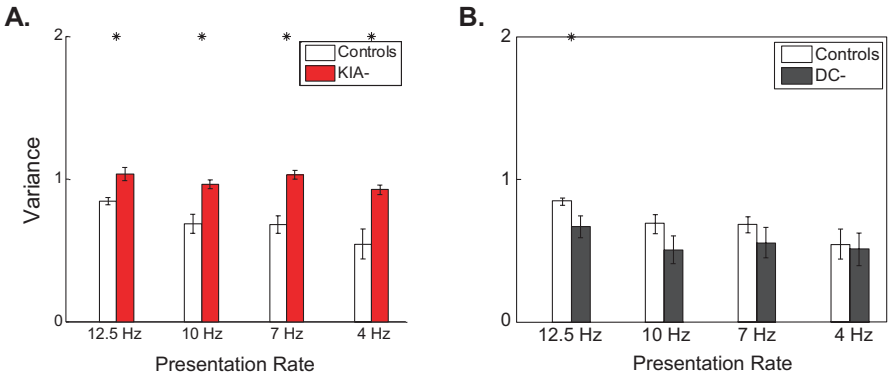

Fig. 4.1 (**a**) Neural responses in rats with reduced *Kiaa0319* expression were less precise than control rats as indicated by increased variance to broadband noise bursts at various speeds; $*p < 0.05$; (**b**) Neural responses in rats with reduced *Dcdc2* expression were just as precise as control rats, except at the fastest speed tested; $*p < 0.05$. All data previously presented (Centanni et al., 2013, 2016)

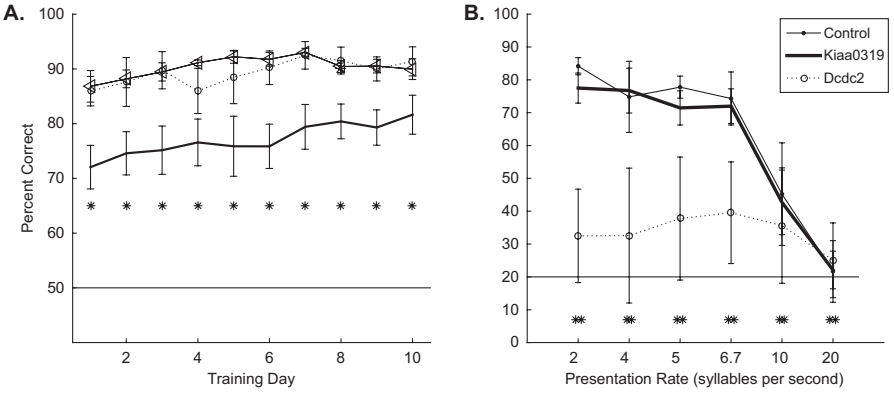

Fig. 4.2 Reduced expression of dyslexia-associated genes leads to nonoverlapping behavioral deficits. All data originally presented in Centanni et al. (2014) and Centanni et al. (2016). (**a**) Rats with reduced expression of *Kiaa0319* were impaired on a phoneme discrimination task, while rats with reduced expression of *Dcdc2* were not impaired at this task. Unpaired *t*-tests between *Kiaa0319* group and control: $*p < 0.05$; (**b**) Rats with reduced expression of *Dcdc2* were significantly impaired at a rapid speech sound discrimination task, while rats with reduced expression of *Kiaa0319* were not impaired. Unpaired *t*-tests between *Dcdc2* group and control: $**p < 0.01$

Kiaa0319 expression, deficits in several tasks were observed, including discrimination of speech sounds in background noise and of isolated phonemes (e.g., /d/ vs. /t/; Fig. 4.2a; Centanni et al., 2014), both of which are difficult for humans with dyslexia (Farquharson, Centanni, Franzluebbers, & Hogan, 2014; Richards & Berninger, 2008; Ziegler, Pech-Georgel, George, & Lorenzi, 2009).

In contrast to the neural profile linked to *KIAA0319*, suppression of the gene *DCDC2* led to strikingly different results in the animal model. While rats with reduced expression of *Kiaa0319* had neural variability and difficulty processing the rapid acoustic information present in individual phonemes, rats with reduced expression of *Dcdc2* had control-level consistency in auditory cortex responses to speech sounds, tones, and broadband noise burst trains (Centanni et al., 2016; Fig. 4.1b). However, it is important to note that studies in mice suggest this gene is important for timing of action potentials (Che, Girgenti, & LoTurco, 2014) and further work is needed to evaluate these apparently contradictory findings. Further, these animals did not have speech-in-noise or phoneme discrimination deficits (Fig. 4.2a) but were severely impaired on a rapid speech sound discrimination task (Fig. 4.2b). During this task, consonant-vowel-consonant (CVC) speech sounds were presented in streams at various presentation rates (Centanni et al., 2016). This profile more closely resembles the rapid naming or fluency deficits seen in some children with dyslexia (Denckla & Rudel, 1976; Korhonen, 1995; Norton & Wolf, 2012). Mutation of *Dcdc2* in the rodent models also leads to impairments in memory (Truong et al., 2014). In a radial arm water maze task, mice without *Dcdc2* were impaired on this task, suggesting deficits in working and reference memory for context cues (Truong et al., 2014). This study and others suggest that this gene does not interfere with relatively simple tasks but does cause deficits in more cognitively demanding tasks (Centanni et al., 2016; Gabel et al., 2011; Truong et al., 2014).

DCDC2 regulates cilia length and function in neurons, both during neural migration and after birth. Work done in cultured cells shows that depending on whether the amount of DCDC2 protein is increased or decreased, the effect on cilia length and function changes (Massinen et al., 2011). Too much DCDC2 protein increased the length of the cilia, triggered increased dendritic branching, and increased signaling of Shh (important for neurogenesis; Choudhry et al., 2014). Reduced DCDC2 protein had no effect on cilia length but increased Wnt signaling, a pathway also critical for neurogenesis but that may also influence synapse formation (Ciani & Salinas, 2005).

Future work in animal models will aid in determining the role of each candidate-dyslexia gene on driving the brain differences and specific deficits in individual children with reading disorders as well as inform which interventions work best for each subtype.

4.2.2 Influence of Dyslexia-Associated Genes on Neural Plasticity: Rat Models

The efficacy of intervention for some children with dyslexia is well-documented, with a growing body of evidence demonstrating changes in the brain as a result of successful intervention (Heim, Pape-Neumann, van Ermingen-Marbach, Brinkhaus, & Grande, 2014; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008; Penolazzi, Spironelli, Vio, & Angrilli, 2010; Temple et al., 2003). In the *Kiaa0319* knockdown

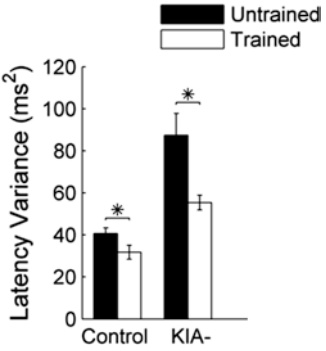

Fig. 4.3 Training-induced plasticity was observed in rats with reduced *Kiaa0319* expression after 4 months. Variability in the onset latency was significantly reduced after extensive behavioral training; $^*p < 0.01$ (Centanni et al., 2014)

rat, the behavioral training paradigm seemed to drive helpful neural plasticity in stabilizing the neural response. Four months of behavioral training was enough to significantly improve neural reliability (Centanni et al., 2014; Fig. 4.3). This result supports the idea that the brain is capable of change even after a genetically inherited brain abnormality. Further work on this gene in humans will help clinicians determine whether children with this genetic marker will best benefit from a specific type of intervention. In the future, this knowledge may even aid in identifying these children prior to the start of reading instruction.

Interestingly, while rats with *Kiaa0319* knockdown benefitted from training, 4 months of behavioral experience actually decreased the precision of speech sound responses in the brains of *Dcdc2* knockdown rats and increased the amount of spontaneous neural firing (Centanni et al., 2016; Fig. 4.4). A separate study suggested that increased neural responses in the *Dcdc2* model may be due to differences at the synaptic level, as mice without this gene had increased numbers of a specific receptor type important for learning and memory [NMDA receptors (Che et al., 2016)]. The observation that *DCDC2* may negatively influence intervention response, if confirmed in additional animal studies and in humans, would provide valuable information about the percentage of children with dyslexia who do not respond to intervention. This double dissociation of the two genes studied in rodents and their respective behavioral deficits demonstrate that genes associated with dyslexia likely influence the disorder in different ways.

4.3 Relating Work in Animal Models to Humans with Dyslexia

Though rodent models are undoubtedly useful for a variety of preclinical studies, including those related to genetics, it is certainly possible that the role of a dyslexia-associated gene may differ between non-primate animal models and humans. Researchers have now begun testing the hypotheses derived from dyslexia work in rats and mice to determine their relevance to humans diagnosed with this reading disorder.

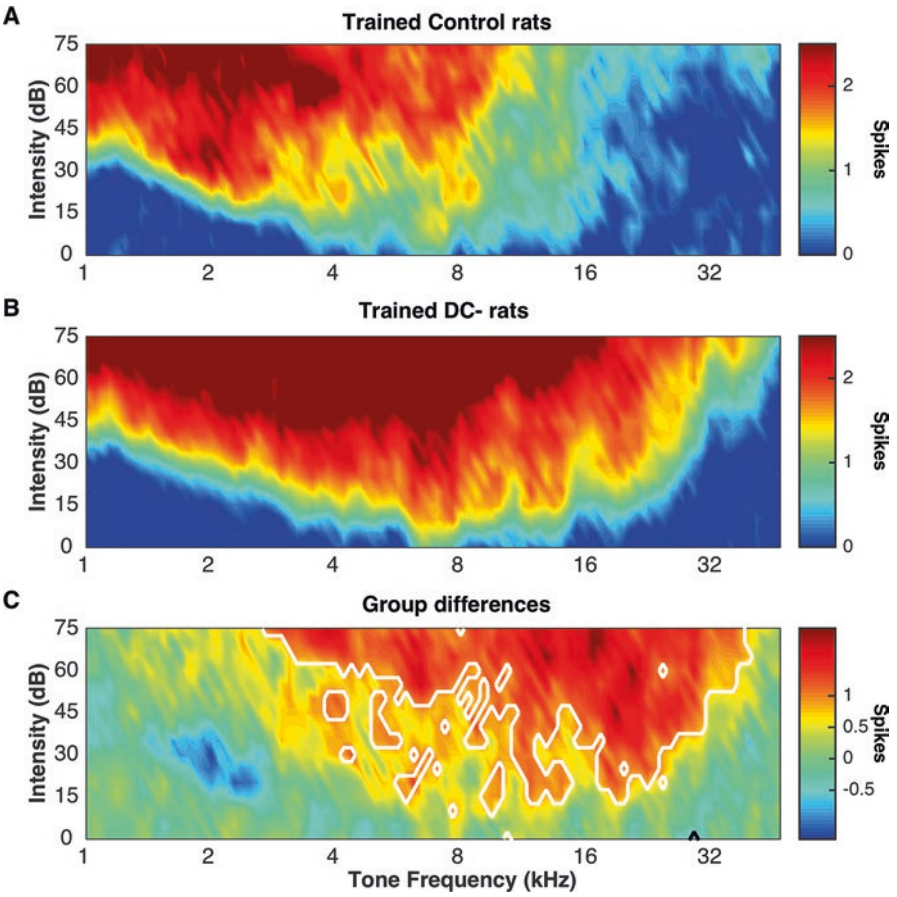

Fig. 4.4 Impaired neural plasticity was evident in rats with reduced expression of *Dcdc2*. Four months of training increased spontaneous and driven firing rates in primary auditory cortex of rats with reduced *Dcdc2* (**b**) compared to trained control rats (**a**), leading to less precise speech sound representations. (**c**) Difference in A1 responses after training in *Dcdc2* suppressed rats compared to genetically intact controls (Centanni et al., 2016)

Almost simultaneously, the first studies demonstrating inconsistent neural responses in the rat (described in a previous section) and in humans with dyslexia were published by different groups (Centanni, Booker, et al., 2013; Hornickel & Kraus, 2013). Hornickel and Kraus (2013) reported that a group of children who were poor readers exhibited reduced consistency in the auditory brainstem response to speech sounds compared to a group of children who were good readers. The auditory brainstem is an early step in the auditory pathway, and the consistency of the response at this level to speech sounds can predict literacy (Neef et al., 2016), suggesting that early auditory areas are critical for reading acquisition in normal hearing individuals.

Following the publication of genetic work in rats suggesting a role of the gene *KIAA0319* on this neural inconsistency, follow-up studies were conducted by both groups. A study in a group of children with a range of reading abilities demonstrated that SNPs in *KIAA0319* corresponded with the degree of auditory brainstem consistency observed as well as behavioral performance on phoneme awareness tasks (Neef et al., 2017). Finally, a study in children with and without dyslexia demonstrated a link between one of these SNPs (rs6935076) and neural inconsistency (Centanni et al., 2018). Importantly, this study also reported heterogeneity in the dyslexia group—approximately half of the children with dyslexia exhibited increased variability, while the remaining half had control-level neural consistency (Fig. 4.5). This body of work, spanning just 5 years across a small number of research groups, demonstrated for the first time the benefit of using rats as a model for studying the gene-brain-behavior relationships in dyslexia.

With respect to these findings, it is important to consider whether inconsistent neural responses to sound may explain other neural differences commonly observed in dyslexia. For example, as described above, early reports of hypoactivation in the left temporal lobe of humans with dyslexia may be an artifact of altered temporal dynamics. If neurons are not firing coherently with one another, the average response across many neurons will generate a lower amplitude than a population of neurons firing simultaneously. Individuals with dyslexia also often exhibit reduced habituation and abnormal mismatch negativity responses compared to their typically

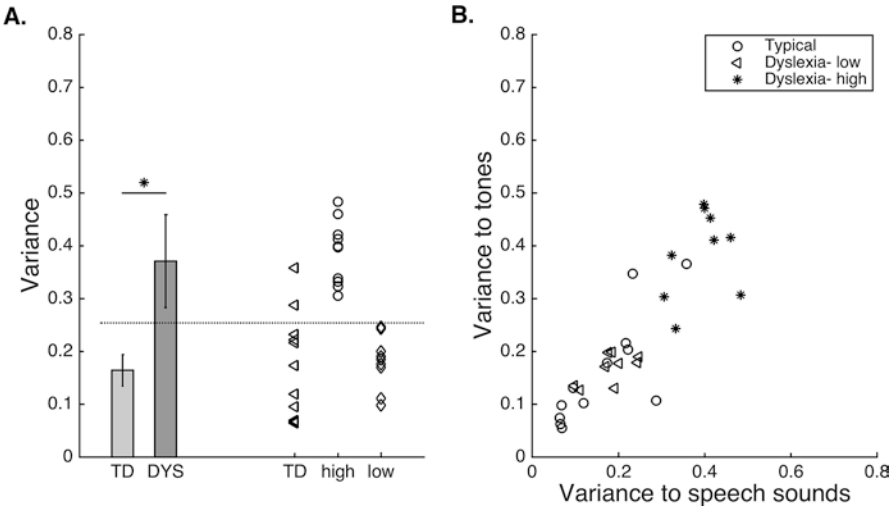

Fig. 4.5 Heterogeneity in neural variability levels in a sample of children with dyslexia. (**a**) Though as a group, children with dyslexia exhibit increased neural variability compared to typical readers, this effect is driven by about half of the population. These children exhibited neural variability in primary auditory cortex that was greater than the control mean + 2 standard deviations. (**b**) Variability in auditory cortex responses is not speech-specific, suggesting that neural variability in dyslexia is a general neural firing property rather than a speech-specific deficit. Data originally presented in (Centanni et al., 2018)

reading peers (Perrachione et al., 2016; Schulte-Körne, Deimel, Bartling, & Remschmidt, 2001; Žarić et al., 2014). In each of these paradigms, a stimulus is presented repeatedly in a single modality. Over successive repetitions, the typically developing brain will respond less strongly, indicating adaptation to repetition as the brain notes a lack of change in the signal. If neurons do not fire consistently to multiple repetitions of the same stimulus, however, it is possible that the brain may not recognize each stimulus as a repeat but rather as a similar but slightly different event. Therefore, rather than habituating to a repeated stimulus, the brain maintains its state of arousal as each stimulus is perceived as a separate and unique item. Future work in humans should evaluate the relationship not only between neural timing variability and habituation but also between habituation and *KIAA0319* variants to determine if this basic neural firing property is related to these other deficits seen in dyslexia.

The other main gene discussed in this chapter, *DCDC2*, has also recently been studied in humans in addition to work done in the rat and mouse models. In children with varied reading abilities (but not diagnosed with dyslexia), SNPs in *DCDC2* were associated with slower reading speeds and impaired spelling performance but did not influence consistency of the neural response (Neef et al., 2017). The work in rat models supports the hypothesis that this gene influences rapid processing, as reduction of Dcdc2 protein degraded speech sound discrimination performance in rapid streams and did not influence neural variability (discussed in previous section, Centanni et al., 2016, but see Che et al., 2014). In humans with dyslexia, this gene is associated not only with reading speed (Neef et al., 2017) but also errors in untimed single-word reading in English (Lind et al., 2010; Paracchini et al., 2008; Scerri et al., 2011) and Mandarin (Zhang et al., 2016), as well as motion perception deficits (Cicchini, Marino, Mascheretti, Perani, & Morrone, 2015; Gori, Mascheretti, & Giora, 2014). In addition to behavioral associations, *DCDC2* variants are also associated with differences in neural migration, observed in reduced volume in various white matter tracts critical to the language and reading networks (Burbridge et al., 2008; Darki & Peyrard-Janvid, 2014). These varied findings could be due to differences in when the gene's expression became abnormal, where in the brain these mutations occur, and/or whether the mutation causes an increase or decrease in DCDC2 protein.

4.4 Other Genes of Interest: *DYX1C1*, *ROBO1*, *FOXP2*, and *CNTNAP2*

Though *KIAA0319* and *DCDC2* are the most commonly studied genes of interest in dyslexia, there are several others that have been identified. Given the genetic complexity of this disorder, it is likely that these other genes play a role in causing many cases of dyslexia, and understanding their relationships to neural activation and to

reading ability is just as important. Two additional neuronal migration genes have both been linked with dyslexia (Galaburda et al., 2006). *DYX1C1* is associated with white matter structure in language areas in humans (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012) and spatial working memory in rat models (Szalkowski et al., 2012; Threlkeld et al., 2007), though this gene is not consistently found in varying populations of individuals with dyslexia (Marino et al., 2005; Zou et al., 2012). The second gene, *ROBO1*, is associated with the ability to hold phonemes in working memory (Bates et al., 2011; Lamminmäki, Massinen, Nopola-Hemmi, Kere, & Hari, 2012), but again, this gene has not been consistently linked with dyslexia across different samples.

There are also two additional genes associated with reading, neither of which is involved in neural migration—*FOXP2 and CNTNAP2*. First reported in connection to a speech articulation disorder, *FOXP2* (located at chromosome 7q31) is a large protein that functions as a regulatory factor for neurogenesis during development (Tsui, Vessey, Tomita, Kaplan, & Miller, 2013) and for other genes later in life (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). *CNTNAP2* (also located at chromosome 7q31) has a number of roles related to cell-cell adhesion including mediating myelination (Poliak & Gollan, 2001) and the localization of potassium channels (Rasband, 2004). *CNTNAP2* is regulated by *FOXP2*, which was first identified as a language gene when it was linked to a severe speech and articulation disorder present in the famous KE family (Lai et al., 2001; Vernes et al., 2008). These genes have been consistently linked to disorders related to speech production and articulation, such as childhood apraxia of speech (Centanni et al., 2015; Peter et al., 2011; Raca et al., 2013), and their roles in motor movement for communication have been validated in multiple animal models including songbirds and rodents (Condro & White, 2014; Groszer et al., 2008; Haesler et al., 2007).

Regarding a relationship to reading, many have found that these genes correspond to deficits in individuals with dyslexia during tasks involving speech production, including stuttering (Petrin et al., 2010) and reading out loud (Peter et al., 2011). Though it is possible that these genes are related to these tasks due to the motor speech production component of both tasks, imaging in humans also suggests links between these genes and abnormalities in reading network regions. For example, a SNP in *FOXP2* was associated with decreased activation in the angular and supramarginal gyri during a rhyming task (Wilcke et al., 2012). Two SNPs in *CNTNAP2* have been associated with increased activation during a silent sentence completion task in right frontal regions (Whalley et al., 2011) that are often hyperactivated in individuals with dyslexia, perhaps as a compensatory mechanism (Hoeft et al., 2011). The role of these genes in the neural mechanisms of dyslexia will require further study to disentangle whether these genes are related to deficits on

tasks that rely on motor production of speech or whether these genes influence the reading network specifically.

4.5 Additional Model Systems for Studying Dyslexia-Associated Genes

This chapter spends a great deal of time devoted to rodent model work on dyslexia genes of interest, largely due to the ease with which genes are modified in these models. However, translational work on these genes has also been conducted in *C. elegans*, drosophila, nonhuman primates, and cell cultures. For example, work in *C. elegans* demonstrated that overexpression of the gene *DCDC2* caused ectopic branching at the cell body and in the dendrites, leading to an abnormal neuronal morphology which was similar to that seen in a similar experiment in rat neurons (Massinen et al., 2011). Drosophila models demonstrated that the fruit fly version of *ROBO1* (*Robo*) interfered with axons crossing the midline during development (Kidd et al., 1998). This finding has been confirmed in rodent models (Ypsilanti, Zagar, & Chedotal, 2010) as well as in humans using auditory perception studies that require neural signals to cross at the midline (Lamminmäki et al., 2012).

In human cell cultures, a risk haplotype of the gene *KIAA0319* led to reduced expression of the gene (Dennis et al., 2009; Paracchini et al., 2006), which supports the use of genetic suppression and genetic knockout rodent models described above, as these models likely mimic the functional consequences of *KIAA0319* SNPs in dyslexia. Interestingly, one specific deletion in *DCDC2* (intron 2) that is strongly associated with dyslexia is associated with increased expression of the gene in cultured cells (Meng et al., 2011), while many of the studies conducted in mice and rats involve reducing or eliminating the expression of this gene (Burbridge et al., 2008; Centanni et al., 2016; Che et al., 2014; Wang et al., 2011). Additional work is needed to better understand the functional consequences of the mutations in dyslexia genes on protein expression in humans so that the most accurate animal models can be used. Future translational work on the gene *DCDC2* between rodent models and humans with dyslexia will need to consider this issue carefully to maximize usefulness of rodent model work.

Since these genes are relatively well conserved from the simple worm to the human, it allows researchers to study these genes in multiple model systems to determine how they evolved across species and determine how they may relate to speech and language in humans. Expression patterns for many of the genes discussed in this chapter (*KIAA0319*, *DCDC2*, *ROBO1*, *FOXP2*, and *CNTNAP2*) were examined in the common marmoset to investigate their overlap with humans (Kato

et al., 2014). This study found genetic expression patterns in the marmoset that overlapped those seen in humans, including in the auditory, visual, and motor pathways, and suggests that transgenic marmosets (Sasaki et al., 2009) may become a valuable tool as researchers move from basic elements of reading work in rodents to more humanlike aspects of language and reading.

4.6 Limitations of Translational Research in Dyslexia

Though the genes *KIAA0319* and *DCDC2* may contribute to dyslexia in unique ways, as demonstrated in rat models, one important limitation of the current research in animal models is that these two genes (as well as many others) interact with each other and can therefore alter the severity of the observed phenotype of an individual with dyslexia. At the time of this chapter's publication, no studies have been published on animal models expressing combinations of genetic variants. Since communication disorders are caused by multiple genes and these genes vary across individuals, understanding gene-gene interactions is critical in our quest to understand the biological mechanisms of this disorder. It will also be critical when studies of customized interventions are more common and attempt to provide meaningful recommendations to clinicians based on an individual child's constellation of deficits.

One such interaction between genes concerns the two most commonly studied dyslexia-associated genes: *KIAA0319* and *DCDC2*. A small variant in *DCDC2* (a small section that is copied and repeated) known as READ1 interacts with a region upstream of *KIAA0319* that has been previously reported as a risk marker for dyslexia (Francks et al., 2004; Powers et al., 2016). Different alleles (variations in the genetic code) of READ1 appear to have different effects on *KIAA0319* expression and the severity of the dyslexia phenotype. Certain alleles of READ1 increase the effect of the risk haplotype (a set of genetic variations that tend to be inherited together) at *KIAA0319* and lead to a more severe reading disability. Other alleles of READ1 negate the effect of the risk haplotype and have a protective effect (Powers et al., 2016). Therefore, the relationship between each of these genes and the brain-behavior relationships reported in animal models should be interpreted with caution until they are fully tested in humans. Animal models, including rats and mice, could be used in future research to further evaluate the mechanisms by which these genes interact and whether they influence neural responses to speech sounds or plasticity during training.

In addition to genetic susceptibility, it is important to note that nongenetic environmental factors such as socioeconomic status (SES), access to services, and home literacy environment (among others) are also highly related to dyslexia risk. Though some parents are able to seek additional tutoring and therapy, the extra cost of this

approach leaves many children, especially those from lower SES households, behind in their reading skill. Children with dyslexia from lower-SES backgrounds exhibit different patterns in neural plasticity following intervention compared to higher-SES children, highlighting the need to better understand how this environmental variable influences gene expression and brain activation in dyslexia (Romeo et al., 2017). There is some controversy, however, about the role of SES on brain activation in dyslexia, as not all researchers find SES effects in visual or auditory tasks (Monzalvo, Fluss, Billard, & Dehaene, 2012). Importantly, these factors are difficult to study using a rat model and so can only be evaluated through studies in humans. By evaluating the role of individual genes on brain, behavior, and plasticity in the rat model, we may be better able to account for these variables in future studies in humans on factors like SES and home literacy environment.

4.7 Conclusion

Given the high degree of heterogeneity in the population of individuals with dyslexia, it is not surprising that there is some degree of inconsistency when it comes to intervention response. In many schools, speech and language pathologists do not have the time or resources to offer a customized approach to intervention for dyslexia and instead offer a single intervention option for children diagnosed with this disorder. Through a careful study of the biological mechanisms driving dyslexia, specifically the gene-brain-behavior relationships underlying the disorder, we may be able to provide clinicians with a set of guidelines that may not only improve early diagnostic success of these children but also improve the selection of intervention. Customizing interventions for each child based on their specific biological and behavioral need will improve outcomes for many children. Using animal models to disentangle the gene-brain-behavior relationships and genetic interactions will provide translatable and testable predictions that can then better inform studies in humans with dyslexia. Rats may not be able to read, but they can still tell us a great deal about how humans learn this critical skill.

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Chapter 5
The Role of Memory Systems in Neurodevelopmental Disorders of Language

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Abbreviations

DD	Developmental dyslexia
DLD	Developmental language disorder
PDH	Procedural deficit hypothesis
SLI	Specific language impairment
TD	Typical development/typically developing

5.1 Introduction

Neurodevelopmental disorders cover a broad range of deficits in the development of the nervous system, which may persist into adulthood to various degrees. These disorders are typically apparent early in development, often before the child starts school, and may impede personal, social, academic, and occupational functioning. The range of developmental deficits varies from specific limitations in a certain domain (e.g., executive function) to global impairment of intelligence or social skills. For certain disorders, the clinical manifestation includes symptoms of deficits and delays in achieving expected milestones (American Psychiatric Association, 2013).

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https://doi.org/10.1007/978-3-030-35687-3_5

Developmental speech and language disorders pertain to developmental deficits in processes supporting speech, language, reading, writing, and social communication. Most of these disorders are well characterized, as in the cases of developmental language disorder (DLD), developmental dyslexia (DD), and motor speech disorders. In a 30-year follow-up study, a majority of young adults who had been originally diagnosed with speech and language impairments as children reported literacy difficulties, unemployment, and low socioeconomic status (Elbro, Dalby, & Maarbjerg, 2011). Increased efforts are thus required to address the long-term social and economic consequences for both the individual and society.

Nevertheless, there is still very limited collaboration between basic and translational research on these disorders: on the one hand, professionals identify the symptoms and the diverse profiles of children with neurodevelopmental disorders and implement interventions, while, on the other hand, basic researchers investigate the brain and behavioral correlates of specific symptoms or broader syndromes. Collaboration between these two parts is required, in order to design appropriate approaches for more efficient intervention in children with these disorders.

The goal of this chapter is to review a selection of key research findings in DLD and DD from the perspective of the cognitive neuroscience of learning and memory, as well as to highlight possible implications for clinical practice, especially in providing a more efficient delivery of intervention in children with DLD and DD.

5.1.1 Developmental Language Disorder

In this chapter, we will focus on "primary language impairment," specifically on DLD. "Language impairment" pertains to significant delays in a child's language skills relative to those of children of the same age. The diagnosis is typically made by means of a combination of formal evaluation, observations of linguistic performance, and professional assessment. Language impairment is often described as being either "primary" or "secondary." "Primary language impairment" refers to language impairment that cannot be explained by sensory or cognitive deficits. "Secondary language impairment" pertains to language deficits associated with conditions affecting a broader range of domains (e.g., cerebral palsy, autism, and hearing loss).

The term "developmental language disorder (DLD)" has been recently put forth to replace "specific language impairment (SLI)" (Bishop et al., 2017). DLD is characterized by difficulties in receptive and/or expressive language in the presence of adequate levels of intelligence scores and in the absence of hearing or other developmental difficulties (Conti-Ramsden, Ullman, & Lum, 2015). DLD has been estimated to affect approximately 3–7% of children (Tomblin et al., 1997) or to have a prevalence of 5–7% of the population (Leonard, 2014). It represents a developmental disorder that comprises the largest disability group in preschool-aged children (Laasonen et al., 2018).

5.1.2 Developmental Dyslexia

In the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), DD can be found under the category of "Specific Learning Disorders," which also includes difficulties in mathematics, reading and writing. In the new International Classification of Mental Disorders (ICD-11; World Health Organization, 2019), it is classified as a distinct category: "Developmental learning disorder with impairment in reading." In both diagnostic manuals, the criteria for DD include difficulties in academic skills regarding word-reading accuracy, reading fluency, and understanding. These characteristics should not be explained by intellectual or sensory impairment, neurological disorder, lack of educational provision or language proficiency, or by psychosocial adversity.

DD is one of the most common learning difficulties and has been estimated to affect 5–10% of the general population, depending on the definition used (Siegel, 2006). In the UK, DD has been estimated to affect the literacy skills of 4–8% of children and that it can reduce lifetime earnings by £81,000 (Cooper, Field, Goswami, Jenkins, & Sahakian, 2008). DD has been reported across languages, whether they have more regular grapheme phoneme correspondences (e.g., French and Portuguese), use a different script (e.g., Arabic and Hebrew), or are non-alphabetic (e.g., Chinese) (Goulandris, 2003; Siegel, 1998).

5.2 Memory Systems in Neurodevelopmental Disorders

A central dichotomy in cognitive neuroscience has been that between "declarative" and "procedural" learning and memory. According to the declarative/procedural model (Ullman, 2001, 2004), declarative memory relies on hippocampal, entorhinal, perirhinal, and parahippocampal cortical structures within the medial temporal lobes, whereas specific cortico-basal ganglia-thalamocortical and cortico-ponto-cerebello-thalamo-cortical circuits are often discussed as the basis of procedural memory.

The procedural memory system is involved in the acquisition of new motor and cognitive skills, such as typing, walking and riding a bicycle, as well as the control of already established ones (Mishkin, Malamut, & Bachevalier, 1984; Schacter & Tulving, 1994; Squire & Knowlton, 2000; Squire, Knowlton, & Musen, 1993). A fundamental property of procedural memory is that it is formed gradually and is ultimately characterized by automaticity, operating below the level of conscious awareness ("implicit memory"). It is important for acquiring skills related with sequencing, serial or abstract, sensorimotor or cognitive (Aldridge & Berridge, 1998; Boecker et al., 2002; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Saint-Cyr, Taylor, & Lang, 1988; Willingham, 1998). On the other hand, declarative memory pertains to facts and events that can be consciously recalled ("explicit memory"), and, as such, includes both episodic and semantic memories (Eichenbaum, 2012; Ullman & Pullman, 2015).

Importantly, different aspects of speech and language are supported in different degrees by the procedural and the declarative memory systems. For instance, the procedural system primarily supports the acquisition and automatization of articulatory sequences, and the implicit acquisition of grammatical rules, whereas the declarative memory system mainly supports the acquisition of word forms, their semantic properties, form-meaning associations, and also information pertaining to irregular morphological forms and larger arbitrary form-meaning mappings, such as idioms (Ullman, Earle, Walenski, & Janacsek, 2020).

The declarative/procedural model has provided the basis for the development of the "procedural deficit hypothesis" (PDH) (Ullman & Pierpont, 2005), whereby DLD and DD, among other neurodevelopmental and adult-onset disorders of speech and language, are characterized by dysfunction in the procedural memory system. Underlying such dysfunction would be structural and functional abnormalities primarily in cortico-basal ganglia-thalamocortical circuitry, primarily involving Broca's area and the caudate nucleus. On the other hand, declarative memory is posited to remain intact, even playing a compensatory role in these disorders (the "declarative memory compensation hypothesis"; Ullman & Pullman, 2015).

A line of work that has partly overlapped with that of the PDH framework within the context of DD studies has been the research supporting the "automatization deficit hypothesis" (Nicolson & Fawcett, 1990) and the concomitant "cerebellar deficit hypothesis" (Nicolson, Fawcett, & Dean, 2001). According to this work, the core deficit underlying DD is the lack of automaticity, which is attributed to impairment of procedural learning circuits supported by cerebellar circuitry (for an up-to-date account of the successor of this theoretical framework, see Fawcett & Nicolson, 2019).

Nevertheless, it is of importance to note at this point that the PDH has not been universally accepted in the field of neurodevelopmental disorders of speech and language. For example, there are ongoing debates in the literature regarding the appropriate tests in assessing declarative and procedural learning (e.g., Conway, Arciuli, Lum, & Ullman, 2019; West, Vadillo, Shanks, & Hulme, 2018). Nevertheless, it is beyond the scope of this chapter to assess the explanatory capacity of the PDH framework as compared to that of other approaches with respect to either DLD or DD. For instance, DLD has been investigated on the basis of grammar-deficit hypotheses (whereby the acquisition and processing of particular grammatical operations is delayed and/or deficient—e.g., Clahsen, 1989; Rice & Oetting, 1993) and hypotheses positing broader processing limitations in DLD children (e.g., Norbury, Bishop, & Briscoe, 2001). However, these hypotheses have been criticized for either failing to account for non-linguistic deficits in DLD or for their preserved linguistic and non-linguistic capacities (Ullman & Pierpont, 2005). In DD, phonological deficits are reported in the majority of studies. Indeed, one of the most prominent accounts of the causes of DD is the "phonological (deficit) theory," whereby the underlying deficit in DD is related to problems in phonological processing (Vellutino, Fletcher, Snowling, & Scanlon, 2004). In this respect, individuals with DD exhibit difficulties in grapheme-to-phoneme conversion due to a specific impairment in the processing of phonemes, leading to difficulties in reading. Another prominent account of DD is the magnocellular deficit account, whereby

reading problems derive from impaired sensory processing. This deficit results from the impaired development of timing systems in the central nervous system, which are mediated by large "magnocellular" neurons throughout the brain (for an up-to-date account, see Stein, 2019). Nevertheless, other aspects of cognitive impairment are also commonly reported. For instance, there has been evidence for impairment in motor skills (Fawcett & Nicholson, 1995), naming speed (Wolf & Bowers, 1999), processing speed (Nicolson & Fawcett, 1994), and implicit structure and sequence learning (Howard, Howard, Japikse, & Eden, 2006; Pavlidou, Williams, & Kelly, 2009). As in the case of DLD, the PDH framework attempts to account for both the linguistic and non-linguistic deficits that DD individuals present with (Ullman et al., 2020).

We turn to a series of studies that the PDH has motivated on the procedural and declarative learning capacities of children with DLD and DD relative to those of typically developing (TD) children. Below we briefly present some highlights of such research.

5.2.1 Procedural Learning in Developmental Language Disorder

Consistent with the predictions of the PDH, DLD groups have been shown to perform poorly relative to TD groups in tasks assessing procedural learning and memory, such as probabilistic classification (Kemény & Lukács, 2010), serial reaction time tasks (Gabriel et al., 2013; Hedenius et al., 2011; Lum, Conti-Ramsden, Page, & Ullman, 2012; for a meta-analysis, see also Lum, Conti-Ramsden, Morgan, & Ullman, 2014), artificial grammar learning (Plante, Gomez, & Gerken, 2002), and implicit statistical learning tasks (Evans, Saffran, & Robe-Torres, 2009). In some of these studies, evidence has also been presented for a compensatory role of declarative learning in DLD: for instance, in Lum et al. (2012), grammatical abilities (a composite score derived from both expressive and receptive tasks) were associated with procedural memory (assessed with a serial reaction time task) in TD children, whereas they were associated with declarative memory (assessed with standardized neuropsychological tests of episodic memory) in children with DLD. Similar relationships were identified in a subsequent study (Conti-Ramsden et al., 2015), whereby receptive grammar in TD children was only predicted by procedural memory (assessed, again, with a serial reaction time task) out of three memory measures (verbal working memory, verbal declarative memory, and non-verbal procedural memory), whereas it was only predicted by declarative memory (assessed with standardized neuropsychological tests of verbal episodic memory) in children with DLD.

Evidence from studies on the neuroanatomy of DLD is also consistent with the core premises of the PDH: a systematic review of 18 articles (Mayes, Reilly, & Morgan, 2015) has identified atypical brain structure and function in key regions supporting the procedural memory system for language, such as the caudate nucleus, the inferior frontal gyrus, and the posterior superior temporal gyrus.

5.2.2 *Procedural Learning in Developmental Dyslexia*

Similar to the findings on DLD, a meta-analysis of 14 studies employing serial reaction time tasks demonstrated that, as compared to TD controls, individuals with DD showed on average worse procedural learning abilities (Lum, Ullman, & Conti-Ramsden, 2013). In another study, implicit sequence learning was assessed in children with DD relative to TD children beyond a single session, also examining the effects of overnight consolidation as well as those of further practice on a subsequent day. Despite a trend toward poorer learning in the DD group in the first learning stage, the sequence learning impairment became significant only after extended practice, including an overnight interval (Hedenius et al., 2013). Dovetailing with the "declarative memory compensation hypothesis" (Ullman & Pullman, 2015), another study demonstrated that, when an implicit task of artificial grammar learning was made explicit, learning differences were no longer seen in a group of adults with DD relative to TD adults (Kahta & Schiff, 2016). Moreover, better performance has been reported for DD relative to TD children in a visual object recognition memory task (Hedenius, Ullman, Alm, Jennische, & Persson, 2013).

Consistent with both the PDH and the cerebellar deficit hypothesis, structural abnormalities in DD have been reported in the neostriatum (caudate nucleus and putamen), the cerebellum, and the superior temporal/temporoparietal and inferior/ventral temporal regions (Brown et al., 2001; Eckert et al., 2005; Eckert, Berninger, Vaden Jr., Gebregziabher, & Tsu, 2016; Pernet, Poline, Demonet, & Rousselet, 2009). Likewise, functional abnormalities have been reported in in the caudate nucleus and the lentiform nuclei (putamen and globus pallidus), motor and inferior frontal regions, and the aforementioned temporal cortical regions (Paulesu, Danelli, & Berlingeri, 2014; Richlan, Kronbichler, & Wimmer, 2011).

5.3 Implications for Designing Intervention Programs

The PDH framework has generated a series of promising translational predictions regarding the diagnosis of and interventions for DLD and DD. To begin with, the neural system-level analysis of frequently interrelated and comorbid neurodevelopmental disorders may in the future provide an alternative classificatory system that complements the current symptom-based one. Implications of such a framework for the diagnostic approach to neurodevelopmental disorders might be more fruitful in revealing a range of cognitive strengths and weaknesses that are to be addressed by intervention. It may be possible that diagnosis could also be based on the presence of particular neuroanatomical anomalies in procedural memory structures (and lack thereof elsewhere) as well as by the presence of deficits (e.g., long-distance grammatical dependencies) that are difficult to compensate for in declarative memory (Ullman et al., 2020; Ullman & Pullman, 2015). Moreover, the findings of deficits extending beyond language in both DLD and DD highlight the need for a thorough

assessment of cognitive strengths and weaknesses of the child, in particular their non-linguistic declarative and procedural learning capacities.

Another promising field that requires further research is the design of intervention programs based on the potential utility of pharmacological agents in enhancing procedural and declarative memory. For instance, levodopa (a precursor to the neurotransmitter dopamine) has been shown to enhance (at least feedback-based types of) procedural learning in healthy young adult humans (De Vries, Ulte, Zwitserlood, Szymanski, & Knecht, 2010), whereas administration of methylphenidate has been shown to trigger amplified long-term plasticity in the hippocampus of preadolescent rats (Dommett, Henderson, Westwell, & Greenfield, 2008) and also enhance memory in healthy humans (Repantis, Schlattmann, Laisney, & Heuser, 2010; Ullman & Lovelett, 2018), and clinical research is required to assess their efficacy in DLD and DD.

Moreover, theoretical frameworks like the PDH may inform therapists in selecting from the currently available intervention programs, and may also provide the basis for the design of novel programs that take into account the (declarative, procedural) learning capacities of a specific child. Though the field is still in its infancy, the PDH has generated a number of pedagogical predictions for enhancing (primarily declarative) learning and longer-term retention within the context of first and especially second language acquisition, based on independent findings from the memory enhancement literature. Nevertheless, these predictions may be translated into interventions for language recovery and rehabilitation in both neurodevelopmental and later-onset disorders (Ullman & Lovelett, 2018). Indeed, introducing principles of unimpaired learning into language treatment is an under-researched yet promising way of enhancing the efficacy of language interventions (Alt, Meyers, & Ancharski, 2012). Given the "declarative memory compensation hypothesis" pertaining to several neurodevelopmental disorders of speech and language (Ullman & Pullman, 2015), the efficacy of such interventions deserves further exploration within the context of enhancing declarative learning and memory in DLD and DD: According to the PDH, for instance, DLD children should be able to compensate to a certain extent for their grammatical deficit by acquiring and employing strategies (such as chunking, whereby "the dog" and "barked" are stored as chunks and are not derived from the particular lexical and grammatical morphemes involved) and explicit rules (e.g., "add -ed to the end of the verb when the event has already happened") in declarative memory (Ullman, 2004; Ullman & Pullman, 2015). Enhancing declarative learning and memory in children with DD or DLD may thus maximize the extent to which they can compensate for their impaired procedural learning in language.

These behavioral interventions may pertain to enhanced learning in an individual ("learner-level" approaches) or enhanced acquisition and retention of specific memoranda ("item-level" approaches) (Ullman & Lovelett, 2018). The former may involve (1) syndrome-specific educational strategies integrating sleep, time course, and time of day in the child's learning schedule (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2017); (2) physical activity intervention (aerobic exercise), given the evidence for a causal relationship with hippocampal structure and memory

performance in children (Chaddock et al., 2010); and (3) diet—for instance, the positive effects of flavonoids that have been reported on declarative memory in both TD children (Whyte & Williams, 2015) and older adults (Brickman et al., 2014) should be further assessed in children presenting with DLD and DD.

With respect to item-level approaches, these would involve (1) "deep encoding," i.e., ensuring semantically rich processing of the memoranda (Craik & Lockhart, 1972; Galli, 2014); (2) mnemonic strategies such as the method of loci, also known as "memory palace," which involves mentally mapping the memoranda onto imageable locations (Legge et al., 2012); (3) gesture-based learning ("the enactment effect"), such as accompanying word learning with contextually appropriate gestures (Kelly, McDevitt, & Esch, 2009); (4) spaced repetition ("distributed practice," "spacing effect"), i.e., the introduction of temporal gaps between brief, iterated presentations of the same memorandum (Gerbier & Toppino, 2015); and (5) retrieval practice ("testing effect"), i.e., retrieving learned information from memory instead of restudying it (Roediger & Butler, 2011) (for further discussion, see Alt et al., 2012; Ullman & Lovelett, 2018).

The design and implementation of such interventions in the case of neurodevelopmental disorders of speech and language require considering their fundamental differences from interventions for later-/adult-onset speech and language disorders: the former are characterized by deviations in the development of cognitive and linguistic skills, resulting in deficiencies of the skills. The latter involve typically intact premorbid abilities. With respect to disorders in children, we have to develop the ability, while in adults we have to restore the ability in question. Overall, we suggest that such interventions should be embedded within the context of naturalistic approaches taking into consideration the following: (1) the mental and physical health of the child (e.g., high levels of stress or overall poor physical condition would diminish their ability to actively participate in the therapeutic process and develop new skills); (2) the environmental setting: this should be compatible with the child's age, cognitive processing level, as well as their personal interests, providing them with opportunities to explore the environment and acquire experiences; and (3) the involvement of family members, which should be in accordance to their own abilities, opportunities, and wishes to support the therapeutic process. The ability of the therapist to identify an optimal way for family members to support the process is an important point in the naturalistic approaches.

5.4 Conclusion

The PDH represents an explanatory framework for the brain and behavioral correlates of DLD and DD with substantial translational potential. Further investigation is required in terms of both basic and translational research, in order to assess its capacity to explain DLD and DD and also to guide the design of successful interventions.

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Chapter 6
Transcranial Direct Current Stimulation (tDCS) and Language/Speech: Can Patients Benefit from a Combined Therapeutic Approach?

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Abbreviations

AoS	Apraxia of speech
atDCS	Anodal transcranial direct current stimulation
BA	Brodmann area
ctDCS	Cathodal transcranial direct current stimulation
DLPFC	Dorsolateral prefrontal cortex
F	Female
h	Hours
HD tDCS	High-density transcranial direct current stimulation
IFG	Inferior frontal gyrus
ITG	Inferior temporal gyrus
LTD	Long-term depression
LTP	Long-term potentiation
M	Male
M1	Primary motor cortex
min	Minutes

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_6

MTG	Middle temporal gyrus
NMDA	N-Methyl-D-aspartate
PFC	Prefrontal cortex
PML	Principles of motor learning
pSTG	Posterior superior temporal gyrus
STG	Superior temporal gyrus
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation

6.1 Introduction

The modulation of cognitive functions by noninvasive stimulation of the human brain has gained increasing attention over the last few decades. The two most known neuromodulation techniques are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). The popularity of tDCS compared to TMS is due to its safety, portability, and cost-effectiveness. Moreover tDCS is an easy-to-use, painless, tolerable corticomotor modulation technique with no or minimal side effects (Bolognini, Pascual-Leone, & Fregni, 2009). While TMS implicates more artefacts such as acoustic noise and muscle twitching, only minor adverse effects are reported from tDCS (Fertonani, Ferrari, & Miniussi, 2015; Poreisz, Boros, Antal, & Paulus, 2007).

tDCS can be used to probe and modulate cortical plasticity (Prehn & Flöel, 2015) that is defined as the capacity of the brain to develop new neuronal-synaptic interconnections and thereby develop and adapt new functions or reorganize/compensate for changes. During tDCS, weak polarizing direct currents are delivered to the cortex via two electrodes placed on the scalp. The current induces changes in the resting membrane potential of the neurons. This means that tDCS does not directly elicit action potentials but changes the amount of additional input needed to generate an action potential in neuronal populations. In other words, tDCS changes the likelihood that an incoming action potential will result in postsynaptic firing both immediately during stimulation and a short period of time after stimulation. Therefore, tDCS has an impact on two neurophysiological mechanisms: (1) subthreshold alterations of the resting membrane potential involving ionic concentration shifts within the extracellular fluid ("primary effect") and (2) the synaptic plasticity of glutamatergic connections (i.e., *N*-methyl-D-aspartate (NMDA) receptor-dependent processes) ("aftereffect") (Prehn & Flöel, 2015). Since tDCS acts upon the resting membrane potential and NMDA-receptor activity, it promotes synaptic plasticity of glutamatergic connections (namely, synaptic long-term potentiation (LTP)-/long-term depression (LTD)-like mechanisms) that can outlast the duration of stimulation for several hours (Stagg & Nitsche, 2011). In general, the resting membrane potential is lowered underneath the anode, inducing higher excitability, while it is heightened underneath the cathode, inducing lower excitability. While these neurophysiological effects are well understood, little is known about

the long-term effects, especially with respect to cognitive enhancement (Holland, Leff, Penny, Rothwell, & Crinion, 2016).

Studies show a high variability in terms of the methodological approach, the characteristics of the study group, the targeted cognitive functions (Cappon, Jahanshahi, & Bisiacchi, 2016), and the outcome measures used. To the best of our knowledge, there is no standard protocol to evaluate the impact of tDCS. A standard protocol is arguable considering the differential impact and the diversity of the research, but a road map focusing on different parameters and their impact might be a valuable starting point (Jacobson, Koslowsky, & Lavidor, 2012). In this chapter, we provide a critical review on all the influencing parameters, along with a draft for such a road map. In the Appendix in the Back matter of this book, a non-exhaustive overview of studies using tDCS to study/boost language functions in healthy (Appendix A: Tables A1 and A2) and patient (Appendix B: Tables B1, B2, and B3) populations is included, which will give the reader a general idea of the demographic characteristics of the targeted population (Tables A1 and B1) and the methodological (Tables A2 and B2) and therapeutic (Table B3) approach of the current studies.

6.2 Variability in Methodological Approach

6.2.1 tDCS Protocol

Zooming in on the methodological approach, many parameters pertaining to the tDCS device may influence its impact: (1) the stimulation schedule (frequency, duration, and type), (2) the current of the stimulation (intensity, density, and total charge), (3) the targeted area of stimulation (left/right, frontal/temporal), (4) the used electrodes (montage, material, sizes, and shape), and (5) the combination of tDCS and therapy (online or offline stimulation, impact of stimulation on task performance).

Stimulation Schedule

The stimulation schedule has three general dimensions: frequency, duration, and type. ***Frequency*** pertains to the amount of tDCS sessions a participant gets. In literature, one session is often used for healthy participants and repeated sessions are used in participants with speech-language impairments. In research, sessions are often separated by at least four hours since the cortical excitability alterations can last for over an hour after the end of the stimulation (Westwood & Romani, 2017). In practice, sessions are often separated by a minimum of 24 h or even one week. In clinical practice, daily sessions are recommended to evoke a cumulative and long-term effect. Repeated stimulations after a short interval of 20 min (i.e., during the

aftereffects of stimulation) result in initially reduced yet ongoing excitability enhancement (LTP-like plasticity), while temporally contiguous stimulation and repeated stimulation after a prolonged time interval (i.e., after the aftereffects have disappeared) might result in a reversal of neuroplasticity (Monte-Silva et al., 2013). This suggests that, in a clinical population, studies need to focus not only on the frequency but also on the interval time between consecutive sessions, so that optimal neuroplasticity effects can be induced.

By ***duration*** we mean the total number of time one session takes. This parameter ranges in the literature from 6 to 30 min, with a mean duration of 20 min.

Different ***types*** of stimulation can be used: anodal tDCS (atDCS), cathodal tDCS (ctDCS), and placebo (sham). From a neurophysiological point of view, the type of stimulation refers to the polarity of the current and thereby to the way neurons are influenced. However, a nonlinear system like the brain is unlikely to have a linear response to an externally applied electric current (Westwood & Romani, 2017). In general, anodal stimulation increases cortical excitability, whereas cathodal stimulation decreases it (Fiori et al., 2011). In literature, however, there is a consensus about the stimulation effect of *atDCS* (e.g., Alberto Pisoni et al., 2015; Jacobson et al., 2012), but there is no consensus about the effect of *ctDCS. Sham* is the placebo stimulation where the electrodes are also attached on the head, but the current is turned on for a maximum period of one minute. The current is quickly ramped up and down in the beginning (and in some studies in the end as well) of each stimulation session. This technique is useful within a research context, since it blinds the participant from knowing whether they are actively stimulated or not, by giving them the initial sensation of the current building up (Gandiga, Hummel, & Cohen, 2006). Bastani and Jaberzadeh (2012) state that the application of tDCS is associated with minimal or no somatosensory input, implicating that the stimulation remains imperceptible by most people during its application. However, some participants do report an itching sensation beneath both electrodes during the early rising phase of the current. This tingling sensation elicited on the scalp lasts only for the first few seconds and then disappears (Nitsche et al., 2003). However, the research of O'Connell et al. (2012) showed that participants receiving both types of stimulation can easily discriminate between real and sham stimulation. When participants only received one type of stimulation, blinding was much more reliable (Russo, Wallace, Fitzgerald, & Cooper, 2013). Unreliable blinding may play a role in data variability present in current tDCS literature. In a research context, often different types of stimulation are used with the order of sessions counterbalanced across participants to control for learning effects. However, in clinical practice, repeated sessions of one type of stimulation are the most favorable approach in order to accumulate the most positive effect. The assumption that atDCS enhances and ctDCS diminishes cortical excitability (Nitsche & Paulus, 2000) has been mainly supported by studies that focus on the effects of tDCS on motor functions. However, a meta-analysis of tDCS studies found that the probability of achieving this classical "anodal-facilitatory/cathodal-inhibitory" effect on motor outcomes was only 0.67 and for cognitive outcomes only 0.16 (Jacobson et al., 2012). The underlying explanation might be that the anodal electrode increases further neuro-

nal firing of a previously activated region, contributing to a greater facilitation of (cognitive) performance of this area. Decreased neural firing, resulting from the cathodal electrode, cannot generate sufficient inhibition when the initial rate is already high, since subjects are engaged in cognitive tasks. Moreover, since cognitive functions are not restricted to a specific brain area but rather to a brain network, these functions may be immune to inhibitory stimulation.

Stimulation Current

The applied current can be defined by its intensity, density, and total charge. The current ***intensity*** varies from 1 to 2 mA. Although stimulation with a stronger current over a longer period of time is more intense, it is unknown whether stimulation is also more effective (Prehn & Flöel, 2015). Vöröslakos et al. (2018) found that current intensities conventionally used in tDCS studies are insufficient to affect neuronal circuits directly, suggesting that reported behavioral and cognitive effects result from indirect mechanisms. The current intensity has an impact on local (i.e., modulation of endogenous low-frequency oscillations) brain areas (Hartwigsen, 2015), within network connectivity (Meinzer et al., 2012), as well as on functionally connected, remote brain areas (i.e., spreading via excitatory and inhibitory neural pathways (Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012)); the exact amount of the impact is still questionable. Therefore, researchers often define the current ***density***, i.e., the stimulation intensity (mA) per area of stimulating electrode size (cm^2). This density is independent of the duration of the stimulation. Densities below 25 mA/cm^2 are considered safe, since 25 mA/cm^2 is the threshold for brain tissue damage in rats. Electrode sizes of 25–35 cm^2 are commonly used with a constant current of 2 mA intensity, resulting in a current density of 0.080–0.057 mA/cm^2 at the skin which will not induce brain tissue damage. Nonetheless, the intensity of current that reaches and affects the cortex below the electrodes is difficult to determine. It is typically inferred from physiologic outcomes such as functional imaging, which is not necessarily linear or even monotonic with local current intensity, or from behavioral changes, where the relationship with regional current flow is yet less clear (Edwards et al., 2013). Moreover, Sandars, Cloutman, and Woollams (2016) reported that even though current density is uniform, between 41% and 61% of the applied current does not penetrate the skull. This limited spatial accuracy is a potential limitation of tDCS (Raffin & Siebner, 2014). In order to overcome this limitation, high-density (HD) tDCS is required, which can be achieved by using smaller electrodes, in configurations that yield more focal stimulation (Datta, Baker, Bikson, & Fridriksson, 2011). While the exact amount and the spreading of the current are hard to define, the maximum effect may not be below the electrode pads as assumed, making it more complicated to choose the appropriate stimulation site. Precise modeling studies might be essential for future research to employ stimulation parameters that optimize current density distribution. Therefore, researchers also report the ***total charge*** of the current, i.e., the amount of current that is applied

over the head during the session and is determined by the duration of the session and the current intensity.

Area of Stimulation

The next important question is the area of stimulation, since therapeutic goals and outcomes of tDCS are linked to the targeted brain regions**.** For this parameter as well, there is no consensus about the optimal location of the electrodes. The placement of the tDCS electrodes is usually guided by the 10–20 EEG system, since this is a helpful and easy-to-use technique facilitating the incorporation of tDCS in day-to-day clinical practice (Meinzer, Darkow, Lindenberg, & Flöel, 2016). As outlined earlier, the stimulated area is a window onto a large-scale functional network, rather than on an isolated site (e.g., Bikson, Datta, Rahman, & Scaturro, 2010; Manjaly et al., 2005; Moliadze, Antal, & Paulus, 2010). So the question is: which is the ideal network to stimulate in order to obtain the maximum out of tDCS? Many researchers stimulate the ***left frontal*** cortex, since this includes the area of Broca, which is important for speech production, i.e., speech repetition, reading, writing, and naming (Bashir & Howell, 2017). The frontal cortex is 1/3 of the cortex and electrodes are 25–35 cm^2, so a more specific spot needs to be chosen. For example, Meinzer et al. (2014) have shown that tDCS over the *primary motor cortex* (M1, C3) induces long-lasting changes in cortical excitability and can improve word retrieval in healthy participants. Besides the primary motor cortex, the *left dorsolateral prefrontal cortex* (DLPFC, Fp1/AF3) (Manenti et al., 2015; Saidmanesh, Pouretemad, Amini, Nillipour, & Ekhtian, 2012; Shah-Basak et al., 2015; Wirth et al., 2011) or the *inferior frontal gyrus* (F5) (e.g., Campana, Caltagirone, & Marangolo, 2015; Fiori et al., 2013; Pisoni, Papagno, & Cattaneo, 2012; Vestito, Rosellini, Mantero, & Bandini, 2014) are frequently targeted areas of stimulation. Depending on the behavioral task administered during stimulation, researchers also stimulate other brain areas beyond the frontal cortex, such as the ***left temporal*** region. Sparing, Dafotakis, Meister, Thirugnanasambandam, and Fink (2008), for example, applied tDCS over the *posterior perisylvian region*, i.e., an area which includes Wernicke's area (T5), and reported an impact on lexical-phonological retrieval. Besides the therapeutic goals and outcomes, interindividual variability may also influence the impact of tDCS. Therefore, studies that employed similar areas of stimulation resulted in highly variable stimulation effects (de Aguiar, Paolazzi, & Miceli, 2015). Klaus and Schutter (2018) argue that the placement of the active electrode over the targeted region and the reference electrode over the contralateral supraorbital region yields the highest field strengths anterior to the targeted region as well as additional frontal effects in the right hemisphere. These wide electrical field distributions may cause collateral activation of surrounding tissue and contribute to the heterogeneous findings reported in previous studies. It remains to be tested whether additional modifications of the montages (e.g., by using smaller electrodes or a HD tDCS setup) further reduce induced field strengths in regions peripheral to the targeted region. The area chosen for stimulation also depends on the location of the reference

electrode. Most researchers place the reference electrode on the contralateral (right) supraorbital region (e.g., Buchwald et al., 2019), whereas others place it on the contralateral (right) homologue area (e.g., Marangolo et al., 2013).

Electrodes

Different electrodes, i.e., different montages, materials, shapes, and sizes**,** vary across studies. Different ***montages*** are available: (a) *bipolar* (two cephalic electrodes) (e.g., Marangolo et al., 2013) or (b) *unipolar* (one cephalic and one extracephalic electrode) (e.g., Nitsche & Paulus, 2000). The magnitude of the tDCS-elicited changes in cortical excitability depends on the electrode montage, due to the interdependence between neuronal orientation and the orientation of the induced current (Wagner et al., 2007). At present, different electrode arrangements have been evaluated – this has been done mainly for stimulation of the primary motor cortex, less for non-motor areas. Since language is a complex cognitive task involving language networks, not specific areas, in recent literature, researchers have investigated the added benefits of bilateral/bipolar stimulation over unilateral stimulation (e.g., Li et al., 2015; Moliadze et al., 2010). Regarding the ***material*** of the electrodes, two types are most often used: nonmetallic, conductive rubber electrodes, covered by saline-soaked sponges or rubber electrodes used with conductive gel (Prehn & Flöel, 2015), minimizing chemical reactions at the electrode-skin interface.

Looking at the ***size and shape*** of the electrodes, two large electrode pads with areas of several tens of cm^2 are used (Saturnino, Antunes, & Thielscher, 2015). This conventional tDCS electrode montage results in very diffuse brain current flow, with areas of clustering ("hot spots") and ineffective pervasion of the targeted area (Edwards et al., 2013). When using the conventional large stimulation electrodes (i.e., 25–35 cm^2), tDCS is less suitable to investigate functional-anatomic subdivisions within language areas, but it might be preferable for therapeutic, longitudinal purposes (Monti et al., 2013).

Combination of tDCS and Behavioral Task

The fifth variable concerns the combination of tDCS and the behavioral task; researchers distinguish between online and offline tDCS. ***Online*** tDCS implicates that the tDCS stimulation is given during a therapy session, therefore potentially optimizing the effects of language therapy, whereas ***offline*** tDCS implicates that the tDCS stimulation is given before a therapy session, potentially priming the language system in preparation for the task used during treatment (de Aguiar, Paolazzi, & Miceli, 2015). Behavioral priming results in improved performance due to repeated encounters with the same or related stimuli and is caused by a reduction in task-dependent neural activity (Holland et al., 2011). Neural priming is the neurophysiological explanation of the cumulative effect of tDCS on behavior. Since the human brain consists of dense neuronal tissue, it operates on limited neural resources

and thereby consists of overlapping neural networks (Brem, Unterburger, Speight, & Jäncke, 2014). In cognitive and neurobiological models, cognitive functions are supported by distributed, interconnected, overlapping, and highly parallel processing networks (Hebb, 1949; Horwitz, Heng, & Quazi, 2003). In these networks, higher-order cortices can be involved in a flexible, context-dependent manner in different functions (Behrens & Sporns, 2012; Bressler & Menon, 2010). For example, the language and motor action systems feature tight functional connections and share neural resources (Willems & Hagoort, 2007). This implicates that enhancement of cognitive functions by means of tDCS is never isolated. The facilitated switching between the overlapping neural systems involved during the behavioral task explains the improved behavioral performance afterwards. In this way, priming cortical excitability using tDCS optimizes the learning processes involved in language therapy and leads to more distinct and long-term functional communication gains (Bolognini et al., 2009). However, the exact cumulative mechanism of the externally applied tDCS, the internal modulation of neuronal activity, and the impact on an individual's behavior has yet to be determined (Holland et al., 2016). Since Monti et al. (2008) suggest the absence of effects of offline perilesional atDCS, recent studies have focused on online atDCS in elderly participants with or without aphasia (e.g., Binney et al., 2018).

Based on the results of the literature, we believe that the following tDCS parameters should result in the most effective outcome: multiple stimulation sessions (>5) should be used, each lasting for at least 20 min, with a short time interval (~24 h), so that neurons are triggered effectively. The current strength is set at 2 mA and the 25–35 cm^{2-}electrodes are placed in saline-soaked sponges to obtain an optimal current flow. The area and the type of stimulation are linked to the training/therapeutic goal (Table 6.1). This leads to determining the influencing parameters of one specific behavioral task.

6.2.2 Behavioral Task

To the best of our knowledge, there is no consensus on what the behavioral task, i.e., the speech-language therapy, should be. Nonetheless, selecting the correct pairing between the area of stimulation and the behavioral task may crucially influence the therapeutic outcome and thereby its efficiency. The goals of speech-language therapy may be better achieved if tDCS is delivered to an area putatively involved in the task at hand, as this ensures that electrical stimulation is paired with ongoing synaptic activation, a seemingly necessary factor for lasting effects (Fritsch et al., 2010).

In an ideal cumulative situation, tDCS enhances corticomotor excitability and augments the efficacy of therapeutic approaches inducing lasting neurobiological effects (Hummel & Cohen, 2006). Different tasks might be differentially sensitive to performance changes induced by tDCS. Moreover, there is an economical argument as well: therapists have less time to treat patients and limited funding is available. Therefore, clinicians are looking for the most ideal therapy program to

Table 6.1 Recommended tDCS parameters based on current literature results

tDCS parameter	Settings
Intensity	Frequency: >5 sessions Duration: 20–30 min Type: atDCS, ctDCS (or sham)
Current	Intensity: 1.5–2 mA Density: 25 mA/cm^2 Total charge: 0.057 mA/cm^2
Area of stimulation	Left/right/bihemispheric, frontal/temporal Adapted to therapeutic task
Used electrodes	Montage: uni- or bipolar Material: nonmetallic or rubber Covered in saline-soaked sponges or coated with conductive gel Size: 25–35 cm^2 Shape: rectangle
Combination of tDCS and therapy	Online/offline

maximize the patient's communicative skills in as little time as possible and at the lowest possible cost, aiming for the most effective outcome (Maas et al., 2012).

Considering the literature on the cumulative effects of tDCS and behavioral speech-language therapy, researchers have reported cognitive enhancement in healthy participants for different cognitive (e.g., sustained attention, working memory, information processing, and language) and executive (e.g., inhibition and planning) functions. This chapter will focus on language and on motor speech, the two main domains of speech-language therapy.

tDCS and Language

Most studies focus on phonological and semantic aspects of oral language production, examining the effects of tDCS on picture naming (Fertonani, Brambilla, Cotelli, & Miniussi, 2014; Holland et al., 2011; Indefrey, 2011), verbal fluency (e.g., Iyer et al., 2005), or picture-word interference (Indefrey & Levelt, 2004). Few studies focus on the cumulative effect of tDCS and semantic aspects of language comprehension, using lexical decision (Brückner & Kammer, 2017), semantic judgment (McDermott, Petersen, Watson, & Ojemann, 2003), or ambiguous words (Peretz & Lavidor, 2013). Two studies have focused on the syntactic aspects of language (e.g., Cattaneo, Pisoni, & Papagno, 2011; De Vries et al., 2010). Two studies (Dick, Goldin-Meadow, Hasson, Skipper, & Small, 2009; Manuel & Schnider, 2016) have focused on tDCS and nonverbal communication, and three studies have combined tDCS with functional communication (Campana et al., 2015; Marangolo et al., 2014; Marangolo, Fiori, Calpagnano, et al., 2013) (Appendix A).

With respect to ***phonology*** and ***semantics***, several researchers have reported the cumulative effect of tDCS on ***picture naming*** (Fertonani et al., 2014; Holland et al., 2011; Indefrey, 2011). However, no consensus has been reached on the stimulation site,

since a large left frontotemporal network plays an important role in a naming task, including phonological and semantic skills. This network supports many cognitive processes, i.e., word-retrieval processes and different cognitive control processes, the initiation and sequencing of speech, and the motor speech act (Crosson, 2013; Dick, Bernal, & Tremblay, 2014; Eickhoff, Heim, Zilles, & Amunts, 2009). As Westwood and Romani (2017) state, picture naming necessitates cortical excitation (word retrieval) as well as inhibition (fending off alternative competitors). This network consists of the dorsal stream (i.e., left frontal hemisphere, the mapping of sensory input, and phonological information on the articulatory network) and the ventral stream (i.e., bilateral temporal hemispheres, the mapping of sounds onto meanings and meanings onto spoken output) (Hickok & Poeppel, 2000; Sandars et al., 2016). Studies have reported significant effects from applying atDCS over the left superior temporal gyrus and DLPFC on object and action naming (Fertonani et al., 2014; Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Sparing et al., 2008), with tDCS mostly affecting naming latencies, rather than error rates (Table 6.2).

Table 6.2 Combination of behavioral task and targeted stimulation area

Behavioral task		Stimulated brain area	Type of stimulation
Language production (phonology + semantics)	Picture naming	Left STG (word rehearsal) (T7) Right STG (T8) Left DLPFC (word selection) (AF3/Fp1)	ctDCS ctDCS atDCS
	Verbal fluency	Left PFC (switching) (Fp1) Left IFG (word finding) (F5) Left STG (clustering) (T7) Left ITG (semantics) (FT9)	atDCS atDCS atDCS
	Picture-word interference	Left MTG (semantics) (T7) Left STG (phonology) (T7) Left temporal cortex (T7)	atDCS atDCS atDCS
Language comprehension (semantics)	Lexical decision	Left pSTG (T5)	ctDCS
	Semantic judgment	Left IFG (F5)	atDCS
	Ambiguous words	Right STG (T8)	atDCS
Syntax	Grammar	Left IFG (F5)	atDCS
Nonverbal communication	Gesture-language interplay	Left IFG (F5)	atDCS
Functional communication	Conversational therapy	Left IFG (F5)	atDCS

STG superior temporal gyrus, *DLPFC* dorsolateral prefrontal cortex, *PFC* prefrontal cortex, *ITG* inferior temporal gyrus, *MTG* middle temporal gyrus, *STG* superior temporal gyrus, *pSTG* posterior superior temporal gyrus, *IFG* inferior frontal gyrus

Another frequently examined language task pertains to ***verbal fluency*** (e.g., Iyer et al., 2005; Meinzer, Flaisch, et al., 2012). This usually involves a short test in which participants are required to generate as many words as possible from a semantic category (i.e., "semantic fluency," which is a more common task, since we organize our daily lives in semantic categories) or beginning with a specific letter (i.e., "phonemic fluency," a more complex and less familiar task) within a limited period of time. Many cognitive processes are involved in verbal fluency. In order to name as many examples as possible, one has to search the word content, retrieve it, monitor it, and select the appropriate word form from among competing alternatives (Fertonani et al., 2010). Considering its cognitive complexity, many brain areas are involved: (1) the prefrontal cortex ("switching," i.e., changing from subcategories, as seen when one goes from providing examples of one subcategory to another, a more controlled process), (2) the inferior frontal gyrus (finding words), and (3) the superior temporal gyrus ("clustering" of words, i.e., the contiguous generation of words, a more automatic process) (Hirshorn & Thompson-Schill, 2006) (Table 6.2). To make it even more complex, phonemic and semantic word fluency involve partially different neural networks: semantic fluency is associated with a greater activation of the left inferior temporal lobe, reflecting the site of stored information being retrieved (Heim, Eickhoff, & Amunts, 2008). The inferior frontal gyrus is likely to subserve common processes critical for both semantic and phonemic tasks (Costafreda et al., 2006). Clustering and switching processes are also dependent on a number of participant characteristics, such as age and level of education (Vannorsdall et al., 2016). Evidence suggests that older healthy participants switch less frequently on semantic fluency tasks and produce larger clusters on phonemic fluency tasks than younger participants (Troyer, Moscovitch, & Winocur, 1997). While some studies report increased verbal fluency during or after tDCS (inferior frontal gyrus: Cattaneo et al., 2011; Iyer et al., 2005; Penolazzi, Pastore, & Mondini, 2013; Pisoni et al., 2018; DLPFC: Vannorsdall et al., 2012), other studies have not obtained such an effect (inferior frontal gyrus: Cattaneo et al., 2011; Ehlis, Haeussinger, Gastel, Fallgatter, & Plewnia, 2016; Vannorsdall et al., 2016; DLPFC: Cerruti & Schlaug, 2009). A third, less frequently reported language production task is a ***picture-word interference task***. Participants are asked to name pictures while ignoring a visually or aurally presented distractor word. The relatedness of the target and the distractor is systematically varied. Typically, a semantically related distractor increases naming latencies compared to an unrelated distractor, while a phonologically related distractor speeds up naming latencies. Lexical-semantic processing has been associated with the left medial temporal gyrus, while phonological processing has been located in the left superior temporal gyrus (Indefrey & Levelt, 2004) (Table 6.2). Semantically related distractors are examined in more detail in semantic blocking tasks. In such a task, naming latencies are compared between semantically homogeneous (i.e., containing words from the same semantic category) and heterogeneous (i.e., semantically unrelated words) blocks. Retrieving and producing semantically related words in a row typically results in longer naming latencies compared to producing semantically unrelated words. This effect is called "the semantic interference effect" and underlines the competitive selection of target responses. This process is believed to rely on the left temporal

cortex (Indefrey, 2011). Therefore, Indefrey (2011) and Wirth et al. (2011) focused on semantic interference during spoken word production using continuous and blocked cyclic naming paradigms (Damian, Vigliocco, & Levelt, 2001; Howard, Nickels, Coltheart, & Cole-Virtue, 2006). The underlying explanation is that in order to map a conceptual representation onto a speech representation, lexical-semantic encoding needs to take place (Belke & Stielow, 2013). However, on the one hand, researchers still have to unravel the precise functionality of the human brain. For example, Indefrey (2011) suggests that more research is needed to disentangle the precise role of subregions of the left inferior frontal gyrus and of the inferior parietal cortex in word production. On the other hand, the setup of the language task itself is still open for debate. Belke and Stielow (2013) demonstrate that the study of semantic context effects on object naming has proven to be a powerful tool for investigations in language production, although the persistency of semantic context effects still remains to be elucidated.

While there is an abundance of literature on language production, less is known on language comprehension, on syntax, on nonverbal communication, or on functional communication. Looking at ***language comprehension***, Brückner and Kammer (2017) focused on the relationship between a ***lexical decision*** task and ctDCS across the left posterior superior temporal gyrus. McDermott et al. (2003) focused on ***semantic judgment*** and the specific role for the left inferior frontal gyrus, while Yang, Fuller, Khodaparast, and Krawczyk (2010) reported a positive effect of atDCS over Broca's area while performing a figurative language comprehension task (Table 6.2). Peretz and Lavidor (2013) focused on ***ambiguous words*** while using a semantic decision task. De Vries et al. (2010) and Cattaneo et al. (2011) focused on ***syntax***: they combined implicit artificial grammar learning with atDCS of the inferior frontal gyrus.

Only one study (Dick et al., 2009) focused on ***nonverbal communication***. They reported the cumulative effect of gesture-language interplay, in which the inferior frontal gyrus plays a critical role.

Looking at ***functional communication***, Marangolo, Fiori, Campana, et al. (2014); Marangolo et al. (2013); and Campana et al. (2015) combined tDCS with activity-based intensive conversational therapy. They used short video clips to set up a natural conversation and encouraged the individual to use a broad range of communicative means (e.g., gestures, drawings, orthographic or phonological cues) to exchange salient information about the video clip. They concluded that atDCS delivered over Broca's area improved informative speech, i.e., individuals used more and more communicative units and the improvement persisted after 1 month (Table 6.2).

tDCS and Motor Speech Act

Recently tDCS has also been used in normal motor control (e.g., Grimaldi et al., 2016; Kang, Summers, & Cauraugh, 2016; Lefaucheur, 2016). The literature on the effects of tDCS on the motor speech act is far more scarce compared to tDCS and language. Five studies have combined tDCS with repeating orally presented words

(Bashir & Howell, 2017; Buchwald et al., 2019; Chesters, Hsu, Bishop, Watkins, & Mottonen, 2017; Fiori, Cipollari, Caltagirone, & Marangolo, 2014; Simione, Fregni, & Green, 2018) and only one study has combined tDCS with oral reading (Wong, Chan, Ng, & Zhu, 2019). Their overall focus was on maximizing speech motor performance, i.e., the fluent and accurate articulation of sequential sounds in words, measured by acquisition, retention, and generalization of speech motor performance (e.g., Maas, 2015; Marangolo, Fiori, Campana, et al., 2014). Although speech production is a habitual and unique form of human daily communication, it is a complex behavior requiring the integration of concurrent linguistic, cognitive, attentional, and sensorimotor processes (Oh, Duerden, & Pang, 2014; Simione et al., 2018). When speaking, one should carefully plan and program precise muscle instructions, and oral movements must be highly coordinated.

During the last two decades, studies (Adams & Page, 2000; Bislick, Weir, Spencer, Kendall, & Yorkston, 2012; Ito, Coppola, & Ostry, 2016; Jones & Croot, 2016; Lisman & Sadagopan, 2013; Steinhauer & Grayhack, 2000; Wong, Whitehill, Ma, & Masters, 2013) have primarily focused on the integration of training principles in the nonspeech domains of motor learning, i.e., *principles of motor learning* (PML) (Schmidt, 1988; Schmidt & Lee, 2005). These PML are derived from relatively easy motor tasks, implicating that they cannot be directly translated to such complex motor tasks as the speech motor act, which possibly depends on a separate and unique motor system (Ziegler, 2003). PML specify (1) the structure of the practice, i.e., practice amount, distribution, variability and schedule, attentional focus, and target complexity, and (2) the nature of feedback, i.e., type, frequency, and timing, in order to enhance the learning capabilities for novel movements (Bislick et al., 2012). Although the application of these PML in speech motor learning has shown positive results in a healthy population, further investigation is warranted (Bislick et al., 2012; Maas, 2015), including replication of current research, extension of investigations of young healthy participants to older healthy participants, extension of investigations to motor speech disorders (e.g., ataxic dysarthria), and investigations of additional PML in both healthy participants and participants with motor speech disorders. In this way, PML can function as a theoretical framework, generating specific hypotheses that need to be investigated in more detail in different populations.

Recently, Buchwald et al. (2019) found that atDCS over the left motor cortex (C3) can improve speech motor learning in an offline condition, which makes it a possible stimulation target to enhance the performance in pure speech motor processing, such as syllable repetition or nonword repetition (Fuertinger, Horwitz, & Simonyan, 2015). Fiori et al. (2014) have confirmed critical involvement of the left premotor region (BA 6), including Broca's area (BA 44/45), in speech repetition (e.g., Baddeley, 2010; Trost & Gruber, 2012). They showed that speech accuracy and vocal reaction times while repeating tongue twisters during atDCS significantly improved during and 1 h after the stimulation. On the contrary, ctDCS significantly reduced speech articulation performance, while sham had no influence on speech articulation. Moreover, they showed generalization effects to untreated language production skills, which underlined the fact that speech engages motor and linguistic networks (Simione et al., 2018).

tDCS and Task Complexity

Besides the specific speech-language task, the ***complexity of the task*** influences the effect of tDCS and thereby the functional outcome. de Aguiar, Paolazzi, and Miceli (2015) reported that atDCS may be more suitable for easy tasks, while ctDCS may be more appropriate when the task is difficult. The question remains which task is easy and which task is not. Difficulty is not a one-way scale from "easy" to "complex ", and different multi-way parameters have an impact on the level of complexity in different ways. First, the ***input***, i.e., the way the task is delivered, might affect task complexity and thus the effectiveness of tDCS. A visually presented task, such as a reading task, impacts other, more occipital brain areas than an aural task, such as a repetition task, which impacts more temporal brain areas (Church, Coalson, Lugar, Petersen, & Schlaggar, 2008). For example, in a recent study, Rollans, Cheema, Georgiou, and Cummine (2017) suggested that the left inferior fronto-occipital fasciculus is more sensitive to overt response times that reflect slower and nonautomatic processes. Secondly, ***cueing*** and ***feedback***, i.e., the way the task is supported, can be defined in different ways to influence the level of complexity. Miniussi, Harris, and Ruzzoli (2013) created a cueing strategy for a picture naming task, while Peach and Chapey (2008) postulated a cueing hierarchy of different semantic, orthographic, and phonological cues for the same task. Thirdly, the ***output***, i.e., the way the task is performed, will impact which brain regions will be involved. For example, an oral response induces activity in other brain regions than a written response, the same for a verbal response versus a nonverbal response. Finally, the ***training material*** itself might impact task complexity. A consistent finding has been that when naming objects in context with other items from the same semantic category, response time increases compared to naming in unrelated contexts (Gauvin, Meinzer, & de Zubicaray, 2017).

6.2.3 Study Group

Besides stimulation- and task-related parameters, one should also take into account interindividual variability. Individual cortical susceptibility to stimulation may differ, inducing different levels of excitability among participants (Krause & Cohen Kadosh, 2014; Parazzini, Fiocchi, Liorni, & Ravazzani, 2015).

Mattson (2015) and Rabipour, Wu, Davidson, and Iacoboni (2018) report a list of interindividual differences: (1) general physiognomic differences, such as the morphology of the individual's brain (Kim et al., 2014); (2) cognitive differences, such as information processing capacity, processing speed, attention, episodic memory, decision making, executive control functions, emotion processing, regulation, and lifelong cognitive stimulation; (3) demographic differences, such as age, gender (Madhavan, McQueeny, Howe, Shear, & Szaflarski, 2014), and level of education (El Hachioui et al., 2013); (4) social differences, such as social support and lifestyle factors; (5) medical differences, such as diabetes, overweight, or the use of medica-

Table 6.3 Checklist of interindividual differences impacting the responsiveness to tDCS

Interindividual differences	Examples
Physiognomic differences	Morphology of the brain
Cognitive differences	Information processing capacity and speed Attention Memory Executive functioning Lifelong cognitive stimulation
Demographic differences	Age Gender Level of education
Social differences	Social support Lifestyle factors
Medical differences	Diabetes Overweight Use of medication
Physical differences	Physical activity
Psychological differences	Motivation Expectation Emotional state

tion; (6) physical differences, such as physical activity; and (7) psychological differences, such as motivation, expectations of outcomes, and affect (Table 6.3).

Physiognomic Differences

Regarding ***physiognomic differences***, interindividual differences in cranial and brain anatomy can influence the impact of tDCS by inducing variability in the actual current received by the brain, even when the same electrical dose is administered. Some examples of these physiognomic differences are skull thickness and cerebrospinal fluid thickness (Opitz, Paulus, Will, Antunes, & Thielscher, 2015), subcutaneous fat (Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013), gyral pattern (Datta, Truong, Minhas, Parra, & Bikson, 2012), local tissue heterogeneities (Shahid, Wen, & Ahfock, 2014), and orientation of neurons (Arlotti, Rahman, Minhas, & Bikson, 2012). Anatomical factors do not always have the expected influence. For example, Opitz et al. (2015) demonstrated that a thicker skull resulted in a more complex relationship between skull thickness and current density.

Cognitive Differences

As for ***cognitive differences***, Smith and Clithero (2009) demonstrate that both atDCS and ctDCS over the left DLPFC can enhance performance in attention tasks, working memory, planning abilities, information processing capacity, and speed. For example, sustained attention is an influencing factor in the rehabilitation process, since it is a prerequisite of cognitive relearning.

Demographic Differences

With respect to ***demographic differences***, such as *aging*, researchers often start with healthy, young participants. Nevertheless, Summers, Kang, and Cauraugh (2016) underline that the neuroplasticity of the elder brain differs from that of a younger brain. They reported that it is more difficult for older participants to retrieve proper names in a naming task and that their verbal fluency is slowing down. This implicates that test results of a younger population cannot be extrapolated to an older population. At the neurophysiological level, aging negatively impacts gray and white matter integrity and neurotransmitter activity (Gutchess, 2014). The impact ranges from a loss of neurons and cortical thinning over impaired neurotransmitter-receptor binding and signaling and an accumulation of neurofibrillary tangles and amyloid plaques to altered concentrations of various brain metabolites (Jagust, 2013). Tatti, Rossi, Innocenti, Rossi, and Santarnecchi (2016) suggested this results in reduced hemispheric lateralization in cognitive aging, which leads to a complex relationship between functional overactivation, structural integrity, and cognitive abilities. Meinzer, Lindenberg, Antonenko, Flaisch, and Floel (2013) showed that elderly participants present with greater bilateral prefrontal activation than young adults and that this correlated with poorer performance in semantic word generation. In word-retrieval studies, decreased accuracy (Meinzer et al., 2009) and increased reaction times (Wierenga et al., 2008) have been noted for older populations. Right frontal activity has only been found in more demanding tasks, i.e., when the older participants produced fewer correct responses compared to the young adults (Meinzer et al., 2009; Meinzer, Flaisch, et al., 2012). This increased bilateral activity is explained by enhanced cognitive demands. According to Meinzer et al. (2014), there might be a co-interference of aging and challenging task conditions. They reported enhanced activity in right prefrontal areas in healthy older compared to younger participants when performing a language task. This enhanced activity might be due to an age-related phenomenon or it might reflect task difficulty effects. Moreover, control processes may have been more challenged in the older group due to deterioration of specialized neural populations in left frontal areas (Park & Reuter-Lorenz, 2009) or medial temporal structures (Pihlajamäki et al., 2000). Changes in hippocampal functions (Pihlajamäki et al., 2000) may also explain selectively impaired semantic word generation in healthy older participants. This may result in local changes in brain activity and also disruption of coordinated activity between different brain regions. Bennett and Madden (2014) have also demonstrated widespread changes in structural connectivity in aging, which has been linked to behavioral impairment and changes in functional networks, such as frontoparietal attention networks. Taking this into account, researchers agreed that atDCS is a viable tool to improve language function in aging (Fertonani et al., 2014; Perceval, Flöel, & Meinzer, 2016).

Moreover, cognitive performance declines with age (Mattson, 2015), although this decline does not affect all individuals equally (Berryhill & Jones, 2012). This decline is due to structural changes, i.e., neural atrophy from prefrontal and parietal regions, as well as functional changes, i.e., the recruitment of additional resources to maintain cognitive task performance (Davis, Dennis, Daselaar, Fleck, & Cabeza,

2008). Besides the impact of age, the *level of education* might impact the functional outcome after tDCS. For example, Katz et al. (2017) show that cognitive training may be more beneficial to those who already have strong cognitive abilities. The advantage of tDCS seemed to increase proportionally with decreasing baseline ability and conferred little additional advantage to a participant who had already performed high at baseline. It is still unclear which specific cognitive ability, such as higher levels of numeracy, literacy, or academic attainment, may mediate the interaction between stimulation and low baseline performance.

Social Differences

Social differences may also affect responsiveness to therapy. Patients with better *social support* experience better and faster recovery (Glass, Matchar, Belyea, & Feussner, 1993). To the best of our knowledge, the specific impact of social differences on tDCS efficacy has not been examined yet, but it is a factor that needs to be taken into account when using tDCS as a therapeutic aid.

Medical Differences

As for ***medical differences***, besides concomitant *diabetes* or *overweight*, *medication* as well can impact the effect of tDCS. Prehn and Flöel (2015) focused on the interference of dopaminergic and serotonergic agents and tDCS, which could change the outcome of the stimulation. More research is necessary to investigate the value of additional biomarkers, such as learning relevant candidate genes, inflammatory markers, neurotransmitter concentrations, markers of cortical excitability and neurodegeneration, as well as neuronal activation patterns in predicting the therapeutic efficacy of tDCS.

Physical Differences

Regarding ***physical differences,*** even something as seemingly minor as hair thickness may impact the outcome of tDCS, since poorer electrode contact can reduce the amount of current passing through the scalp and skull. Other more obvious differences, such as poorer motor coordination or postural control, might influence the impact of tDCS on functional outcome (Uehara, Coxon, & Byblow, 2015).

Psychological Differences

tDCS studies rarely examine ***psychological differences*** such as motivation, expectations of outcome, affect, and attitude which may influence tDCS responsiveness through placebo-like effects. Two findings in the literature have underlined the importance of examining psychological differences in tDCS studies: evidence for

the influence of (1) *expectations* on cognitive interventions (e.g., Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016) and performance (e.g., Schwarz, Pfister, & Büchel, 2016) and (2) factors such as *emotional state* (Sarkar, Dowker, & Cohen Kadosh, 2014) and *motivation* (Jones, Stephens, Alam, Bikson, & Berryhill, 2015) on responsiveness to tDCS.

Brain Lesions

Besides these seven interindividual differences in a healthy population, an extra category of differences is linked to the ***brain lesion*** underlying an acquired speech-language disorder. Focusing on a participant with a brain lesion, a variety of factors has the potential to influence the outcome of speech-language therapy. Relevant roles can be played by:

1. *Stroke severity* (Pedersen, Vinter, & Olsen, 2004): for example, Maas et al. (2012) reported the negative influence of a larger lesion on post-stroke aphasia recovery.
2. *Lesion characteristics* such as site, size (Maas et al., 2012), and type (El Hachioui et al., 2013): looking at the lesion site, lesions of the left hemisphere might provide cortical disinhibition in perilesional structures, thereby increasing activity in left areas involved in language, with this perilesional activation associated with good recovery. However, this lesion can also disrupt the balance of interhemispheric competition. Whether increased right hemisphere activation is beneficial or maladaptive is controversial (Hamilton, Chrysikou, & Coslett, 2011).
3. *Characteristics of the speech-language disorder*: less severe overall aphasic deficits (Pedersen et al., 2004) and sparing of phonological skills (El Hachioui et al., 2013) are significant predictors of recovery.

Several stroke studies showed that participants with larger deficits and less surviving brain structures, assessed by lesion size (Bolognini et al., 2015), white matter tract integrity (Bradnam, Stinear, & Byblow, 2013), or level of impairment (Saucedo Marquez, Zhang, Swinnen, Meesen, & Wenderoth, 2013), appeared to experience less benefit from tDCS. Bradnam et al. (2013) reported that ctDCS on the contralesional hemisphere in severely impaired patients could even have a negative effect. The underlying explanation might be that the contralesional activity is having a compensatory effect rather than impairing recovery of the lesioned hemisphere (O'Shea et al., 2014). Other factors such as time post-onset (Saucedo Marquez et al., 2013) and increased baseline functional connectivity (Rosso et al., 2014) might also confer better responsiveness to tDCS. Knowledge of the mechanisms underlying spontaneous recovery and of those underlying the effect of tDCS is yet insufficient to constrain neurostimulation strategies in participants with post-stroke aphasia.

6.2.4 Outcome Measures

A final methodological variable is the used outcome measure. The reported measures vary across studies and are often not ideal for evaluating the therapeutic goals. Speech-language therapy is a type of neurorehabilitation that focuses not only on the rehabilitation of an impairment but also searches for compensating strategies, implicating a progress in *functional communication*. Therefore, in a picture naming task, researchers should not only evaluate the impairment (i.e., using a picture naming task after naming therapy), but they should also focus on transfer (i.e., does the patient's naming also improve on non-trained words) and generalization (i.e., does the patient use the trained words in functional communication) of the naming abilities. Moreover, researchers should not only focus on naming accuracy but also on the reaction time, since higher reaction times are associated with more fluent language output, which maintains the flow of the conversation. This implicates that they should focus on the functional outcome and on the impact on the participant's *quality of life*. An impairment-based outcome measure has an advantage for the researcher, since it assesses the interplay between the neurophysiological effects of tDCS and levels of cortical excitability. For the clinician and the patient, however, the impairment-based focus is less crucial; they are more focused on improving the functional communication and the patient's quality of life.

Moreover, the outcome measures should not only be evaluated immediately after therapy, but *follow-up* measures should be included as well to determine whether treatment effects endure after treatment. Some studies (e.g., Shah-Basak et al., 2015) have shown only a trend towards improvement immediately after the combination of atDCS and naming therapy, but showed significant improvement at 2 months' follow-up.

6.3 tDCS in Patients with Language/Speech Disorders

6.3.1 Aphasia

The clinical application of tDCS in participants with aphasia was first reported in August 2006 (Hummel & Cohen, 2006). Since then, 44 studies have been published, investigating the therapeutic potential of the technique. These studies have included 394 participants with aphasia due to a vascular lesion. About 76% of the participants ($n = 301$) had chronic aphasia, 17% ($n = 68$) (Hesse et al., 2007; Kang, Kim, Sohn, Cohen, & Paik, 2011; Jung, Lim, Kang, Sohn, & Paik, 2011) had subacute aphasia (4–8 weeks post-stroke), and 6% ($n = 25$) (Rosso et al., 2014) were in the lesion phase (3–6 months post-stroke). To exclude spontaneous recovery, most studies zoom in on participants with chronic aphasia. However, in clinical practice it might be better to combine tDCS with aphasia therapy in the lesion phase so that the cumulative effect of spontaneous recovery and therapy-induced recovery can

merge into the most optimal recovery for the individual participant with aphasia. Zooming in on the tDCS parameters, most of these 44 studies use: (1) multiple tDCS sessions (ranging from 1 to 30 sessions, mean: 7.1 sessions); (2) with a current strength of 1.5 mA (ranging from 1 to 2 mA); (3) the active electrode is most often placed on the left inferior frontal gyrus and the reference electrode is placed on the right supraorbital region; (4) a unipolar montage is used; (5) current is transferred by nonmetallic electrodes covered in saline-soaked sponges of 35 cm^2; and (6) tDCS is combined with online therapy. Most studies focused solely on patients with non-fluent aphasia (n = 172; 44%), i.e., Broca's aphasia, global aphasia, and transcortical motor aphasia (e.g., Marangolo et al., 2014; Marangolo, Fiori, Campana, et al., 2014; Saidmanesh et al., 2012). Fridriksson, Richardson, Baker, and Rorden (2011) reported a study focusing solely on patients with fluent aphasia (n = 8; 2%), i.e., Wernicke's aphasia, amnestic aphasia, and transcortical sensory aphasia. Other studies combine patient groups: non-fluent aphasia (n = 161; 40.5%), fluent aphasia (n = 47; 12%) and mixed aphasia (n = 6; 1.5%) (Baker, Rorden, & Fridriksson, 2010; de Aguiar, Paolazzi, & Miceli, 2015; Jung et al., 2011; Kang et al., 2011; Lee, Cheon, Yoon, Chang, & Kim, 2013; Vestito et al., 2014; Volpato et al., 2013).

With these different methodological approaches in mind, determining a specific pathway for participants with aphasia is far from simple. Aphasia is among the most devastating consequences of stroke, as it affects vocational integration, social life, and psychological well-being on the individual level and places major burdens on the healthcare system. Intensive and deficit-oriented treatment can alleviate aphasia even in the chronic stage, but treatment effect sizes are often modest (e.g., Brady, Kelly, Godwin, & Enderby, 2012; Wilssens et al., 2015); hence there is a pressing need to explore new strategies to enhance treatment efficacy in chronic aphasia. The combination of tDCS and behavioral therapy might be important in evidence-based language therapy (Marangolo, 2017). Multisession tDCS has been shown to induce more permanent behavioral and neural modulation (Meinzer, Darkow, et al., 2016). Therefore, interest in tDCS as a therapeutic tool for aphasia is booming (e.g., Crinion et al., 2006; Holland & Crinion, 2012; Tippett, Niparko, & Hillis, 2015), based on its potential to guide neuroplasticity in recovery and thereby facilitate learning during behavioral therapy.

Recent neuroimaging and behavioral data have indicated that considerable changes in the cortical representation of language processing can occur in the days, weeks, and months following stroke in the left hemisphere, and the degree of language recovery after stroke depends significantly on the degree of *neuroplasticity* in the participant's brain (Hamilton et al., 2011). Three kinds of changes in neural activity after stroke may be most relevant for aphasia recovery: (1) recruitment of perilesional left hemisphere regions for language-related tasks; (2) acquisition, unmasking, or refinement of language processing ability in the nondominant right hemisphere; and (3) dysfunctional activation of the nondominant hemisphere that may interfere with language recovery. Evidence indicates that unilateral injury, such as left hemispheric stroke, can lead to cortical disinhibition in at least two regions:

(1) neighboring ipsilesional cortical areas and (2) contralesional homotopic areas connected via the corpus callosum (Bütefisch, Kleiser, & Seitz, 2006).

It is well established that activity in one cerebral hemisphere affects activity in the other one via a rich network of *interhemispheric connections* and that these interactions represent a dynamic process that can be flexibly modulated based on task demands or by exogenous stimulation (Chrysikou & Hamilton, 2011). The inhibitory interplay between homologous hemispheric regions likely contributes to normal performance on a variety of tasks and can be manipulated with tDCS. Unilateral stroke gives rise to maladaptive patterns of interhemispheric competition. In the healthy brain, there is a mutual inhibitory control between the two hemispheres, mediated by transcallosal connections (Bütefisch, Weβling, Netz, Seitz, & Hömberg, 2008). Thus, a unilateral left-side lesion reduces transcallosal inhibition of the right hemisphere by the left hemisphere and therefore increases activity in the intact right hemisphere. Since the right hemisphere can still send transcallosal inhibitory impulses to the left hemisphere, activation in the damaged left hemisphere is further reduced (de Aguiar et al., 2015; de Aguiar, Paolazzi, & Miceli, 2015).

Appendix A shows an overview of the heterogeneous literature on tDCS and aphasia. The first reports focused on the safety of the tDCS device in participants with aphasia (e.g., Hesse et al., 2007). Since 2011, the focus has moved from the most ideal stimulation site over to the most ideal task and the most ideal stimulation schedule. Unfortunately, researchers do not formulate a clear step-by-step protocol that fits all patients, due to all the interrelated methodological variables. In Sect. 6.4, we will present a road map for determining a tDCS protocol that can be used in therapy.

6.3.2 Motor Speech: Dysarthria/Apraxia of Speech (AoS)

As in the case of aphasia, it is complex to specify a pathway for participants with isolated motor speech disorders, i.e., dysarthria (Duffy, 2013) or apraxia of speech (AoS), or for individuals with motor speech disorders in the presence of aphasia (Wambaugh, Duffy, McNeil, Robin, & Rogers, 2006).

In daily clinical practice, many treatment approaches have been developed to remediate motor speech disorders. For dysarthria, the application of PML can be interesting as a therapeutic approach (Austermann Hula, Robin, Maas, Ballard, & Schmidt, 2008; Ballard, Maas, & Robin, 2007; Kaipa & Peterson, 2016; Van der Merwe, 2011; Wambaugh et al., 2017, 2018; Wambaugh, Nessler, Cameron, & Mauszycki, 2013; Wambaugh, Nessler, Wright, & Mauszycki, 2014; Whitfield & Goberman, 2017). Systematic reviews (Mitchell, Bowen, Tyson, Butterfint, & Conroy, 2017) have indicated that people with AoS benefit from articulatory treatment at the impairment level. However, no data are available about the impact of motor speech disorders and/or motor speech disorder therapy on functional communication (Wambaugh & Mauszycki, 2010) and well-being.

To the best of our knowledge, no research data exist about the impact of tDCS on speech motor performance for participants with dysarthria. For AoS, Marangolo and colleagues are the only researchers who have studied the impact of tDCS in this patient population (Marangolo et al., 2016, 2011; Marangolo, Fiori, Cipollari, et al., 2013). Marangolo et al. (2011) treated three right-handed native Italian speakers (2 M, 1 F, mean age 66 years) with stroke-induced (ischemic lesion, $n = 2$; hemorrhagic lesion, $n = 1$) chronic non-fluent aphasia and severe AoS. All three had a lesion in the left hemisphere involving damage to (1) structures functionally connected with Broca and (2) the insula. None of them showed damage to the inferior frontal gyrus. In a randomized double-blinded experiment, all three underwent online intensive articulatory training with online tDCS for 2 weeks. The tDCS protocol involved sessions (atDCS, 20 min, 1 mA) followed by a 6-day intersession interval and another five sessions (sham tDCS, 20 min, 1 mA) or vice versa. The behavioral task was an aurally presented repetition task of speech stimuli ($n = 40$ per condition) ranging from consonant-vowel (CV) syllables to CVCCV disyllabic words. The word list was adapted for each participant according to their own specific motor speech disorder. Training was delivered in five different steps: (1) the patient could watch the articulatory movements of the clinician; (2 and 3) the patient repeated this focusing on syllable-segmentation, vowel-sound prolonging and exaggerating the articulatory gestures; and (4 and 5) the patient fluently repeated this. The stimulating electrode (atDCS) was positioned over the left inferior frontal gyrus (inferior frontal gyrus, F7), and the cathodal electrode was placed over the contralateral supraorbital region. The accuracy of training was measured pre- and post-treatment. Results showed a significant acquisition effect indicated by a higher accuracy of syllable/word repetition in the post-training phase in both tDCS conditions. Moreover, the mean percentage of correct responses was greater after atDCS than after sham. Language measures showed generalization effects to oral (i.e., reading aloud) and written (i.e., writing to dictation) production tasks. None of the participants improved on oral naming. Marangolo et al. (2011) conducted three follow-ups (1 week, 1 and 2 months), which resulted in significantly better retention effects after atDCS than after sham. However, study results established significant improvements on acquisition, retention, and generalization of training in both atDCS and sham.

Marangolo and colleagues replicated these findings in a group of 17 right-handed subjects (9 M, 8 F, mean age 56.71 years) with chronic, ischemic stroke. All 17 were native Italian speakers with non-fluent aphasia and severe AoS (Marangolo et al., 2016; Marangolo, Fiori, Cipollari, et al., 2013). All 17 had a lesion in the left hemisphere involving damage to (1) structures functionally connected with Broca and (2) the insula. These studies as well resulted in improved accuracy of speech articulation and generalization effects. The studies of 2013 and 2016 differ at some methodological variables from the study of 2011:

1. tDCS parameters, i.e., (a) the intensity of the current is now set at 2 mA (instead of 1 mA); (b) the treatment intensity is augmented from five to 15 sessions; and (c) bihemispheric stimulation (instead of unihemispheric stimulation) is used.

This means that the anode was placed over the ipsilateral and the cathode over the contralateral IFG (F7 and F6).

2. The outcome measures: two tasks, i.e., vocal reaction times and picture description, were added and only one follow-up (after 1 week) was performed. Vocal reaction times declined after atDCS and 11 out of 17 patients improved on the picture description task after atDCS.

In the 2016 study, Marangolo et al. (2016) included fMRI data and showed that atDCS boosted the recovery process by increasing functional connectivity in the left lesioned cerebral hemisphere. After sham stimulation, on the other hand, functional connectivity increased in the right intact cerebral hemisphere.

6.4 Road Map

In Fig. 6.1 we have constructed a road map, summing up all the variables and linking them in a patient-centered virtuous circle. We believe that speech-language therapy should be an iterative process where the clinician is in constant dialogue with the patient. (A–B) The clinician should formulate shared, monitored, accessible, relevant, transparent, evolving, and relationship-centered (SMARTER: Hersh, Worrall, Howe, Sherratt, & Davidson, 2012) *therapeutic goals* taking into account interindividual differences and the *patient's expressed needs* (Table 6.3). (C) These goals should be linked to *therapy*, identifying the therapeutic material that is relevant for each particular patient in each particular stage of their rehabilitation. Meanwhile, the clinician should consider how they will present the material to the patient (nonverbal, oral, or written input), how they will support the patient (cueing and feedback), and how the patient should respond (nonverbal, oral, or written

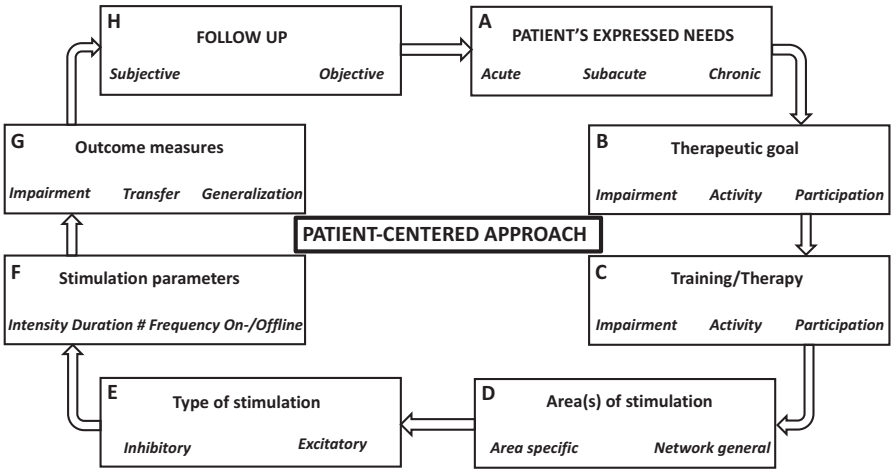

Fig. 6.1 Road map for tDCS implementation in speech-language therapy

output). (D) The clinician should choose the *area of stimulation*, identifying the brain regions that are involved in the language processes in question (Table 6.2). Here, a specific brain area or a language network can be targeted. To optimize the effects of tDCS on impaired networks and to choose the relevant targeted area and polarity, clinicians need a better understanding of brain reorganization, the time course of the reorganization, and the involvement of perilesional and contralesional cortices, in addition to the precise molecular mechanisms associated with tDCS (Biou et al., 2019). Moreover, the right Broca homologue and supplementary motor area seem to be involved in the subacute phase of stroke, and language reorganization needs these divergent processes before a normalization and reshifting of cortex activity towards the left can occur at the chronic stage (Saur, 2006). Klaus and Schutter (2018) showed in their meta-analysis a small, but reliable effect of online tDCS on language production. On the other hand, Westwood and Romani (2017) found no effect of tDCS on performance in language production and reading tasks. (E) The clinician has to determine the *type of stimulation*, taking into account the location and the severity of the stroke. Different strategies can be used through inhibition of interfering areas or excitation of compensating/perilesional tissue. This will depend on several different factors (e.g., timing of stimulation and area of stimulation). (F) The clinician has to establish the *stimulation parameters*, determining the intensity, current, and area of stimulation; the placement, type, size, and shape of the electrodes; and linking these settings with the therapeutic goal (Table 6.1). (G) The most sensitive *outcome measure* should be chosen with a focus on the impairment, the transfer, or the generalization to functional communication. (H) *Follow-up* is needed to evaluate if the progression remains or possibly augments. Here, it is also important to take into account the patient's subjective feeling of progress and well-being. In close consultation with the patient, new therapeutic goals can be set, thereby repeating the circle.

6.5 Discussion

These heterogeneous influencing parameters illustrate the difficulties associated with tDCS in anticipating the direction and the magnitude of its behavioral effects (Jacobson et al., 2012; Oldrati & Schutter, 2017). Recent publications have highlighted substantial variability among reported stimulation effects in healthy participants (e.g., Wiethoff, Hamada, & Rothwell, 2014), criticized methodological reasons (Antal, Keeser, Priori, Padberg, & Nitsche, 2015), or even questioned the potential of tDCS to induce behavioral effects on cognition and on motor function (Horvath, Forte, & Carter, 2015). They have motivated reflections on the use and the efficacy of tDCS and prompted urgent calls for more rigorous methodology (e.g., within-subject instead of between-subject designs), including replication studies (Fertonani & Miniussi, 2017) and extension of investigations to older participants, to other language disorders (e.g., semantics or syntax) and other motor speech disorders (e.g., ataxic dysarthria), and to specific behavioral tasks (e.g., investigations

of additional PML in participants with motor speech disorders). However, the more parameters one can distinguish as impacting the functional outcome, the more complex it becomes to find homogeneous groups in order to unravel the cumulative effect of speech-language therapy and tDCS.

Moreover, the complexity of the brain network which controls speech and language remains largely unknown. Functional MRI (fMRI) data highlight (1) the existence of a shared core network of segregated local neural communities in the primary sensorimotor and parietal regions, in which the left primary motor cortex plays an important role in the speech network organization; (2) the flexibility of these strong interconnected local neural communities based on their participation in several functional domains across different networks; and (3) the capacity to adaptively switch long-range functional connectivity, depending on the nature of the task. This means that each behavioral task addresses a different functional network which is related to a different neural community structure (Fuertinger et al., 2015). For example, the motor speech production network and the real-life language network share high-strength neural communities but also recruit function-specific non-shared network nodes. Predicting the efficacy of tDCS over a specific region will therefore depend on our knowledge about the exact involvement of that region in the task that will be used in combination with tDCS. Especially in patients, the underlying neural mechanisms are usually not easy to determine or understand. Therefore, besides as an interventional tool, tDCS should also be used as a research tool to complete neuroimaging approaches, neurophysiological parameters, and behavioral measures and thereby unravel the mechanism of neuroplasticity (Hartwigsen, 2015). This more fundamental methodological approach could be developed in parallel with clinical practice, in which therapy goals should be carefully planned and training should be impairment, activity, or participation oriented.

6.6 Conclusion

Considering patients with aphasia, atDCS over the left inferior frontal gyrus (F5) associated with naming therapy can result in higher naming accuracy for right-handed participants with chronic non-fluent vascular aphasia. Patients with severe AoS and chronic non-fluent vascular aphasia might benefit more from atDCS associated with articulation therapy, i.e., oral repetition. However, the generalizability of the tDCS findings to other aphasic symptoms or to other speech motor impairments in other stages of rehabilitation might be limited. Concerning tDCS parameters, bihemispheric stimulation might be more efficient than unihemispheric stimulation (Marangolo et al., 2016; Marangolo, Fiori, Cipollari, et al., 2013). These findings are in line with the interhemispheric inhibition hypothesis and confirm the importance of activating perilesional brain tissue for enhanced speech-language outcome. The stimulation schedule should include repeated sessions of tDCS that might induce more permanent behavioral and neural long-term effects in the stimulated network (Meinzer et al., 2014; Meinzer, Darkow, et al., 2016; Reis et al., 2009). To

determine the appropriate behavioral task, reactivation or (mal-)adaptation strategies should be monitored. More evidence from behavioral treatment studies in speech motor learning could help in exploring the impact of tDCS. However, the impact of tDCS with modality- and task-specific speech-language therapy remains limited and equivocal. Interindividual differences should be taken into account; in tDCS studies only demographic information about age, gender, and education has been well reported. Since it is known that the neuroplasticity of the elder brain differs from that of a younger brain, further research is warranted in all age categories of a healthy population (Summers et al., 2016).

However, it is impossible to set up a standard protocol since many parameters co-interfere with the behavioral task and interindividual variability and therefore hamper comparability between studies. While there is study-specific evidence for the efficacy of tDCS in language production research, the methodological variability between studies is large. Therefore, a patient-centered road map has been described in this chapter, which can be used as a guideline to determine the tDCS protocol with the most potential for each individual patient. This road map has been constructed as a virtuous circle since the needs of the patient and the neural complexity of the damaged network will change over time. This also allows for timely evaluation of the efficacy of the tDCS protocol and makes it possible to adjust if needed.

In general, further research should bridge the gap between tDCS and neuroimaging, neurophysiological, and behavioral findings in speech-language therapy, while using a more homogeneously constructed research methodology. The implementation of tDCS in the clinical speech-language therapy is promising, but remains experimental. Many research questions still need to be addressed: (1) More research is required to study the advantages of high definition tDCS, which can be used to stimulate more focally. (2) More research is needed for specific patient populations. There is evidence to promote online tDCS in participants with chronic non-fluent aphasia (combined with severe AoS), but up until now, there is less to no evidence to promote online tDCS in other patient populations, such as individuals with dysarthria. And (3) research should focus more on functional communication, well-being, and follow-up results, instead of focusing only on the impairment.

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Chapter 7
Transcranial Magnetic Stimulation in Aphasia Rehabilitation

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Abbreviations

cTBS	Continuous theta-burst stimulation
IFG	Inferior frontal gyrus
iTBS	Intermittent theta-burst stimulation
LH	Left hemisphere
RH	Right hemisphere
rTMS	Repetitive transcranial magnetic stimulation
TBS	Theta-burst stimulation

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
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7.1 Introduction

Aphasia is a highly prevalent acquired language disorder usually caused by damage induced after a stroke or traumatic brain injury to a network of areas (with various topographical patterns) of the left cerebral hemisphere (LH); it is mainly characterized by impairments in the production and comprehension of speech, word-finding difficulties, and difficulties in reading and writing (Harley, 2001: 23).

Recovery and rehabilitation of language abilities in aphasia has been a challenge for clinicians and researchers, as is evident in a plethora of studies focused on the effectiveness of different therapeutic approaches (for discussion, see Gauvreau, Le Dorze, Croteau, & Hallé, 2019; Wortman-Jutt & Edwards, 2019). In addition, the increasing number of stroke patients due to the aging of the population and lifestyle changes (high levels of stress and/or generally unhealthy lifestyle) has resulted in a rise of public health cost. There is a need for an alternative or adjunct therapy in addition to behavioral therapy techniques. In the past decade there has been a significant rise in the use of therapeutic brain stimulation protocols for aphasic populations. In the present chapter, we discuss the treatment approaches used in individuals with stroke-induced nonfluent aphasia with agrammatism, who show a pattern of erroneous sentence production and comprehension in grammatically complex constructions (Caramazza & Zurif, 1976; for a review, see Bastiaanse & Thompson, 2012). We focus on noninvasive neuromodulatory techniques and, in particular, repetitive transcranial magnetic stimulation (rTMS), which has recently generated considerable clinical and research interest.

Language therapeutic interventions have traditionally focused on improving communication abilities in stroke-induced aphasia by alleviating certain symptoms. Behavioral treatments have been used to address either lexical deficits (Herbert, Best, Hickin, Howard, & Osborne, 2003; Hillis, 1998; Kiran & Bassetto, 2008) or sentence-level deficits (Murray, Timberlake, & Eberle, 2007; Schwartz, Saffran, Fink, Myers, & Martin, 1994; Thompson & Shapiro, 1994, 1995; Thompson, Shapiro, & Roberts, 1993; Thompson, Shapiro, Tait, Jacobs, & Schneider, 1996; Webster & Whitworth, 2012). With respect to lexical deficits, interventions typically focus on improving semantic processing by investigating the effectiveness of semantic and/or phonological cues for lexical retrieval. For example, Marshall, Pound, White-Thomson, and Pring (1990) investigated the effectiveness of semantic and phonological cueing by asking the patient to provide an appropriate name for a visually presented picture after reading aloud two semantically related words, an unrelated word and the target. Semantic feature analysis training has also been employed in aphasia therapy for improving naming disorders. This approach aims at strengthening the semantic, pragmatic, and cultural associations of lexical items within semantic networks to enhance retrieval ability by increasing the level of activation. Most of the intervention studies within this framework have dealt with single-word training, which positively impacts on single lexical item retrieval, with nevertheless inconsistent application of this retrieval in oral speech (see Antonucci, 2009).

Regarding sentence-level deficits, Thompson and colleagues have conducted several behavioral studies investigating the effects of training on language (re)learning and generalization in aphasia (Thompson et al., 1993, 1996; Thompson & Shapiro, 1995), applying a behavioral linguistic intervention focusing on specific grammatical aspects. Specifically, in these studies, agrammatic speakers were trained to produce *wh*-questions (e.g., *who did the woman kiss at the park?*), relative clauses (e.g., *Peter saw the woman who kissed the boy at the park*), and passive constructions (e.g., *the woman was kissed by the man at the park*). Training was explicitly focused on the underlying linguistic properties that take place during the production of those constructions, specifically, on training linguistic movement, which is the underlying mechanism generating those constructions. These studies have suggested that linguistically related structures recover together; in other words, positive outcomes can be generated in structures that entail similar movement operations (*wh*-questions, relative clauses, since they both entail *wh*-movement). However, no generalization is observed to unrelated movement structures (e.g., in passives, since they entail noun phrase (NP) movement, which is a different movement type) (see Thompson & Shapiro, 2005). More importantly, training complex structures results in generalization to less complex forms, as long as they share linguistic properties; nonetheless, the opposite pattern (simple-to-complex generalization) rarely occurs (Thompson et al., 2003; Thompson & Shapiro, 2007). "Treatment of Underlying Forms" has proven to be successful over the years, leading to robust treatment and generalization effects in people with mild-to-moderate agrammatism (Dickey & Yoo, 2010). Relatively little is known, however, about whether (a) there is a change in the processing system in response to such behavioral treatments and (b) neural changes resulting from training can be traced in the brain.

Evidence from recent studies suggests that online sentence processing abilities in agrammatic aphasia can be modulated and become more "normalized" following behavioral treatment that targets impaired linguistic processes and representations. Specifically, with respect to sentence comprehension, Dickey and Thompson (2004) found that agrammatic listeners became better at detecting syntactic anomalies in noncanonical sentences after receiving behavioral treatment. Similarly, Mack and Thompson (2017) showed that online sentence comprehension strategies normalize following treatment; more typical eye movements (i.e., agent-first looking patterns in correct responses) were recorded after treatment in an online sentence-picture matching task in ten individuals with chronic agrammatic aphasia. Similar improvements and shifts to more typical sentence processing have been reported for sentence production as well. In a recent study, Mack, Nerantzini, and Thompson (2017) used a structural priming task with eye tracking to monitor treatment-induced changes in online sentence production in nine aphasic speakers. Before and after language treatment (which trained production and comprehension of complex passive constructions), participants' eye movements were tracked as they produced active and passive sentences. Prior to treatment, the aphasic speakers showed poorer production of passive sentences and an abnormal eye-tracking pattern in the encoding of agent and theme noun phrases. Posttreatment, however, not only did they show improved sentence production, but they managed to fixate on the agent more

often in active sentences than in passive, reflecting improved encoding of the sentence subject. These findings indicate that behavioral treatment not only improves offline sentence comprehension and production but also that it results in shifts to more normal sentence processing strategies.

Neural activation also seems to shift as a result of behavioral treatment. Language therapy-induced reorganization can elicit measurable changes in brain function (i.e., brain regions that have not been used previously in language processing can undertake new compensatory roles; see Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013; Saur et al., 2006). The contribution of each hemisphere to aphasia rehabilitation, however, is highly controversial, since both hemispheres participate in the recovery process. After LH damage, the region's activity is downregulated and left functional recovery can occur in different ways. Some studies show that the right hemisphere (RH) can undertake language functions that are typically mediated by the LH. Specifically, studies with children or adults, with hemispherectomy of the dominant hemisphere for language (LH) or injury in the LH, have shown stronger engagement of the RH in language processing (Bulteau et al., 2017; Calvert et al., 2000; Danelli et al., 2013; Moosa et al., 2013; de Mendonça, 2014, for discussion). Alternatively, LH areas are being recruited, with increased activation (i.e., upregulation) of non-lesioned tissue in the LH, in nearby perilesional areas (Fridriksson, Richardson, Fillmore, & Cai, 2012; Meinzer et al., 2008) or the residual LH structures that may have been involved in language function previously (Heiss & Thiel, 2006; Saur et al., 2006). However, although some studies have shown that better recovery and spontaneous recovery is mainly associated with the restoration of function by the LH (de Mendonça, 2014; Fridriksson et al., 2013; Heiss & Thiel, 2006; Saur et al., 2006; Schlaug, Marchina, & Wan, 2011), contralesional areas (homologous to language and speech-motor regions) in the RH (Heiss & Thiel, 2006; Kiran, Meier, Kapse, & Glynn, 2015; Thompson, den Ouden, Bonakdarpour, Garibaldi, & Parrish, 2010; Thompson, Riley, den Ouden, Meltzer-Asscher, & Lukic, 2013) are also recruited in the recovery process to compensate for the lost function.

Thompson et al. (2006) examined the effects of training on neural activation patterns and found that treatment gains map onto perilesional (LH) tissue as well as RH homologues of LH language areas, even in chronic patients. In a more recent study, Barbieri, Mack, Chiappetta, Europa, and Thompson (2019) reported upregulation in the activation of RH region homologues of LH regions involved in both sentence processing and domain-general functions after training production and comprehension of complex passive constructions in 14 agrammatic speakers. These findings provide compelling evidence for treatment-induced neural plasticity in chronic aphasia and highlight the role of language networks in the restoration of normal-like sentence processing patterns in chronic aphasia.

More importantly, the effectiveness of treatment and aphasic speakers' ability to recover can vary across individuals due to factors including: (1) participant demographic characteristics (i.e., age, sex, years of education) (e.g., Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Pedersen, Vinter, & Olsen, 2004); (2) severity type, related to lesion size and site (e.g., Lazar et al., 2010; Maas et al., 2012;

Marchina et al., 2011; Pedersen et al., 2004); (3) time post-onset (e.g., Bakheit, Shaw, Carrington, & Griffiths, 2007); (4) the anatomical characteristics of the right auditory-motor white matter tracts (e.g., arcuate fasciculus) (Forkel et al., 2014; Marchina et al., 2011); and (5) the integrity of tissue within specific brain regions, such as the middle/superior temporal gyrus and the basal ganglia (Bonilha, Gleichgerrcht, Nesland, Rorden, & Fridriksson, 2016; Fridriksson et al., 2012).

In light of these individual factors which can interfere with the prognosis of aphasia treatment, and in order to ensure that the treatment approach used results in maximal gains in the treated modality, an important development in language intervention for both focal and neurodegenerative diseases is the use of noninvasive brain stimulation. This can be applied in conjunction with or independently from behavioral treatments. In the remainder of the paper, we will review studies using rTMS as a tool for language intervention in aphasia.

7.2 TMS in Aphasia Rehabilitation

TMS is a noninvasive neuromodulatory technique that has been utilized recently to target pathologies for therapeutic gains, including therapy for depression, and rehabilitation of both developmental (Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014) and acquired disorders (Khedr et al., 2014; Lisanby, Kinnunen, & Crupain, 2002; Loo & Mitchell, 2005; Otal, Olma, Flöel, & Wellwood, 2015; Perera et al., 2016; Ren et al., 2014). In addition to its use in brain navigation and mapping (Ahdab et al., 2014; Weiss Lucas et al., 2016), rTMS has been effectively employed to facilitate language recovery by noninvasively manipulating cortical excitability in targeted focal brain regions in order to enhance neuronal plasticity at the level of synaptic communication, strengthening the connections within language networks (Hattori, Moriwaki, & Hori, 1990; Liebetanz, Nitsche, Tergau, & Paulus, 2002; Moriwaki, 1991). The procedure entails no significant risk to the recipients and has proven to be a beneficial intervention tool for different stages of aphasia recovery. Importantly, there are specific safety guidelines (Krishnan, Santos, Peterson, & Ehinger, 2015) that need to be followed with respect to intensity, frequency, and intertrain interval, in order to eliminate the risk of developing adverse effects such as fatigue, headache, nausea, seizures, and deterioration of language abilities.

Noninvasive brain stimulation protocols have been used to either increase excitation in ipsilesional cortical regions by applying high-frequency stimulation (>5 Hz) or decrease excitation in contralesional cortical regions by applying trains of low-frequency stimulation (1–4 Hz) resulting in inhibitory effects for several minutes after stimulation (Pobric, Lambon Ralph, & Jefferies, 2009). The use of inhibitory brain stimulation can be beneficial since it suppresses inhibitory effects from the intact hemisphere onto the perilesional cortex of the affected hemisphere. Facilitatory high-frequency stimulation, on the other hand, can also improve language skills in patients with stroke-induced aphasia. Recently, a few clinical studies have tried to directly compare the effects of low- and high-frequency rTMS in stroke-induced

aphasia (Chieffo et al., 2014; Hu et al., 2018); their findings are discussed in the next section. Besides classic inhibitory and excitatory stimulation approaches, a few other rTMS protocols have been successfully applied in post-stroke neurorehabilitation: (a) intermittent theta-burst stimulation (iTBS), an excitatory form of high-frequency repetitive stimulation (Szaflarski et al., 2011); (b) continuous theta-burst stimulation (cTBS), an inhibitory form of high-frequency rTMS (Kindler et al., 2012); and (c) paired-pulse stimulation, in which stimulus pulses are administered concurrently, or at varying intervals (Vuksanović et al., 2015; for combined iTBS and cTBS).

7.2.1 Stimulation Parameters (Intensity and Stimulation Site)

The vast majority of published studies have examined the inhibitory effects of rTMS in stroke patients by applying low-frequency 1 Hz stimulation to the intact homologous areas of the RH in the inferior frontal gyrus (IFG) (Abo et al., 2012; Barwood et al., 2011, 2012, 2013; Garcia, Norise, Faseyitan, Naeser, & Hamilton, 2013; Hamilton et al., 2010; Heiss et al., 2013; Martin et al., 2009, 2014; Medina et al., 2012; Naeser et al., 2005, 2011, 2012; Schlaug et al., 2011; Thiel et al., 2013; Tsai et al., 2014; Wang et al., 2014; Weiduschat et al., 2010; Winhuisen et al., 2005; (for a review see Li, Qu, Yuan, & Du, 2015; Otal et al., 2015; Ren et al., 2014)), while fewer studies have used high-frequency (≥3 to 20 Hz) rTMS applied to the LH, to investigate whether stimulating perilesional regions can boost recovery (Dammekens, Vanneste, Ost, & De Ridder, 2014; Khedr et al., 2014; Schlaug et al., 2011), probably due to the fact that the safety of the former is higher in this population compared to high-frequency rTMS. Note that there are also studies that combine low- and high-frequency stimulation in an attempt to maximize the effectiveness of treatment (Chieffo et al., 2014; Hu et al., 2018; Kakuda, Abo, Momosaki, & Morooka, 2011). With respect to the stimulation site, studies that use low-frequency rTMS mainly target the triangular part of the right IFG (Barwood et al., 2013; Hartmann, Rubi-Fessen, & Heiss, 2013; Heiss et al., 2013; Seniów et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011), and not the right pars opercularis (following Naeser et al., 2011), with the exception of Waldowski, Seniów, Leśniak, Iwański, and Członkowska (2012) that also included the pars opercularis.

Specifically, Naeser et al. (2011) showed that rTMS suppression of the right pars triangularis, through 1 Hz stimulation, significantly increased picture naming accuracy with simultaneous decrease in response time, in eight nonfluent chronic patients with aphasia. By contrast, while inhibitory effects on the right pars opercularis led to a significant increase in response times, there was no impact on participants' accuracy in picture naming. These results were interpreted as showing that specific RH areas may be more appropriate for optimal language recovery. Similar beneficial effects of the inhibitory stimulation over the contralesional pars triangularis have been reported by Tsai et al. (2014), who demonstrated significantly better performance on object naming, compared to sham stimulation, in a group of 56

patients with nonfluent aphasia after treatment. These changes persisted for at least 3 months.

On the other hand, Dammekens et al. (2014) conducted a case study using high-frequency stimulation to the damaged left IFG in post-stroke nonfluent aphasia. The application of 10 Hz rTMS was shown to be beneficial, since it decreased activity in the right IFG, while increasing activity in the right supplementary motor area and functional connectivity between the left and right IFG, and to improve participants' performance in repetition, naming, and comprehension tests.

Previously, Kakuda et al. (2011) had employed high- and low-frequency stimulation, which was applied to the right IFG of four individuals with chronic aphasia. In addition to the rTMS therapeutic protocol (18 sessions, in total, consisting of 10 min 6 Hz priming stimulation followed by 20 min 1 Hz low-frequency rTMS), intensive speech therapy was provided. Improvement was reported in both expressive and receptive language modalities in all patients (Kakuda et al., 2011). Furthermore, Khedr et al. (2014) also employed a bi-hemispheric stimulation paradigm in 30 patients with subacute post-stroke nonfluent aphasia. The researchers performed combined sequential stimulation of both hemispheres during 10 TMS sessions (5 sessions per week). A session consisted of one continuous train of low-frequency inhibitory (1000 pulses) rTMS (1 Hz) over the RH homologue of Broca's area (500 pulses over pars triangularis and 500 pulses over the pars opercularis) followed by 10 trains of high-frequency 20 Hz rTMS stimulation over the left Broca's area of the affected hemisphere (five trains over pars triangularis followed by five trains over pars opercularis). Speech and language training for 30 min followed this application. The results indicated significant gains in linguistic abilities as shown by the aphasia severity rating scale. Interestingly, these researchers reported therapeutic gains maintenance over 2 months after the therapeutic protocol application.

In an attempt to directly compare the effects of excitatory (10 Hz), inhibitory (1 Hz), and sham rTMS over the right homologous Broca's region, Chieffo et al. (2014) investigated the performance of five chronic post-stroke patients with aphasia in a picture naming task, before and immediately after three sessions of rTMS separated by a 6-day washout period to eliminate any carryover effects. Patients were assessed with the naming task immediately before and after the stimulation session. The authors reported that only the excitatory 10 Hz stimulation induced significant improvements in picture naming performance, compared to baseline and pre-rTMS evaluations, and that this effect was larger than that observed with inhibitory rTMS. This proves that excitatory stimulation can also induce facilitatory effects in chronic aphasia.

In a recent study, Hu et al. (2018) examined the efficacy of different frequencies of rTMS applied to the contralesional hemisphere in stroke patients with nonfluent aphasia. Patients were assigned to four groups: (a) a high-frequency rTMS group (10 Hz; $n = 10$); (b) a low-frequency rTMS group (1 Hz; $n = 10$); (c) a sham stimulation group ($n = 10$); and (d) a control group ($n = 10$). All patients received additional therapy including speech and language therapy services at the time of the study. Greater improvement was noted for the low-frequency rTMS group in expressive and receptive language abilities as compared to the high-frequency group, even 2

months posttreatment. Notably, as compared to the control group, the group that received high-frequency stimulation showed significantly better performance on repetition and aphasia quotients as evident on follow-up testing (2 months after treatment). Based on these results, the authors suggested that while both low- and high- frequency rTMS might be beneficial, the former results in both immediate- and long-term benefits, whereas the latter produces only long-term benefits (Hu et al., 2018).

7.2.2 Language Domains Affected

Most of the intervention studies with rTMS in stroke-induced aphasia have focused on *fluency* and *word-finding* difficulties, showing facilitation in naming after rTMS (Barwood et al., 2011; Martin et al., 2009; Naeser et al., 2005; Weiduschat et al., 2011, among others). A few studies, however, have also shown improvements in spontaneous speech and picture description tasks, calculated by word number, sentence length and function word use (Barwood et al., 2011; Hamilton et al., 2010; Martin et al., 2009; Naeser et al., 2005), articulatory agility (Naeser et al., 2005), discourse productivity (Medina et al., 2012), expressive and receptive language abilities (Barwood et al., 2013), as well as repetition (Barwood et al., 2011).

For instance, Medina et al. (2012) applied 1 Hz rTMS daily (1200 pulses) at different sites in the right IFG in order to identify the optimal target for stimulation in ten nonfluent aphasic speakers for ten sessions over 2 weeks. Half of the participants initially received sham stimulation and 2-month follow-up after they received real rTMS. These researchers explored whether narration could be affected after right IFG rTMS. Significant improvement was observed after real stimulation in several aspects of discourse production as compared to baseline performance. However, there were no differences in accuracy rates concerning grammatical and sentential aspects.

7.2.3 Studies with Combined Speech and Language Therapy and Stimulation

Neuromodulatory techniques have been employed in different research designs either by using rTMS independently as a treatment tool (Garcia et al., 2013; Hamilton et al., 2010; Medina et al., 2012; Tsai et al., 2014; Weiduschat et al., 2010) or in combination with speech and language intervention practices (Abo et al., 2012; Heiss et al., 2013; Rubi-Fessen et al., 2015; Thiel et al., 2013; Yoon, Han, Yoon, Kim, & Yi, 2015; Wang et al., 2014; for a review see Heikkinen et al., 2019) in order to maximize the efficacy of the behavioral intervention while producing more sustained improvements.

Specifically, Abo et al. (2012) applied ten 40-min sessions (2400 pulses) of low-frequency stimulation (1 Hz) to the IFG in 14 patients with chronic nonfluent aphasia and to the superior temporal gyrus in ten patients with fluent aphasia, combined with intensive speech and language therapy (60 min), for 11 consecutive days, after selection of the stimulation area using fMRI. Nonfluent participants showed significant improvement of auditory and reading comprehension, as well as repetition 4 weeks after stimulation, while fluent aphasic patients showed significant improvement in spontaneous speech. It is worth noting that no control group was included in this study.

Thiel et al. (2013) applied inhibitory 1 Hz rTMS over the right triangular part of the posterior IFG, in 13 patients with subacute stroke-induced aphasia of different types, followed by 45 min of speech and language therapy for ten sessions. Significant improvements were observed in their overall performance in the Aachen Aphasia Test, with improved naming, comprehension, and writing abilities, and higher scores in the Token Test, after real stimulation as compared to participants who had received sham stimulation (n = 10). Similarly, Heiss et al. (2013) applied inhibitory stimulation over the contralesional IFG in 29 right-handed subacute post-stroke participants with aphasia, who received either 10 sessions of speech and language therapy following 20 min of stimulation (n = 15) or ten sessions of speech and language therapy following sham stimulation (n = 14). Positron emission tomography (PET) was used prior to and after therapeutic interventions to assess language activation alterations. Significant improvements were observed in their overall performance in the Aachen Aphasia Test, after real stimulation compared to sham; picture naming was particularly improved. Additionally, changes in activation volume indices were significantly greater after real stimulation compared to pretreatment or in sham condition. These results provide evidence for network activity shift toward the left, ipsilesional hemisphere.

Seniów et al. (2013) administered a 3-week rehabilitation program with speech and language therapy combined with 30 min inhibitory stimulation (1 Hz, 1800 pulses) to the anterior portion of the right Broca's area homologue (pars triangularis) or sham stimulation. There were 40 participants with different aphasia types in the subacute phase. All participants showed improvement in linguistic abilities. However, treatment was not equally effective for all patients. Notably, severely aphasic patients showed greater improvement than patients receiving sham stimulation in repetition tasks. The authors argued that not all aphasic patients benefit similarly from the inhibition of the right hemisphere.

Although it is common for speech and language therapy to follow rTMS (Heiss et al., 2013; Rubi-Fessen et al., 2015; Thiel et al., 2013), one study has tested the efficacy of synchronous verbal picture naming training during rTMS in patients with chronic, nonfluent aphasia (Wang et al., 2014). Wang and colleagues recruited 45 Chinese patients with stroke-induced aphasia and assigned them to three groups: (1) a group that underwent contralesional 1 Hz rTMS over the Broca homologue (i.e., contralesional pars triangularis) for 20 min for ten daily sessions coupled with a synchronous picture naming training (online model), (2) a group that underwent stimulation followed by a picture naming activity (offline model), and (3) a group

that underwent sham stimulation combined with a concurrent naming activity. Their performance was assessed before, immediately, and 3 months following the intervention. The group who had received stimulation and picture naming therapy simultaneously showed significant improvements in their overall scores of the Concise Chinese Aphasia Test, as well as in expression and description subtests, and in action and object naming activity, as compared to the two other groups. Treatment gains were maintained for 3 months, in comparison with the sham group.

To the best of our knowledge, the available studies that combine brain stimulation and speech therapy do not allow us to separate the effects of each therapeutic intervention (rTMS and intensive language therapy) on language function. Thus, the positive outcomes reported should be interpreted with caution, since intensive language therapy alone can also improve language function in the chronic phase of stroke. Note also that the content, as well as the duration and frequency of the language therapy provided, differs across studies. Bhogal, Teasell, and Speechley (2003) have reported a correlation between the duration of language therapy (total number of hours) and the extent of improvement. In an attempt to compare the efficacy of rTMS with speech and language intervention, Yoon et al. (2015) showed that nonfluent aphasic patients who received only speech and language therapy for a 4-week period demonstrated no significant improvement, whereas patients who received inhibitory 1 Hz rTMS for 20 min (1200 pulses) (once per day, five times per week, for 4 weeks), alongside speech and language therapy, significantly improved their performance in repetition and naming. This indicates that rTMS, when used as an adjunct method to speech and language therapy, can boost recovery and language improvement.

7.2.4 TBS

There are only a few studies that have investigated the impact of TBS on aphasic patients' recovery and language functioning. Szaflarski et al. (2011) explored the potential improvements in language skills in chronic post-stroke nonfluent aphasia, using an excitatory stimulation protocol combined with fMRI to localize LH Broca's area. The protocol included 10 daily treatments of 200 s each, using iTBS. The target of stimulation was the left Broca's area. The sample included eight patients with moderate or severe aphasia, at least 1 year following left middle cerebral artery stroke. The results revealed that six patients demonstrated significant improvements in semantic fluency when comparing pre-rTMS and post-rTMS language performance. In addition, patients reported improvement in their language and communication skills after treatment completion. Comparisons between pre- and post-rTMS fMRI maps indicated higher activation for the left fronto-temporo-parietal language networks with a significant LH shift in the left frontal and temporo-parietal regions poststimulation (Szaflarski et al., 2011).

Kindler et al. (2012) examined the effects of TBS by employing an inhibitory protocol with a shorter application time than the common 1 Hz protocol. Eighteen

patients with aphasia in different post-stroke phases participated in the study. They were tested by means of a naming task before and after TBS over the intact right Broca's homologue. Patients' overall naming performance was significantly enhanced post-TBS. Notably, the best responders were the subacute phase patients. In addition to the positive effects of this protocol on language function, its short application time makes it quite suitable for clinical practice as argued by these researchers (Kindler et al., 2012). In addition, Vuksanović et al. (2015) have developed a novel approach, i.e., a bilateral sequential TBS protocol, combining iTBS and cTBS. The authors stimulated the LH Broca's area by iTBS and its right homologue by cTBS. The patient who received this treatment (in 15 daily sessions) was a chronic nonfluent post-stroke right-handed person with aphasia. Posttreatment assessment indicated improvement in several language functions, mostly in propositional speech, semantic fluency, short-term verbal memory, and verbal learning (Vuksanović et al., 2015).

7.2.5 Final Remarks

As discussed in this chapter, recovery of language functions is possible in the chronic phase of stroke-induced aphasia using neuromodulatory techniques, either independently or combined with speech and language therapy. We also know that the shorter the time post-stroke, the easiest it is to achieve the maximal modulation of plasticity (Kindler et al., 2012). There are only a few studies investigating the rehabilitation effects of neuromodulation involving patients in the subacute stage (Heiss et al., 2013; Rubi-Fessen et al., 2015, 2017; Seniów et al., 2013; Weiduschat et al., 2011), which report similar beneficial outcomes. Weiduschat et al. (2011), for instance, applied inhibitory 1 Hz rTMS over the homologue to pars triangularis combined with speech and language therapy in six patients with various types of aphasic in the subacute stage, while other four patients received sham stimulation over the vertex instead of the RH IFG. Significant changes in language performance were observed in both the TMS and the control groups, possibly due to the fact that behavioral treatment was administered to the control group as well. However, improvements in naming performance and in the Aachen Aphasia Test total score were confirmed only for the TMS group. Nevertheless, our current knowledge regarding the optimal period for stimulation is limited due to the absence of randomized clinical trials directly comparing the effects of treatment in patients with chronic aphasia and those in the subacute stage.

Despite the positive outcomes of the reported rehabilitation studies, there are certain methodological limitations. Firstly, the majority of studies have employed small samples and varying protocol designs. Specifically, the studies have used heterogeneous protocols in terms of the number of pulses and the duration of the intervention, which act as significant confounders in the interpretation of the reported outcomes. For instance, while some studies include a number of 1200 pulses of 1 Hz rTMS (Heiss et al., 2013; Medina et al., 2012) for 20 min daily for 10 days

(Garcia et al., 2013; Rubi-Fessen et al., 2015; Thiel et al., 2013), others use a different protocol with, e.g., 1 Hz rTMS for 40 (Hara et al., 2015) or 30 min (Waldowski et al., 2012).

Additionally, not all of those studies have shown generalization to other tasks or have reported sufficient long-lasting effects. A successful treatment involves improvement in speech output that can be generalized to untrained language structures and contexts (Thompson & Shapiro, 2007). Some studies report benefits of the treatment in language functions evidenced only by using formal neuropsychological testing. Moreover, most studies have not followed up patients for a long enough period of time posttreatment to determine the longer-term outcomes of intervention; typically, the reported studies include only modest follow-up lengths with few studies exceeding 1 year (see Martin et al., 2009). Results from studies comparing real and sham rTMS showed that patients undergoing real stimulation had significantly better performance in language tests (Garcia et al., 2013; Tsai et al., 2014; Weiduschat et al., 2010), which was permanent at 2 (Barwood et al., 2010; Garcia et al., 2013; Hamilton et al., 2010; Naeser et al., 2005), 3 (Tsai et al., 2014), 6 (Garcia et al., 2013; Hamilton et al., 2010), 8 (Barwood et al., 2012; Naeser et al., 2005), 10 (Hamilton et al., 2010), 12 (Barwood et al., 2013), 16 (Martin et al., 2009), and 43 (Martin et al., 2009) months of follow-up evaluation. Thus, it is hard to ultimately assess the effectiveness of neuromodulatory interventions in stroke-induced aphasia.

The majority of the studies includes patients with nonfluent post-stroke aphasia (Naeser et al., 2011; Seniów et al., 2013; Tsai et al., 2014; Vuksanović et al., 2015) and only a few participants with fluent post-stroke aphasia (Abo et al., 2012). To the best of our knowledge, there is only one study including both fluent and nonfluent aphasic participants (Abo et al., 2012), showing differential outcomes after 10 treatment sessions (40 min 1 Hz rTMS and 60 min intensive speech therapy); nonfluent aphasic patients showed significant improvement in auditory comprehension, reading comprehension, and repetition, whereas fluent aphasic patients showed significant improvement in spontaneous speech.

Finally, the majority of relevant studies report data from right-handed patients with LH dominance (Chieffo et al., 2014; Hara et al., 2017; Heiss et al., 2013; Kindler et al., 2012; Waldowski et al., 2012). Heiss et al. (2013) included two left-handed patients with stroke-induced aphasia in the subacute stage, in addition to 29 right-handed patients, providing results that can be informative for future studies. Both groups improved in language functioning, but right-handed patients demonstrated better recovery.

7.3 Conclusion

This chapter aimed at providing an up-to-date narrative literature review of the findings from the application of rTMS in aphasia therapy. While this technique has only recently been applied in the aphasia intervention research context, its contribution

appears positive as shown by its effects, particularly in patients in the chronic stage. Crucially, the combination of rTMS with traditional behavioral intervention methods results in an additive improvement of patients' linguistic abilities. This literature review revealed certain limitations, including the application of the method to small samples and specific aphasia types, which pose challenges for further research.

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Chapter 8
The Cerebellum: A Therapeutic Target in Treating Speech and Language Disorders

Maria Leggio, Giusy Olivito, Michela Lupo, and Silvia Clausi

Abbreviations

ASD	Autism spectrum disorders
BOLD	Blood oxygen level dependent
CBI	Cerebellar brain inhibition
cTBS	Continuous theta-burst stimulation
DTI	Diffusion tensor imaging
FC	Functional connectivity
GM	Gray matter
iTBS	Intermittent theta-burst stimulation
MEPs	Motor-evoked potentials
PASAT	Paced auditory serial addition task
PASST	Paced auditory serial subtraction task
PSP	Progressive supranuclear palsy
rs-fMRI	Resting-state functional magnetic resonance imaging
rTMS	Repetitive transcranial magnetic stimulation
SCA	Spinocerebellar ataxia
TBS	Theta-burst stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VWM	Verbal working memory

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_8

8.1 Introduction

Approaches to thinking about the cerebellum have historically been overshadowed by the view that it is a structure mainly involved in motor control and coordination (Manto & Mariën, 2015). However, during the past decades, neuroanatomical, neuroimaging, and clinical studies have substantially modified this traditional view and provided new insights and a body of evidence for cerebellar involvement in a wide range of nonmotor processes, such as cognitive, affective, and social processes (Clausi, Iacobacci, Lupo, et al., 2017; Clausi, Olivito, Lupo, et al., 2019; Lupo, Troisi, Chiricozzi, et al., 2015; Stoodley & Schmahmann, 2010; Tedesco, Chiricozzi, Clausi, et al., 2011). Within the broad range of functions in which the cerebellum is involved, several clinical studies have shown the occurrence of different types of speech and language impairments subsequent to cerebellar damage (Mariën & Borgatti, 2018).

In the first part of the present chapter, we briefly summarize the motor and nonmotor language impairments that have been reported after cerebellar damage in adults and the associated cerebello-cerebral network alterations. Starting from these clinical and neuroimaging data regarding the "linguistic cerebellum," in the second part of the chapter, we provide an overview of the studies that used noninvasive transcranial neuromodulation techniques to further investigate the cerebellar role in speech and language domains. Furthermore, we show the current state of the art and translational potential of the use of cerebellar neuromodulation to improve speech and language functions after cortical and subcortical damage.

8.2 Cerebellar Topographical Organization: An Outline

The neuroanatomical substrate of the cerebellar role in motor, cognitive, and affective processing consists of the proven existence of connections between the cerebellum and the motor, paralimbic, and association cortices (Strick, Dum, & Fiez, 2009). Indeed, the cerebellum receives inputs from the cerebral cortex via cortico-pontine-cerebellar pathways and sends them back to the same cortical areas via cerebello-thalamic-cortical pathways (Schmahmann, 1996). Each cerebellar hemisphere mainly sends information to and receives information from the contralateral cerebral hemisphere.

Neuroanatomical and neurophysiological studies have shown a specific topographical and functional organization of the cerebellar regions as follows: the anterior cerebellar lobe (lobules I–V and extending into medial lobule VI and lobule VIII) is involved in motor functions, the posterior cerebellar lobe (Crus I, Crus II, lobules VI, VIIb, and IX) is involved in cognitive functions, and the posterior vermis is involved in affective functions (Stoodley & Schmahmann, 2010).

Over the years, among the functions in which the cerebellum plays a role, speech and language processes have received high levels of attention. A number of studies

have shown cerebellar involvement in both motor and nonmotor aspects of the linguistic domain. These functions have been anatomically localized mainly in the right hemispheric cerebellar regions (Stoodley & Schmahmann, 2009), although bilateral cerebellar involvement has also been described (Mariën, Engelborghs, Fabbro, & De Deyn, 2001; Murdoch & Whelan, 2007).

8.3 Role of the Cerebellum in Speech and Language Impairments: Evidence from Clinical Studies

Evidence for a cerebellar role in the speech and language domains derives predominantly from evaluations of patients with various cerebellar pathologies in which different language problems have been identified (Mariën & Borgatti, 2018). Indeed, according to the most relevant literature, several types of motor and nonmotor language impairments have been reported after cerebellar damage, as outlined in the next sections. When language function is considered a highly complex skill that incorporates different subskills, evidence about specific alterations observed after a cerebellar lesion can lead to new considerations for possible treatments.

8.3.1 Motor Speech Planning

This term refers to an implicit knowledge of the language regularities in motor patterns that are established during speech acquisition (Mooshammer, Goldstein, Nam, et al., 2012). A cerebellar lesion may cause ataxic dysarthria, a speech disorder traditionally ascribed to motor execution impairments and characterized by distorted articulation and prosody. In the last decade, the view of ataxic dysarthria as a mere motor execution problem has changed, and it is now considered to also encompass deficits in motor speech programming (Mariën & Verhoeven, 2007; Spencer & Slocomb, 2007).

8.3.2 Verbal Fluency

Impairments in verbal fluency tasks are commonly reported in patients affected by focal or degenerative cerebellar damage (Leggio, Silveri, Petrosini, & Molinari, 2000; Schweizer, Alexander, Gillingham, et al., 2010; Stoodley & Schmahmann, 2009). Performance differences between semantic and phonological fluency tasks have been described in patients affected by cerebellar lesions with a specific trend for disruption of phonological processing (Leggio et al., 2000). Although there is a general agreement on such impairment in phonological fluency after a cerebellar

lesion, less clear is the cerebellar lateralization effect (Leggio et al., 2000; Murdoch & Whelan, 2007).

8.3.3 Grammar Processing

Since the 1990s, a growing number of clinical studies have provided evidence for a possible role of the cerebellum in morphological and syntactic aspects of language processing in terms of deviations from predicted grammar rules such as subject-verb agreement or canonical word order (Mariën, Baillieux, De Smet, et al., 2009; Silveri, Leggio, & Molinari, 1994). Regarding grammatical problems, most of the cases in the literature presented after a right cerebellar lesion (Mariën, Engelborghs, Pickut, & De Deyn, 2000; Silveri et al., 1994). However, left cerebellar hemisphere involvement has also been described (Fabbro, Moretti, & Bava, 2000; Justus, 2004).

8.3.4 Writing

Among language deficits, writing disorders have been frequently reported after cerebellar lesions. Consequent to focal or diffuse cerebellar damage in adults, different studies have described the presence of disorders in the coordination, planning, and execution of writing movements, such as spatial agraphia, apraxic agraphia, micrographia, and neglect dysgraphia (Mariën, De Smet, de Smet, et al., 2013; Silveri, Misciagna, Leggio, & Molinari, 1999), which are not linked to the typical motor impairments due to cerebellar damage. More central processes of writing are also affected by cerebellar lesions (Lupo et al., 2019). These are commonly included in the cluster of graphical buffer deficits (i.e., spelling process, lexical agraphia, deep agraphia, phonological or semantic agraphia) (Haggard, Jenner, & Wing, 1994; Silveri et al., 1999). Although writing problems are mainly described after a right cerebellar lesion, there is no agreement on cerebellar lateralization in this function (Fabbro et al., 2000; Mariën et al., 2009).

8.3.5 Reading

Reading difficulties after cerebellar damage in adults have been reported less often. In the last decade, Moretti, Torre, Antonello, et al. (2002) provided evidence for problems in the reading of letters and words in a population of cerebellar patients with vermal lesions. Furthermore, Mariën et al. (2009) described visual dyslexia in a patient affected by an ischemic infarction in the territory of the right superior cerebellar artery.

8.3.6 Verbal Working Memory

Verbal working memory (VWM) is the ability to temporarily store and manipulate verbal information. Data from studies in adult patients showed that the presence of cerebellar pathology can have a mildly to moderately severe negative impact on VWM (Chiricozzi, Clausi, Molinari, et al., 2008; Hokkanen, Kauranen, Roine, et al., 2006; Ravizza, McCormick, Schlerf, et al., 2006). The shared hypothesis about the cerebellar role in VWM has been that the cerebellum could participate in the articulatory control system and/or the phonological storage system (Chiricozzi et al., 2008; Ravizza et al., 2006) described by Baddeley (2003). Ravizza et al. (2006) suggested that the cerebellum may be involved in creating a memory trace during the first stage of articulatory control when verbal information is translated into a phonological representation. Furthermore, impairment in encoding phonological traces has also been described as a consequence of cerebellar damage (Chiricozzi et al., 2008).

8.4 Structural and Functional MRI Alterations in the Cerebello-Cerebral Circuitry Related to Speech and Language Deficits

In the context of language deficits related to cerebellar alterations, further support has been provided by structural and functional neuroimaging studies. Starting from the evidence that the cerebellum has a clear topographical organization of functions, linguistic abilities may be selectively affected based on the site of the cerebellar lesion. As proposed by Mariën et al. (2000) and Mariën, Saerens, Nanhoe, et al. (1996), after cerebellar damage, a reduction in excitatory impulses through the cerebello-ponto-thalamo-cortical pathways may result in language disturbances that reflect a remote effect on supratentorial language areas. Consistent with the presence of contralateral projections between the cerebellum and left-lateralized language regions in the cerebral cortex (Hubrich-Ungureanu, Kaemmerer, Henn, & Braus, 2002; Jansen, Flöel, Randenborgh, et al., 2005), different studies in cerebellar-damaged patients have shown that language deficits (in particular impaired verbal fluency and agrammatism) occur more often after damage of the right posterior cerebellar lobe (Schmahmann & Sherman, 1998; Tedesco et al., 2011). This evidence has been further supported by neuroimaging studies in patients with cerebellar damage using voxel-based lesion-symptom mapping that have shown a link between damage to the right Crus I and verbal fluency deficits (Richter, Gerwig, Aslan, et al., 2007), while damage to right lobules VII through IX was associated with poorer scores on the Boston Naming Test (Stoodley, MacMore, Makris, et al., 2016). As suggested by a whole-brain voxel-based morphometry study (Clausi, Bozzali, Leggio, et al., 2009) in patients affected by isolated cerebellar damage, gray matter (GM) changes may occur in supratentorial regions due to

the reduced input via cerebello-cortical pathways and result in the observed functional impairment. Specifically, reduced GM volume in the left superior temporal gyrus has been shown after isolated right cerebellar damage and correlated with verbal fluency deficits in patients (Clausi et al., 2009). It is worth noting that, although most studies have indicated crossed cerebro-cerebellar language lateralization (Méndez Orellana, Visch-Brink, Vernooij, et al., 2015; Starowicz-Filip, Chrobak, Moskała, et al., 2017), clinical and neuroimaging findings have also suggested that the left cerebellar hemisphere contributes to the mediation of language via ipsilateral cerebello-cortical pathways (Murdoch & Whelan, 2007).

From a structural point of view, further support comes from a diffusion tensor imaging (DTI) study that investigated the patterns of microstructural integrity within cerebellar white matter tracts connecting the cerebellum with higher-order cerebral regions, including those relevant to language (Olivito, Lupo, Iacobacci, et al., 2017). In particular, in patients with cerebellar neurodegenerative pathology, specific alterations of diffusion-derived measures within the right superior cerebellar peduncle correlated with verbal and phonological fluency (Olivito et al., 2017). Moreover, cerebellar mutism syndrome has been described in patients with a significant reduction of diffusivity values (i.e., fractional anisotropy) in the superior cerebellar peduncle (McEvoy, Lee, Poliakov, et al., 2016).

Taken together, these observations suggested that altered interactions within specific cerebello-cortical modules may be related to language and speech deficits, both in primary cerebellar pathology and other pathological conditions in which cerebellar damage is reported. In this framework, functional connectivity (FC) studies have provided great insight into the dissection of the complex interactions between the cerebellar and cerebral cortex that may subserve linguistic abilities and have informed our understanding of the cerebello-cerebral functional alterations underlying language and speech dysfunctions. FC refers to synchronous neural activity between anatomically separated brain regions (Biswal, Van Kylen, & Hyde, 1997) and can be analyzed by means of resting-state functional magnetic resonance imaging (rs-fMRI). This approach focuses on spontaneous, low-frequency fluctuations (<0.1 Hz) in the blood oxygen level-dependent (BOLD) signal at rest and allows the detection of synchronous activations between regions that are spatially distinct (Biswal et al., 1997). Over the years, an increasing body of rs-fMRI studies in healthy subjects have revealed the presence of functional intrinsic connectivity networks involving the cerebellum and cerebral cortex regions related to language (Buckner, Krienen, Castellanos, et al., 2011; D'Mello & Stoodley, 2015; O'Reilly, Beckmann, Tomassini, et al., 2010). Connectivity alterations within cerebello-cerebral networks have been specifically linked to language deficits reported in autism spectrum disorders (ASD) (Khan, Nair, Keown, et al., 2015; Verly, Verhoeven, Zink, et al., 2014). By using a seed-based approach, Verly et al. (2014) reported a significant reduction in the FC strength between the right posterior cerebellum (Crus I and Crus II) and cortical language regions, including the left inferior frontal gyrus, dorsolateral prefrontal cortex, left premotor, and supplementary motor area. All these cortical regions are related to different language domains (Alario, 2006; Duffau, 2003), thus suggesting that FC within specific cortico-cerebellar modules

might play a crucial role in distinct abnormal language functions in ASD. Further support for these observations has been derived from evidence that FC strength between different cerebello-cortical nodes correlates with distinct expressive and receptive language domains (see Verly et al., 2014 for a review). Overall, the structural and functional observations derived from neuroimaging studies highlight the centrality of the cerebellum in regulating language networks and may provide important therapeutic indications in the context of language deficits, particularly when the increasing interest of cerebellar neuromodulation to treat different motor and cognitive disturbances is considered (D'Mello, Turkeltaub, & Stoodley, 2017; Ferrucci, Bocci, Cortese, et al., 2016; Leow, Marinovic, Riek, & Carroll, 2017).

8.5 Cerebellar Neuro-Stimulation Techniques

As reported in the previous sections, a number of clinical and neuroimaging studies point toward a central role of the cerebellum in regulating speech and language functions. Specifically, the evidence regarding impairments after cerebellar lesions and the activation of specific regions of the cerebellum in speech and language tasks may provide the foundations for developing novel treatments.

The cerebellar anatomical location, right beneath the skull, makes the cerebellum accessible to noninvasive neuro-stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (van Dun, Bodranghien, Manto, & Mariën, 2017), which have been recognized as promising techniques to modulate neuronal activity in both healthy and patient populations (van Dun, Mitoma, & Mario Manto, 2018). Indeed, modeling studies have shown that both TMS and tDCS are capable of inducing electric currents inside the cerebellar cortex (Hardwick, Lesage, & Miall, 2014; Parazzini, Rossi, Ferrucci, et al., 2014). Moreover, if we consider the very high concentration and organized distribution of neurons in the cerebellar cortex, together with the properties of plasticity in the cerebellar microcircuits, these techniques may be very effective when targeting the human cerebellum, with consequent effects on cognitive domains in which the cerebellum plays a role, such as speech and language (van Dun et al., 2017; van Dun, Bodranghien, Mariën, & Manto, 2016).

Before examining the cerebellar neuro-stimulation effects on speech and language abilities, it is useful to briefly describe the main characteristics of TMS and tDCS over the cerebellum.

8.5.1 Cerebellar Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a safe and noninvasive neuro-stimulation technique that allows both activation and modulation of the excitability of neurons depending on the intensity and frequency of the pulses (Sandrini, Umiltà,

& Rusconi, 2011; Walsh & Cowey, 2000). It is administered by using a magnetic coil placed on the scalp to induce weak electric currents in the brain sites beneath the coil. It can be administered as a single pulse (single-pulse TMS) with an excitatory effect or as a series of pulses with different frequencies. Similarly, the effects of repetitive TMS (rTMS) on neuronal activity depend on pulse frequency: high-frequency rTMS (usually 50 Hz) excites and low-frequency rTMS (usually 1 Hz) inhibits neuronal activity (Hallett, 2007). A variation in the rTMS protocol is theta-burst stimulation (TBS), which uses bursts of high-frequency stimulation (3 pulses at 50 Hz) at a 1–5 Hz rhythm. It can be given in a continuous (cTBS, inhibitory) or intermittent (iTBS, excitatory) manner (van Dun et al., 2016, 2018); rTMS is often used in cognitive research to induce a reversible "virtual lesion," as its effects outlast the period of stimulation by some minutes (Walsh & Cowey, 2000).

To date, although most TMS studies have been directed at the cerebral cortex, there is growing interest in applying TMS over the cerebellum to investigate the effects of cerebellar stimulation on cognitive functions, including language processing (Grimaldi, Argyropoulos, Boehringer, et al., 2014). It has been proposed that single-pulse TMS over the cerebellum activates Purkinje cells, with increased inhibition of the dentate-thalamo-cortical facilitatory connections that affect the contralateral primary motor and prefrontal cortex (Ugawa & Iwata, 2005). Moreover, different studies on motor and cognitive processes have inferred suppression of the activity of the cerebellar cortex after cTBS (Koch, Mori, Marconi, et al., 2008; Picazio, Oliveri, Koch, et al., 2013).

However, there is no consensus on the effects of rTMS and cTBS of the cerebellum on cerebral cortex function. Indeed, both facilitation and inhibition of motor-evoked potentials (MEPs) have been reported after cerebellar stimulation (van Dun et al., 2017). The situation becomes more complex in cognitive studies, in which behavioral measures are used. In this case, physiological measures of cortical function, i.e., electroencephalogram, should be encouraged, and several methodological issues need to be considered, such as the type of coil, the intensity, and site of stimulation (Tomlinson, Davis, & Bracewell, 2013).

8.5.2 Cerebellar Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that induces site-specific, polarity-dependent modulation of cortical excitability. However, tDCS is not as powerful as TMS in inducing action potentials (Woods, Antal, Bikson, et al., 2016). Two electrodes of different polarities (most frequently used electrode sizes are 25–35 cm^2), the "anode" and the "cathode," are connected to a 9 V battery-driven direct current stimulator and used to deliver a low-intensity constant current of 1–2 mA for 8–25 min. One electrode is placed over the cerebral area of interest and the other electrode over a reference site, which can be on the scalp for bicephalic stimulation (Grimaldi & Manto, 2013) or on a different body part, such as the deltoid muscle, for monocephalic stimulation (Ferrucci,

Marceglia, Vergari, et al., 2008). The current flow passes from one electrode to the other and in the opposite direction for anodal versus cathodal tDCS, affecting the sodium and calcium channels and altering resting membrane potentials (Nitsche, Cohen, Wassermann, et al., 2008; Woods et al., 2016).

In general, in healthy subjects, anodal tDCS leads to neuronal membrane depolarization and increases neural excitability, whereas cathodal tDCS leads to neuronal membrane hyperpolarization and decreases neuronal excitability (Bikson, Inoue, Akiyama, et al., 2004). The effects of tDCS can occur both during and after stimulation (e.g., in the motor cortex, the effect can last up to 90 min) (Nitsche & Paulus, 2001) and might result in enhanced or impaired task performance, depending on the stimulated neuronal circuitry (Antal, Nitsche, Kincses, et al., 2004; Rogalewski, Bretenstein, Nitsche, et al., 2004).

In recent years, the cerebellum has been considered an ideal target for tDCS due to its high neuronal concentration and anatomical location. Indeed, as shown in animal studies, the cerebellum is highly susceptible to polarizing currents (Grimaldi, Argyropoulos, Bastian, et al., 2016). Although the unique and complex cytoarchitecture of the cerebellum makes it difficult to predict tDCS outcomes (Rahman, Toshev, & Bikson, 2014), cerebellar tDCS has been increasingly used in both healthy subjects and patients to study the functional connectivity of the cerebellum with other parts of the brain and its effects on motor, cognitive, or affective functions.

The effect of tDCS over the cerebellum in humans has been indirectly investigated by studying its effect on "cerebellar brain inhibition" (CBI) (Galea, Jayaram, Ajagbe, & Celnik, 2009; Ugawa, Uesaka, Terao, et al., 1995), which is the inhibitory action that the cerebellum exerts on the contralateral cerebral cortex by means of inhibitory output from Purkinje cells to the disynaptic dentate-thalamo-cortical facilitatory connections (Oulad Ben Taib & Manto, 2013; Ugawa, Genba-Shimizu, Rothwell, et al., 1994). Specifically, the cerebellar cortex sends efferent fibers to the cerebral cortex through the cerebellar nuclei, on which it exerts inhibitory action. Since the cerebellar nuclei exert excitatory effects on the thalamo-cortical pathway, their inhibition results in reduced dentate-thalamo-cortical facilitation (Schmahmann, Smith, Eichler, & Filley, 2008). Galea et al. (2009), using a conditioning paired-TMS protocol, showed that cerebellar tDCS induces amplitude changes in MEPs elicited from the contralateral primary motor cortex. In particular, they demonstrated that cerebellar cathodal stimulation decreased the ability of TMS to elicit CBI of M1, whereas anodal stimulation had the opposite effects. Although the exact physiological impact of tDCS over the cerebellum is not yet completely understood, it has been proposed that it produces its effects by polarizing Purkinje cells and changing the levels of activity in the deep cerebellar output nuclei, affecting distant plasticity in human cortical areas (Galea et al., 2009). Moreover, cerebellar tDCS might affect the transmembrane polarization resulting in prolonged spiking activity in Golgi inhibitory cerebellar neurons that can explain the long-lasting aftereffects (Grimaldi et al., 2016).

One limitation of cerebellar tDCS is that although modeling studies have demonstrated that the electric field effectively reaches the cerebellum, only the lobules in proximity to the skull, such as the posterior portions of the cerebellum, are accessible

(Ferrucci, Brunoni, Parazzini, et al., 2013; Rahman et al., 2014). Moreover, cerebellar tDCS effects also depend on the electrical field orientation. The position of the reference electrode is thus of critical importance: for example, positioning it on the ipsilateral buccinator muscle or on the shoulder might alter the stimulation effect (Ferrucci, Cortese, & Priori, 2015). Another issue that must be taken into account is that there have been no unambiguous conclusions about the polarity-specific effects of cerebellar tDCS. Indeed, while some studies reported polarity-specific effects (Galea et al., 2009; Pope & Miall, 2015), with anodal cerebellar stimulation increasing and cathodal stimulation decreasing CBI, other studies found no differences between anodal and cathodal cerebellar stimulation (Ferrucci et al., 2008; Hamada, Strigaro, Murase, et al., 2012).

In conclusion, cerebellar tDCS can be considered safe and is not associated with long-lasting negative side effects. However, it is important to carefully consider each stimulation parameter to guarantee the health and safety of subjects undergoing stimulation. In particular, the possible short-term side effects (i.e., itching, tingling, burning, mild intensity pain sensations, sensation of a metallic taste, and redness under the electrode) and subject exclusion criteria (i.e., brain surgery, head trauma, or tumor, metal in the head, implanted medical devices, central nervous system-effective medication, pregnancy, scalp sensitivity) have to be taken into account (Grimaldi et al., 2016).

8.6 Cerebellar Stimulation to Modulate Speech and Language Abilities in Healthy Subjects

The following subsections will be focused on the studies that used TMS and tDCS to investigate the cerebellar role in speech and language domains. We will provide also an overview of the studies that combine these neuromodulation techniques with neuroimaging analyses to investigate the effect of cerebellar stimulation on the cerebral areas involved in speech and language functions.

8.6.1 Cerebellar TMS Effects

Different studies have used TMS to investigate the role of the cerebellum in specific cognitive domains, including speech and language functions (Arasanz, Staines, Roy, et al., 2012; Argyropoulos, Kimiskidis, & Papagiannopoulos, 2011; Tomlinson, Davis, Morgan, & Bracewell, 2014). In particular, to investigate language abilities, tasks assessing working memory, verbal fluency, and lexical decision tasks have been administered before and after different types of cerebellar stimulation. A summary of the studies that investigated the effects of cerebellar TMS on speech and language functions is reported in Table 8.1a.

Table 8.1 Summary of the studies that investigate the effect of the cerebellar TMS (part A) and tDCS (part B) on speech and language functions

Part A

TMS study	*Participants*	*Stimulation type*	*Task*	*Sessions*	*Position of coil*	*Effects*
Allen-Walker et al. (2018)	*N* = 19 (9 M, 10 F) Mean age ± s.d.: 24.2 ± 2.1	cTBS 55% of MMO	Lexical decision task (backward associative priming at short SOAs)	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	1 cm below, 3 cm L or R from inion	Significant increase in backward priming at short SOAs after the stimulation of L CB relative to R CB
Arasanz et al. (2012)	*N* = 27 (9 M, 18 F) Age: range 20–35 years *N* = 14: L stim *N* = 13: R stim	cTBS 80% of AMT	Phonetic and semantic fluency tasks	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	1 cm below, 3 cm L or R from inion	Lower switching scores in first 15 s of phonemic fluency task after R stimulation Increased number of words produced in phonemic fluency task after R or L stimulation in the late phase of the task No effect on semantic fluency task
Argyropoulos et al. (2011)	*N* = 8 (n.s.) Mean age ± s.d.: 26.9 ± 8.6 years	cTBS 45% of MMO	Lexical decision task with associative (e.g., "gift"-"horse") or semantic (e.g., "swan"-"chicken") prime	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	Lateral: 1 cm below, 4.5 cm R from inion Medial: 1 cm below, 1 cm R from inion	Selective increase of associative priming size after medial CB stimulation Selective decrease in accuracy rate after medial CB stimulation in the first session

(continued)

Table 8.1 (continued)

Part A

TMS study	*Participants*	*Stimulation type*	*Task*	*Sessions*	*Position of coil*	*Effects*
Argyropoulos et al. (2011)	*N* = 24 (n.s.) Mean age ± s.d.: 26.9 ± 8.6 years *N* = 12: lateral stim *N* = 12: medial stim	cTBS 45% of MMO	Lexical decision task with associative (e.g., "gift"-"horse") or semantic (e.g., "swan"-"chicken") prime	3 pulses at 30 Hz every 100 ms (801 pulses) (offline)	Lateral: 1 cm below, 4.5 cm R from inion Medial: 1 cm below, 1 cm R from inion	Impaired learning after medial CB stimulation (lack of decrease in RT for those receiving medial TMS during first experimental session) No effect on priming size
Argyropoulos and Muggleton (2013)	*N* = 50 (n.s.) Mean age ± s.d.: 22.7 ± 5.4 years *N* = 12: R lateral stim *N* = 11: R medial stim *N* = 23: no stim	cTBS 45% of MMO	Lexical decision task with associative (e.g., "chef"-"cooking") or semantic (e.g., "theft"-"stealing") prime	3 pulses at 50 Hz repeated at a 5 Hz rhythm for 40 s (600 pulses) (offline)	Lateral: 10 cm R from inion Medial: 1 cm below, 1 cm R from inion	Selective enhancement of semantic associative noun-to-verb priming after R CB stimulation No effect on semantic categorical priming
Brusa, Ponzo, Mastropasqua, et al. (2014)	*N* = 10 (4 M, 6 F) patients affected by PSP Mean age ± s.d.: 59.3 ± 6.6 years	iTBS 80% of AMT	Clinical rating scale for PSP	2 weeks—10 sessions 2 trains (L and R) of 3 pulses at 50 Hz in 20 trains of 10 bursts with 8 s intervals (600 pulses) (offline)	L and R CB	Improved dysarthria
Desmond, Chen, and Shieh (2005)	*N* = 17 (8 M, 9 F) Mean age ± s.d.: 24.9 ± 6.9 years	Single-pulse TMS 120% of MT	Verbal working memory task	1 pulse immediately after encoding (online)	R superior lobule VI/Crus I	Increased RTs during CB stimulation
Farzan, Wu, Manor, et al. (2013)	*N* = 1 F Patient affected by cerebellar ataxia Age: 62 years	TMS 100% of MMO	Clinical observation	3 weeks—21 sessions 5 pulses with 6-s ISI (offline)	Lateral: 4 cm L or R from inion Medial: over inion	Improvement of speech after CB stimulation

Gilligan and Rafal (2018)	*N* = 41 (20 M, 21 F) Mean age ± s.d.: 23.4 ± 5.5 years	cTBS 80% of MT	Lexical decision task with associative prime	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses) (offline)	1 cm below, 3 cm R or L of the inion	Decreased priming after L CB stimulation and increased priming after R CB stimulation
Lesage, Morgan, Olson, et al. (2012)	*N* = 22 (n.s.) Mean age = 20.5 years; *N* = 21: vertex; *N* = 22: stim	1 Hz rTMS 55% of MMO	Visual world task	10 min—600 pulses (offline)	1 cm below, 3 cm R of the inion	Increased fixation latencies for predictive condition after R CB stimulation
Oliveri, Bonnì, Turriziani, et al. (2009)	*N* = 24 (n.s.) Age: range 20–35 years	1 Hz rTMS 90% of MT	Spatial-temporal association of linguistic tenses	10 min—600 pulses (offline)	1 cm below, 3 cm L or R of the inion	Selective impairment in RTs to future tense of action verbs after R CB stimulation Selective decrease in accuracy after R and L CB stimulation
Rami, Gironell, Kulisevsky, et al. (2003)	*N* = 16 M Mean age ± s.d.: 26.63 ± 4.57 years	5 Hz rTMS 10% below MT	Verbal working memory (digits forward and backward) Phonetic fluency task	Trains of 10 s with 30 s ISI (online)	2 cm below, 3 cm R of the inion	No effect
Runnqvist, Bonnard, Gauvin, et al. (2016)	*N* = 16 (6 M, 10 F) Mean age ± s.d.: 24 ± 3 years	1 Hz rTMS at 60% of MMO	Speech production task	1 session divided in two parts: (1) 15 min stimulation (900 pulses) followed by the task (2) 15 min stimulation (to the opposite hemisphere) followed by the task	R and L CB (lobules Crus I–II)	Impaired language production after R compared to L CB stimulation

(continued)

Table 8.1 (continued)

Part A						
TMS study	*Participants*	*Stimulation type*	*Task*	*Sessions*	*Position of coil*	*Effects*
Tomlinson et al. (2014)	*N* = 10 (4 M, 6 F) Age: range 18–35 years	cTBS 80% of AMT	Sternberg task	3 pulses at 50 Hz, repeated at 5 Hz rhythm for 40 s (600 pulses)	1 cm below and 6 cm R or L of the inion	Decreased accuracy on verbal working memory after R CB stimulation
Part B						
tDCS study	*Participants*	*Stimulation*	*Task*	*Number of Sessions*	*Position of the electrodes*	*Effects*
Boehringer, Macher, Dukart, et al. (2013)	*N* = 40 (20 M, 20 F) Mean age ± s.d.: 25 ± 3 years	tDCS (2 mA)	Digit span	1 session (25 min) offline	Cathode: R CB Anode: R buccinators muscle	Reduced forward digit span Blocked the practice-dependent increase in backward digit span
Ferrucci et al. (2008)	*N* = 17 (n.s.) Age: range 19–32 years	tDCS (2 mA)	Sternberg task	1 session (15 min) offline	Anode/cathode: bilateral CB Cathode/anode: R deltoid muscle	Impaired practice-dependent effects after CB stimulation
Macher, Boehringer, Villringer, and Pleger (2013)	*N* = 19 (9 M, 10 F) Mean age ± s.d.: 26 ± 4 years	tDCS (2 mA)	Sternberg task	1 session (25 min) offline	Anode/cathode: R CB Anode/cathode: n.s.	Impaired item recognition after the anodal CB stimulation
Marangolo, Fiori, Caltagirone, et al. (2018)	*N* = 12 (6 M, 6 F) patients with left-brain-damaged affected by chronic aphasia Age: range 48–70 years	tDCS (2 mA)	Verb generation task Verb naming task	5 daily sessions of 20 min for 4 weeks (online)	Cathode/sham: R CB Anode: R deltoid muscle	Improvement in verb generation task at the end of the treatment with the cathodal stimulation

Miall, Antony, Goldsmith-Sumner, et al. (2016)	*N* = 73 (17 M, 56 F) Mean age ± s.d.: 19.8 ± 2.7 years *N* = 26 anodal stim *N* = 26 cathodal stim *N* = 20 sham	tDCS (2 mA)	Manual version of the visual word task	1 session (20 min) online	Anode/cathode: R CB Cathode/anode: R shoulder	Decreased response time advantage for the predictable sentence items after the cathodal stimulation
Pope and Miall (2015)	*N* = 66 (12 M, 54 F) *N* = 22 (6 M, 14 F) anodal stim Age: mean 21 years *N* = 22 (2 M, 20 F) cathodal stim Age: mean 20 years *N* = 22 (4 M, 18 F) sham Age: mean 21 years	tDCS (2 mA)	PASAT/PASST/verb generation task	1 session (20 min) offline	Anode/cathode: R CB Anode/cathode: R deltoid muscle	Improvement in PASST and verb generation task after the cathodal stimulation
Turkeltaub, Swears, D'Mello, and Stoodley (2016)	*N* = 76 (30 M, 46 F) Mean age ± s.d.: 23.7 ± 6.2 years *N* = 15 sham *N* = 30 anodal (15 anterior-medial, 15 right posterolateral) *N* = 30 cathodal (15 anterior-medial, 15 right posterolateral)	tDCS (2 mA)	Phonemic fluency task	1 session (20 min) offline	Anode/cathode: anterior-medial or R posterolateral CB Anode/cathode: R deltoid muscle	Improved phonemic fluency after anodal R posterolateral CB stimulation

Studies conducted in patients are reported in gray rows

AMT active motor threshold, *CB* cerebellum, *C* conditioning stimulus, *cTBS* continuous theta-burst stimulation, *F* female, *ISI* inter-stimulus interval, *iTBS* intermittent theta-burst stimulation, *L* left, *M* male, *MEP* motor-evoked potential, *MMO* maximum machine output, *MT* motor threshold, *n.s.* not specified, *PASAT* paced auditory serial addition task, *PASST* paced auditory serial subtraction task, *PSP* progressive supranuclear palsy, *R* right, *RT* reaction time, *rTMS* repetitive transcranial magnetic stimulation, *SCA* spinocerebellar ataxia, *SOAs* stimulus onset asynchrony, *stim* stimulation, *tDCS* transcranial direct current stimulation, *TS* target stimulus

The effects of cerebellar TMS on verbal working memory, measured by the Sternberg task, have been reported in two studies, and they demonstrated increased reaction times after single-pulse TMS over the right superior cerebellum (Desmond et al., 2005) and an impairment in accuracy after cTBS over the same site (Tomlinson et al., 2014).

As reported in Sect. 8.3, cerebellar damage may also result in verbal fluency impairments. Arasanz et al. (2012) investigated the impact of cerebellar stimulation on both phonetic and semantic fluency tasks, focusing on the number of category switches, that is, the exhaustion of a phonemic or semantic cluster and the shift to another. They compared two groups of healthy subjects who completed phonemic and semantic fluency tasks before and after cTBS: one group received stimulation over the right cerebellar hemisphere and the other over the left cerebellar hemisphere. The results showed that cTBS over the right posterolateral cerebellum induced lower switching scores during the first 15 s of phonemic fluency performance, with no effect on semantic fluency. These data confirmed previous studies showing that the cerebellum is involved in phonemic but not semantic fluency (Leggio et al., 2000), and these studies probe the effects of cerebellar stimulation on the executive control of word generation.

Another language ability that has been reported as impaired in cerebellar patients and in which the cerebellum seems to play a role is reading ability (see Sect. 8.3), in which lexical aspects are crucial. Since 2011, Argyropoulos and colleagues have used cTBS to investigate the role of the cerebellum in the lexical domain. In particular, in an initial study (Argyropoulos, 2011), cTBS was applied over the right medial and lateral cerebellum to investigate its effect in a lexical decision task by using lexical associative priming. The author found that medial cerebellar stimulation led to a significant enhancement of associative priming when it was based on the co-occurrence of words in idiomatic speech. These results suggest that the cerebellum has a role in predictive aspects of language processing. Moreover, in the same study, the authors found that, when right medial stimulation was administered before (first session) the lateral stimulation (second session), the subjects showed a significant drop in the post-stimulation lexical decision task accuracy. This aspect was further addressed in a subsequent study (Argyropoulos et al., 2011) in which the effects of the right cerebellar cTBS on *practice-induced acceleration of lexical decisions* were investigated. Right medial and right lateral cerebellar sites were stimulated, and a visual lexical decision task was used. The results showed that the practice effects on the lexical decision task were reduced after medial cTBS, suggesting a cerebellar role in acquiring, storing, and/or retrieving associative memories. Moreover, Argyropoulos and Muggleton (2013), using cTBS and a lexical decision task, demonstrated that stimulation of the right lateral cerebellum enhanced noun-to-verb semantic associative priming. These findings were recently reinforced by Gilligan and Rafal's (2018) study. These authors provided evidence that left cerebellar hemisphere cTBS decreased, and right hemisphere stimulation increased, associative word priming in a lexical decision task.

Recently, Allen-Walker and colleagues (2018) showed that cTBS over the left cerebellar hemisphere influenced backward associative priming with short stimulus

onset asynchrony (SOA) in a lexical decision task. They found a significant increase in the priming size only for backward related stimuli after the stimulation of the left cerebellar hemisphere and no changes for forward priming. This is in line with a previous fMRI study in which activation of the left cerebellum was found for backward priming at short SOA, together with brain areas involved in lexical processing system (such as the right occipitotemporal network) (Terrien et al., 2013). It has been hypothesized that the presence of automatic and fast feedback loops in the left cerebellum could be involved in the backward priming and seem to be dissociated from forward connections (Allen-Walker et al. 2018).

These results are in line with clinical (Mariën et al., 2001) and neuroimaging (Murdoch & Whelan, 2007) data, indicating the involvement of both cerebellar hemispheres in the language domain. Taking the combined results of these studies in consideration, the right cerebellum is clearly involved in lexical associative computations and the left cerebellum seems to have a selective role in backward priming.

Consistent with the above, Lesage et al. (2012) provided evidence that low-frequency rTMS over the right cerebellum affected predictive processes in a task of sentence comprehension. The results showed that after cerebellar stimulation, participants were significantly slower at predicting the final noun of an auditorily presented sentence. The authors argued that the right cerebellum might contribute to language prediction, providing an efferent copy of internalized speech, due to its connections with cortical language areas such as Broca's area. This idea is in line with language processing theories proposing that the self-monitoring of language production is achieved through internal modeling, in a manner similar to other somatic actions (see Argyropoulos, 2016 for discussion). In this light, Runnqvist et al. (2016) studied the possibility of a causal role of the right posterior cerebellum in self-monitoring of speech errors. They applied low-frequency rTMS over the right or left cerebellar hemisphere (lobules Crus I and II) and used a speech production task. The authors found that language production was impaired after right cerebellar stimulation and interpreted this result as evidence for direct cerebellar involvement in language production *"in terms of internal modeling of upcoming speech through a verbal working memory process used to prevent errors"* (Runnqvist et al., 2016, p. 203).

Finally, Oliveri et al. (2009) investigated the possible involvement of the cerebellum in spatial-temporal interactions in language, linking this aspect with the grammatical aspects in which the cerebellum plays a role. In this study, the subjects were asked to indicate whether a stimulus was past or future tense with right and left response buttons. The participants were faster and more accurate if the left button was associated with the past and the right with the future tense, showing a spatial-temporal association of linguistic tenses. rTMS over both cerebellar hemispheres decreased this enhanced accuracy for identifying future (right) and past (left) tense. In addition, stimulation of the right cerebellum selectively slowed down responses to the future tense of action verbs. The authors interpreted these findings as a demonstration of a cerebellar role in *establishing the grammatical rules for verb conjugation*. They also suggested that the right cerebellum may be important in anticipating future events based on past experiences, in line with the hypothesis that

the cerebellum acts as a predictive device across different domains (Leggio & Molinari, 2015; Miall, Weir, Wolpert, & Stein, 1993; Roth, Synofzik, & Lindner, 2013).

In this complex set of findings, when we look at cerebellar speech and language functions, in most of the studies, the right lateral cerebellum (lobule VIIa/Crus I) appears to be the preferred target for the TMS. This region has been implicated in a range of language tasks by both lesion and imaging studies (Mariën et al., 2001). However, starting from these studies, specific conclusions are difficult to draw. Indeed, in some experiments, low-frequency rTMS or cTBS led to enhanced performance (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), whereas in others, there was a disruptive effect (Argyropoulos et al., 2011; Desmond et al., 2005; Lesage et al., 2012; Oliveri et al., 2009; Tomlinson et al., 2014). These findings may be due to the excitatory and inhibitory connections that the cerebellum has with different cerebral areas; thus, the stimulation effects may depend on the targeted pathways and on their contribution to the studied task. Therefore, a number of variables must be taken into account to design therapeutic protocols, and the few negative results reported in the literature need to be examined. In one relatively early study, Rami et al. (2003) did not find any effect of online high-frequency rTMS over the right cerebellar hemisphere in phonetic fluency and episodic memory tasks. These results could be due to differences in the timing or types of TMS protocols.

8.6.2 Cerebellar tDCS Effects

A novel line of research is also represented by the study of cerebellar tDCS effects on cognitive functions (Ferrucci & Priori, 2014). In the present section, we will focus on the studies in which the effect of cerebellar tDCS on speech and language abilities was investigated to understand the potential use of this technique as a treatment intervention. A summary of the studies that investigated the effects of cerebellar tDCS on speech and language functions is reported in Table 8.1b.

Studies have primarily focused on the effects on verbal working memory task performance (i.e., Sternberg task) (Ferrucci et al., 2008; Macher et al., 2013). In particular, Ferrucci et al. (2008) found that both anodal and cathodal cerebellar stimulation impaired practice-dependent improvements, significantly affecting the reaction times, but with no effect on task accuracy.

In 2013, Boehringer et al. (2013) found that cathodal tDCS over the right cerebellum decreased forward digit span task performance and blocked the practice-dependent increase in verbal working memory for backward digit spans, with no effect on word reading, finger tapping, and visually cued sensorimotor tasks. These findings are in line with those that demonstrated an impairment of the practice-induced facilitation in word-generation tasks after cerebellar damage (Fiez, Petersen, Cheney, et al., 1992; Gebhart, Petersen, & Thach, 2002). In the same year, in contrast with the absence of an effect on accuracy reported by Ferrucci et al. (2008), Macher et al. (2013) reported a positive effect of right anodal cerebellar stimulation

on the recognition of items of medium difficulty in the Sternberg task, with no effect on the items of easy or hard difficulty level. These results seem to indicate that task complexity might influence the effects of cerebellar tDCS and explain the absence of a significant effect of cerebellar stimulation on accuracy in the study by Ferrucci et al. (2008), in which intermixed Sternberg stimuli of three difficulty levels were used. A task-difficulty influence on cerebellar tDCS findings has also been demonstrated by Pope and Miall (2015). In this study, the authors reported an effect of tDCS over the right cerebellum on the difficult paced auditory serial subtraction task (PASST), but not on the easier paced auditory serial addition task (PASAT). In particular, the authors observed an improvement of the performance and a reduction in verbal response latency on the PASST selectively after cathodal stimulation. The authors suggested that cerebellar stimulation affects distinct levels of executive demand and memory load, hypothesizing that when cognitive load is high, cathodal depression of the right cerebellar cortex may release cognitive resources by disinhibiting the left prefrontal cortex and enhancing performance (Pope & Miall, 2015). Moreover, in the same study, the authors found a facilitatory effect of cathodal tDCS over the right cerebellum on the rate and consistency of subjects' verbal responses in a verb generation task. They explained these facilitatory effects as a result of disinhibition of the left prefrontal cerebral cortex. Indeed, the inhibitory effect of the cathodal tDCS on the cerebellar cortex releases the cerebellar nuclei, thus resulting in enhanced activity in the projections to cerebral areas (Pope & Miall, 2015). These results are in line with the enhanced lexical associative priming observed after the cerebellar cTBS that has an inhibitory effect on the cerebral cortex as well (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). In a more recent study, Turkeltaub et al. (2016) demonstrated that anodal tDCS over the right posterolateral cerebellum significantly improved phonemic fluency (the same trend was found for cathodal stimulation).

As shown in studies that investigated the cerebellum's role in language abilities by using cerebellar TMS (reported in Sect. 8.6.1) and in line with recent hypotheses (Argyropoulos, 2016; Miall et al., 2016; Moberget & Ivry, 2016), the cerebellum might support predictive and learning mechanisms involved in linguistic processing (Lesage et al., 2012), as it does on motor control, to optimize the behavior. In this framework, Miall et al. (2016) investigated the polarity-specific effects of cerebellar tDCS on linguistic prediction, hypothesizing that cathodal polarity should impair and anodal polarity should facilitate linguistic prediction. Their experimental design also tested whether tDCS modulated associative learning in a manual variation of the visual world paradigm used by Lesage et al. (2012). Consistent with the previous TMS study by Lesage et al. (2012), the authors found that cathodal stimulation decreased and anodal stimulation enhanced the response time advantage for the predictable sentence items, without changing performance for the nonpredictable ones. These results are consistent with a role for the right posterolateral cerebellum beyond motor aspects of language and suggest that internal models of linguistic stimuli in the cerebellum might also support semantic prediction, due to the cerebellar functional connectivity with cerebral cortical language networks.

As evidenced by the studies reported above, there have been inconsistent reports on whether anodal or cathodal tDCS over the cerebellum improves or disrupts language processing. Thus, additional studies are needed to clarify the polarity-specific effects of the cerebellar tDCS on cognitive processing.

8.6.3 Cerebellar TMS/tDCS Effects on Cerebro-Cerebellar Networks

As shown in Sect. 8.4, neuroimaging studies clearly demonstrated that the cerebellum is a component of distributed language networks (Buckner et al., 2011; O'Reilly et al., 2010), but the functional relationship between the cerebellum and cerebral areas involved in language processing remains to be further elucidated. A novel approach to this issue has been recently employed, by combining brain stimulation and neuroimaging techniques to precisely investigate how magnetic or electrical stimulation over the cerebellum may affect this structure, the rest of the brain, as well as the interaction between them. A summary of the studies that combine cerebellar TMS or tDCS with neuroimaging analyses to investigate the effect of cerebellar stimulation on the cerebral areas involved in speech and language functions is reported in Table 8.2.

Interestingly, some studies have shown that the application of TMS and tDCS over the cerebellar cortex might determine changes in the activity not only of cerebellar output (Das, Spoor, Sibindi, et al., 2017; Oulad Ben Taib & Manto, 2013) but also of the cortical areas targeted by the cerebellar projections (Cho et al., 2012; Macher et al., 2014).

In a combined rTMS and positron emission tomography study, Cho et al. (2012) observed increased glucose metabolism in cognition- and language-related areas, such as the left superior temporal gyrus (Wernicke's area) and left inferior frontal gyrus (Broca's area), when 1 Hz rTMS was applied over the left cerebellum. Taking into account the data showing co-activation of Broca's area and the cerebellum during language-related tasks (Honey, Bullmore, & Sharma, 2000; Majerus, Laureys, Collette, et al., 2003; Paulesu, Frith, & Frackowiak, 1993), the authors hypothesized that rTMS works as a cerebellar "virtual lesion" and compensatory neuronal activity can occur in other brain areas to maintain the functional state. It has to be underlined that this result is to be seen in the context of the ongoing debate about the role of left and right cerebellar hemispheres in linguistic abilities (Gebhart et al., 2002). Indeed, although cerebellar language-related deficits have been observed more often after lesions of the right lateral cerebellum (Baillieux, De Smet, Dobbeleir, et al., 2009; Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004), and some studies have demonstrated activation of the right cerebellar hemisphere during language tasks (Hubrich-Ungureanu et al., 2002; Jansen et al., 2005), both clinical and neuroimaging studies have provided evidence for a role of the left cerebellar hemisphere in the language domain (Gebhart et al., 2002).

Table 8.2 Summary of studies that combine cerebellar TMS or tDCS with neuroimaging analyses to investigate the cerebellar role in speech and language domains

Study	Participants	Type of stimulation	Measuring method	Task	Timing of neuroimaging signal	Location of the stimulation	Activations
Brusa et al. (2014)	10 (4 M, 6 F) PSP Mean age ± s.d.: 59.3 ± 6.6 years	iTBS 80% of AMT 2 weeks—10 sessions 2 trains (L and R) of 3 pulses at 50 Hz in 20 trains of 10 bursts with 8 s intervals, 600 pulses (offline)	rs-fMRI	No task	Before and after the iTBS sessions	L and R CB	Increased activation of the caudate nuclei Alleviated dysarthria
Cho, Yoon, Bang, et al. (2012)	*N* = 12 (6 M, 6 F) Mean age ± s.d.: 23.7 ± 2.6 years	1 Hz rTMS (900 pulses) 90% of MT Active or sham offline	PET	No task	Within 5 min after stimulation (10 min scans)	L CB	Increased glucose metabolism in cognition and language-related areas (e.g., left superior temporal gyrus, left inferior frontal gyrus, after CB stimulation
D'Mello et al. (2017)	*N* = 35 (12 M, 23 F) Mean age ± s.d.: 23.7 ± 2.7 years *N* = 15 sham stim *N* = 20 anodal stim	tDCS (1.5 mA) 1 session (20 min) offline	Task-based and rs-fMRI	Sentence completion task	Before and after tDCS	Anode: R CB Cathode: R clavicle	Increased activation in R Crus I/II during semantic prediction after anodal stimulation Enhanced FC between nodes of the predictive reading/language network and regions involved in second language learning and syntactic and semantic processing, after anodal stimulation

(continued)

Table 8.2 (continued)

Study	Participants	Type of stimulation	Measuring method	Task	Timing of neuroimaging signal	Location of the stimulation	Activations
Macher, Boehringer, Villringer, and Pleger (2014)	*N* = 16 (8 M, 8 F) Mean age ± s.d.: 26 ± 3.4 years	tDCS (2 mA) 1 session (25 min) offline	Task-based fMRI	Sternberg task	After tDCS	Anode/cathode: R CB Anode/cathode: R buccinators muscle	Reduced item recognition capacity and attenuated neural signal from the R CB (lobule VIIb), during the late encoding phase, after anodal stimulation Affected task-associated FC between R CB lobule (VIIb) and the posterior parietal cortex, after anodal stimulation
Turkeltaub et al. (2016)	*N* = 76 (30 M, 46 F) Mean age ± s.d.: 23.7 ± 6.2 years *N* = 15 sham *N* = 30 anodal (15 anterior-medial, 15 R posterolateral) *N* = 30 cathodal (15 anterior-medial, 15 R posterolateral)	tDCS (2 mA) 1 session (20 min) offline	rs-fMRI	Phonemic fluency task	Before and after tDCS	Anode/cathode: anterior-medial or R posterolateral CB Anode/cathode: R deltoid muscle	Improved phonemic fluency after anodal R posterolateral CB stimulation Increased FC between the R posterolateral CB and frontoparietal cognitive networks

CB cerebellum, *F* female, *FC* functional connectivity, *fMRI* functional magnetic resonance imaging, *ISI* inter-stimulus interval, *iTBS* intermittent theta-burst stimulation, *L* left, *M* male, *MT* motor threshold, *PET* positron emission tomography, *PSP* progressive supranuclear palsy, *R* right, *rs-fMRI* resting state fMRI, *rTMS* repetitive transcranial magnetic stimulation, *tDC* transcranial direct current stimulation

Brusa et al. (2014) administered daily iTBS sessions over the cerebellum for 2 weeks in patients with progressive supranuclear palsy (PSP). The CBI measure (to investigate the interaction between the cerebellum and M1), rs-fMRI and a clinical rating scale were involved both pre- and post-iTBS. The authors observed an increase in CBI and alleviation of dysarthria. Moreover, the rs-fMRI showed an increased BOLD signal in the caudate nuclei, suggesting an enhanced functional connectivity between the cerebellar hemispheres, caudate nuclei, and cortex.

Furthermore, combining right cerebellar tDCS with fMRI in healthy adults, Macher et al. (2014) found an impaired digit recognition performance in a modified Sternberg task after anodal cerebellar stimulation. They also found attenuated hemodynamic signal in the right lobule VIIb and decreased FC between this lobule and the posterior parietal cortex during the late encoding phase. However, in a more recent study, Turkeltaub et al. (2016) demonstrated that anodal tDCS over the right posterolateral cerebellum modulated rs-fMRI FC in language networks, increased the FC between the cerebellum and language and speech motor regions, and improved verbal fluency.

In a subsequent study combining tDCS over the right posterolateral cerebellum and fMRI, D'Mello et al. (2017) showed that anodal tDCS increased activation in right Crus I/II during semantic prediction and enhanced resting-state FC between hubs of the reading/language networks. Interestingly, they observed that cerebellar tDCS did not broadly increase activation throughout the brain; indeed, the effects of tDCS were focal to language-associated regions of the cerebellum and cerebral cortex. This is consistent with the previous study by Turkeltaub et al. (2016) showing that cerebellar tDCS over the posterolateral cerebellum altered FC in cerebro-cerebellar association networks without affecting somato-motor networks.

All in all, these studies further confirm that the cerebellum has functional links to the cerebral areas involved in specific aspects of language processing and that electric or magnetic stimulation applied over the cerebellum affects these cerebello-cerebral networks.

8.7 Cerebellar Stimulation to Modulate Speech and Language Abilities in Patients

In recent literature, studies have applied TMS or tDCS over specific cerebral areas, such as the left dorsolateral prefrontal cortex or posterior perisylvian area in patients presenting with language deficits to investigate the effect of neuromodulation on specific language tasks, often obtaining therapeutically promising improvements in linguistic performance (Monti, Ferrucci, Fumagalli, et al., 2013).

Regarding the cerebellum, initial studies reported an improvement in ataxic gait after 21 days of rTMS over the cerebellum in patients with spinocerebellar ataxia (SCA) (Shiga, Tsuda, Itoyama, et al., 2002; Shimizu, Tsuda, Shiga, et al., 1999). Farzan et al. (2013) applied the same protocol on a patient affected by

idiopathic late-onset cerebellar atrophy. The patient presented with scanning speech dysarthria, a type of ataxic dysarthria in which spoken words are broken up into separate syllables, often separated by a noticeable pause, and spoken with varying force. During the training sessions, the patient was required to complete one trial of normal walking and one trial of motor-cognitive dual tasking during which they had to name items found in a supermarket while walking. Interestingly, when cerebellar stimulation was applied, the authors found not only an improvement in limb coordination and gait but also in speech, as characterized by a louder and clearer voice. Moreover, the patient named more items in the dual-task condition.

The authors linked this finding to a reduction in CBI due to transient depletion of cerebellar cortical neuro-mediatory mechanisms responsible for suppression of the dentate nucleus consequent to the inhibitory effect of low-frequency stimulation over the cerebellar cortex. Farzan et al. (2013) argued that the low-frequency TMS might exert its therapeutic efficacy by reducing the cerebellar cortical inhibitory control over the dentate nucleus, thereby potentiating the residual activity of the dentate nucleus, resulting in a facilitatory effect on both motor and nonmotor cerebral areas. This hypothesis is in line with studies that described modifications in prefrontal cortical activity and language functions after cerebellar stimulation in healthy subjects (see Sect. 8.6.3). The case study described by Farzan et al. (2013) provides important evidence about the efficacy of cerebellar stimulation as a therapeutic approach in cerebellar degenerative ataxia. These findings have been reinforced by the study of Brusa et al. (2014), in which alleviation of dysarthria was observed in PSP patients after 2 weeks of daily iTBS sessions over the cerebellum.

Recently, cerebellar tDCS has also been used in clinical populations to investigate its potential application as a therapeutic tool in the language domain. Characteristically, Marangolo et al. (2018) investigated the effect of cerebellar tDCS coupled with language treatment in improving performance in a verb generation task in subjects with aphasia by using a randomized, crossover, double-blind design. Each participant received cerebellar tDCS in four experimental conditions (right and left cathodal or sham stimulation), run in five consecutive daily sessions over 4 weeks. tDCS was administered during a verb naming task or a verb generation task. Significant improvements were found only in the verb generation task following the cathodal stimulation conditions. The authors hypothesized that cerebellar tDCS is a viable tool for recovery from aphasia, particularly when the language task also demands the activation of nonlinguistic strategies, as in the case of the verb generation task, which requires executive and memory components.

The studies above provided evidence that cerebellar neuromodulation has the potential to become a treatment tool for speech and language disorders, not only for patients affected by cerebellar pathology but also for other patient populations, such as SCA, PSP, and subjects affected by aphasia.

8.8 Conclusions and Future Directions

Cerebellar involvement in speech and language domains has been largely demonstrated by clinical and neuroimaging studies. These data have been reinforced by the application of neuromodulation techniques, such as TMS and tDCS, which hold a significant advantage over correlational fMRI methods and clinical studies because of the capacity to demonstrate the causal relationship between cerebellar functioning and language abilities (Arasanz et al., 2012; Pope & Miall, 2015). Thus, as described in the present chapter, in recent years, the cerebellum has become an interesting target for these novel and highly promising techniques. Although, to date, these noninvasive tools have been mainly employed in a research context, cerebellar stimulation represents not only an interesting tool to study the role of the cerebellum in language processing but also a therapeutic approach that could be exploited for speech and language disorders (Grimaldi et al., 2016). In the literature, a number of studies have demonstrated a behavioral facilitatory effect of tDCS over different brain areas (Vallar & Bolognini, 2011), in motor and perception tasks (Antal et al., 2004; Fregni, Boggio, Nitsche, et al., 2005), and in working memory and language-related tasks (Fertonani, Rosini, Cotelli, et al., 2010; Fregni et al., 2005). These findings highlight the potential of neuromodulation as a therapeutic intervention in psychiatric and neurological conditions (i.e., depression and stroke) (Flöel, 2014; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). Regarding the speech and language domains, despite some discrepancies in the findings as described in the previous sections, it is clear that both TMS and tDCS over the cerebellum can modulate speech and language functions and also produce improvements in specific abilities (Argyropoulos, 2011; Argyropoulos et al., 2011; Turkeltaub et al., 2016). In this light, very recent studies using cerebellar transcranial stimulation in clinical populations have reported improvements in dysarthria in PSP patients and verb generation in patients with aphasia (Bradnam, Graetz, McDonnell, et al., 2015; Brusa et al., 2014; Marangolo et al., 2018). Considering the cerebellar role in learning and skill acquisition through the error-based adaptation of internal models that enable fluent, optimized performance (Ito, 2008), cerebellar neuromodulation may enhance language abilities, with potential positive effects on aphasia recovery. Indeed, pairing cerebellar tDCS with speech-language therapy might enhance the learning of compensatory strategies and relearning of language mechanisms during aphasia rehabilitation.

In fact, targeting the cerebellum might represent a novel way to modulate the excitability of not only the cerebellum but also remote cortical regions and their functions. Indeed, as evidenced in Sect. 8.6.3, both cerebellar TMS and tDCS are capable of modulating cerebello-cerebral FC, affecting the connectivity between the cerebellum and language networks (D'Mello et al., 2017; Macher et al., 2014; Turkeltaub et al., 2016). Providing sufficient reinforcement of this enhanced network connectivity through multiple sessions of cerebellar stimulation could contribute to long-lasting effects on the reorganization of residual language networks after stroke. However, due to the high variability in the impact of cerebellar TMS and

tDCS on the cortico-cerebellar pathways, studies with more stringent methodological standards (larger sample size, sham-controlled designs) are needed to understand the effects of different experimental protocols (Nordmann, Azorina, Langguth, & Schecklmann, 2015). This information could be crucial to efficiently implement cerebellar TMS and tDCS in therapeutic settings.

In comparison with cortical neuromodulation, cerebellar neuromodulation might have some additional practical advantages as a treatment approach for specific pathological conditions (Turkeltaub et al., 2016), and future potential applications should be considered. For example, in patients with aphasia consequent to a cerebral cortical stroke with encephalomalacia at the lesion site, cerebellar stimulation might represent a useful choice. Indeed, encephalomalacia makes direct perilesional cerebral cortical stimulation difficult (Baker, Rorden, & Fridriksson, 2010; Dmochowski, Datta, Huang, et al., 2013). Targeting the right hemispheric language homologs could be an alternative, but encephalomalacia in the left hemisphere may result in unpredictable patterns of current flow when stimulation is delivered over the right hemisphere (Anglade, Thiel, & Ansaldo, 2014; Gainotti, 2015). As an alternative approach, in the case of right posterolateral cerebellar stimulation, this site is distant enough from the cerebral cortical stroke sites associated with aphasia, and it is unlikely that the electrical current flow would be affected by encephalomalacia, especially when the reference electrode is placed off the head. Furthermore, considering the emerging literature about the possible role of connectivity alterations within cerebello-cerebral networks in language deficits reported in ASD subjects (Khan et al., 2015; Verly et al., 2014) (as described in Sect. 8.4), the neuromodulation of cerebellar activity might represent a potential tool to intervene in autism language disorders.

Before concluding, it is important to warn that prior to using the cerebellar TMS and tDCS as potential treatment techniques in speech and language disorders, both researchers and clinicians have to take into account the working mechanisms and the advantages/disadvantages of each technique. Indeed, while TMS is capable of inducing action potentials by acting on axons and monosynaptic or polysynaptic pathways resulting in genuine neuronal firing, tDCS cannot excite neurons and is mostly used to modulate neuronal excitability. Nevertheless, in many cases, the aftereffects of the two techniques are very similar, probably due to shared electrical characteristics of cerebellar neuronal populations (Grimaldi et al., 2016).

As a therapeutic tool, cerebellar tDCS seems to have some advantages over TMS. The device to administer TMS is sophisticated and costly, while the tDCS device is simple to use and less expensive. In addition, since the device is small and easily portable, no specific room is required for the administration of tDCS, making it easy to combine tDCS with other speech therapies (Priori, Hallett, & Rothwell, 2009). Other practical advantages of cerebellar tDCS over TMS regard the possibilities of implementing sham-controlled and double-blind studies (Hummel, Celnik, Giraux, et al., 2005). Indeed, placebo stimulation, often named “sham” stimulation, is more reliable in tDCS than in TMS, particularly with respect to the extent of the physiological artifacts that cerebellar TMS can generate (Merabet & Pascual-Leone, 2008).

Furthermore, during TMS, the copper wire windings within the coil tense and often produce a brief "click" exceeding 120 dB (Pascual-Leone, Cohen, Shotland, et al., 1992). This noise might represent a potential confound in behavioral performance, especially in speech perception and auditory sentence comprehension tasks. Moreover, because the suboccipital muscles of the neck attach to the skull close to the cerebellum, the magnetic field generated by the electrical current running through the coil can activate local sensory nerves or muscles with an unpleasant effect or induce a startle reaction affecting reaction-time measures (Hummel et al., 2005; Merabet & Pascual-Leone, 2008; Paulus, 2003). These aspects might also compromise the sham condition. In contrast, during tDCS, no sounds are produced, and only mild transient tingling sensations with no twitches may occur during the first few seconds (Ferrucci et al., 2015). One limitation of tDCS is its spatial resolution, which is markedly lower than that of TMS (Jahanshahi & Rothwell, 2000). In this light, the more focal effect of TMS might allow the stimulation of particular cerebellar regions specifically involved in language subcomponents.

In conclusion, cerebellar neuromodulation has enormous potential as a treatment tool in speech and language disorders, not only for patients affected by cerebellar pathology but also for other patient populations. Future placebo-controlled trials in patients with specific diagnoses would permit the identification of individuals who can benefit the most from this therapeutic approach. Furthermore, neuroimaging studies should be implemented to precisely identify the mechanisms of cerebellar TMS and tDCS to guarantee more efficacious personalized treatment protocols.

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Chapter 9
Navigated rTMS for Mapping the Language Network in Preoperative Settings: Current Status and Future Prospects

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Abbreviations

DCS	Direct cortical stimulation
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EMG	Electromyography
FA	Fractional anisotropy
fMRI	Functional MRI
FT	Fiber tracking
MRI	Magnetic resonance imaging
nrTMS	Navigated rTMS
nTMS	Navigated TMS
rTMS	Repetitive TMS
TMS	Transcranial magnetic stimulation
μV	Microvolt(s)

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_9

9.1 Introduction

The extent of resection constitutes a principal prognostic factor for patients with an intrinsic brain tumor (Ius et al., 2012; McGirt et al., 2008, 2009; Sanai & Berger, 2008; Sanai, Polley, McDermott, Parsa, & Berger, 2011; Smith et al., 2008; Stummer et al., 2008; Wisoff et al., 1998). As a consequence, maximal resection with concurrent preservation of functionally important areas is a key treatment goal (Duffau, 2009; Hervey-Jumper et al., 2015; Ojemann & Whitaker, 1978; Stupp et al., 2014; Stupp, Tonn, Brada, Pentheroudakis, & ESMO Guidelines Working Group, 2010; Weller et al., 2014). Over the years, numerous techniques have been developed in order to attain this goal, including intraoperative imaging (magnetic resonance imaging (MRI)) (Black et al., 1997; Foroglou, Zamani, & Black, 2009; Knauth et al., 1999), ultrasound (Rubin & Dohrmann, 1983), and neuronavigation (Golfinos, Fitzpatrick, Smith, & Spetzler, 1995), that are used to assist the intraoperative identification of the neoplastic tissue and guide the operative process. It is axiomatically accepted that brain functions influencing the patient's quality of life postoperatively, like language, should be protected, even though the relevant areas are neighboring to the neoplasm or are infiltrated by the neoplastic process (Watts & Sanai, 2016).

According to recent models of language organization, information is processed through a dorsal sensorimotor stream and a ventral semantic stream (Hickok & Poeppel, 2004; Rauschecker & Scott, 2009), following a hodotopic paradigm (Catani, 2007; Duffau, 2008, 2010). Although traditional models emphasize the prevailing participation of the dominant hemisphere, there is evidence that the non-dominant hemisphere contributes significantly in language function (Baum, Martin, Hamilton, & Beauchamp, 2012; Brennan & Pylkkanen, 2012; Briganti et al., 2012; Cogan et al., 2014; De Witt Hamer, Robles, Zwinderman, Duffau, & Berger, 2012; Desmurget, Bonnetblanc, & Duffau, 2007; Devlin & Watkins, 2007; Schuhmann, Schiller, Goebel, & Sack, 2012; Southwell, Hervey-Jumper, Perry, & Berger, 2016; Thiel et al., 2005; Vigneau et al., 2011). It should be emphasized that the functional brain anatomy of language is characterized by significant intersubject variability. This variability may be even more accentuated in cases where brain plasticity is induced by slowly growing lesions. Accordingly, surgical resection of intrinsic brain lesions is hindered, and functional integrity is put in jeopardy, when the unique language brain anatomy of the patient remains unknown (De Benedictis & Duffau, 2011).

In order to address this issue, a number of techniques for the intraoperative localization of areas relevant to critical functions, like language and motor areas, have been introduced in the neurosurgical armamentarium (Hervey-Jumper et al., 2015; Ojemann & Whitaker, 1978; Sanai et al., 2008). These techniques include intraoperative cortical mapping (Berger, Cohen, & Ojemann, 1990; Rostomily, Berger, Ojemann, & Lettich, 1991), continuous neurophysiological monitoring of the cortex and the subcortical white matter (Keles et al., 2004; Kombos, Suess, Ciklatekerlio, & Brock, 2001), as well as awake craniotomy (Berger, 1994, 1995; Berger, Deliganis, Dobbins, & Keles, 1994; Berger & Ojemann, 1992; Penfield, 1954;

Silbergeld, Mueller, Colley, Ojemann, & Lettich, 1992; Taylor & Bernstein, 1999; Walsh, Schmidt, & Marsh, 1992). Direct cortical stimulation (DCS) is the current gold standard for the accurate localization of functional cortical anatomy (De Witt Hamer et al., 2012). In order to achieve functional mapping of areas relevant to language processing, it is necessary that the patient be awake, cooperative, and concentrated. Therefore, the duration of mapping with DCS during awake surgery is limited by discomfort, distraction of attention, fatigue, or boredom (Kilbride, 2013). It should be noted that the effects of DCS may spread to adjacent and remote cortical areas, a phenomenon which may act as a confounder in the interpretation of results (Borchers, Himmelbach, Logothetis, & Karnath, 2011). It should also be noted that responses to repetitions of DCS at the same site may show significant variation (Lesser et al., 2008; Whitaker & Ojemann, 1977). During object naming, the most effective task for the intraoperative determination of language-related cortex (Petrovich Brennan et al., 2007), each site is stimulated for three nonconsecutive times, and, if a response is elicited at least two times, it is marked as positive.

Apart from intraoperative functional mapping, preoperative knowledge of functional language anatomy may assist surgical planning, reduce mapping time in awake craniotomy, and contribute to patient preparation and counseling. This urgent clinical need is addressed by a variety of methods for the preoperative mapping of functional networks. Among these, navigated repetitive transcranial magnetic stimulation (nrTMS) stands out as a novel, accurate, noninvasive, and feasible method.

The outline of the present chapter is as follows: First, the basic principles of nrTMS and nrTMS-seeded tractography are described. Second, the indications of the method, various methodological issues, and adverse event profile are presented, and the results of the clinical application of nrTMS for language mapping are critically discussed and contrasted with those of other relevant functional mapping techniques. The chapter concludes with a brief remark on the future research perspectives regarding the optimization of this highly promising method.

9.2 Principles of nrTMS

Transcranial magnetic stimulation (TMS) is a noninvasive neurophysiological technique for motor (Barker, Jalinous, & Freeston, 1985) and language network mapping (Pascual-Leone, Gates, & Dhuna, 1991), which is based on the phenomenon of electromagnetic induction (Faraday, 1832; Maxwell, 1865). Briefly, an electric field **E** is induced in the brain by a rapidly changing, high-intensity magnetic field **B** produced by a coil outside the brain and propagating unattenuated through the scalp and the cranium. It is noteworthy that no direct contact of the coil with the patient is needed, no electric current is administered, and the magnetic field has no biological consequence by itself alone. However, the intracranially induced electric field gives rise to the hyperpolarization or depolarization of cortical neurons and, as a result, the formation of action potentials with resultant physiological effects. The size of

the stimulated cortical area depends on the intensity of the TMS pulse (Hannula & Ilmoniemi, 2017).

The action potentials generated by the action of TMS on the motor cortex spread through the pyramidal tract, and their activity can be detected with electromyography (EMG) as motor evoked potentials (MEPs) from peripheral muscles (Rothwell et al., 1999). Concurrently, inhibitory neurons are activated as well, leading to the appearance of the cortical silent period (CSP), which is recorded as an attenuation of the signal after the MEP (Saisanen et al., 2008).

Among various stimulating coil configurations, the figure-of-eight coil (Ueno, Tashiro, & Harada, 1988) is widely used to focus the induced electric field on a specific point. In order to accurately position the focused electric field on a point in the cortex, a frameless stereotactic neuronavigation system with the investigated subject's reference MRI is employed (navigated TMS (nTMS)) (Ilmoniemi, Ruohonen, & Karhu, 1999; Karhu, Hannula, Laine, & Ruohonen, 2014; Krings et al., 2001; Ruohonen & Ilmoniemi, 1999; Ruohonen & Karhu, 2010). Regarding the estimation of the stimulated cortical area, two methods of navigation have been proposed. Line navigation assumes that the target lies on a line perpendicular to the plane of the coil and passing through its center, and it may lead to inaccuracy in targeting (Sollmann et al., 2016). Alternatively, the more accurate **E** field navigation is based on computational modelling of the electric field, taking into consideration the characteristics, position, and orientation of the coil, the anatomy of the patient, and the characteristics of the tissues (Picht et al., 2011). Locally spherical (Nummenmaa et al., 2013; Picht et al., 2011), boundary element (Nummenmaa et al., 2013), or finite element models (Opitz, Windhoff, Heidemann, Turner, & Thielscher, 2011) can be applied, the latter two in off-line mode only, each with its own advantages and disadvantages.

Instead of using single TMS pulses, which is the norm in motor mapping, language mapping uses repetitive TMS (rTMS) pulses (Espadaler & Conesa, 2011; Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994; Michelucci et al., 1994; Pascual-Leone et al., 1991). In a similar procedure to DCS during awake craniotomy, patients execute language-related tasks, and, simultaneously, rTMS attempts to disrupt language function (Devlin & Watkins, 2007; Epstein et al., 1996; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011).

TMS and rTMS have similar physiological effects to those of DCS by inducing a reversible disturbance in the language processing networks. Although it is not yet entirely understood how rTMS impairs language functioning, it seems that language networks are temporarily inhibited by focal depolarizations (Epstein et al., 1996). With regard to the underlying neural processing mechanism, theories put forward suggest that (1) rTMS evokes a "virtual transient lesion" by reducing signal strength, i.e., by causing a transitory interruption of ongoing neural processing which may act synergistically with signal noise without actually introducing one (Harris, Clifford, & Miniussi, 2008), (2) rTMS evokes a "virtual transient lesion" by introducing noise to the signal (Walsh & Cowey, 2000), or (3) rTMS does not evoke a "virtual lesion," but instead it induces behavioral effects by differentially activating functionally distinct neural populations (Silvanto & Muggleton, 2008).

It should be noted that, similarly to DCS, the effects of rTMS may spread to cortical areas other than the stimulated one (Ilmoniemi et al., 1997; Robertson, Theoret, & Pascual-Leone, 2003; Valero-Cabre, Payne, Rushmore, Lomber, & Pascual-Leone, 2005; Walsh & Cowey, 1998).

The accuracy of a nTMS system, defined as the root of the sum of squared errors from all sources, can be as low as 5.7 mm, with possible sources of error being the localization of the coil (optical tracking, manufacturing tolerances for the coil and coil trackers), the movement of a head tracker, the computation model for the **E** field, and the registration of the system to the reference MRI (Ruohonen & Karhu, 2010). The mean distance between a stimulated site in nTMS and DCS in motor cortex tumor surgery has been reported to lie between 4 and 8 mm (Krieg et al., 2012; Paiva, Fonoff, Marcolin, Cabrera, & Teixeira, 2012; Picht et al., 2009, 2011; Takahashi, Vajkoczy, & Picht, 2013). The minimum spatial resolution of nrTMS during language network mapping, defined as the smallest distance of a positive and a negative stimulation point that can be distinguished by the system, ranges from 10.8 ± 4.8 to 16.6 ± 4.8 mm, comparable to the width of a gyrus (Sollmann et al., 2016). Thus, nrTMS is able to discriminate between two adjacent gyri regarding their relevance to language.

However new it may be as a technique, nTMS has already proven its safety (Tarapore et al., 2016a, 2016b) and has been widely utilized for the preoperative noninvasive mapping of motor and language networks (Conti et al., 2014; Frey et al., 2012; Krieg et al., 2012; Picht, Frey, Thieme, Kliesch, & Vajkoczy, 2016; Tarapore et al., 2013; Weiss et al., 2015).

9.3 nrTMS-Seeded DTI FT

Of its own accord, nrTMS is capable of mapping cortical areas in a depth of a few centimeters. However, it can be further extended by providing seeding points for diffusion tensor imaging (DTI) fiber tracking (FT). The latter is based on the anisotropic diffusion of water in the white matter, as observed with diffusion-weighted imaging (DWI) MRI (Moseley et al., 1990). The diffusion tensor, its principal axis following the direction of the fascicles, and the degree of anisotropy, namely, fractional anisotropy (FA), for each voxel, are computed from the DWI data (Basser, Mattiello, & LeBihan, 1994). The estimation of the white matter tracts from the diffusion tensors is performed using either a probabilistic or a deterministic algorithm. In order to limit tracking to fibers belonging to the language network, landmarks based on general anatomical models of language (Catani, Jones, & ffytche, 2005; Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005; Stieglitz, Seidel, Wiest, Beck, & Raabe, 2012) or on the unique language brain anatomy of the subject, as determined with functional techniques, like nrTMS, are used as seeds (Negwer et al., 2017). The distinction between voxels in the tract and those out of the tract is achieved by applying termination criteria, such as a turning angle threshold or a minimal FA threshold (Negwer et al., 2017; Soares, Marques, Alves, & Sousa, 2013).

9.4 Indications of nrTMS

It is conceivable that nrTMS for preoperative mapping of the language network is indicated for lesions in areas traditionally associated with language function, such as the cortex around the Sylvian fissure in the dominant hemisphere (Broca, 1861; Hervey-Jumper et al., 2015; Wernicke, 1874). As evidence for the participation of the non-dominant hemisphere in language organization is increasing (De Witt Hamer et al., 2012; Desmurget et al., 2007; Southwell et al., 2016), it seems plausible that the treatment of lesions in both hemispheres would benefit from mapping.

Like all techniques utilizing strong magnetic devices, nTMS is contraindicated in case the patient has metallic implants, foreign metal cranial bodies, or implanted electronic devices like cardiac pacemakers (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), while its use with proper parameters and precautions is allowed in childhood (Rejno-Habte Selassie, Pegenius, Viggedal, Hallbook, & Thordstein, 2018; Rosenstock, Picht, Schneider, Koch, & Thomale, 2019). Further, the unproblematic use of nTMS has been reported in patients with ventriculoperitoneal shunts (Lavinio et al., 2008; Lefranc et al., 2010), aneurysm clips (Hsieh et al., 2012), or deep brain stimulation electrodes (Kuhn & Huebl, 2011). It should be noted that attempts to map the language network with nrTMS are unreliable in severe aphasia and cognitive impairment due to an increased number of naming errors that are independent from stimulation(Schwarzer et al., 2018).

9.5 Methodology

A variety of protocols for language mapping have been used in the literature (Hauck et al., 2015a, 2015b; Hernandez-Pavon, Makela, Lehtinen, Lioumis, & Makela, 2014; Krieg et al., 2014; Lioumis et al., 2012; Picht et al., 2013; Rogic, Deletis, & Fernandez-Conejero, 2014; Tarapore et al., 2016a, 2016b; Vitikainen, Makela, Lioumis, Jousmaki, & Makela, 2015; von Campe & Jehna, 2017; Weiss et al., 2013). Since the differences between the various protocols make the comparison between their results difficult and hinder the clinical application of nrTMS for language mapping, a group of leading nTMS centers across the world has recently published a consensus for nTMS mapping of motor and language functions. The focus of that protocol was to standardize the procedures followed during nTMS for mapping the motor and language network in the preoperative setting of neurosurgical patients (Krieg et al., 2017).

In a nutshell, a reference MRI is performed before the nrTMS examination. It includes at least three-dimensional high-resolution structural data for nTMS, nrTMS, and intraoperative neuronavigation, while DWI data for DTI FT can be obtained in the same session. The common reference MRI is fed into the navigation system of the TMS setup (Lefaucheur & Picht, 2016; von Campe & Jehna, 2017).

Throughout the nrTMS examination, the patient should be comfortably seated and concentrated. The entire procedure of the examination is explained beforehand. Surface EMG electrodes are attached to small hand muscles for the purpose of motor cortex threshold determination (*vide infra*). The navigation MRI is registered to the head of the patient. Thereafter, in certain setups, the induced **E** field is calculated by the system and visualized on the MRI in real time (Jarmo Ruohonen & Ilmoniemi, 2005) (Fig. 9.1).

Language network mapping with nrTMS can be performed after motor cortex mapping with nTMS, which may be indicated depending on the location of the lesion. Even if full mapping of the motor cortex is not attained, the resting motor threshold (rMT) for the hand muscles bilaterally (abductor pollicis brevis (APB), first dorsal interosseous (FDI), or abductor digiti minimi (ADM)) is determined using nTMS before language network mapping (Krieg et al., 2017; Lefaucheur & Picht, 2016; von Campe & Jehna, 2017). According to the International Federation of Clinical Neurophysiology (IFCN) definition (Rossini et al., 2015), the rMT corresponds to the stimulus intensity that elicits a motor evoked potential of a predefined size, typically 50 μV peak to peak, with a 50% probability. The stimulated

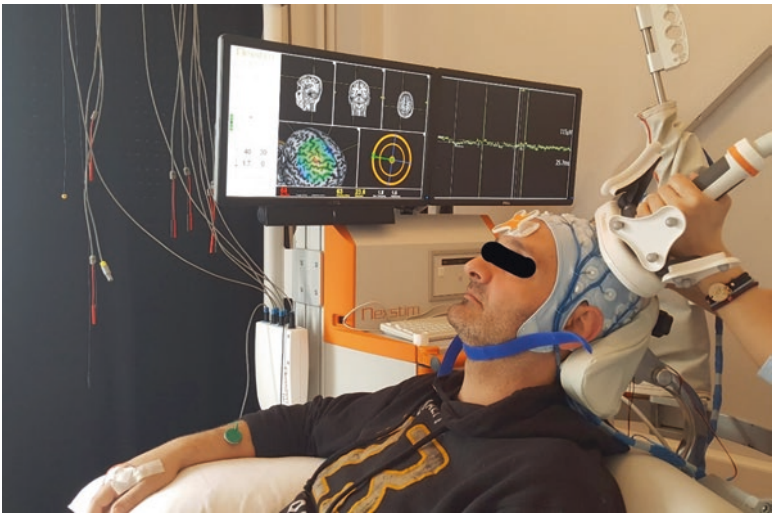

Fig. 9.1 Examination setup for preoperative language network mapping with nrTMS (eXimia system, version 5.1, Nexstim Plc, Helsinki, Finland). The first stage of the procedure corresponds to motor threshold determination. The patient sits comfortably and the head tracker is attached on the forehead. The exact position of the nTMS coil above the left central area is tracked by the navigation system, and the stimulation target is visualized on the registration three-dimensional MRI. The EMG surface electrodes are attached on the right FDI muscle. EEG is concurrently recorded in cases with epileptic seizures to maximize safety but also to avoid the confounding effects of epileptiform discharges (TMS-induced or spontaneous) in the interpretation of the results. At the second stage, pictures for the confrontational object naming task will be shown on a display in front of the patient

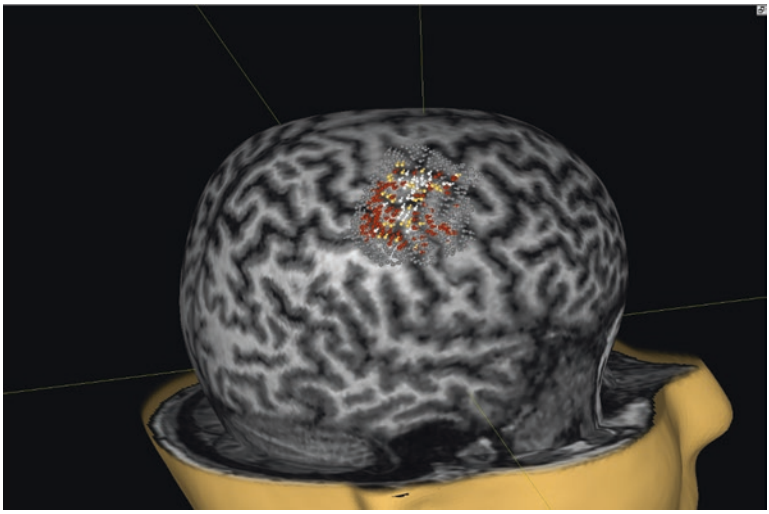

Fig. 9.2 Right hemispheric motor cortex mapping, from FDI, APB, and ADM muscles, with nTMS. Colors of stimulated sites correspond to the MEP voltage (gray, 0–50 μV [no response]; red, >50–500 μV; yellow, >500 μV–1000 μV; white, >1000 μV)

muscle must be at rest, and the so-called hotspot (the site with the maximal motor response) should be determined beforehand (Rossini et al., 1994) (Fig. 9.2).

Due to its effectiveness during DCS, its acceptance by the patients, and its ability to examine various aspects of language (Hauck et al., 2015a; Hernandez-Pavon et al., 2014; Hervey-Jumper et al., 2015; Petrovich Brennan et al., 2007), confrontational object naming has prevailed in rTMS language mapping as well (Lioumis et al., 2012). Moreover, it seems that it is more sensitive than action naming (Hauck et al., 2015b; Hernandez-Pavon et al., 2014). Either color (Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010; Mäkelä & Laakso, 2017) or black-and-white pictures (Krieg et al., 2017; von Campe & Jehna, 2017) are displayed on a computer screen with an interpicture interval (IPI) of 2500 ms and a picture presentation time (PPT) of 700 ms. The picture set contains only objects without synonyms. The patient is instructed to name the objects as rapidly and correctly as possible (Krieg et al., 2017). The session is video recorded, and the response is classified as no response (speech arrest or aphasic anomia), performance error (dysarthria or speech apraxia), hesitation, circumlocution, semantic paraphasia, phonological paraphasia, neologism, or normal (Corina et al., 2010; Picht et al., 2013) (Fig. 9.3).

Before actual mapping takes place, a baseline session is performed thrice without rTMS stimulation, and all pictures with a response other than normal (i.e., erroneously named, named with hesitation, or unnamed) are discarded from the actual mapping. During baseline session, IPI and PPT are adjusted to fit patient competence.

During rTMS language mapping, the remaining pictures in the set are presented. The stimulation is performed in synchrony with the appearance of the pictures, with a picture-to-rTMS trigger interval (PTI) of 0 ms (Fischer, Hess, & Rosler, 2005; Ille

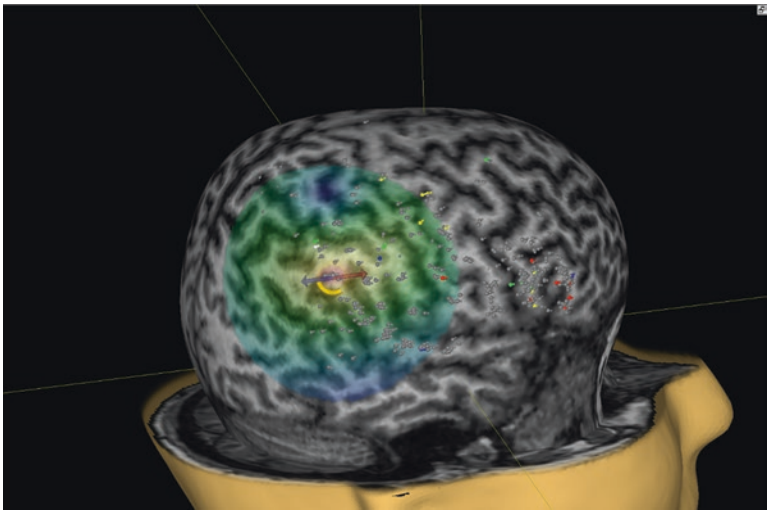

Fig. 9.3 Language network mapping with nrTMS. The figure illustrates the participation of the non-dominant hemisphere (right) in language function. The direction of the stimulating **E** field is depicted with a red arrow (corresponding to the stronger stimulation direction) and blue arrow (indicating the weaker stimulation direction). The faded colors of the arrows indicate that the coil is suboptimally positioned on the scalp. Colors of stimulated sites correspond to the type of the response (red, unclear; gray, no error; white, no response; green, performance error; blue, semantic error; orange, muscle stimulation; yellow, others)

et al., 2015a, 2015b; Krieg et al., 2014; Krieg, Tarapore, et al., 2014; Sollmann et al., 2017), a stimulus intensity equal to the rMT for the ipsilateral small hand muscles, a frequency of 5 Hz, and a duration of 1000 ms. If the stimulation is not efficient, the IPI, frequency, PTI, intensity, and PPT may be increased in small steps, until an abnormal response is observed (Krieg et al., 2017). It should be noted that the employed stimulation parameters (intensity, frequency), stimulation onset time, and coil orientation critically affect the rate and type of produced errors (Hauck et al., 2015a; Sollmann et al., 2015). Importantly, emerging evidence suggests that stimulation parameters should be determined separately for the anterior and the posterior language regions. For instance, a recent study recommends as optimal stimulation protocol for language mapping the use of 100% rMT with 5 Hz for anterior stimulation and 10 Hz for posterior stimulation and a coil orientation perpendicular (90° or 270°) to the underlying stimulated gyrus (Sollmann, Fuss-Ruppenthal, Zimmer, Meyer, & Krieg, 2018).

Between the presentation of the pictures, the TMS coil is moved manually over a wide cortical area around the Sylvian fissure, covering all regions of surgical interest. In all, 40–80 sites in each hemisphere are triggered three nonconsecutive times each, achieving a total of 120–240 stimulations. The stimulation sites are spaced at a distance of 10 mm from each other, while over and around the surgical lesion, the distance is reduced to 3–5 mm. The coil is held at such a direction that the induced **E** be perpendicular to the adjacent sulcus in an anteroposterior orientation (Krieg

et al., 2017). If the response cannot be undoubtedly classified as positive or negative, the direction of the coil may change, in an effort to induce a clear response (Sollmann, Ille, Obermueller, et al., 2015).

After the examination has been completed, the video-recorded responses of the stimulation are reviewed along with the video recording (Lioumis et al., 2012), in order to avoid misinterpretation of errors due to discomfort, distraction of attention, fatigue, boredom, or perseveration (Krieg et al., 2017). The patient may even assist in the distinction of true responses to stimulation from errors due to pain. Furthermore, errors such as paraphasias and performance errors may be recognized more readily in the video and audio recording than during actual stimulation (Mäkelä & Laakso, 2017). The accurate measurement of delays in the responses may even be assisted by the automated analysis of laryngeal vibrations using an accelerometer, which defines objectively speech response latencies (Vitikainen et al., 2015). Subtle disturbances are detected by the comparison of the responses between baseline and stimulation sessions (Corina et al., 2010; Picht et al., 2013). Every site where an error is elicited at least two times is marked as positive.

The language network maps are stored in Digital Imaging and Communications in Medicine (DICOM) format. They are further integrated with the MRI used for neuronavigation. The positive sites are also used as seeds for DTI FT (Frey et al., 2012; Negwer, Ille, et al., 2017; Negwer, Sollmann, et al., 2017; Raffa et al., 2016; Sollmann et al., 2015, 2016).

9.6 Adverse Effects and Problems

Although the possibility of epileptic seizures emerging due to nrTMS cannot be excluded and the TMS operators should be prepared for the unlikely event of a seizure, such seizures have been reported very rarely and usually with frequencies exceeding those commonly used (Rossi et al., 2009). Neurocardiogenic syncope due to anxiety or discomfort, with recovery within seconds, may also be observed. It is more common than seizures, and the operating personnel should also be prepared (Grossheinrich et al., 2009).

Discomfort or pain due to temporalis muscle contractions or stimulation of trigeminal branches may be observed, to the degree that mapping may be unattainable in the temporal region (Krieg et al., 2016), although it is rarely distressing (Tarapore et al., 2016a, 2016b). However, it should be noted that pain and discomfort can usually be avoided in most settings by changing the position and/or the location of the coil.

A small range of technical problems might restrain the efficacy of nrTMS mapping of the language network. It should be noted, for example, that the effect of nrTMS can reach several millimeters in depth. As a result, at times, it may not be fully clear whether a response originates from a specific gyrus or an adjacent one (Mäkelä & Laakso, 2017). Furthermore, the stimulation of temporomesial or deep frontal cortex is not feasible (Krieg et al., 2017). Finally, as with all other imaging information gathered

preoperatively, nTMS mapping may become inaccurate during surgery for tumor resection, because of brain shift (Hastreiter et al., 2004; Suess et al., 2007).

9.7 Results

Several studies have compared language network mapping using nrTMS with DCS in patients harboring brain tumors (Ille et al., 2015a, 2015b; Picht et al., 2013; Tarapore et al., 2013) or epilepsy (Babajani-Feremi et al., 2016; Lehtinen et al., 2018). Sensitivity of nrTMS language network mapping to detect sites of language disturbance in DCS mapping ranged from 67% to 98%, specificity from 15% to 90%, positive predictive value (PPV) from 24% to 69%, and negative predictive value (NPV) from 84% to 99% (Table 9.1). The substantial variability in specificity could be perhaps attributed to differences in experimental setup across the studies. The steadily high NPV provides evidence for the correlation of nTMS negative language mapping with DCS; thus it is highly improbable that language function will be revealed intraoperatively with DCS at a cortical area marked as negative for language processing with preoperative nTMS (Krieg, Tarapore, et al., 2014; Picht et al., 2013). Moreover, an isolate positive site in a cortical area warrants further clarification with DCS, while clusters of positive sites in an area constitute a clearer indication of the participation of the area in language function.

The positive sites for language mapping with nrTMS show significant interindividual variation (Hernandez-Pavon et al., 2014), even though the perisylvian areas in the dominant hemisphere are the areas where most positive sites are mapped. Although nTMS may provide information regarding hemispheric lateralization on language (Ille et al., 2016), it should be noted that positive sites are also mapped in the non-dominant hemisphere (Ille, Kulchytska, et al., 2016; Rosler et al., 2014; Sollmann et al., 2014). This is even more evident in patients with dominant hemisphere tumors (Krieg et al., 2013; Rosler et al., 2014), giving hints toward the functional brain plasticity associated with slowly growing brain tumors. The type of the response may differ in each stimulation of a cortical site. Moreover, positive responses to nTMS are more frequent in patients who already have language disturbances in relation to those without speech problems (Rosler et al., 2014).

Table 9.1 Studies validating nrTMS for language mapping preoperatively in brain tumor or epilepsy patients against DCS; *PPV* positive prognostic value; *NPV* negative prognostic value

Study	Sample size	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Picht et al. (2013)	20	90	24	36	84
Tarapore et al. (2013)	12	98	90	69	99
Ille et al. (2015a, 2015b)	27	97	15	34	91
Babajani-Feremi et al. (2016)	6	67	66	24	95
Lehtinen et al. (2018)	20	68	76	27	95

9.8 Clinical Advantages

The patient that undergoes a preoperative nrTMS examination is prepared for the procedures of the awake craniotomy that will follow, and they are further familiarized with the picture set and the various types of language disturbance.

The risks that accompany tumor resection or epilepsy surgery are assessed preoperatively and can be explained to the patient as well, in order to offer more accurate information regarding individual functional anatomy in relation to the tumor and expectations about a complete resection or a possible tumor remnant. It is evident that nrTMS has the potential to help surgical planning, as the approach to the lesion and the strategy for the actual resection can be adjusted to the unique anatomy of the patient. Thus, decisions concerning the aimed extent of tumor resection can be made together with the patient in a more individualized way, and unexpected results can be minimized (Ringel, 2017).

Information regarding hemispheric dominance and the degree of language shift toward the non-dominant hemisphere in patients with intrinsic brain tumors can be derived from nrTMS language network mapping (Krieg et al., 2013; Rosler et al., 2014) and interhemispheric connectivity assessed with nrTMS-seeded DTI FT (Sollmann et al., 2017). Thus, information regarding status of language function (Ille, Engel, Kelm, Meyer, & Krieg, 2018), compensation of language functions by the non-dominant hemisphere (Ille, Kulchytska, et al., 2016), and interhemispheric connectivity (Sollmann, Negwer, et al., 2017) might be related to the risk for new postoperative language disturbance, especially in patients harboring perisylvian lesions in the dominant hemisphere.

The language network maps resulting from nTMS are imported into the neuronavigation system and used during surgery for the detection of functional areas to be spared during tumor resection or epilepsy surgery (Makela, Vitikainen, Laakso, & Makela, 2015). At present, due to its low specificity and PPV and to inaccuracy introduced by brain shift during surgery, nrTMS is not routinely used as a replacement to DCS mapping and intraoperative monitoring, but rather as an adjunct (Sollmann et al., 2018). Therefore, during awake craniotomy, language function mapping with DCS starts at these nrTMS-positive sites (Ottenhausen, Krieg, Meyer, & Ringel, 2015; Sollmann et al., 2015). The same object naming task is performed with the same picture set used during the nrTMS session. This process gives a boost to the detection of DCS-positive sites and decreases intraoperative time spent on cortical mapping (Sollmann, Ille, Hauck, et al., 2015).

The DTI created using positive nrTMS language sites as seeds is also used during tumor resection or epilepsy surgery as the most helpful source of information regarding subcortical white matter tracts available preoperatively (Frey et al., 2012; Sollmann, Negwer, et al., 2016). Although anatomical landmarks can be used, the opportunity to use the unique functional anatomy of the subject, as outlined by nrTMS, offers the advantage of an individualized, accurate, and precise determination of seed points and, consequently, estimated subcortical tracts (Negwer, Ille, et al., 2017; Negwer, Sollmann, et al., 2017). A recent refinement of the technique

suggests that it is possible to use different error categories as regions of interest (ROIs) for nrTMS-DTI and thereby visualize the predominantly relevant fascicles (for instance, when focusing on performance errors only, the superior longitudinal fascicle, which is involved in articulatory processes, is preferentially visualized). Accordingly, nTMS-based function-specific tractography may provide even more detailed and reliable intraoperative guidance in patients undergoing surgery of tumors affecting language areas (Sollmann et al., 2018). Still, intraoperative direct electrical stimulation (DES) and monitoring remain the most definitive techniques to determine functional cortex and subcortical fascicles (Bello et al., 2007, 2014; Seidel, Beck, Stieglitz, Schucht, & Raabe, 2013; Soffietti et al., 2010). Therefore, nTMS-seeded tractography provides information regarding the whereabouts of a fascicle and subcortical DES attempts to locate the tract with higher accuracy. Usually, the electric current threshold to stimulate a specific fascicle is proportionate to the distance from the fascicle with a ratio of about 1 mA for every 1 mm of distance. Stimulation starts with a current of 10–15 mA and gradually decreases in order to determine the current threshold and, therefore, the distance to the fascicle. As resection proceeds, the current threshold is measured periodically until it reaches the value of 5 mA, to ensure the integrity of the white matter tract (Kamada et al., 2009; Mäkelä & Laakso, 2017).

Regarding postoperative outcome, patients with preoperative mapping of language with nrTMS have smaller craniotomy and better early postoperative language outcome than patients without nrTMS mapping, but the residual tumor, total peri- and postoperative complications, postoperative Karnofsky performance score, inpatient stay, and long-term language outcome are not significantly different (Sollmann, Ille, Hauck, et al., 2015). It should also be noted that the use of nrTMS for the preoperative mapping of language networks before asleep craniotomy without cortical or subcortical DES has been reported without permanent postoperative deficits (Ille et al., 2016; Raffa et al., 2018). Although awake craniotomy is the state of the art for surgery in areas relevant for language processing, when it is not feasible, asleep surgery with preoperative nrTMS mapping of language networks may be the best available alternative (Milian, Tatagiba, & Feigl, 2014; Nossek et al., 2013; Picht et al., 2013; Rosenstock et al., 2019; Sanai et al., 2008). Nevertheless, it should be kept in mind that due to the low PPV (but relatively high NPV) of nrTMS, such a strategy would result in low risk of new postoperative language disturbances but also in increased residual tumor (Ringel, 2017).

9.9 Comparison with Other Functional Mapping Techniques

A number of studies have compared nrTMS with other functional techniques for mapping the language network, the results of which are briefly summarized as follows.

9.9.1 Wada Test

Intracarotid amobarbital injection, namely, the Wada test (Wada, 1949), is a standard procedure for the determination of language lateralization preoperatively (Baxendale, 2009; Haag et al., 2008). However, in recent years, this invasive method is being increasingly replaced by other, noninvasive alternatives, for instance, functional MRI (fMRI) or magneto-encephalography (MEG) (Papanicolaou et al., 2014). Although a number of nrTMS studies examining language hemispheric dominance have been published (Krieg et al., 2013; Rosler et al., 2014), their results have not been insofar directly compared with this technique (Ringel, 2017).

9.9.2 fMRI

Blood oxygen level-dependent (BOLD) fMRI is based on the difference in magnetic properties between oxyhemoglobin and deoxyhemoglobin (Pauling & Coryell, 1936). As the level of oxygenation of hemoglobin changes in a cortical area during an activity relevant to this area, fMRI can be used for the indirect mapping of several functional brain networks at the cortical level, such as those pertinent to language organization (Kwong et al., 1992; Ogawa, Lee, Nayak, & Glynn, 1990). It has also been proposed as a technique for the determination of language lateralization (Abou-Khalil, 2007; Bauer, Reitsma, Houweling, Ferrier, & Ramsey, 2014; Binder et al., 1996; Deblaere et al., 2004; Kloppel & Buchel, 2005).

fMRI is easy to carry out in standard MRI scanners, without the use of an intravenously administered contrast medium. It is readily available, it can be used for various functional networks, and it does not cause any discomfort to the patient. On the contrary, nrTMS requires equipment unavailable to many centers, and it may result in discomfort or pain due to temporalis muscle contractions or stimulation of trigeminal branches. In comparison to nrTMS, fMRI for the preoperative mapping of language functions near brain tumors and other highly vascularized lesions seems to be less accurate (Sollmann et al., 2013) and less sensitive (but more specific) (Ille et al., 2015a, 2015b) and lead to false-negative results (Giussani et al., 2010). This could be attributed to its dependence on tissue oxygenation (Giussani et al., 2010; Ille et al., 2015a, 2015b; Picht et al., 2013) and the fact that it represents an indirect means of functional mapping, contrary to nrTMS. Indeed, preoperative mapping of language networks with fMRI does not seem to correlate well with the intraoperative mapping achieved with DCS in the setting of awake craniotomy (Giussani et al., 2010).

9.9.3 MEG

MEG is based on the noninvasive measurement of the magnetic field around the head produced by the electrical activity of the neurons (Cohen, 1968). It has also been proposed as a technique for the determination of language lateralization (Findlay et al., 2012; Salmelin, 2007; Tarapore et al., 2013). In comparison to nTMS, MEG seems to be less accurate for the mapping of language networks in a preoperative setting (Tarapore et al., 2013). Moreover, MEG scanners are quite sophisticated and expensive devices to be easily implemented in routine clinical practice, and, therefore, their use is still not widespread.

9.10 Further Research Perspectives

Although it is already part of clinical practice, preoperative nrTMS language network mapping is also a field where multiple questions remain unanswered. A primary goal, in order to make the most of TMS in this area, is the improvement of specificity and PPV (Tarapore & Berger, 2017). Although it seems quite improbable that nrTMS could fully replace DCS as the principal technique in pre−/intraoperative language network mapping, it would improve results in cases where awake craniotomy is not feasible. Language network mapping with nTMS exhibits low specificity particularly in the posterior speech area, in contrast with anterior sites that demonstrate a higher correlation with intraoperative DCS (Nummenmaa et al., 2014). Low specificity in posterior sites may be overcome by applying a different stimulation protocol (cf. Sect. 9.5) or a different task (for instance, a semantic task rather than the commonly employed object naming) (Picht et al., 2013). The latter suggestion is based on the observation that different task types influence to varying degrees the efficacy of nrTMS to produce errors (Tarapore et al., 2013). Action naming produces the highest errors in the posterior language areas, whereas object naming is the most sensitive task in general to reveal language-positive errors (Hauck et al., 2015b). Further, DTI FT could be routinely incorporated into the nTMS/nrTMS procedure, in order to target a predefined white matter tract. In this direction, it would be helpful to pre-compute the optimal location and orientation of the coil with simulation models combining different spatial arrangements of the nrTMS coil and DTI FT (Nummenmaa et al., 2014). Lastly, further studies comparing nrTMS language network mapping with methods that evaluate hemispheric dominance, such as Wada testing, are warranted. The primary benefit from this type of studies would be the assessment of whether inferences regarding the adequacy of language compensation by the non-dominant hemisphere can be drawn from nrTMS data (Ringel, 2017).

9.11 Conclusions

Language network mapping using nrTMS can nowadays be considered a mature neurophysiological technique. It has proven its efficacy and safety in the preoperative setting of brain tumors and epileptic disorders, and its acceptance by practitioners and patients is constantly increasing. Although, at present, its requirement for special training and extra equipment might be regarded as drawbacks, the benefits in decision-making, surgical planning, patient counseling, and awake mapping optimization are expected to overcome any remaining doubts regarding its application in resective brain surgery. In recent years, nTMS emerged as a clinically applicable method that allows the reliable noninvasive mapping of language networks and thereby gained acceptance among clinicians. In addition, it has attracted the interest of researchers of diverse backgrounds that explore its potential and attempt to standardize its use in an era when functional mapping is increasingly integrated with neurosurgery.

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Chapter 10
Presurgical Language fMRI in Epilepsy: An Introduction

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Abbreviations

(f)MRI	(Functional) magnetic resonance imaging
AFNI	Analysis of Functional Neuroimages (software)
BOLD	Blood oxygenation level dependent
ECS	Electrical cortical stimulation
EEG	Electroencephalography
FSL	FMRIB software library (software)
GLM	General linear model
HRF	Hemodynamic response function
ISA	Intracarotid Sodium Amytal procedure (colloquially 'Wada test')
SPM	Statistical Parametric Mapping (software)
TE	Echo time
TLE	Temporal lobe epilepsy
TR	Repetition time

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_10

10.1 Introduction

Neurosurgery has the potential to both cure epilepsy and cause irreversible loss of cognitive skill. The ability to predict decline in language and memory is thus fundamental to patient care in neurosurgical planning. Defining this risk requires a unique form of assessment: a procedure that relates physiological change (removal of a brain area) to a change in a psychological property (decline in cognition). In the 1980s, the key method for doing so was invasive, unpleasant, and costly: the Intracarotid Sodium Amytal procedure (ISA or 'Wada testing') involved directly anesthetizing each cerebral hemisphere in an awake patient to see if they could still speak and understand others. As such, when functional magnetic resonance imaging (fMRI) was developed to map the brain-cognition relationship in the early 1990s, it did so in the context of a clear clinical need. It was soon shown to identify the language-dominant hemisphere effectively (e.g., Binder et al., 1995) and to predict language impairment after temporal lobe surgery (Sabsevitz et al., 2003) and, in January 2007, received the critical codes required in the USA for widespread clinical adoption and billing (Bobholz, Rao, Saykin, & Pliskin, 2007). This remarkable and rapid translation from a research setting to the clinic sets fMRI apart as a model for translational neuroscience in acquired language and speech disorders.

The goal of this chapter is to orient the reader to the clinical purpose of fMRI, the practicalities of fMRI task design and data analysis, and the basics of reviewing and interpreting these data in the clinic. While we have chosen these topics, it is notable that the knowledge and skills required to conduct clinical language fMRI accurately and safely are still in the process of being defined. Many different disciplines have issued guidelines on aspects of fMRI, including Neuropsychology (Bobholz et al., 2004), Radiology (e.g., ACR-ASNR-SPR, 2017), and Neurology (Szaflarski et al., 2017). This captures the fact that clinic-quality fMRI:

> […] requires expertise and knowledge in an array of areas, including neuroanatomy, the organization of functional brain systems, brain-behavior relationships, statistical approaches for detecting and localizing brain activation, a basic understanding of MR physics and of image acquisition and reconstruction artifacts tha[t] can confound data interpretation, and in the use and development of psychological tools to optimally probe brain regions and systems of interest […] Execution of fMRI requires a multidisciplinary, collaborative approach […]. (Bobholz et al., 2004, pp 349–350)

This chapter is thus designed as an overview of critical aspects of fMRI from a number of these different perspectives, with direction to further accessible resources at relevant junctures.

10.2 Language fMRI: Clinical Utility in Epilepsy Surgery

Focal-onset epilepsy involves the presence of a pathological region in the cerebral cortex (or a discrete, lateralized network of such regions) which generates abnormal electrical activity and manifests clinically as epileptic seizures. The clinical mani-

festation of seizures depends largely on the brain areas and networks that they involve and are generated from. A clinically useful distinction is often made between seizures arising from primary epileptogenic regions/networks involving temporal structures (temporal lobe epilepsy (TLE)) and extratemporal regions (extratemporal lobe epilepsy), including frontal, central, parietal, and occipital regions. TLE is the most frequently encountered focal-onset epilepsy among the population of patients with chronic and drug-resistant epilepsies. Likewise, temporal lobectomy (and its variations) is the most commonly performed surgical procedure for epilepsy (Blumcke et al., 2017; Lueders, 2008). Medial temporal sclerosis, developmental lesions (such as focal cortical dysplasia), and low-growth tumors are the most frequent epileptogenic substrates of focal-onset epilepsy (Blumcke et al., 2017). A detailed account of seizure types can be found in Fisher et al. (2017).

Traditionally, standard temporal lobe resections are planned to avoid "conventional" posterior language regions, i.e., the middle and posterior parts of the superior temporal gyrus, as well as the supramarginal and angular gyri (Lueders, 2008). However, postoperative language (especially naming) deficits are documented in neuropsychological assessment in as many as 40% of patients subjected to left temporal lobe resection (Busch et al., 2016; Ives-Deliperi & Butler, 2012).

This means that, despite avoiding conventional posterior language areas, cortical systems related to language function are present in more anterior and basal temporal regions and their removal may lead to a decline in naming ability. fMRI and electrophysiological evidence supports the existence of a "semantic language network" located within the temporopolar and the anterolateral temporal neocortex (Binder, 2015; Binder et al., 2011), and a "basal temporal language area" in temporo-occipital cortex (Krauss et al., 1996; Schaffler, Luders, Morris, & Wyllie, 1994; Trébuchon-Da Fonseca et al., 2009). These regions will be discussed in the following sections.

Besides naming, verbal memory deficits of variable severity are also encountered following standard, especially left-sided, temporal lobectomies (Alpherts et al., 2006; Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003; Stroup et al., 2003). These are attributed to resection of medial temporal regions, i.e., the hippocampus and the adjacent parahippocampal gyrus (the entorhinal, perirhinal, and parahippocampal cortices). Predictive models, including fMRI data, for postoperative deficits in naming and verbal memory, have been put forth (Baxendale, Thompson, Harkness, & Duncan, 2006; Bonelli et al., 2010; Stroup et al., 2003).

The clinical utility of language fMRI in the presurgical evaluation in epilepsy is determined by its reliability in identifying (1) the language-dominant hemisphere (given the higher risk for language deficits following operations on it) and (2) a language network comprising "clinically meaningful" language regions, damage in which is very likely to be accompanied by severe language deficits and should thus be carefully avoided in the operation.

Accordingly, the first step in evaluating the utility of language fMRI, as regards presurgical epilepsy evaluations, is to examine its sensitivity and specificity in determining hemispheric language dominance vis-à-vis established gold standards. These involve the Intracarotid Sodium Amytal procedure (ISA or 'Wada test') and

electrical cortical stimulation (ECS) used for mapping cortical regions related to language.

10.2.1 Concordance with the Intracarotid Sodium Amytal (Wada) Test

In the context of epilepsy, the ISA, pioneered by Juhn Wada in the 1940s, is an historic gold standard (van Emde Boas, 1999). Conceptually, the procedure involves anesthetizing one hemisphere and testing a patient's ability to use language and remember new material using the other. A radiologist typically runs a catheter from the femoral artery up to the internal carotid artery and then injects sodium amytal (a short-acting barbiturate), until loss of contralateral grip strength and possibly electroencephalography (EEG) data indicate the ipsilateral hemisphere is anesthetized. A neuropsychologist, typically, administers a battery of simple language tests (e.g., involving naming, repetition, and comprehension tasks). The patient's ability to perform in those tests after sequential injection and inactivation of both hemispheres is assessed, and by comparing left vs. right hemisphere-based performance, an estimate of language lateralization (i.e., hemispheric dominance with respect to language function) is achieved. Relatively simple lateralization indices, depending on the proportion of correct vs. false responses for each hemisphere, are utilized in the ISA. After recovery, recall of the named items is used to index hemisphere memory function. This gives a gross measure of which hemisphere is "dominant," i.e., critical, for these processes. Poor standardization of the ISA protocol was a major confound early in its development, with widely varying rates of left, right, and bilateral dominance occurring across centers. The development of highly standardized procedures such as the Medical College of Georgia (MCG) protocol has supported reliable and valid use in clinical care (see Loring and Meador (2015) for an accessible outline of the protocol and related evidence).

For fMRI language lateralization, "dominance" is most often determined by visual review of images (Benjamin et al., 2018a). In contrast, the literature validating language fMRI relies on quantitative indices based on the count of task-activated voxels. Patients are usually assigned to "left hemisphere-dominant," "right hemisphere-dominant," and "mixed" (or "bilateral") language categories. The principal role of the left hemisphere in language processing has been confirmed by early language fMRI studies (Springer et al., 1999), with 94% of normal right-handed individuals showing left hemispheric dominance and 6% bilateral. In the same study, among right-handed epileptic individuals, left-sided dominance was established in 78%, and it was bilateral in 16% and right-sided in 6%, thus confirming language reorganization processes taking place in epileptic brains. Ninety-four percent of normal right-handed individuals show left hemispheric and 4% right hemispheric fMRI language lateralization, while among left-handed and ambidextrous individuals, 70% show left hemispheric, 15% right hemispheric, and 15% bilateral fMRI language lateralization.

As far as the focal-onset epilepsy population is concerned, several studies comparing hemispheric dominance derived from the ISA with that from fMRI across many language paradigms report an overall concordance of 80–90% (Arora et al., 2009; Janecek et al., 2013a, 2013b). More specifically, and according to a recently published American Academy of Neurology meta-analysis of relevant studies (Szaflarski et al., 2017), the concordance rate has been estimated to be close to 87% for cases with medial TLE and close to 81% for cases with extratemporal epileptogenic zones. Discordance is highest in cases characterized by either test as having "bilateral language" and is predicted by a rightward shift of language dominance in fMRI, thus suggesting a higher sensitivity of fMRI to right hemisphere language processing (Janecek et al., 2013a, 2013b).

Language fMRI studies comparing healthy controls with focal epilepsy patients reveal that lateralization is weaker in epilepsy and the variance larger, particularly in the inferior frontal (Broca's) area (Tailby, Abbott, & Jackson, 2017). Between 15% and 50% of epilepsy patients depart from normality, with atypical patterns more often occurring in posterior temporal (Wernicke's) areas. Dissociation of lateralization between anterior and posterior language areas, rarely observed in controls, is also more frequently encountered in epilepsy patients.

Overall, language fMRI lateralization studies suggest a high degree of concordance with the—so far—"gold standard" ISA. They also suggest language network organization departs from normality in a considerable proportion of epilepsy patients. This is to be expected given the known reorganization of language that can occur in epilepsy patients, secondary to epileptogenic pathology and epileptiform activity.

10.2.2 Areas Activated by Language Tasks in Normal Controls

There is a wide variety of language tasks utilized among different centers to activate language networks in fMRI, making it hard to homogenize results across studies. Meta-analytic data may enable a rough approximation and mapping of areas coactivated during the administration of related tests (Laird et al., 2011; Smith et al., 2009). While there can be considerable variation among independent observers as to what constitutes a "language-related" component in a given fMRI language map, most language fMRI studies consistently activate "conventional" anterior and posterior language areas (Binder, Swanson, Hammeke, & Sabsevitz, 2008; Swanson, Sabsevitz, Hammeke, & Binder, 2007). The former include the posterior inferior frontal gyrus (pars triangularis) (corresponding to the classic Broca's area), and the latter can be considered to include the posterior superior and middle temporal gyri, as well as the supramarginal and angular gyri (corresponding, as a complex, to the traditional Wernicke's area).

The reader should keep in mind the considerable change of views that has recently taken place regarding the relationship between particular aspects of language comprehension and production and the components of Wernicke's area com-

plex (e.g., Binder, 2015). Additional activated areas include the posterior portion of the middle frontal gyrus (Exner's area) and the medial frontal region (supplementary motor area), and regions of the basal temporal lobe (corresponding to the basal inferior temporal and fusiform gyri) (Benjamin et al., 2017) and less consistently the hippocampus and the parahippocampal gyrus (Binder et al., 2008; Szaflarski et al., 2008). These findings suggest that a network of interconnected brain areas, far more extensive than the simplistic "Broca's-Wernicke's" model, participate in language function. While this does not necessarily imply that every activated area plays a crucial role in language processing, lesion studies suggests that Broca's, Wernicke's, and Exner's areas are indispensable in this regard, while activations in the hippocampus and parahippocampal gyrus are most likely related to memory or associative processes. Lesions to the basal temporal language area may be associated with either persistent or transitory naming deficits, while lesions in the dominant-side supplementary motor area do not, as a rule, result in permanent language dysfunction (e.g., Zentner, Hufnagel, Pechstein, Wolf, & Schramm, 1996).

10.2.3 How Do Epileptogenic Lesions Affect Language Network Organization?

Several important parameters need to be considered in relation to language reorganization secondary to epileptogenic lesions, especially with respect to the effects of the lesion side and location, the nature of the lesion (congenital versus acquired, histopathology type), and the abnormal electrophysiological activity induced by the lesion. "Atypical language representation" secondary to most common epileptogenic pathologies is characterized by one of the following patterns: (1) atypical lateralization, (2) crossed dominance, and (3) intrahemispheric changes in language representation (Dijkstra & Ferrier, 2013).

Left hemispheric lesions are more often associated with atypical language representation, as compared to right hemispheric ones; this is particularly true with early-life frontal and temporal lobe lesions, as compared to other lobes (Korman et al., 2010). Medial temporal sclerosis (the most frequent pathology in intractable TLE) merits particular reference: when it occurs in the left hemisphere, it is associated with bilateral or right side-dominant language representation in 20–25% of cases (Briellmann et al., 2006; Janszky et al., 2003; Rathore, George, Kesavadas, Sankara Sarma, & Radhakrishnan, 2009). Besides hemispheric shift, however, medial temporal sclerosis can also be associated with intrahemispheric changes in language organization, in particular a wider dispersion of posterior language sites over the superior temporal sulcus and the middle temporal gyrus. Such a posterior intrahemispheric shift has been independently confirmed in patients with medial temporal sclerosis using ECS, and it seems that both mechanisms (lateralization shift and intrahemispheric shift) may be operative, although it is difficult to predict which

direction language representation will follow (Hamberger et al., 2007; Hamberger & Cole, 2011).

Lesion timing, severity, and extent appear to relate to reorganization patterns. Destructive and extensive early-life cerebral lesions (e.g., perinatal strokes, trauma, infections) are more often associated with atypical lateralization, in contrast to static/slowly evolving developmental lesions (such as focal cortical dysplasia, polymicrogyria, tumors, and arteriovenous malformations) or lesions acquired at an older age. The latter are less likely to induce significant reorganization, and language cortex may well be identified in their vicinity (by both fMRI and ECS) if located close to expected language areas.

10.2.4 Concordance with Electrical Cortical Stimulation (ECS)

Although fMRI-defined language network maps may be consistent with those disclosed by other methods, the issue of whether they can be utilized independently to locate language-critical cortex is far from unequivocal. Ideally, language maps should be a safe guide for shaping resection borders, especially for lesions located close to activated voxels. Even if we assume that fMRI can correctly locate language areas, the extent and borders of language cortex will vary with methodological factors including the task, analysis, and thresholding used. ECS is the imperfect "gold standard" (Hamberger, Williams, & Schevon, 2014) for mapping and defining the borders of "eloquent" cortex related to language, sensorimotor, and visual function. It remains invasive and is associated with significant risks, time, and expense, however.

In ECS, testing is implemented in a surgical (extraoperative or intraoperative) setting. Neurosurgery is first undertaken to implant intracranial electrodes over selected cortical regions. In the extraoperative setting, following electrode placement, the patient is brought to the epilepsy monitoring unit where he/she undergoes ECS across one or more sessions in the following few days (Ritaccio, Brunner, & Schalk, 2018). The final operation is performed a few days later, with all necessary information in hand. In the intraoperative setting, the patient is awake during the surgery, and ECS is performed in the acute setting. Understandably, extraoperative ECS is superior in that it provides relaxed and controlled testing for both patient and examiner, a flexible time frame, and better chances for test repeatability, conditions which obviously do not exist in the acute intraoperative setting.

During ECS proper, low-intensity and short-lasting electrical stimuli are delivered between successive pairs of adjacent electrodes while the subject is performing a language task (e.g., reading, counting, visual naming, pointing to an object in response to a verbal description). Disruption of task performance upon stimulation implies the presence of language-related ("language-positive") cortex beneath the stimulating electrodes. Resections at a distance within 1–2 cm of language-positive

electrodes are accompanied by language deficits, and this is a border which most neurosurgeons respect during resection (Haglund, Berger, Shamseldin, Lettich, & Ojemann, 1994; Rolinski et al., 2019). In this way, a cortical map is derived, depicting cortical regions over which stimulated electrodes disrupt performance in language tasks. This template helps as a guide for the neurosurgeon to avoid resecting regions related to language function. It is important to remember, however, that even if the operation spares all language-positive electrodes in ECS, postoperative naming deficits may still occur (Hamberger et al., 2014; Rolinski et al., 2019). Moreover, ECS and fMRI do not test exactly the same aspects of a given function: it is argued that ECS, through its inhibitory effect, identifies areas that are *essential* for language, while fMRI discloses regions which *contribute*, in variable degrees, to language function. Lastly, language activation tasks utilized in fMRI are not identical to those utilized for evaluating language integrity with ECS.

What is the relation of ECS-defined language areas to language task-activated fMRI networks? While this question has not been answered definitively and will vary with the ECS and fMRI protocols used, evidence from several studies suggests that the two modalities show a considerable although not complete degree of concordance. In a recent extraoperative ECS study, fMRI sensitivity approached 80% (i.e., almost 20% of language-positive electrodes would not intersect with an fMRI-positive region) (Austermuehle et al., 2017); fMRI specificity was close to 73% (i.e., almost 27% of non-positive electrodes would in fact intersect with a positive fMRI region). Importantly, in patients with no language-positive electrodes in ECS, fMRI specificity across selected thresholds was very high, ranging between 86% and 97%, indicating that fMRI may be useful for confirming that certain regions are non-eloquent. In the acute intraoperative ECS setting for brain tumor surgery, sensitivity and specificity rates as high as 100% and 68% for Broca's area, respectively, and 65% and 85% for Wernicke's area have been reported (Bizzi et al., 2008); results among other areas vary widely, however, including studies with much lower sensitivity and specificity rates (Giussani et al., 2010).

10.2.5 fMRI Utility in Predicting Language Outcome Following Epilepsy Surgery

Our knowledge regarding postoperative naming decline derives mainly from TLE patients subjected to temporal lobectomy. fMRI-independent predictive models, exclusively based on clinical data, have shown that naming decline is rare following right-sided resections, not exceeding the level expected by chance (Sherman et al., 2011). On the contrary, left-sided resections are associated with naming decline in as many as 40% of cases. The extent of decline is related to later age at seizure onset, older age at surgery, and higher preoperative naming ability. These factors predicted correctly naming decline in 68% of patients (though language preservation is better predicted than decline) (Busch et al., 2016).

How much can fMRI add to, or shape, our predictions on postoperative naming decline? In cases of left temporal lobectomy, evidence suggests that a strong lateralization of preoperative language fMRI to the left (surgical) hemisphere is related to poorer naming outcome, whereas lateralization toward the right (nonsurgical) hemisphere is associated with less or no decline. Preoperative fMRI has been shown to contribute significantly to prediction of naming ability outcome, doing so more effectively than prediction based on age at seizure onset and preoperative naming performance alone (Sabsevitz et al., 2003).

What is the outcome of resecting language fMRI-activated regions? A recent study by Rolinski et al. (2019) provides evidence for the complementary role fMRI and ECS may have: if the fMRI-activated region overlaps with language-positive responses on ECS and this region is resected, this is highly predictive of a postoperative naming decline. On the contrary, the predictive value of resecting fMRI-activated regions without language-positive responses on ECS, or regions with language-positive response on ECS without colocalized language fMRI activations, is much lower (the last combination also casts doubt on the utility of ECS as the gold standard for identifying eloquent cortex). The same study also calls our attention to the significance of the basal temporal language area: its resection may be accompanied by persistent naming deficits. Given that the basal temporal cortex is not always covered by intracranial electrodes (and thus ECS is not always performed), it is important for an fMRI language protocol to reliably identify this region. Other fMRI factors related to postoperative naming decline include the amount of tissue resected in Wernicke's area and the percentage of the most activated (top 10%) voxels resected (You et al., 2019).

Language task-based fMRI is thus a valuable and increasingly utilized method in presurgical evaluation of epilepsy for identifying language networks, aiding in surgical plans, and predicting postoperative language deficits. It is currently validated for lateralization only, and cannot yet replace ECS for language localization. The evidence to date suggests the tools are complementary, especially in the subset of cases where the anticipated area of resection is close to eloquent cortices.

10.3 Task Design and Cognitive Protocols

Central to all forms of cognitive assessment, including fMRI, is the development of standardized methods that allow the same cognitive processes (and brain regions) to be elicited in the same way, in any patient (this is the focus of the field of psychometrics, e.g., see Wood, Garb, & Nezworski, 2012). Similarly, the way in which stimuli are arranged and presented in functional MRI will determine whether task-related signal will be strong enough to be detected.

10.3.1 fMRI Requires Two Conditions

Functional MRI is inherently comparative: the signal, the units of which are an arbitrary measurement representing blood oxygenation (discussed further below), is only meaningful when different conditions are compared. As a result, it is vital to ensure that two conditions—both the language *task* and the alternative cognitive state it is being compared with (the *control* or *baseline*)—are designed to selectively isolate specific cognitive processes. These two brain states will then be contrasted in an analysis to identify brain regions considered significantly more or less active in one cognitive state relative to the other.

The timing of stimuli (onset and duration) within these conditions turns out to be vital in maximizing the ability to identify task-related changes in blood flow. The two archetypal task designs are, simply, *block* and *event-related* in nature. In the former, trials are presented in blocks of (typically) 20–40 s duration. Having the patient continually complete a task for this period causes a large, drawn-out increase in blood flow in related brain regions. Presenting stimuli in blocks does not easily allow the response in different trials (e.g., correct vs. incorrect) to be identified, however; this is the focus of *event-related* designs. Here trials from multiple conditions are presented in a staggered, pseudo-randomized manner to maximize the difference in blood flow between conditions (Dale, 1999). Block designs are overwhelmingly used in clinical fMRI (95% of epilepsy presurgical sites) (Benjamin, Dhingra, et al., 2018a), likely due to these signal benefits and potentially their allowing simpler instructions for patients.

10.3.2 Cognitive Protocols in Clinical Language fMRI

As the focus of clinical fMRI is on the ability to reliably and reproducibly engage certain cognitive processes and brain regions, the cognitive protocol can be considered to include all aspects of fMRI that determine "how the patient thinks" during the assessment. The most obvious elements, here, include (1) the task instructions and directions, both those given pre-scan and in-scanner, and (2) the stimuli used in the paired fMRI "task" and "control" conditions. Each of these factors determines the cognitive strategy patients will use during testing and the brain regions they do and do not engage.

The importance of the instructions and training is highlighted by studies showing that when individuals experience identical stimuli but are given different instructions, patterns or the extent of neural activation can differ. For example, when subjects are shown a line with a mark near the center, fMRI activation differs depending on whether they are asked to judge if the mark is in the center or if the lines on either side of the mark are equal in length (Fink, Marshall, Weiss, Toni, & Zilles, 2002). Similarly, when a rest condition varies and patients are told to either "relax and be still" or relax and "ignore" background scanner noise, patterns of connectivity differ

(Benjamin et al., 2010). It is therefore essential that all patient instructions be carefully considered and standardized, ideally so that the lowest functioning patients will comprehend them. Given that surgical teams, explicitly or implicitly, often use fMRI to guide surgical margins (Benjamin et al., 2018b), such variation has the potential to directly change fMRI activation boundaries and patient outcomes.

A wide range of cognitive protocols are currently in use in clinical fMRI. These include over 19 different cognitive tasks in which patients alternately listen to stories and judge whether words are synonyms or if words rhyme, and most (95%) of surgical programs use multiple protocols (Benjamin, Dhingra, et al., 2018a). Control conditions are equally variable and include silently viewing a crosshair, listening to white noise, and watching bouncing squares. These protocols may give consistent estimates of language dominance if used in a standardized manner, but will differ markedly in the patterns of activation within the dominant hemisphere (Binder et al., 2008) (Fig. 10.1d). The current diversity in protocols likely reflects the rapid translation of fMRI from a research to a clinical tool: fMRI was available to many epilepsy programs prior to its clinical validation, so that programs often independently validated (and remain most confident with) their own protocols.

Perhaps the best validated protocols are the semantic decision-making paradigm developed by Jeff Binder and colleagues (Binder et al., 1995) and the combination of verbal fluency and noun-verb generation (Bonelli et al., 2012). These cognitive protocols are indeed the three most widely used (by 36%, 59%, and 66% of sites, respectively). Note, though, that unless all aspects of a protocol are replicated (cognitive instructions and tasks, analysis steps and settings), results will vary, and at most 7% and 5% of sites are using the full protocols published by those authors (Benjamin, Dhingra, et al., 2018a). Here we review what we consider the best-validated approach and an alternative, freely available protocol we use based on an approach developed by Susan Bookheimer at UCLA (Benjamin et al., 2017).

Semantic Decision-Making Task

This protocol was designed to isolate the processing of semantic information from other functions including attention, working memory, and motor responses. After many years of proving its reliability and reproducibility, it is being used in variations in multiple sites and institutions. A valuable practical discussion of the method in surgical planning for those seeking to use it has recently been published (Swanson, Binder, Raghavan, & Euler, 2015).

This protocol begins with a detailed set of instructions prior to scanning. A program is run for approximately 6–7 min in which the patient is initially oriented to the task and control conditions. These begin with simple instructions, to minimize any anxiety (e.g., “listen to these sounds; we will call them tones”). In the task, patients hear the names of animals and are required to press a button if the animal is both found in the USA and commonly used by humans. The patient has 3 s to respond to each animal name, in blocks of eight animals/trials (24 s). In the control condition, they hear brief sets of 3–7 high (750 hz) and low (500 hz) tones.

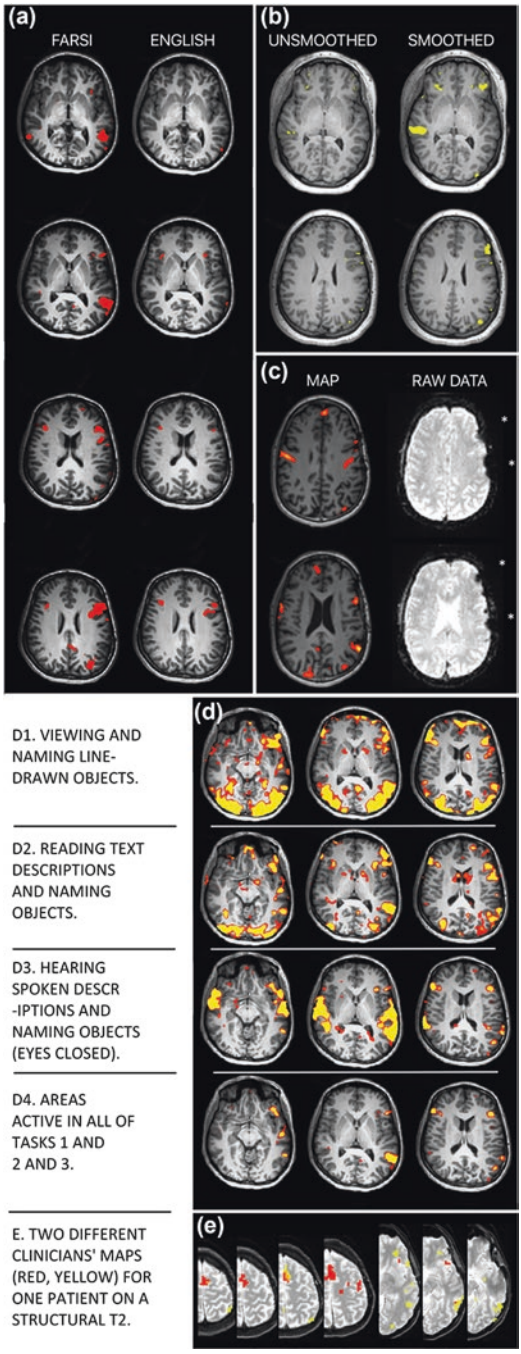

Fig. 10.1 How cognitive and technical variables can change language fMRI results. Language maps will vary in clinically meaningful ways due to multiple variables. Surgical teams can manage

Low tones form the majority, and the patient must press the button if he/she hears two high tones in a sequence. By comparing the animal to the tone task, it is hypothesized that the contrast of "Task > Control" will reveal regions involved in higher-order language but not lower-order auditory processing and response selection. This protocol reliably activates regions including the dominant superior temporal gyrus, inferior frontal and parietal cortex, angular gyrus, and temporo-occipital cortex.

The key appeal of this protocol is the exceptional work completed to validate its use and its reasonably objective output—a laterality index—to minimize subjective interpretation. The protocol has perhaps most notably been validated against the ISA for the prediction of postoperative naming decline in temporal lobe resection (Sabsevitz et al., 2003). It has also been shown to be comparable to the ISA when lateralizing language in a cohort of 229 patients (Janecek et al., 2013a, 2013b) and to be superior at predicting outcome when fMRI and ISA conflict (Janecek et al., 2013a, 2013b). It is highly standardized, with computer-based training for patients pre-scan, which improves reliability. Patient accuracy is directly assessed during the protocol (button presses), though these data are not used to modify the analysis and are not used clinically in a standardized manner.

There are some lesser, though significant, limitations to its application. As is inevitable with an extensively studied protocol, the imaging and analytic processes are dated. Sabsevitz et al. (2003) used a TR of 3 s with a voxel size 3.75 × 3.75 × 7 mm, with 19 image slices (presumably also true of Janecek et al., 2013a, 2013b). This is difficult to justify in contemporary sites, where newer sequences allow dramatically improved acquisition times (e.g., TR < 1 s) and spatial resolution (e.g., 2.5 mm^3 or 2 mm^3 voxels; >50 slices). Perhaps more importantly, the analytic processes are heavily customized, use custom regions of interest and a correlation coefficient, and used historic analysis software (e.g., Analysis of Functional NeuroImages; AFNI, pre-2003). We now know clinical teams infrequently use AFNI (8% of programs), correlation coefficients (26%), or laterality indices (35%) (Benjamin, Dhingra,

Fig. 10.1 (Continued) these factors by using experts in both imaging (e.g., radiology) and cognition (e.g., neuropsychology) in clinical fMRI design, analysis, and interpretation. (**a**) Language skill. A patient's language ability will change their activation map. Maps using the same tasks in Farsi and English from a patient who reported fluency in and made medical decisions in English. (**b**) Data analysis. Each analysis step changes the map. Data "smoothing" removes noise. Whether it is appropriate, and to what degree, is debated. The degree of smoothing in commercial software may be unspecified. Identical analysis without (left) and with (right) smoothing (8 mm kernel). (**c**) Data quality. A statistical map (left) does not show where raw data are missing (right, asterisks). These areas will not be active even if they are language-critical. This map (left) was presented to a surgical team for surgical planning without caveat. (**d**) Cognitive task. Different language tasks give different maps. Subtle changes in task instructions, patient motivation, and cognitive strategy change language maps. (D1) Visual object, (D2) text reading, and (D3) auditory tasks are shown as well as (D4) the intersection of these. (**e**) Analyst expectations. The analyst's perceived goal will change the activation map. Two overlaid maps (red; yellow) generated independently by two clinicians for the same patient (see Benjamin et al., 2017). Analysts were blind to case details. One prioritized frontal (red) and the other temporal (yellow) regions, as when mapping frontal tumor versus temporal lobectomy cases. Overlap in orange (Source: Figure and caption reprinted from Benjamin, C., Li, A., et al., "Presurgical language fMRI..." (2018); Creative Commons Attribution-Non-Commercial-NoDerivs License)

et al., 2018a). Instead, they prefer a range of software packages (most often Statistical Parametric Mapping (SPM), 27% of programs), overwhelmingly model the data using a general linear model (76%), and interpret the data by visual review at the team's conference (78%). In contrast to available evidence, data are often (~50% of programs) used, like stimulation maps, to localize language cortex.

The validation data supporting this task are the best available, though at times key publications appear to use slightly different analyses and vary classification criteria for language dominance (e.g., for laterality indices); classification and prediction accuracy may differ slightly across papers due to this. In our experience, many (particularly lower-functioning) patients also find the task overwhelming during both practice and imaging, even if the task is simplified (e.g., to "press the button if the animal is used by humans"). Consistent with this, when predicting post-surgical decline, Sabsevitz et al. (2003) excluded such patients (FSIQ $\leq$ 70). Another point is that the patient is asked to press the button with their non-dominant hand (Swanson et al., 2015), which will introduce bias from motor activation in some patients, as handedness and language dominance are not perfectly correlated. Finally, the task is culturally biased, making translation or use across different English language-speaking countries somewhat complex.

None of these points detract from the fact that this is the best validated protocol, and its direct replication is ideal. Replicating the method does require reverting to historic MR sequences and software, though, acquiring the publishing team's anatomical and region of interest templates, and determining what the precise analysis steps were to write custom protocols. It also requires moving surgical teams toward the use of laterality indices rather than visually reviewing images.

Naming: Open Multilingual fMRI Battery

Many researchers have used protocols focused on the primary cognitive process impaired after dominant temporal lobe surgery (Sherman et al., 2011): object naming. The naming of visually presented objects was used in early PET imaging approaches to language mapping (e.g., Bookheimer et al., 1997; Rutten, Ramsey, van Rijen, & van Veelen, 2002), as was the naming of objects in response to written or auditorily presented descriptions (e.g., "a tall pink bird") (Gaillard et al., 2001, 2002). A recent approach used by us integrates these protocols to provide more focal maps of the language system (Benjamin et al., 2017). This has since been modified into a standardized approach to map six known language regions.

Specifically, the patient begins with standardized instruction in each of the three protocols they will complete. They are explicitly told that this is to orient them to the tasks; that they do not need to remember the instructions, as they will be given again immediately prior to imaging; and that they will make errors—which is fine—and that in these instances they should just relax and try to get the subsequent items. The patient is also informed about the purpose of the task and control conditions and the need to remain attentive and engaged through both. A brief example of each task is given, and the patient then completes practice trials.

After moving to the imaging suite, each of the three tasks is given. Before each, a 1-min audio reminder is provided, and the patient is required to describe, in their own words, what they will need to do (while a summary is presented on screen). This provides an opportunity to correct (not infrequent) misunderstandings. (1) The visual object naming task (OBJ) also includes a verb generation component: patients are shown line-drawn black-and-white objects and required to sub-vocalize the object name and something they can do with it (a related verb). The control condition involves visual scrambles of the same stimuli, with the patient instructed to just watch the stimuli and relax. (2) In the "visual responsive naming" (VRN) task, the patient reads a short description of an object (e.g., "you write with it") and sub-vocalizes the name ("pen"). The control is as for the task, though the patient is instructed to sweep their gaze across the scramble, as in reading (to engage the frontal eye fields). Finally, (3) in the "auditory responsive naming" (ARN) task, the patient hears descriptions (similar to VRN) and sub-vocalizes the object name. The control involves the same auditory stimuli, scrambled (white noise). In analysis each task is first contrasted with its paired control. The results are thresholded at different levels to determine the threshold that best reveals six known language regions, and any run that is particularly poor is excluded. Ideally, at least one visual and one auditory protocol are included, as forming a conjunction of the corresponding activations removes lower-order sensory processing. The conjunction of the selected maps is then interpreted. As such, this approach involves some experience.

In the original version of the task the control conditions were rest, instructions were not given in scanner, and stimuli were presented in 10 s blocks (3 × 3 s stimuli) with an initial 1 s written cue (e.g., "read this") (Benjamin et al., 2017). An updated version (www.cogneuro.net) includes the above-described pre-scan and in-scan instructions with higher-level control conditions; 24 s blocks of stimuli with no text cue (to increase signal and avoid signal blurring); more trials (48 vs. 36); translations in 15 languages; and both standard (3 s) and slower (4 s, 6 s) trials. This is intended to be used with an updated acquisition sequence (~297 images/51 slices/TR ~1 s rather than 100 images/28 slices/TR = 2.5 s); analyzed with contemporary (SPM12) rather than custom software; and with a standard processing pipeline (e.g., including realignment, coregistration, smoothing). Note the translated protocols are yet to be validated but are provided given the widespread use of custom protocols and ad-hoc use of translators to read text during scanning.

This protocol is highly standardized and designed to decrease patient anxiety. For lower-functioning patients, it is easier and can be easily slowed when required. By taking the conjunction of three different tasks (two visual, one auditory), lower-order visual and auditory sensory information is removed leaving a cleaner, modality-independent image of the regions involved in naming. The task is validated to identify six known language-critical regions, and the use of three tasks yields higher confidence in the result. It is available in 15 languages and at multiple speeds. It has been validated against the ISA when read visually—the way in which most language fMRI protocols are used—rather than using a laterality index.

While the original protocol is validated against the ISA, the updated version is not. Given that interpretation is based on visual inspection of the maps

(not a laterality index), it is whether this will change markedly is debatable. It has not been validated for predicting post-surgical decline in the same fashion as the semantic decision-making task. The non-English language versions are yet to be validated, and while the slowed versions can be valuable for low-functioning patients, varying stimulus speed may alter the resulting maps. A measure of in-scanner accuracy is not obtained (though a "post-test" is included to obtain an estimate after the scan). Given that there are three ~5-min runs, the protocol also takes approximately 20 min rather than the ~6–7 min of the semantic decision-making protocol. Importantly, while the protocol reliably identifies activation consistent with six known language regions, the fact that those identified are language-critical remains to be shown.

10.3.3 Resources

Both of these protocols, as well as two well-known, validated alternatives—verbal fluency and verb generation (the versions validated in Bonelli et al., 2012)—can best be obtained directly from the relevant authors. In an effort to make protocols more readily available, we have developed a battery containing versions of these tasks (the Open Multilingual fMRI battery) which is freely available at www.cogneuro.net/omfmri.

10.4 Basic fMRI Data Analysis

A second central requirement for successful clinical fMRI is knowledge of the basics of the MR signal and image analysis. While these areas are fields in their own right, a conceptual understanding of the steps required and parameters used is both necessary and reasonably straightforward.

10.4.1 Key Principles

A functional MRI scan yields a series of MR images, each composed of many slices. The smallest volume unit (or element) within an image is referred to as a "voxel," the size of which indexes the resolution of the scan.

The MR Signal

While a detailed overview of MR physics is beyond the extent of this chapter, we direct the interested reader to the many available overviews (e.g., Buxton, 2013). Briefly, functional MR acquisition works by taking advantage of the magnetic

properties of the tissues to be mapped. Firstly, the MRI scanner maintains a large, static magnetic field parallel to the bore (B0) with strength 1.5 or 3 T which aligns the small net magnetization of nuclei in the brain with it. In fMRI, as well as in most MRI acquisitions, hydrogen is selected as the nuclei to magnetize and measure as it has a small net magnetic charge (magnetic moment) making it rapidly precess around its axis. Then, a weaker, perpendicular radio frequency magnetic field in the frequency of the precession of hydrogen is applied to tilt the hydrogen nuclei within the scanner's field to a varying degree (the flip angle). At this point the overall magnetization includes two components: a small residual longitudinal magnetization along B0 and a greater perpendicular transverse magnetization. When the transient perpendicular field is removed, the nuclei gradually realign with the B0 field (the relaxation period), and this time is measured.

The time taken for the longitudinal magnetization to recover gives an index referred to as "T_1 time," while the time taken for the transverse magnetization to decay is referred to as "T_2 time." While it would seem that T_1 and T_2 times should be the same, the lack of a perpendicular magnetic field means that the magnetization of the hydrogen nuclei interacts with that of the surrounding nuclei, making decay faster. As a result, the T_2 time depends largely on the surrounding tissue (gray or white matter, or tumorous tissue). In fMRI, the T_2 time is measured because it decays faster as the oxygenation level of the blood decreases (Norris, 2015; Uludağ, 2015).

The time taken to acquire an entire brain volume (all slices) is a key metric referred to as the "repetition time" (TR). The time between the application of the perpendicular radio frequency magnetic field and the measurement (the time at which the signal induced in the coils peaks) is called "echo time" (TE). Other key values that must be determined are the thickness of the slices acquired (the greater the number of slices, the longer the TR) as well as the in-plane resolution. Jointly, these values will determine the voxel size. Ultimately, the correct set of parameters to use in clinical fMRI is that used in the study validating your protocol. This aside, it can be difficult to balance the trade-off between speed (a low TR) and resolution. When clinicians in the field are surveyed, they report using isotropic voxels (72% of programs), with a voxel size of 3 mm^2 (41%); a TR of 3, 2, or 2.5 s (47%, 25%, 22%); and a modal duration of 5 min (Benjamin, Dhingra, et al., 2018a).

What Would Task-Related Brain Activity Look Like in fMRI Data?

After we run a clinical language fMRI protocol, we typically have two things: (1) the timing of the blocks of events in our language and control conditions (e.g., 0.00 s, 40.00 s, 80.00 s, etc.) and (2) a set of images of the brain collected during these conditions (say, 300 images). Because fMRI measures blood flow, in fMRI analysis, we most often use our onset times to create the time course (model) of what blood flow will look like in brain regions engaged in our condition(s). Throughout our patient's brain (in each voxel), we then compare these expected time course(s) with the actual signal obtained across our (e.g., 300) images.

This makes it equally important to have both good-quality, high-resolution brain images and a good-quality, high-resolution model of the expected fMRI signal. In obtaining an accurate model, we rely on (1) accurate onset times and durations for our tasks and (2) an accurate model of how blood flow changes when brain regions are active. The latter is referred to as the "hemodynamic response function" (HRF) and has been the subject of extensive research (e.g., Buxton, Uludağ, Dubowitz, & Liu, 2004). The HRF appears to exhibit a brief initial dip, followed by a marked increase in signal that peaks 4–8 s after stimulus presentation, ultimately followed by a slow drop to below baseline levels and subsequent recovery. A common approach is to use a "double gamma" function which models both the major peak and the post-peak drop in signal (see Poldrack, Mumford, and Nichols (2011) for discussion). Each fMRI analysis program has its own default settings (the software package SPM uses a default HRF peaking at 6 s after onset).

While this is a good starting point, it is valuable to realize the canonical HRF is not perfect. The response function differs to varying degrees both across brain regions and across individuals (Aguirre, Zarahn, & D'esposito, 1998). It is possible to address this in analysis by including (for example) temporal derivatives in modeling, through mapping each individual patient's own HRF for use in analysis (Aguirre et al., 1998) or through setting aside the HRF-based approach and using a model-free approach such as finite impulse response modeling.

For most cases, however, this critical assumption will be reasonable and unlikely to have a significant effect when tasks use a block design (below); and, to our knowledge, variants of the canonical HRF are routinely used in clinical fMRI. In statistical analysis (below), at each voxel, the fit between this predicted time course and the actual observed time course will be compared to identify voxels we will consider involved in our task.

10.4.2 Software

The steps involved in fMRI analysis can be completed with numerous software packages. While good commercial software is available, the open packages initially written by the neuroimaging community and used to validate clinical fMRI are extremely well established, continually reviewed and improved, and freely available. Among these, University College London's SPM (www.fil.ion.ucl.ac.uk/spm), Oxford FMRIB's FSL (www.fsl.fmrib.ox.ac.uk/fsl), and the NIH-funded AFNI (https://afni.nimh.nih.gov) all have devout adherents. While these packages require a reasonable understanding of fMRI and image analysis to use, this understanding is essential if the results of fMRI and the attendant caveats and potential confounds are to be appreciated. Instead of purchasing commercial licenses, teams can benefit significantly from investing funds in training their own staff or funding associated neuroscientists to assist in clinical fMRI using these freely available packages. An accessible, detailed introduction is provided in Poldrack et al. (2011).

10.4.3 Data Analysis: Preprocessing

Standard analysis of clinical language fMRI data involves (1) cleaning the fMRI data (preprocessing) so that (2) the task and the control can be statistically compared (modeling) and finally (3) reviewed, interpreted, and reported. The value of understanding these steps is illustrated in Fig. 10.1, which demonstrates how altering preprocessing parameters (Fig. 10.1b) and reviewing the raw data (Fig. 10.1c) can alter results and clinical interpretation.

Preprocessing can be conceptualized by considering the problems it addresses. One begins analysis with one or more runs of raw functional data, one or more high-resolution structural images, and the task's timing data. The end goal is a set of clean images of the brain, aligned in space, that can be statistically modeled and overlaid on the structural image for interpretation. After a preliminary analysis step that involves reviewing the raw data for unusual artifacts and stripping the skull from the images, the main preprocessing begins.

Aligning Functional Images: Registration and Interpolation

During acquisition of the functional data, the patient's head will have moved as they cough or shift during the task. So that a given brain region is in a consistent location (and its time course can be evaluated), the first step of preprocessing is frequently to align the functional images. The process of bringing the images into alignment (into the same coordinate system) is referred to as *registration*. When one image is aligned to a template, the precise values at each voxel are at first unknown. The new values must therefore be estimated. This is typically accomplished by inserting new values calculated from the closest voxels in the registered version of the non-aligned image (*interpolation*). As interpolation will calculate new values from a combination of the originals, this will effectively degrade (smooth) the data. Thus while these processes are essential, if possible it is best to calculate all registrations and interpolations required for the image throughout the analyses and at the end of analysis combine and apply them in a single step. Realignment is completed near universally in clinical language fMRI (84% of programs; Benjamin, Dhingra, et al., 2018a).

Aligning Functional and Structural Images: Coregistration

Additionally, the functional and structural data are almost certain to be mis-aligned initially. While the interpolation required for alignment can further degrade the data (if applied sequentially), aligning these images helps ensure functional activation is accurately located on the structural reference. Most presurgical clinical programs include coregistration to one of the patient's structural images (81% of programs;

Benjamin, Dhingra, et al., 2018a). Ensuring the structural image has been skull-stripped (above) prior to processing can dramatically decrease processing time, here.

Importantly, non-linear distortion and dropout impact EPI fMRI images due to the air-filled cavities (e.g., sinuses) near the base of the brain but not structural T_1 images. This means the results of standard functional analysis cannot be accurately aligned with a reference MPRage and are misleading. Thus while most clinicians do use an MPRage a high-resolution T_1 image as a reference (94%), some use a T_2 image as a structural reference with a more similar distortion profile (6%) (Benjamin, Dhingra, et al., 2018a). An alternate approach is to try to remove the distortion from the EPI data (using a field map), but this approach is not in widespread clinical use.

Removing Noise from the Data: Smoothing

Finally, as with any signal, fMRI data include noise when first collected. The most common form of statistical analysis—general linear modeling—requires data to have minimal, normally distributed noise, so the data are frequently *smoothed* to meet this requirement. Conceptually, smoothing is a form of averaging, whereby the BOLD value at each voxel throughout the brain is transformed into a weighted average of the voxel itself and that of its neighbors. Most clinical programs include smoothing in their analysis pipelines (81% of programs; Benjamin, Dhingra, et al., 2018a). Notably, the extent to which data are smoothed (the smoothing kernel used) varies markedly, with the most frequently used value being 8 mm (the default value in key software; SPM).

Slice-Timing Correction, Normalization, and Temporal Filtering

A set of additional steps can be completed, but whether they need to be included is more readily debated. *Slice-timing correction*. Each slice of a single fMRI volume is acquired at a different point in time, so that a single image consists of slices of data acquired from the beginning to the end of the acquisition (e.g., potentially 1–2 s apart in time). By considering the value of a voxel (in a given slice) across the duration of the scan, it is possible to calculate the predicted value at any other point during the acquisition period. In *slice-timing correction*, variants of this process are used to change the values of each voxel to the same point in time. This is not a significant issue when a block design is used, as in the vast majority of images (during a 20 s block of task, or a 20 s block of control), the predicted BOLD signal value changes little. Because it also further smoothes the data, we do not include this step though a majority of programs (57%) do.

If slice-timing correction is used, the order of motion and slice-timing correction can alter the data in an unpredicted way. When realignment (or coregistration) is applied, brain regions are moved between slices. As such if slice-timing correction is later performed, it will falsely assume all voxels in each slice were acquired simultaneously. Conversely, if slice-timing correction is applied first, as different

volumes are not aligned, signal from different brain regions (in different images) can be blurred. In both cases, this will introduce error. An alternative is to include temporal derivatives in the statistical model (GLM, below) as this will accommodate variation in both time and the shape of the patient's hemodynamic response.

Temporal filtering can also be used to remove noise from the data, though is often not used with block designs. In this case signal variation occurring more slowly than your task conditions can be removed using a high-pass filter with a cutoff of the stimulus frequency. A low-pass filter is not advised since a BOLD signal is a slow wave and by applying low-pass filter useful information may be lost (Buxton et al., 2004).

Normalization, also not typically used in clinical fMRI, is used to register the patient's brain to a reference image. This is usually completed so that a patient's brain can be compared with that of other patients or so that structures can be labelled using a reference brain (such as the Montreal Neurological Institute's template of 152 averaged brains [MNI152]). To accomplish this, images are usually warped (undergo non-linear registration). Normalization is not typically used in clinical fMRI as the surgical team usually wish to compare the fMRI results to other imaging collected in the patient's own brain space (e.g., structural MRI, PET imaging, SPECT imaging). The exception here is when laterality indices are calculated (as at 35% of programs). In this case, a reference brain with paired regions of interest is used. The reference (and regions of interest) can be normalized to the patient's brain, allowing the number of voxels in each region to be calculated.

Conclusions: Preprocessing

As such, a typical preprocessing pipeline in clinical fMRI, when a block design task is used, might include performing (1) brain extraction on each structural image; then (2) realigning all functional images to their mean; (3) coregistering these to a reference structural image; and (4) smoothing the data prior to statistical analysis. Temporal filtering may also be included, and if laterality indices are to be calculated, the reference (and related regions of interest) should also be aligned with the patient's structural image.

10.4.4 Statistical Analysis

With the data cleaned, each voxel's time series can be compared to the conditions' predicted BOLD time course. We will focus here on the analysis of a single subject's data (first-level analysis), and the interested reader is directed to one of the many good books covering this topic for additional detail (e.g., Jenkinson, Bijsterbosch, Chappell, & Winkler, n.d.; Poldrack et al., 2011).

The most common form of modeling used to identify task-related BOLD activity in clinical fMRI is the general linear model. This relies on the user identifying all

factors that will impact blood flow and creating a time course of their presence. A simple clinical language task may include only two initial regressors for the task and control conditions.

Other sources of predictable variance can be added, including indices of movement obtained during preprocessing. These may represent the translation and rotation in *X*, *Y*, and *Z* dimensions through the scan and potentially their derivatives, to accommodate non-linear motion effects. If periods of significant movement occur, analysts often decrease the impact of these by including a regressor for each impacted image that takes the value of 0 for all images except that to be removed (where it is 1). As each additional regressor decreases statistical power (decreases the degrees of freedom of the model residual) (Lazar, 2008), one approach is to begin with relatively few regressors and then add regressors as needed to remove sources of artifact.

When the model has been fully specified, the regressors are convolved with the canonical hemodynamic response (above) to capture the delay between an event and the resulting blood flow response. At each voxel, the ability of these final regressors (X) to predict the blood flow course (Y) is independently determined, giving a beta weight for each regressor. Conceptually, the beta weights summarize the ability of their condition to predict blood flow. If the beta weight for a task regressor is 1 and that for a control regressor is 0, then, at that voxel, the task perfectly predicts blood flow.

To test hypotheses, the beta weights for different conditions are directly compared to evaluate their relative ability to predict blood flow. For instance, if our model has two regressors of interest (task, control), we could identify models (voxels) where the task predicts blood flow more than the control by assigning the beta weight for task a value of +1 and that for the control a −1 giving a contrast vector [+1–1]. To test if this contrast is different, a t-statistic is calculated by taking the beta weights multiplied by their contrast values and dividing the result by (the square root of) the associated variance.

A final, key issue in interpretation of fMRI is how the resulting t maps should be thresholded. For example, when a *p*-value of 0.05 is used to threshold a statistical map containing 100–200,000 voxels, 5% of the voxels will be active simply by chance, leading to 5–10,000 false-positive results. While the field of neuroscience has focused on approaches that tend to be very stringent, the opposite is true in clinical fMRI. While the focus of research is on avoiding false-positive findings, in the clinical setting, false-negative findings (overlooking actual language areas) are of central concern. As such, the majority (79%) of those completing clinical fMRI vary thresholds "dynamically" (i.e, on a case-by-case basis; Benjamin, Dhingra, et al., 2018a), and professional groups actively recommend this (ACR-ASNR-SPR, 2017). Such approaches mean the results will turn fundamentally on the expectations and knowledge of the operator, a factor which can change the extent of, and even areas identified in, a scan (Fig. 10.1e). In spite of this, it is notable that the approaches used in the work validating fMRI do use fixed thresholds (Sabsevitz et al., 2003).

10.4.5 Conclusions

In this section, we have reviewed the core procedures required for clinical functional MRI analysis. While many more sophisticated analyses exist, the above steps should currently be sufficient for most cases so long as the clinician reviewing the data fully understands the analysis completed and how the decisions made here have shaped their results. Perhaps the best way to expand one's knowledge from here is to download Matlab (www.mathworks.com) and the SPM software package and complete the practice fMRI analyses included in the manual, with a clear but comprehensive reference such as Poldrack et al. (2011) in hand.

10.5 Reporting

10.5.1 Quality Assurance

Interpretation of fMRI results is also complex, as numerous variables impact the results and must be considered. These include, for instance, behavioral performance, effort and attention, mood state, strategy to perform task, extent of brain pathology, medication effects, and education level. When analysis has been completed and the results are ready to be reviewed, detailed quality control is imperative given the potential cost of errors. After data collection, we typically preprocess and analyze all tasks using an automated pipeline (steps noted above) and then review the data as follows.

Raw data: artifact. An essential initial step is reviewing each task run's raw data to identify artifacts. This can be achieved by (1) reviewing a single image from the functional run in detail through all (coronal, sagittal, axial) orientations and (2) watching the entire fMRI run loop, as a movie. In both cases, it is valuable to have the aligned (coregistered) MPRage and T_2 images open to locate artifacts. While this can be done in any package, the viewer included with FSL (currently "FSLeyes") is extremely useful. It is valuable to review the basal temporal and anterior frontal lobes to determine the extent of signal loss (dropout). Similarly, signal in regions of pathology should be reviewed. Reviewing the images as a movie gives an appreciation of likely movement artifact, and images with major artifact contamination—visible as (for example) high- and low-intensity stripes through the image—can be seen.

Image orientation: when data are analyzed outside a closed radiology system and custom analyses are used, it is important to ensure image orientation is preserved (e.g., not left-right flipped). While (very) unlikely to be an issue, this was a significant concern in early stages of the field. Given this error can be undetectable and the consequences catastrophic, the simple step of placing a vitamin E capsule (or similar) on (for example) the left of the patient's forehead is advisable. During quality checking, the laterality of the images should then be reviewed.

Coregistration and skull-stripping: Failures in the registration of the functional runs to a structural image (coregistration) and the removal of non-brain structures (skull-stripping) can misplace or obscure language activation. Given the (often implicit) tendency for clinicians to interpret fMRI results as localizing, it is imperative that any mismatch be outlined. Ideal points for checking coregistration include the boundaries of the ventricles and the edges of each lobe (particularly the temporal lobes).

Image mask: during the final stages of analysis (modeling, estimation, thresholding), the voxels included in and excluded from analysis are identified using an image mask. Reviewing this with the aligned structural and functional images allows areas that were excluded to be identified (e.g., due to pathology or movement). For instance, while a map may not show any temporal lobe activation, this may occur because the voxels in this area were not included in analysis.

Movement and signal variation. While movement artifact was appreciated when the raw data were reviewed, several packages provide a quantitative estimate of the extent of such artifacts (e.g., www.nitrc.org). One of the available options is that provided by the Gabrieli Lab at MIT (Drs. Whitfield-Gabrieli, Mozes, and Castañón; www.nitrc.org/projects/artifact_detect). This provides both an estimate of the percentage of images exceeding set criteria (e.g., movement of >1 mm; MR signal drift >3 SD) and corresponding regressors that can be included in analysis (modeling) to attempt to remove their impact. If we find that significant movement artifact is present, we typically re-run the statistical analyses (Sect. 4.4) and incorporate these regressors. This step can be automated so that both corrected and uncorrected maps can be reviewed after analysis.

Laterality-based approaches: alignment of regions of interest. If you are using a laterality index-based approach, it is essential to confirm the regions of interest are accurate. Errors may occur, for instance, if the registration of your patient's structural image to the reference image fails.

10.5.2 Reporting

In order to prepare for reporting, it is valuable to review the factors known to modify the base rates of atypical language dominance, such as the patient's handedness and the age of any neuropathology (or seizure onset). To obtain this information we complete a brief questionnaire with patients (Appendix C). We also review the details of the fMRI acquisition, including notes on details such as the patient's comprehension of the task, engagement, and movement.

The resulting language maps can then be reviewed and interpreted. With an approach using *laterality indices*, this may be as simple as visually reviewing the data for any unexpected results and reporting the laterality index itself along with the result of any equation predicting the probability of language decline (Swanson et al., 2015).

If visually examining tasks, it is useful to review the statistical maps from each run independently (the use of a panel of tasks is known to improve accuracy; Gaillard et al., 2004). We review lower-order sensory cortices to determine if expected visual and/or auditory activation has occurred. If a patient has not completed the tasks, this is often apparent (e.g., visual activation may be absent); runs of data may also be unusable due to patient movement, artifact, or other causes. For each run, we also informally evaluate whether expected language areas (below) are identified. This allows one to determine consistency across runs and decide whether each run should be reported, reanalyzed to address artifact, or excluded from reporting.

As is essential in clinical fMRI (ACR-ASNR-SPR, 2017; Benjamin, Dhingra, et al., 2018a)—though anathema to the research enterprise—we review each map at a series of thresholds to decide which best represents the language network (see Sect. 4.4) (Benjamin et al., 2017). As noted, "dynamic" thresholding is completed at a majority (79%) of programs in an attempt to ensure no language areas are omitted. This is an inherently subjective approach, though we have attempted to standardize this to minimize variation (Benjamin et al., 2017) and are developing this further currently. When the protocol is adapted to be completed with a multiband sequence (TR < 1 s) and analyzed using a standard SPM pipeline, we typically find that (1) thresholding tasks at around $p < 0.005$ and (2) taking the conjunction (intersection) of three tasks yield a sensible map (this approach was used in all cases in Fig. 10.2). Our experience is that this gives clearly lateralized maps in a majority of cases.

When evaluating language dominance, it is important to note that laterality is not a unitary construct. There is a degree of bilaterality in essentially all individuals (Tailby et al., 2017), and numerous known patterns of language dominance across (at least) Broca's and Wernicke's areas can be identified (Berl et al., 2014). As such, while in many cases there is much greater activation in one hemisphere (one hemisphere is clearly dominant), discriminating borderline cases can be complex. When a clinician remains uncertain after reviewing multiple tasks at multiple thresholds and makes a dominance determination anyway, a forced decision is more likely to be at odds with ISA-determined language dominance (Benjamin et al., 2017). In such cases it is advisable to either repeat fMRI or complete the ISA.

Identifying language areas. Before discussing the possible use of fMRI for identifying specific areas of language cortex, it is vital to note that, while fMRI can lateralize language, it *is not yet validated for language localization*. It is likely that maps generated from many protocols, such as ours (Fig. 10.2), do not identify all language areas (e.g., anterior temporal language cortex), and fMRI-positive language tasks are not necessarily language-critical (Benjamin, Li, et al., 2018b). When it is necessary to confirm specific cortex is not language-positive, it is advisable to rely upon ECS (in spite of all its flaws; Hamberger et al., 2014). Having said this, there is evidence that activation consistent with a number of language regions can be routinely identified on clinical language fMRI. The process of identifying these and differentiating them from artifact involves extensive experience, reading on the

functional neuroanatomy of language, ideally supervised training, and continual access to an excellent atlas (e.g., Moeller & Reif, 2007).

Specifically, there is evidence that fMRI may be sensitive to (1) Broca's area in the posterior third of the inferior frontal gyrus; (2) Exner's area in the posterior middle frontal gyrus; (3) the supplementary motor area; (4) the angular gyrus; (5) Wernicke's area, which can be separated into bilateral anterior superior temporal gyrus and lateralizing posterior superior temporal gyral—supramarginal gyral components; and (6) the basal temporal language area in the posterior temporo-occipital cortex. An overview of these regions, and directions on how to identify these, is given in Fig. 10.2 and Table 10.1.

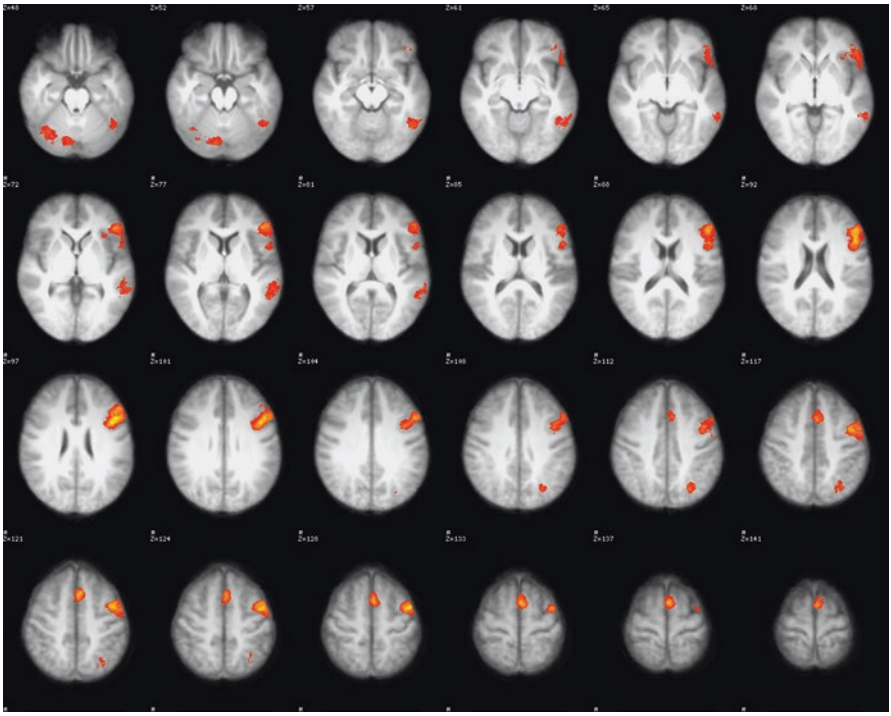

Fig. 10.2 Axial sections showing six language regions identifiable by fMRI in patients with epilepsy (radiological conventions: right of image is left of brain). Broca's area (approximately row 1 slices 4–6; row 2 slices 1–6); Exner's area (row 3 slices 1–6; row 4 slices 1–5); basal temporal language area (row 1 slices 1–3); Wernicke's area (row 1 slices 5–6; row 2 slices 1–3); supplementary speech area (row 3 slices 5–6; row 6 slices 1–6); angular gyrus/parietal cortex (row 3 slices 4–6, row 4 slices 1–2). Locations approximate. Areas of activation correspond to known language-critical regions. Note, however, that it has not been demonstrated that the areas identified via fMRI are critical, and other language-critical regions (e.g., in anterior temporal cortex) are likely not identified by this protocol. This map is the summed conjunction maps from 17 left language-dominant presurgical epilepsy patients, thresholded to show only the areas activated in a majority of subjects ($n > 9$). All patients were left dominant as determined by invasive methods or independently acquired and reported fMRI. Each patient completed the object naming, verbal responsive naming, and auditory responsive naming protocols of the Open Multilingual fMRI battery (versions updated from the protocol used in Benjamin et al. (2017) and analyzed with a standard processing pipeline in SPM12). Background image is the averaged group MPRage in MNI space

Table 10.1 Structural and functional descriptions of six language regions identifiable by fMRI in patients with epilepsy

Region	Structural definitions	Functional notes
Broca's area BA 44, 45, 47	Broca's area sits within, approximately, the posterior third of the inferior frontal gyrus (IFG). On axial MR images, identify the inferior-most slice containing the ventrolateral PFC (BA 47). Moving superiorly, some orbital frontal language cortex will then often be seen before Broca's area proper can be visualized in the posterior IFG. From the posterior-most extent of IFG moving anteriorly, Broca's area contains pars opercularis, pars triangularis, and pars orbitalis ("lip," "triangular," and "orbital" parts)	Functionally Broca's area can be broken into at least three components (Bookheimer, 2002) 1. *Posterior* regions tend to be engaged more readily in phonological processing 2. Pars triangularis by *syntactic processing* 3. More *anterior* orbital regions by semantic processing
Wernicke's area, inferior BA 22 (extends to 41, 42)	Anatomical demarcation of Wernicke's has been difficult historically as the area is defined functionally rather than anatomically (Bogen & Bogen, 1976). Historical definitions have variously included the posterior superior and potentially middle temporal, angular, and supramarginal gyri. Using fMRI, two temporo-parietal regions can usually be identified. On axial MR images, the *inferior component* can typically be identified across the superior temporal sulcus and middle temporal gyrus. It is posterior and adjacent to the primary auditory cortex	In our experience, this *inferior region* frequently activates bilaterally. As this region abuts the primary auditory cortex—an area that will be engaged by auditory stimuli (regardless of whether they are linguistic)—it is critical to understand the cognitive nature of the task being used to be certain activation reflects linguistic and not basic auditory processing. At times activation here becomes continuous with either activation in Wernicke's area's superior region or the basal temporal language area (see below). Clinically, damage to this region results in comprehension deficits and classical Wernicke's-type aphasia (e.g., word salad, etc.)
Wernicke's area, superior: supramarginal gyrus BA 41/42, 40	A separate component of Wernicke's area is located *superiorly*. This region sits in the temporo-parietal junction, extending from the posterior superior temporal gyrus to include the supramarginal gyrus and potentially cortex deeper within the intraparietal sulcus	This *superior region* tends to be involved more in phoneme selection and sequencing and in reading. Damage to this region can lead to neologistic paraphasic errors. In our experience, object and word naming tasks tend to activate this region poorly. On fMRI, activation may occur laterally and also deeper within the sulci

(continued)

Table 10.1 (continued)

Region	Structural definitions	Functional notes
Angular gyrus (AG; BA 39)	Frequently included in definitions of Wernicke's area, the angular gyrus sits within the inferior parietal lobule (or parietal operculum). It can perhaps best be identified on structural MRI (axial sections) where it appears very posteriorly in the parietal region. After identifying the intraparietal sulcus, the angular gyrus can be identified just below this. It forms an "n" shape on axial sections just posterior to the "m" of the supramarginal gyrus and continues inferiorly. Note that on maps with significant visual activation, it can prove difficult to distinguish this region from occipital visual activation	Historically considered to be jointly involved in word recognition, these gyri have been argued to support orthography-phonology mapping (i.e., letter-to-sound rules). Separately they have been argued to be differentially involved in semantic and phonological processing with the *supramarginal gyrus* suggested to support phonological processing to a greater extent (Stoeckel, Gough, Watkins, & Devlin, 2009; Devlin, Matthews, & Rushworth, 2003), while the *angular gyrus* may be differentially more engaged in semantic components of word processing (Stoeckel et al., 2009; Devlin et al., 2003)
Basal temporal language area (BA 20, 37)	This region is located in the posterior and inferior temporal lobe, just anterior to the pre-occipital notch. Moving superiorly from the most inferior temporal axial slice, this region is located at the temporal-occipital border on the inferior to lateral surface, lateral to the fusiform gyrus	Not recognized in early language network models, this region is critically involved in naming, i.e., the linking of semantics with nouns. It is thus not engaged in tasks such as verb generation. It may be omitted from fMRI images given its proximity to MR field inhomogeneities caused by the brain/air (sinus) interface The region has previously been studied as Mills' Naming Center and Nielsen's language formulation center. It is close to, but distinct from, the fusiform gyrus' "visual word form area"

(continued)

Table 10.1 (continued)

Region	Structural definitions	Functional notes
Supplementary speech area BA 6	An area which can be described as the "supplementary speech area" (SSA) sits immediately anterior to the supplementary motor area in the superior frontal gyrus. Using functional MRI, it can be identified on axial images from the most (or near most) superior axial slice. This activation often extends inferior to the cingulate cortex	Functionally, this area's role in motor planning and sequencing means is engaged by language tasks drawing on these skills. There is a general trend for activation to follow the pattern of hemispheric dominance (e.g., in patients with left hemisphere language dominance, activation is more prominent in the left hemisphere), although it can occur bilaterally. Such tasks include initiation or planning of speech. It is just anterior to what is typically termed the "supplementary motor area" (SMA). As with primary motor and sensory areas, regions of the body are organized in a homunculus within the SMA
Exner's area BA 6, 8, 9	Exner's area is located at the junction of Broca's areas 6, 8, and 9. This region is again best identified using axial structural and functional MRI. It lies both superior and posterior to Broca's area and anterior to the hand motor area in the premotor region (Exner, 1881). After finding the motor strip's "hand knob," Exner's area can typically be found as an island of functional activation in the middle frontal gyrus anterior to this	This region is integral to phoneme-grapheme conversion (Keller & Meister, 2014). Functionally it is associated with the cognitive aspect of writing and reading, while it does not seem to be involved in motor control in itself; it is likely involved in motor programming for this purpose (Matsuo et al., 2003). We have observed patients who can continue to write during direct stimulation of this region while incorrectly mapping phonology to orthography (e.g., writing cat as "kat")

BA Brodmann area (Reprinted Supplementary Material (2) from Benjamin, C., et al., "Presurgical language fMRI..." (2017); Creative Commons Attribution-Non-Commercial-NoDerivs License)

Written reports. Clinical fMRI can be reported in a range of ways, and general guidelines on reporting imaging are available (American College of Radiology, 2014). From a neuropsychological, statistical, and clinical perspective, key points may include the following:

- *The referral question* should be noted (e.g., "language lateralization," "laterality of Broca's area," "location of Wernicke's area relative to temporal tumor"). This is important as the analyst's expectations and goals will impact the language map and may result in over- or under-representation of language cortex in specific regions (see Benjamin et al., 2017). Note that fMRI is currently validated for lateralization but not for localization (cf. the referral to "localize Wernicke's area"). The results may be informative, however, in conjunction with methods validated for language localization (electrical stimulation mapping).
- *Clinical information impacting language organization:* A brief review of details that change the base rate for atypical language organization should be included. This might include handedness, age of pathology or seizure onset, and pathology location. Handedness may be quantified using the brief, free Edinburgh Handedness Inventory—Short Form (Veale, 2014).
- *Relevant cognitive data:* Other data that may indicate poor lateralization or atypical results include intellectual disability, reading disability, and language impairment, as well as patient engagement and anxiety level.
- *Analysis quality:* A statement on the tasks completed, language used, data quality, and patient engagement and accuracy (if judged to impact findings).
- *Results:* A simple, clear statement of the findings. This can include statements of overall dominance or dominance by language region as relevant for the patient. (see Berl and colleagues (2014) for a discussion of patterns of dominance through Broca's and Wernicke's areas).
- *Limitations:* A brief statement of limitations of the study and fMRI itself—notably, the fact that fMRI is lateralizing, but not localizing. It is essential these be conveyed simply. Over-emphasizing a study's limitations renders a study useless to the referring clinician (the result will not be relied on), while under-emphasizing them can lead to the data being incorrectly used for localization or potentially (if the scan is invalid) for lateralization. As protocols will often not show all known language areas, this point can be critical to note. If areas of the map are blank due to artifact, it can be useful to include an image showing the mask overlaid on a structural image to indicate areas where data exist.

An example of such a report is provided in Appendix D.

10.6 Conclusion

Clinical fMRI requires a broad body of knowledge that encompasses the fundamentals, not only of cognitive design, MR imaging, and analysis, but also of epilepsy, the language system, and of how to interpret and communicate fMRI findings in a

clinically meaningful manner. This chapter has provided a survey of these issues and, we hope, directed you to further readings—and ideally software—that you can use to expand your knowledge of this invaluable clinical tool.

Acknowledgments This work was supported in part by an American Academy of Neurology Clinical Research Training Scheme award (2018; Benjamin).

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Chapter 11
Lesion-Symptom Mapping in Speech and Language Disorders: A Translational Perspective

Georgios P. D. Argyropoulos

Abbreviations

CT	Computed tomography
fMRI	Functional magnetic resonance imaging
LSM	Lesion-symptom mapping
MRI	Magnetic resonance imaging
NPM	Non-parametric mapping
PLORAS	Predict language outcome and recovery after stroke
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VLBM	Voxel-based lesion-behavior mapping
VLSM	Voxel-based lesion-symptom mapping

11.1 The Significance of Lesion-Symptom Mapping in Speech and Language Disorders

The overarching goal of lesion-symptom mapping (LSM) studies is the generation of inferences on the neuroanatomy of functions (or processes supporting these functions) of interest (e.g., sensorimotor, cognitive, affective) by investigating relationships between damage to different brain regions and the resulting behavioral deficits. LSM studies provide a unique bridge between basic and clinical neuroscientific research, with their findings holding the potential for translation into improved patient care by guiding prognosis and treatment (Vaidya, Pujara, Petrides, Murray, & Fellows, 2019).

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3_11

LSM is the primary tool employed to draw inferences on the causality of brain relationships with speech and language:

1. Manipulations of brain activity in non-human primates are often used to test causal predictions about relationships between brain activity and symptoms in neurological and psychiatric populations (Vaidya et al., 2019). However, a fundamental issue with speech and language is that, unlike other functional domains (e.g., episodic memory, short-term/working memory, and executive function), manipulation of brain activity in non-human primates cannot be used to directly assess such relationships, given the uniqueness of speech and language to the human species.
2. Likewise, in humans, modern brain stimulation techniques, despite their substantial advantages over patient studies (Argyropoulos, 2015), may still be limited by several factors. For instance, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) induce transient alterations of brain function that may also help establish a causal relationship between brain anatomy and behavior. Nevertheless, they remain limited by the restricted extent and our currently little understanding of their effects [see Pustina, Avants, Faseyitan, Medaglia, & Branch Coslett, 2018 for discussion].
3. Finally, unlike correlations between behavior and activation in functional neuroimaging, LSM provides evidence for causal relationships between lesions and symptoms. Thus, LSM arguably remains the most crucial and prevalent method for studying causal relationships between brain damage and speech and language deficits.

11.2 Historical Background: Postmortem Analyses

In the speech and language domain, the origins of LSM are traditionally traced back to the origins of modern aphasiology in the late nineteenth century, primarily with the work by Broca (1861) and Wernicke (1874). Broca was clearly not the first to identify relationships between speech/language impairment and brain lesions: there has been recognition that the early history of aphasiology can be traced back to even before the Hippocratic writings (c. 400 BC), as early as c. 1700 BC (Benton & Joynt, 1960; Prins & Bastiaanse, 2006). Moreover, the early nineteenth-century Paris, especially since Gall's emigration to France in 1806 and the broad acceptance of phrenology, had become a beacon for early LSM studies. For instance, Bouillaud (1825) described a series of patients with speech impairment who, upon autopsy, were revealed to have damage in anterior portions of the brain [see Luzzatti & Whitaker, 2001 for discussion]. Before the advent of modern neuroimaging, these early studies de facto relied on the posthumous autopsy of brain damage in cases of documented speech and language deficits. Nevertheless, this work formed the foundations not only for understanding the neural substrates of language but also for a scientific approach for addressing a broad range of brain-behavior questions

(Baldo, Wilson, & Dronkers, 2012), often referred to in the recent literature as the human "lesion method" (Rorden & Karnath, 2004).

Broca (1861, 1865), in particular, suggested that lesions in anterior portions of the left hemisphere were most critical for producing such difficulties with articulation. "Broca's area," the area associated with speech production, has since been defined as the pars opercularis (corresponding to Brodmann area 44) and the pars triangularis of the inferior frontal gyrus (corresponding to Brodmann area 45). Wernicke (1874) described a left posterior region for processing sensory aspects of language related to the auditory word form. "Wernicke's area," the area associated with comprehending speech, is traditionally defined as the posterior part of Brodmann area 22 which encircles the auditory cortex on the Sylvian fissure near the junction between the temporal and parietal lobes, although its precise location remains controversial [see discussions in Mesulam, Thompson, Weintraub, & Rogalski, 2015 and Wang et al., 2015].

11.3 In Vivo Imaging and the Lesion Overlap Approach

The development of computed tomography (CT) scanning in the 1970s and the expanded use of magnetic resonance imaging (MRI) in the 1980s enabled detailed LSM analyses of speech and language deficits on the living brains of groups of patients (Baldo, Wilson, & Dronkers, 2012). Importantly, they have helped us re-evaluate the relationships between brain lesions and speech/language deficits posited in the nineteenth century, especially with respect to Broca's and Wernicke's areas. Several findings have highlighted the oversimplified nature of such relationships—for instance, (1) damage to these areas may not always impair language function (Kreisler et al., 2000; Mohr et al., 1978); (2) speech comprehension and production deficits could be triggered by lesions in several different areas, since performance in any given language task (e.g., naming) relies on the integrity of several cognitive processes (from access to conceptual knowledge to motor coordination of speech articulators), which may be supported by multiple brain regions and networks thereof (Hillis, 2007; Newhart, Ken, Kleinman, Heidler-Gary, & Hillis, 2007); and (3) lesions in Broca's original patients have been shown to extend to multiple gray and white matter structures far beyond the posterior portions of the left inferior frontal gyrus (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007; Signoret, Castaigne, Lhermitte, Abelanet, & Lavorel, 1984).

Originally, two LSM approaches were commonly used: (1) patients were grouped on the basis of lesion site [e.g., frontal vs. temporal, anterior vs. posterior (Mazzocchi & Vignolo, 1979; Risse, Rubens, & Jordan, 1984)] with comparisons conducted among patient groups and/or against a group of healthy controls on tests assessing the symptoms of interest [as in other domains, including working memory and attention (e.g., Chao & Knight, 1998; Friedrich, Egly, Rafal, & Beck, 1998) and (2) patients were classified according to taxonomic criteria, irrespective of lesion localization (e.g., chronic/acute Broca's/Wernicke's/global/anomic aphasia), and a

common lesion site for patients belonging to the different groups was determined, based on lesion overlap (e.g., Kertesz, Harlock, & Coates, 1979). For instance, two of the earliest applications of this approach to disorders of spoken language understanding (Kertesz, Lesk, & McCabe, 1977; Naeser & Hayward, 1978) demonstrated consistent involvement of the left superior temporal gyrus for patients with Wernicke's aphasia.

In the 1990s, this lesion overlap method was extended and refined to address the lesions associated, not only with clinical syndromes in toto but also with specific deficits (Price, Seghier, & Leff, 2010). For instance, in a series of 25 stroke patients, apraxia of speech was associated with damage in the left precentral gyrus of the insula. In the form of a double dissociation, a complementary lesion overlay was provided for 19 patients lacking the deficit in question, in whom this region was completely spared (Dronkers, 1996). This was a methodologically fundamental improvement within the context of the lesion overlay approach: simple overlay plots for patients presenting with a certain deficit may be misleading, since the regions often highlighted may in fact reflect increased vulnerability of certain regions to injury (e.g., because of their vasculature), rather than a causal relationship with the disorder of interest. A group of control patients who do not present with the deficit of interest is therefore considered to be indispensable for valid anatomical conclusions (Rorden & Karnath, 2004).

Despite their critical contribution in advancing our understanding of the brain basis of speech and language, these LSM approaches were also limited in several regards. For instance:

1. Patients were separated on the basis of binary attributes, such as syndrome labels (e.g., patients with Wernicke's aphasia vs. those without), thus preventing the adoption of more precise quantitative measures (e.g., patients with more or less pronounced deficits in understanding language). This approach entailed grouping together a range of patients with possibly quite distinct clinical syndromes, e.g., Broca's patients capable of generating little more than repetitive utterances were assigned to the same patient group as those presenting with only slight agrammatism.
2. In other cases, identifying patients on the basis of syndrome labels involved the selection of "pure" cases of taxonomies, and the concomitant loss of data from several cases that did not present with the prototypical profiles of such categorizations.
3. The anatomical boundaries that were used to divide patients into groups (e.g., anterior vs. posterior) were often arbitrary, without necessarily reflecting distinctions of significance for the investigation of a particular speech or language deficit (Baldo, Wilson, & Dronkers, 2012).
4. Equally arbitrary in these approaches may be the definition of "impairment": a patient group is often dichotomized into "unimpaired" and "impaired" subgroups, in order to capitalize on the possibility of identifying a group of control patients. In these approaches, cut-off scores are often arbitrarily identified, with great variability across studies: these can be derived from data-driven

(e.g., *k*-means cluster) analyses, a median split, or based on the fifth percentile ($z \leq -1.67$) of the population-based norms of a standardized neuropsychological test; alternatively, identifying patients with unambiguously normal and unambiguously impaired performance in a certain test may entail data loss of cases scoring in the middle.

11.4 Voxel-Based Approaches

Since that time, the lesion overlay method for the analysis of this type of data has been superseded by a technique commonly referred to as "voxel-based lesion-symptom mapping" [VLSM; Bates et al. (2003)]. VLSM employs lesion status at each voxel as a grouping variable, subsequently comparing (*t*-test) the lesioned and non-lesioned groups on a given dependent measure (quantifying the severity of the symptom investigated), which in turn produces an effect-size statistic for each voxel. As such, VLSM employs continuous behavioral and lesion information (Bates et al., 2003), avoiding the data loss associated with the often arbitrary dichotomization of patients into groups on the basis of lesion location or diagnosis/behavioral performance, thus increasing sensitivity and power (however, VLSM also caters for binary comparisons using binomial tests). Moreover, this approach allows for statistical rigor: to define a "significant" voxel, a statistical threshold cut-off is often determined based on permutation testing (e.g., $n = 1000$), whereby patients' scores are randomly reassigned across the voxels 1000 times, and, for each permutated dataset, statistics are re-run, and the top 5% of *t*-values are calculated (corresponding to family-wise error correction; for a discussion of other methods for correction for multiple comparisons, see Baldo, Wilson, and Dronkers (2012); see also Fig. 11.1).

In the first large-scale application of VLSM, Bates et al. (2003) investigated the neural correlates of auditory language comprehension in 101 patients with chronic aphasia following left hemisphere stroke. The resulting map disclosed that damage to the left posterior middle temporal gyrus was most predictive of comprehension deficits, a more ventral lesion localization than might have been expected based on traditional models. VLSM has thus helped uncover additional areas that are critical for speech and language processes beyond the traditional areas of Broca and Wernicke, since it does not rely on a priori regions of interest or specific language diagnoses. Since then, VLSM has been broadly used to investigate causal relationships between focal lesions and impaired performance in tasks involving language comprehension (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004), grammaticality judgments (Wilson & Saygin, 2004), conversational speech production (Borovsky, Saygin, Bates, & Dronkers, 2007), verbal fluency (Baldo, Schwartz, Wilkins, & Dronkers, 2006), and picture naming (Baldo, Arévalo, Patterson, & Dronkers, 2013).

This voxel-by-voxel analysis employed by VLSM has substantially enhanced the spatial precision of lesion-symptom relationships. Moreover, it has enhanced the

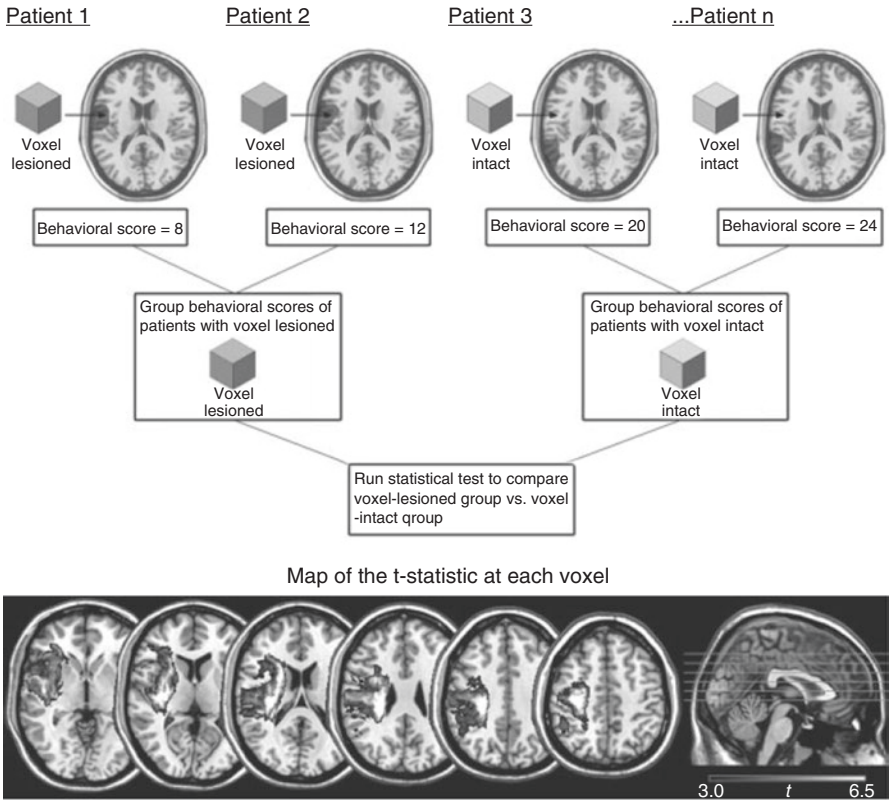

Fig. 11.1 Typical steps of a VLSM analysis. Patients' lesions are first reconstructed onto a standardized template (e.g., MNI) and are introduced in the analysis (top). A *t*-test is then conducted for every voxel, comparing patients' behavioral scores (e.g., in tasks of language comprehension or production) with and without a lesion in that voxel. The resulting statistics at every voxel are subsequently color-coded and visualized (bottom). Statistical corrections may then be applied to correct for the number of comparisons conducted, so that only voxels meeting a pre-specified significance level are displayed [Figure adapted from (Baldo, Wilson, & Dronkers, 2012), p. 585, with permission (Copyright © 1969, John Wiley and Sons)]

comparability between the results of LSM and those of functional neuroimaging studies: as in the latter, patients' lesions are reconstructed in a standard space (e.g., MNI), and voxels reflecting significant lesion-symptom relationships are highlighted, with color-coded maps reflecting statistics of relevance. This enables the combination of insight into the neural organization of speech and language. Similar techniques have since been implemented, such as non-parametric mapping (NPM) (Rorden, Karnath, & Bonilha, 2007), a program included with MRIcron for LSM analysis, and Brainvox (Frank, Damasio, & Grabowski, 1997). Characteristically, Rorden et al. (2007) have introduced the non-parametric rank order Brunner-Munzel test (Brunner & Munzel, 2000) in their software (NPM) as a complementary alternative to parametric tests for LSM. NPM thus enables voxel-based analyses using

non-parametric statistics that do not make the parametric *t*-test assumptions regarding the distribution of the behavioral data that VLSM involves, since the distribution of behavioral scores from brain-damaged subjects may often violate the assumptions of normality. LSM analyses conducted on a voxel-by-voxel basis, such as VLSM, NPM, and Brainvox, are often referred to as "voxel-based lesion-behavior mapping" (VLBM) methods [e.g., (Karnath, Sperber, & Rorden, 2019)].

Similar approaches involving continuous behavioral measures have been adopted using voxel-based morphometry (VBM) (Ashburner & Friston, 2000). VBM estimates the relative gray and white matter concentrations for every voxel throughout the brain. Once each brain has been segmented into gray and white matter maps, we can analyze whether different groups of people (patients vs. demographically matched healthy controls) have different concentrations or volumes of these tissues in a voxel-wise fashion across the whole brain. VBM is ideal for measuring subtle differences in gray and white matter. Within the context of LSM studies, VBM is optimized for detecting gray matter volume reduction in degenerative conditions, such as Alzheimer's disease and semantic dementia (Mummery et al., 2000). For instance, Amici et al. (2007) studied the performance of 51 patients with neurodegenerative disease presenting with predominant speech and language symptoms on four different language tests: (1) confrontation naming, (2) repetition, (3) sentence comprehension, and (4) language fluency in spontaneous speech production. The study identified positive correlations between (1) naming and the bilateral temporal lobes; (2) sentence repetition and the left posterior portion of the superior temporal gyrus; (3) sentence comprehension and the left dorsal middle and inferior frontal gyri; and (4) fluency and the left ventral middle and inferior frontal gyri (Amici et al., 2007). While VBM is also commonly employed in conditions of focal damage [e.g., hippocampal atrophy due to autoimmune limbic encephalitis, as in Argyropoulos et al., 2019], the automated tissue segmentation and image registration routines required in the VBM processing pipeline may not be ideal in the presence of more profound focal lesions (Rudrauf et al., 2008), such as stroke or damage following tumor resection.

11.5 Translational Potential

Beyond aiding the understanding of normal brain function and uncovering the neural foundations of speech and language, LSM studies afford us substantial translational insight. In principle, information disclosed by modern LSM studies could be used to identify potential loci for neurosurgical intervention or noninvasive brain stimulation (e.g., TMS, tDCS) (Vaidya et al., 2019). Moreover, we can identify key structures, the integrity of which may determine the extent of possible recovery from language impairment. For instance, Campana and colleagues have showed that beneficial effects after anodal tDCS over the left inferior frontal gyrus depended on the anatomical integrity of different left hemispheric structures and, in particular, the basal ganglia, the insula, and the superior and inferior longitudinal fasciculi (Campana, Caltagirone,

& Marangolo, 2015). Furthermore, LSM studies on the negative sequelae of surgical excision of tumors on speech and language may identify critical structures in which surgical damage should be minimized [e.g., (McEvoy et al., 2016)].

LSM also enables the investigation of interactions between lesion location and medication with respect to recovery of language functions. In a report of two longitudinal studies, Hillis et al. (2018) identified two factors at onset that were associated with recovery of naming in the first 6 months post-stroke: (1) damage to left posterior superior temporal gyrus and/or superior longitudinal fasciculus/arcuate fasciculus and (2) selective serotonin reuptake inhibitor (SSRI) use. Preservation of these structures and use of SSRIs were associated with naming recovery, such that patients with damage to these areas showed better outcome if they took SSRIs for 3 months post-stroke. These associations were independent of lesion volume, time since stroke, and depression. While such preliminary findings are often based on small numbers of patients, they hold substantial translational potential and require replication in larger randomized controlled trials.

Importantly, the insight provided by LSM methods can be used to inform patients, carers, and therapists on the probability, the possible extent, and the anticipated timeframe of speech and language recovery, as well as to identify the therapeutic interventions that may accelerate this. Providing such information would not presuppose the adoption of a theoretical model of the implementation of language in the brain, i.e., a "model-led" approach. Instead, the information would be provided to patients and carers by the clinician on the basis of data from other patients with a similar lesion and symptom profile (a "data-led" approach; Price et al., 2010). The implementation of such an approach is not a hypothetical scenario. Indeed, new data-led systems that predict language outcome on the basis of lesion site have begun to emerge over the last couple of decades. A characteristic example is the "Predict Language Outcome and Recovery After Stroke" (PLORAS) study (Price et al., 2010). This large, multi-site study in the UK had involved brain imaging and behavioral data from 330 patients on the database by the end of 2009 (Price et al., 2010) and had already recruited 750 patients as of early 2015 (Seghier et al., 2016). One of the fundamental goals of these endeavors is to be translated to a larger scale and become available over the web, with data becoming available to the broader research community. This study thus offers the potential of setting up a data-led system for predicting language outcome and recovery after stroke and involves (1) a database of structural MRI and (2) behavior from standardized neuropsychological assessments in several hundreds of stroke patients, as well as (3) software to measure and compare lesions in different patients. These analyses are expected to enable the estimation of the expected language outcome for each new patient by (1) conducting a high-resolution MRI scan for the new patient; (2) comparing their lesion site with that of all the other patients in the database; (3) selecting patients in the database who are most similar to the new patient, in terms of their lesions and presenting symptoms; and (4) extracting the language scores, over time, for these similar cases of patients on different aspects of speech and language functions (e.g., articulation, comprehension, reading, etc.). This procedure would provide information on the percent of patients with the same lesion that had made a full recovery within a particular timeframe (Price et al., 2010).

11.6 Challenges and Future Directions

Despite their substantial advantages over previous LSM methods and their translational potential, VLBM studies are still faced with a number of challenges. If not overcome, these challenges may compromise the predictions given to patients and carers on the functional outcome associated with certain lesions, the likelihood and extent of anticipated recovery, and the interventions associated with the best outcome in each lesion profile (Price, Hope, & Seghier, 2017). Below I outline a select number of those:

11.6.1 Statistical Power

While VLBM enables the identification of lesion effects on function with much greater precision than earlier methods, it requires substantially large sample sizes for several interconnected reasons. Patient pools do not include a randomized set of lesions that cover the entire brain (Baldo, Wilson, & Dronkers, 2012). In most studies, the lesions do not even span across the entire structure of interest, preventing the assessment of the impact of lesions involving all voxels of that structure. In particular, VLBM analyses are restricted to those voxels that involve a reasonable number of patients with and without a lesion. In other words, brain voxels with a lesion overlap below an arbitrarily defined minimum number of cases are excluded from the analysis, hence avoiding markedly unbalanced comparisons (e.g., 1 lesioned patient versus 90 non-lesioned patients). For example, brain damage due to stroke is more common in some vascular territories than others, and, as a result, certain regions, such as the left perisylvian region, are often overrepresented due to the frequency and severity of strokes in the middle cerebral artery territory. On the contrary, damage in other regions that represent less common lesion locations in the patient groups of interest (e.g., infarcts associated with speech and language deficits) cannot be assessed with respect to its effects on speech and language outcomes due to an insufficient number of cases with lesions in those areas. It is thus important to determine the capacity of each VLBM study to detect differences in those regions that are inadequately represented, in order to avoid the misinterpretation of null findings, since the null effects may be attributed to a reduced power profile in such regions. Predictions should instead be confined to brain regions with sufficient power. Ideally, power analyses should be conducted prior to VLBM in order to determine the capacity of the analysis to detect statistical differences across the different voxels/brain regions (Kimberg, Coslett, & Schwartz, 2007). For instance, a map can be generated in order to determine the distribution of statistical power for a study's sample, based on a large effect size (e.g., 0.8) and an alpha of 0.5 (Kimberg et al., 2007). It is important that sufficient power is detected in regions of greatest interest for each study (e.g., exceeding a minimum threshold of 0.8) (e.g., Baldo, Katseff, & Dronkers, 2012). This means that the predictive validity of a database like PLORAS will be higher on frequently occurring than rare lesions (Price et al., 2010).

Indeed, underpowered LSM studies may lead to unreliable results. Characteristically, several underpowered studies have made inappropriate use of the Brunner-Munzel test implemented in the NPM (Rorden et al., 2007). These studies have involved small patient cohorts such that most examined voxels do not meet the necessary criteria (e.g., analyzing voxels with fewer than ten subjects in either the lesion or no lesion group), and inappropriate usage of the Brunner-Munzel test has been shown to involve large type I errors (Medina, Kimberg, Chatterjee, & Coslett, 2010).

Furthermore, studies need to account for the several sources of inter-patient variability in behavioral performance, in order to explain inconsistencies across patients with similar lesions. These pertain to multiple demographic, clinical, and neuropsychological factors, such as age, handedness, gender, education, ethnicity, social and cultural background, and multi-lingual experience, but also time post-lesion, comorbidity, vision and hearing, attention, working memory, premorbid learning ability, motivation to relearn, as well as the administration and extent of speech therapy and pharmacological interventions (Price et al., 2010, 2017). Another such covariate of fundamental significance is that of lesion volume: an equipotentiality model would predict that impairments are a consequence of lesion volume, regardless of location; a locality model would predict that impairments stem from damage to a specific region (Karnath, Himmelbach, & Rorden, 2002). Maximizing the number of sources of inter-patient variability is expected to reveal consistent lesion-outcome relationships at least for some lesion sites (Price et al., 2017). The number of factors that can be reasonably added in the analysis as between-subjects covariates depends on the size of the patient group analyzed.

11.6.2 Preprocessing

Moreover, VLBM studies require the accurate delineation of the brain lesion, either manually or with automated means. Prior to the analysis, patients' lesions must be reconstructed and standardized into a common stereotaxic (e.g., MNI) space to allow for statistics across several subjects. T_1-weighted MRI scans are most appropriate when lesions are traced directly on to digital images. Lesion masks are recommended during the normalization process so that the lesion itself does not bias the transformation into normalized space (Brett, Leff, Rorden, & Ashburner, 2001). Automated segmentation algorithms have been developed, although it is still argued whether such programs are sufficiently accurate and preferable to a skilled rater (Kimberg et al., 2007). Moreover, the delineation of the lesion site as a three-dimensional volume needs to be conducted without losing information on the relative degree of damage in each part of the lesion. Given the difficulties in determining the exact border of a lesion, recommendations have been made for using probabilistic maps based on a range of scores (e.g., 0 for no lesion, 0.5 for possible lesion, and 1.0 for a certain lesion), with voxels along the lesion border being assigned a score of either 0 or 0.5 (Kimberg et al., 2007). The accuracy of VLBM studies is thus a function of the quality of preprocessing pipelines, but also image

resolution. Studies require T_1- and T_2-weighted structural MRIs at higher field strength and protocols enabling more precise spatial normalization, especially for certain structures, such as the deep cerebellar nuclei (Maderwald et al., 2012).

11.6.3 Network Abnormalities

Nevertheless, the accuracy in the delineation of a focal lesion and its spatial transformation into a standardized template do not suffice in quantifying the extent of damage involved. In particular, the power of traditional VLBM analyses is diminished in the presence of symptoms reflecting broader network dysfunction and diaschitic effects such that injuries to one area can cause dysfunction in remote, non-lesioned areas. For instance, cortical disconnection, i.e., the loss of white matter fibers supporting a cortical region apparently intact after remote focal damage (e.g., following a stroke or tumor excision), contributes to the severity of language impairment, and disconnection or diaschisis may lead to remote cortical dysfunction that can be functionally equivalent to direct cortical lesions. Importantly, post-stroke cortical deafferentation can be pervasive and invisible to conventional structural MRI such as T_1- or T_2-weighted images. Therefore, behaviorally relevant brain damage needs to be understood as a combination of cortical necrosis and disconnection.

Likewise, the plastic responses of the brain following a focal lesion may aid the brain in rapidly reconfiguring following damage. Some first evidence has supported the notion that spared alternative pathways have the capacity to sustain language processing following damage and that recovery from damage to one such component should depend on the integrity of the surviving system (Seghier, Lee, Schofield, Ellis, & Price, 2008). Although such reconfiguration is fundamental for recovery, it impedes the inferences on the premorbid function of the brain (Rorden & Karnath, 2004) and needs to be accounted for in generating individualized predictions on language outcome following lesions (Price et al., 2017). In certain types of lesions, this is of profound significance. For instance, in contrast to acute stroke, tumors that are eventually excised surgically (as in the case of posterior fossa tumors) develop slowly, with symptoms often progressing for long periods before diagnosis. This offers substantial time for the development of compensatory mechanisms, which are difficult to control (Timmann et al., 2009).

These network-wide abnormalities and plastic responses following focal lesions are problematic in the case of traditional LSM approaches, given their implicit assumptions that, after a focal lesion, regions remote from the lesion site continue to function in the same manner as before the lesion. Structural and functional abnormalities remote from the lesion should thus be considered in combination with VLBM. Characteristically, some studies have quantified the integrity of white matter pathways interconnecting the language network using DTI tractography, correlating pathway integrity with behavioral measures of interest, in order to determine whether reduced structural connectivity accounts for behavior above

and beyond the contribution of lesion location and/or total lesion volume (Ellmore et al., 2010; Harvey, Wei, Ellmore, Hamilton, & Schnur, 2013; Rudrauf, Mehta, & Grabowski, 2008).

One of the limitations, obviously, of such multi-modal neuroimaging protocols is that specialized brain scans are required for the collection of such data beyond the routine clinical scans. This approach is thus harder to implement when symptoms are transient or rare or when (prolonged) brain scanning is difficult. With this in mind, a novel approach has been presented and adopted over the last few years, whereby (1) the three-dimensional volume of a lesion is transferred (e.g., using conventional structural MRI) onto a reference brain; (2) the intrinsic functional connectivity of the lesion volume with the rest of the brain is assessed using normative connectome data; and (3) overlapping lesion-associated networks are used to identify regions common to a clinical syndrome. This method has been tested in peduncular hallucinosis, and its generalizability has been also assessed in another three syndromes, one of which was subcortical expressive aphasia. In each syndrome, heterogeneous lesions that themselves had little overlap showed significant network overlap in cortical areas previously implicated in symptom expression (Boes et al., 2015). The combination of LSM analyses with networks of functional neuroimaging maps of interrelated regions ("the connectome") has been held to offer a novel way of understanding neurologic function and disease, including speech and language disorders (Fox, 2018).

11.6.4 Limitations of Mass-Univariate Approaches

Traditionally, most of the VLBM studies have involved the independent analysis of each voxel, adopting what is called the "massively univariate" or "mass-univariate approach." Over the last two decades, this approach has been shown to suffer from substantial limitations that may severely compromise its capacity to map functions onto specific brain areas. As mentioned above, neighboring voxels are frequently correlated with each other, given the non-random nature of lesions that follow the vascular anatomy. As a result, effects located in voxels with a balanced (e.g., 50%:50%) lesion ratio produce higher statistical scores and are more likely to be detected, whereas effects located in voxels with a lower lesion ratio (e.g., 10%:90%) produce lower statistical scores and are less likely to be detected. Even more worryingly, the discrepancy between t-scores becomes larger with the increase of sample size (Pustina et al., 2018). Simulation approaches based on large patient samples with brain lesions have shown a bias within the lesion-deficit maps, displacing inferred critical regions from their true anatomical locations by approximately 16 mm toward areas of greater general lesion affection (Inoue, Madhyastha, Rudrauf, Mehta, & Grabowski, 2014; Mah, Husain, Rees, & Nachev, 2014). Such displacement may lead to irreproducible results and interpretation errors, even in the case of studies employing sizable datasets with adequate voxel-wise power [see Pustina et al., 2018 for elaborate discussion].

Addressing those limitations, the recently developed multivariate methods adopt a different approach to assessing the localization of function. Whereas univariate analyses test for the strongest associations between impairment and damage, multivariate approaches test which patterns of damage cause similar impairment and may be more sensitive than univariate approaches in identifying the lesion-symptom relations. In other words, multivariate approaches no longer rely on the assumption of independent contributions of brain regions, but rather quantify the joint contribution of multiple brain regions in determining behavior (Pustina et al., 2018; Smith, Clithero, Rorden, & Karnath, 2013; Zhang, Kimberg, Coslett, Schwartz, & Wang, 2014). Nevertheless, improvements in univariate VLBM methods that involve taking into account inter-voxel relations in patients' anatomical data (along with lesion size) may also help address the misplacement bias (Sperber & Karnath, 2017).

Evidently, overcoming each of the above challenges requires substantial resources: the patient sample size is obviously a function of the difficulty and expense of recruiting, scanning, and testing patients with diverse lesion sites and iterating this process at different time points. Likewise, the computing power, expertise, and labor required to analyze, integrate, store, and preprocess often multimodal brain imaging data from multiple patients and conduct sophisticated analyses including patients' behavioral data can only be secured with sufficient resources and collaboration [see Price et al., 2010 for discussion].

11.7 Conclusion

Modern LSM studies afford us substantial translational insight for improved patient care, with respect to both symptom prediction and rehabilitation. Overcoming several limitations involved in those studies requires the creation of large databases of behavioral and brain imaging datasets, which in turn relies on the availability of research funding and the possibility of large-scale multicenter collaborations.

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Appendix A: tDCS Studies in a Healthy Population

Table A1 Studies investigating the impact of tDCS on language in healthy populations—demographic information

Article	Language	Participants	Mean age (SD)	Educational level (SD)
Iyer et al. (2005)	English	30 RH (17F; 13M)	38.6 years (12.9 years)	16.2 years (2.6 years)
Sparing et al. (2008)	German	15 RH (5F; 10M)	26.9 years (3.7 years)	n.r.
Cerruti and Schlaug (2009)	English	18 RH (13F; 5M)	25.5 years (2.6 years)	n.r.
de Vries et al. (2010)	English	44 RH (19F; 25M); 10 RH (5F; 5M)	22.6 years (2.1 years); 23.7 years (2.4 years)	15.6 years (1.5 years); 15.3 years (1.3 years)
Fertonani et al. (2010)	Italian	12 RH (8F; 4M); 12RH (6F; 6M)	24.1 years (3.7 years); 21.8 years (1.0 years)	n.r.
Liuzzi et al. (2010)	German	30 RH (18F; 12M)	24.9 years (0.6 years)	>12 years
Ross, McCoy, Wolk, Coslett, and Olson (2010)	English	15 RH (11F; 4M)	25.6 years; range 19–37 years	n.r.
Ross, McCoy, Coslett, Olson, and Wolk (2011)	English	14 RH (7F; 7M)	65 years; range 55–69 years	n.r.
Cattaneo et al. (2011)	Italian	10 RH (6F; 4M)	23.6 years (3.2 years)	Undergraduate students
Fiori et al. (2011)	Italian	10 RH (3F; 7M)	55 years (7.9 years)	14 years (2.4 years)
Holland et al. (2011)	English	10 RH (3F; 7M)	69 years; range 62–74 years	n.r.
Wirth et al. (2011)	German	20 RH (10F; 10M)	23.5 years (3.7 years)	13 years (1.6 years)

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Table A1 (continued)

Article	Language	Participants	Mean age (SD)	Educational level (SD)
Jeon and Han (2012)	Korean	32 RH (20F; 12M)	37.3 years (13.0 years)	≥12 years
Meinzer, Antonenko et al. (2012)	German	20 RH (10F; 10M)	26.7 years (3.8 years)	n.r.
Pisoni et al. (2012)	Italian	12 RH (10F; 2M)	22.4 years (2.94 years)	14.7 years (2.1 years)
Vannorsdall et al. (2012)	English	24 RH (13F; 11M)	35.7 years (10.1 years)	>12 years
Meinzer et al. (2013)	German	20 RH (10F; 10M); 20 RH (10F; 10M)	68.0 years (5.7 years); 26.4 years (3.4 years)	15.9 years (1.2 years); 15.6 years (1.9 years)
Penolazzi et al. (2013)	Italian	90 RH (55F; 35M)	21.6 years (0.2 years)	University students
Peretz and Lavidor (2013)	Hebrew	17 RH (11F; 6M)	24.4 years (3.0 years)	Students
Fertonani et al. (2014)	Italian	20 RH (10F; 10M)	66.5 years (5.5 years)	10.5 years
Henseler, Mädebach, Kotz, and Jescheniak (2014)	German	36 RH (n.r.)	26.2 years (3.0 years)	n.r.
Meinzer et al. (2014)	German	18 RH (9F; 8M)	68.4 years (5.2 years)	n.r.
Ehlis et al. (2016)	German	23 RH (14F; 9M); 23 RH (11F; 12M)	32.1 years (10.5 years); 24.3 years (2.4 years)	n.r.
Manuel and Schnider (2016)	French	13 RH (6F; 7M); 13 RH (9F; 4M)	24 years (5 years); 23 years (3 years)	n.r.
Meinzer, Yetim, McMahon, and de Zubicaray (2016)	English	24 RH (14F; 10M)	24.7 years (4.6 years)	n.r.
Habich et al. (2017)	German	43 RH (22F; 21M	24.8 years (2.9 years)	>12 years
Vannorsdall et al. (2016)	English	14 RH (8F; 6M)	22.3 years (2.4 years)	15.1 years (1.9 years)
Westwood, Olson, Miall, Nappo, and Romani (2017)	English	18 RH (10F; 8M); 20 RH (12F; 8M); 18 RH (13F; 5M)	21 years (2.8 years); 21 years (2.9 years); 19.8 years (2.8 years)	Undergraduate students
Binney et al. (2018)	English	23 RH, 1 AD (20F; 4M)	21.2 years; range 18–30 years	n.r.

AD ambidextrous, *F* female, *M* male, *n.r.* not reported, *RH* right-handed, *SD* standard deviation

Table A2 Studies investigating the impact of tDCS on language in healthy populations—methodological information

Article	Active electrode location (size)	Reference electrode location (size)	Intensity	Type	No. of sessions (duration)
Iyer et al. (2005)	F3 (25 cm^2)	R supraorbital region (25 cm^2)	2 mA	a/c/s	1 session (20 min); 3 groups of 10 people
Sparing et al. (2008)	Wernicke: CP5 (35 cm^2)	CP6 (35 cm^2)	2 mA	a/c/s	1 session (7 min) per type, 4-h interval
Cerruti and Schlaug (2009)	L DLPFC (16 cm^2)	R supraorbital region (30 cm^2)	1 mA	a/c/s	1 session (20 min) per type, 30-min interval
de Vries et al. (2010)	Broca: L BA 44/45 (35 cm^2)	R supraorbital region	1 mA	a/s	1 session (20 min)
Fertonani et al. (2010)	L DLPFC (35 cm^2)	R shoulder (35 cm^2)	2 mA	a/c/s	1 session (8 min); 1 session (10 min)
Liuzzi et al. (2010)	L M1 (25 cm^2)	R supraorbital region (25 cm^2)	1 mA	a/c/s	4 daily sessions (20 min)
Ross et al. (2010)	T3; T4 (35 cm^2)	Contralateral cheek (35 cm^2)	1.5 mA	a/s	1 session (15 min) per montage and type; 1-day interval
Ross et al. (2011)	T3; T4 (35 cm^2)	Contralateral cheek (35 cm^2)	1.5 mA	a/s	1 session (15 min) per montage and type, 1-day interval
Cattaneo et al. (2011)	Broca	R supraorbital region	2 mA	a/s	1 session (20 min) per type, interval n.r.
Fiori et al. (2011)	L STG: CP5	R occipito-parietal region	1 mA	a/c/s	1 session (20 min) per type, 6-day interval
Holland et al. (2011)	L IFG: FC5 (35 cm^2)	R frontopolar cortex (35 cm^2)	2 mA	a/s	2 sessions (20 min) a/s and s/a, 5–7 day interval
Wirth et al. (2011)	L DLPFC (35 cm^2)	R shoulder (49 cm^2)	1.5 mA	a/s	1 session (30 min)
Jeon and Han (2012)	L DLPFC, F3; R DLPFC, F4 (35 cm^2)	Contralateral supraorbital area (35 cm^2)	1 mA	a/s	1 session (20 min)
Meinzer, Antonenko et al. (2012)	Broca: L BA44/45 (35 cm^2)	R supra orbital region (100 cm^2)	1 mA	a/s	1 session (20 min) per type, 1-week interval
Pisoni et al. (2012)	L STG (35 cm^2)	R supraorbital region (35 cm^2)	2 mA	a/s	1 session (20 min) per type, 1-weeks interval
Vannorsdall et al. (2012)	F3 (27.04 cm^2)	Cz (27.04 cm^2)	1 mA	a/c/s	1 session (30 min) per type, 90-min interval

(continued)

Table A2 (continued)

Article	Active electrode location (size)	Reference electrode location (size)	Intensity	Type	No. of sessions (duration)
Meinzer et al. (2013)	L IFG (35 cm^2)	R supraorbital region (100 cm^2)	1 mA	a/s	1 session (30 min)
Penolazzi et al. (2013)	T3-Fz × F7-Cz; T3-F3 × F7-C3; T3-F3 × F7-C3; T3-F3 × F7-C3 (35 cm^2)	R supraorbital area (35 cm^2); R supraorbital area (35 cm^2); T4-F4 × F8-C4 (35 cm^2); R supraorbital area (100 cm^2)	2 mA	a/s	1 session (20 min)
Peretz and Lavidor (2013)	Wernicke (35 cm^2)	R orbitofrontal cortex (35 cm^2)	1 mA	a/c/s	1 session (10 min) per type, 1-week interval
Fertonani et al. (2014)	L DLPFC (35 cm^2)	R shoulder (35 cm^2)	2 mA	a/s	1 session (10 min)
Henseler et al. (2014)	L IFG; L pMTG (25 cm^2)	R supraorbital region (50 cm^2)	2 mA	a/s	1 session (25 min) per montage, 1-week interval
Meinzer et al. (2014)	L M1 (35 cm^2)	R supraorbital region (100 cm^2)	1 mA	a/s	1 session (20 min) per type
Ehlis et al. (2016)	Broca: C3 × F3 × F7 (35 cm^2)	R supraorbital region (35 cm^2)	1 mA	a/c/s	1 session (20 min) per type (a/s or c/s), 48-h interval
Manuel and Schnider (2016)	L PPC, P3; R PPC, P4; L DLPFC, F3; R DLPFC, F4 (35 cm^2)	Contralateral supraorbital region (35 cm^2)	1 mA	a/s	1 session (24 min) per montage and type (L, R, s), 1-week interval
Meinzer, Yetim et al. (2016)	L IFG; L PTC (35 cm^2)	R supraorbital cortex (100 cm^2)	1 mA	a/s	1 session (20 min) per montage and type (IFG, PTC, s), 1-week interval
Habich et al. (2017)	L DLPFC: F3 (35 cm^2)	R supraorbital region (35 cm^2)	1 mA	a/s	1 session (20 min)
Vannorsdall et al. (2016)	L DLPFC (25 cm^2)	Vertex: Cz (25 cm^2)	1 mA	a/c	1 session (30 min); 2 matched groups
Westwood et al. (2017)	L IFG, F7 (9 cm^2); L IFG, F7 (25 cm^2); L pMTG (25 cm^2)	R supraorbital area (35 cm^2); R supraorbital area (35 cm^2); R cheek (35 cm^2)	1 mA; 1.5 mA; 1.5 mA	a/s	1 session (15 min; 25 min; 25 min) per type (a/s), 1-week interval
Binney et al. (2018)	T3-T4; C3-C4; P3-P4 (2 × 5 cm^2)	Fpz; Fpz; Iz (35 cm^2)	2 mA	a/c	1 session (20 min) per montage, interval n.r.

a anodal; *BA* Brodmann area; *c* cathodal; *DLPFC* dorsolateral prefrontal cortex; *h* hour(s); *IFG* inferior frontal gyrus; *L* left; *mA* milliampere(s); *n.r.* not reported; *pMTG* posterior middle temporal gyrus; *R* right; *s* sham; *STG* superior temporal gyrus

Appendix B: tDCS Studies in Aphasic Patient Populations

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Table B1 Studies investigating the impact of tDCS on language in patient populations—demographic information

Article	Language	Patients' handedness (no. of F; no. of M)	Mean age (SD)	Mean level of education (SD)	Type of stroke	Time since stroke	Type of aphasia (*n*)	Lesion area cortex
Hesse et al. (2007)	English	10 n.r. (3F; 7M)	63.3 years; range 32–76 years	n.r.	iCVA	4–8 weeks po	Non-fluent aphasia	L MCA (10)
Monti et al. (2008)	Italian	8 RH (4F; 4M)	60.38 years (11.99 years)	10.62 years (1.72 years)	iCVA (7); hCVA (1)	24–96 months po	Non-fluent aphasia (BA 4, GA 4)	Frontal cortical or subcortical damage + possible damage to parietal and/or temporal areas
Baker et al. (2010)	English	10 n.r. (5F; 5M)	65.50 years (11.44 years)	14.00 years (2.31 years)	CVA	12–240 months po	Fluent (AA: 6); non-fluent (BA: 4)	LH damage
You, Kim, Chun, Jung, and Park (2011)	Korean	21 RH (9F; 12M)	Range 49–82 years	Range 6–16 years	iCVA	Subacute	Global aphasia	L MCA
Fiori et al. (2011)	Italian	3 RH (M)	45 years; 65 years; 74 years	18 years; 13 years; 13 years	iCVA	Chronic	Non-fluent aphasia	Supramarginal gyrus (2); STG (1)
Flöel et al. (2011)	German	12 RH (5F; 7M)	52.3 years; range 39–67 years	n.r.	iCVA	21–71 months po	Non-fluent aphasia	L frontal, temporal, parietal + occipital lesions; no lesion in RH
Fridriksson et al. (2011)	English	8 n.r. (n.r.)	68.13 years (10.40 years)	n.r.	CVA	10–150 months po	Fluent aphasia	L posterior (sub)cortex
Jung et al. (2011)	Korean	37 n.r. (11F; 26M)	>65 years (22); <65 years (15 years)	n.r.	iCVA (20), hCVA (16)	1 months po (13), 1–3 months po (24)	Fluent (10); non-fluent (26) aphasia	Broca's area, Wernicke's area, arcuate fasciculus, insula

Kang et al. (2011)	Korean	10 RH (2F; 8M)	61.9 years (2.7 years)	11.6 years (1.5 years)	iCVA	6–181 months po	Non-fluent (GA 3, BA 4, TMA 1), fluent (AA: 2) aphasia	R Broca's homologue area (F8)
Vines, Norton, and Schlaug (2011)	English (1 Russian-English)	6 RH (M)	56.2 years; range 31.3–80.9 years	n.r.	iCVA	15–120 months po	Non-fluent aphasia	L frontal lobe
Saidmanesh et al. (2012)	Persian	20 RH (8F; 12M)	55.93 years (2.4 years)	n.r.	CVA	60 months po	Non-fluent aphasia	Anteroposterior (9), posterior (11)
Cherney et al. (2013)	Cantonese	1 RH (M)	63 years	15 years	iCVA	204 months po	Non-fluent aphasia	n.r.
Fiori et al. (2013)	Italian	7 RH (2F; 5M)	58.4 years; range 44–71 years	11.1 years; range 5–18 years	iCVA	9–84 months po	Non-fluent aphasia	L hemispheric stroke
Lee et al. (2013)	Korean	11 n.r. (2F; 9M)	52.6 years (13.4 years)	n.r.	CVA	8–180 months po	Non-fluent (BA 4, TMA 2), fluent (AA: 5)	Inferior L MCA (9); L basal ganglia (2)
Marangolo, Fiori, Cipollari et al. (2013)	Italian	8 RH (4F; 4M)	range 37–68 years	Range 5–18 years	CVA	6–74 months po	Non-fluent aphasia	Cortical L fronto-temporo-parietal (6); L fronto-parietal(2)
Marangolo, Fiori, Di Paola et al. (2013)	Italian	7 RH (2F; 5M)	62.4 years; range 46–77 years	13.2 years; range 5–18 years	CVA	7–96 months po	Non-fluent aphasia	LH: frontal, parietal, temporal lobe + subcortical areas
Marangolo, Fiori, Calpagnano, et al. (2013)	Italian	12 RH (4F; 8M)	59.6 years; range 44–71 years	12.2 years; range 5–18 years	CVA	5–84 months po	Non-fluent aphasia	L subcortex (capsula extrema, claustrum, putamen)

(continued)

Table B1 (continued)

Article	Language	Patients' handedness (no. of F; no. of M)	Mean age (SD)	Mean level of education (SD)	Type of stroke	Time since stroke	Type of aphasia (*n*)	Lesion area cortex
Santos et al. (2013)	Brazilian-Portuguese	19 RH (10F; 9M)	53.3 years	> 6 months po	iCVA	Chronic	Non-fluent aphasia (BA: 8), fluent (AA: 7), and mixed aphasia (4)	LH: frontal, parietal, temporal lobe + subcortical areas
Volpato et al. (2013)	Italian	8 n.r. (2F; 6M)	58.6 years; range 42–70 years	12.3 years; range 8–18 years	CVA (6 i; 2 h)	6–126 months po	Non-fluent (TMA: 1); fluent (AA 2, CA 1; WA 2; TSA 1) aphasia	LH: temporo-parietal (2), parietal (1), fronto-parietal (2), temporal (1); subcortical (2)
Marangolo, Fiori, Gelfo et al. (2014)	Italian	7 n.r. (2F; 5M)	57.6 years; range 49–68 years	11.1 years; range 5–18 years	iCVA	10–72 months po	Non-fluent aphasia	LH: fronto-temporo-parieto-occipital cortex (1); fronto-temporo-parieto cortex (4); fronto-parietal cortex (2)
Rosso et al. (2014)	French	25 RH (13F; 12M)	57 years (18 years)	14.6 years (1.2 years)	iCVA	>3 months po (mean: 15 months po)	Non-fluent	Lesion in Broca's area (11); intact Broca's area (16)
Vestito et al. (2014)	Italian	3 n.r. (1F; 2M)	62 years; 65 years; 67 years	n.r.	iCVA (1); hCVA (2)	20–64 months po	Non-fluent (BA: 2), fluent (AA: 1)	Left fronto-temporal (1); left frontal (1); left temporal (1)
Campana et al. (2015)	Italian	20 RH (9F; 11M)	57.1 years; range 37–75 years	12.5 years; range 5–18 years	iCVA	6–84 months po	Non-fluent aphasia	L MCA

Cipollari et al. (2015)	Italian	6 RH (3F; 3M)	59.1 years; range 46–75 years	11.6 years; range 7–16 years	CVA	10–79 months po	Non-fluent aphasia	Fronto-temporo-parietal cortex (4); temporal cortex (1); fronto-parietal cortex (1)
de Aguiar, Bastiaanse et al. (2015)	NA	9 RH (3F; 6M)	57 years; range 45–75 years	> 5 years	CVA (7 iCVA; 2 hCVA)	8–92 months po	Non-fluent (6), fluent (3)	LH
Galletta and Vogel-Eyny (2015)	NA	1 RH (M)	43 years	16 years	CVA	20 months po	Fluent anomic	Temporo-parietal cortex
Richardson, Datta, Dmochowski, Parra, and Fridriksson (2015)	English	8 RH (4F; 4M)	60.6 years (range 48–74 years)	n.r.	CVA	89 months po (range 9–312 months po)	Non-fluent (BA: 5), fluent (AA: 3)	Fronto-parietal cortex
Shah-Basak et al. (2015)	English	12 RH (2F; 10M)	63.6 years; range 53–78 years	n.r.	CVA	7–111 months po	Non-fluent aphasia	L MCA
Wu, Wang, and Yuan (2015)	Chinese	12 RH (2F; 10M)	53.2 years; range 39–57 years	14.8 years; range 9–19 years	CVA (5 iCVA; 5 hCVA)	3–6 months po	Non-fluent (8), fluent (2), mixed (2)	Fronto-temporo-parietal cortex (9); temporo-parietal (1); fronto-parietal (2)
Meinzer, Darkow et al. (2016)	German	26 RH (8F; 18M)	59.9 years; range 38–78 years	11.9 years; range 7–18 years	iCVA (23); hCVA (3)	15–108 months po	Non-fluent (BA 9; GA 6), fluent (WA 9; AA 2) aphasia	LH
Darkow, Martin, Würtz, Flöel, and Meinzer (2017)	German	16 RH (6F; 10M)	56.7 years (10.1)	12.8 years; range 8–18 years	CVA	12–169 months po	Mild aphasia	LH

(continued)

Table B1 (continued)

Article	Language	Patients' handedness (no. of F; no. of M)	Mean age (SD)	Mean level of education (SD)	Type of stroke	Time since stroke	Type of aphasia (*n*)	Lesion area cortex
Marangolo, Fiori, Caltagirone, Pisano, and Priori (2017)	Italian	12 (6F; 6M)	Range 46–70 years	Range 8–18 years	CVA	14–37 months po	Non-fluent aphasia	LH
Norise, Sacchetti, and Hamilton (2017)	English	14 RH (4F; 10M)	63.3 years; range 50–76 years	n.r.	CVA (12 iCVA; 2 hCVA)	8–116 months po	Non-fluent aphasia	LH

AA anomic aphasia; *BA* Broca aphasia; *CA* conduction aphasia; *F* female; *GA* global aphasia; *hCVA* hemorrhagic cerebral vascular accident; *iCVA* ischemic cerebrovascular accident; *L* left; *LH* left hemisphere; *M* male; *MCA* middle cerebral artery; *n* number; *n.r.* not reported; *R* right; *po* postonset; *SD* standard deviation; *TMA* transcortical motor aphasia; *TSA* transcortical sensory aphasia; *WA* Wernicke aphasia

Table B2 Studies investigating impact of tDCS on language in patient populations—methodological information

Article	Active electrode location (size)	Reference electrode location (size)	Intensity	Type	No of sessions (duration)
Hesse et al. (2007)	Lesioned M1: C3 or C4 (35 cm^2)	Contralateral orbital area	1.5 mA	a	30 daily sessions (7 min)
Monti et al. (2008)	T3-Fz + F7-Cz (1); occipital (2) (35 cm^2)	R shoulder (35 cm^2)	2 mA	a/c/s (1); c/s (2)	1 session (20 min)
Baker et al. (2010)	L frontal cortex (25 cm^2)	R shoulder (25 cm^2)	1 mA	a/s	5 daily sessions (20 min) per type, 7-day interval
You et al. (2011)	L STG: CP5 (1.3); R STG: CP6 (2) (35 cm^2)	R supraorbital (1.3); L supraorbital (2)	2 mA	a(1)/c(2)/s(3)	10 daily sessions (30 min)
Fiori et al. (2011)	CP5: Wernicke's area (35 cm^2)	R occipito-parietal	1 mA	a/s	5 daily sessions (20 min)
Flöel et al. (2011)	R temporo-parietal cortex (35 cm^2)	L supraorbital (100 cm^2)	1 mA	a/c/s	3 sessions (20 min)
Fridriksson et al. (2011)	L post c perilesional area (25 cm^2)	Contralateral forehead (25 cm^2)	1 mA	a/c/s	5 daily sessions (20 min) per type, 3-week interval
Jung et al. (2011)	Broca's area: T4-Fz → F8-Cz (36 cm^2)	Orbital (36 cm^2)	1 mA	a-tDCS	10 sessions (20 min)
Kang et al. (2011)	R IFG (25 cm^2)	L orbital (25 cm^2)	2 mA	a/s	5 daily sessions (20 min) per type, 1-week interval
Vines et al. (2011)	R posterior IFG: 2.5 cm posterior to F8 (16.3 cm^2)	L supraorbital (30 cm^2)	1.2 mA	a/s	3 daily sessions (20 min) per type, 7-day interval
Saidmanesh et al. (2012)	L DLPFC (35 cm^2)	R DLPFC (35 cm^2)	2 mA	a/c/s	10 sessions (20 min)
Cherney et al. (2013)	R STC (8/28 cm^2)	Contralateral orbital (48 cm^2)	1 mA	c	30 sessions (13 min)
Fiori et al. (2013)	L IFG, L Wernicke: CP5 (35 cm^2)	Contralateral frontopolar cortex (35 cm^2)	1 mA	a/s	5 sessions (20 min)
Lee et al. (2013)	Single: L IFG, F7 (35 cm^2); bihemispheric, L a-IFG, R c-IFG (35 cm^2)	Single: L buccinator muscle (35 cm^2); bihemispheric, L (cathode) and R (anode) buccinator muscle	2 mA	a/bihemispheric	1 session (30 min) per type; 24-h interval

(continued)

Table B2 (continued)

Article	Active electrode location (size)	Reference electrode location (size)	Intensity	Type	No of sessions (duration)
Marangolo, Fiori, Cipollari et al. (2013)	Anode: L IFG, F5 (35 cm^2)	Cathode: R IFG (35 cm^2)	2 mA	Bihemispheric/s	10 daily sessions (20 min) per type; 14-day interval
Marangolo, Fiori, Di Paola et al. (2013)	Broca, F5; Wernicke, CP5 (35 cm^2)	Contralateral frontopolar cortex (35 cm^2)	1 mA	a/c/s	15 sessions (20 min) per type; 6-day interval
Marangolo, Fiori, Calpagnano et al. (2013)	Broca, F5; Wernicke, CP5 (35 cm^2)	Contralateral frontopolar cortex (35 cm^2)	1 mA	a/s	10 sessions (20 min) per type and montage; 14-day interval
Santos et al. (2013)	L M1 (35 cm^2)	Contralateral supraorbital region (35 cm^2)	2 mA	a	10 sessions (20 min)
Volpato et al. (2013)	L Broca's area: T3-F7 (35 cm^2)	Contralateral supraorbital region (35 cm^2)	2 mA	a/s	5 weekly sessions (20 min)
Marangolo, Fiori, Gelfo et al. (2014)	L IFG, L Wernicke's area (35 cm^2)	R IFG (35 cm^2)	2 mA	a/s	10 sessions (20 min)
Rosso et al. (2014)	L IFG (35 cm^2)	Contralateral supraorbital region (35 cm^2)	1 mA	c/s	1 session (10 min); 1-h interval; 1 session (10 min)
Vestito et al. (2014)	L IFG (25 cm^2)	Contralateral supraorbital region (25 cm^2)	1.5 mA	a/s	10 sessions (20 min)
Campana et al. (2015)	L IFG (35 cm^2)	Contralateral frontopolar cortex (35 cm^2)	2 mA	a/s	10 sessions (20 min)
Cipollari et al. (2015)	R IFG (35 cm^2)	Contralateral frontopolar cortex (35 cm^2)	2 mA	a/s	15 sessions (20 min)
de Aguiar, Bastiaanse et al. (2015)	Individually determined (35 cm^2)	Individually determined (35 cm^2)	1 mA	a/c/s	10 sessions (20 min)
Galletta and Vogel-Eyny (2015)	L Broca/L Wernicke (35 cm^2)	R Broca/R Wernicke (35 cm^2)	1 mA	a/s	10 sessions (20 min)
Richardson et al. (2015)	L posterior cortex (35 cm^2)	R supraorbital region (35 cm^2)	2 mA	a/HD	5 sessions (20 min)

Shah-Basak et al. (2015)	L DLPFC, R DLPFC	Contralateral mastoid	2 mA	a/c/s	10 sessions (20 min)
Wu et al. (2015)	L posterior perisylvian region (24.75 cm^2)	R shoulder (24.75 cm^2)	1.2 mA	a/s	20 sessions (20 min)
Meinzer, Darkow et al. (2016)	L M1: C3 (35 cm^2)	R supraorbital region (100 cm^2)	1 mA	a/s	8 sessions (20 min) (2 × 1.5 h/day)
Darkow et al. (2017)	L M1 (35 cm^2)	R supraorbital region (100 cm^2)	1 mA	a/s	2 sessions (20 min)
Marangolo et al. (2017)	R cerebellar cortex (35 cm^2)	R deltoid muscle (35 cm^2)	2 mA	c/s	5 daily sessions (20 min) per type; 6-day interval
Norise et al. (2017)	a-L IFG (n = 3); c-L IFG (n = 3); a-R IFG (n = 1); c-R IFG (n = 1)	Contralateral mastoid	2 mA	a/c/s	10 daily sessions (20 min)

a anodal; *c* cathodal; *DLPFC* dorsolateral prefrontal cortex; *h* hour(s); *IFG* inferior frontal gyrus; *L* left; *M1* primary motor cortex; *mA* milliampere(s); *n* number; *n.r.* not reported; *R* right; *s* sham; *STG* superior temporal gyrus

Table B3 Studies investigating impact of tDCS on language in patient population—therapeutic information

Article	Intervention	Outcome measures	Outcome	Follow-up
Hesse et al. (2007)	Online naming therapy (nouns)		Significant improvement after atDCS (n = 3)	None
Monti et al. (2008)	No behavioral treatment	Picture naming (accuracy + response times)	Significant improvement after ctDCS (n = 6)	None
Baker et al. (2010)	Online picture-word matching (nouns)	Picture naming (accuracy)	Accuracy improved significantly for treated items after atDCS	1 week
You et al. (2011)	Online SLT (a (n = 10), c (n = 11), s (n = 12))	Korean WAB	Significant improvement after ctDCS	None
Fiori et al. (2011)	Online naming therapy (nouns)	Picture naming (accuracy + response time)	atDCS might have an important effect on recovery of anomia	None
Flöel et al. (2011)	Online naming therapy (nouns)	Picture naming	Significant improvement on naming, especially after atDCS	3 × 2 weeks
Fridriksson et al. (2011)	Online spoken word-picture matching (nouns)	Picture naming (accuracy + response time) + picture description	atDCS > naming reaction time	2 × 3 weeks
Jung et al. (2011)	Online SLT (according to needs of PWA)	Aphasia quotient + Korean WAB	Most important prognostic factor: initial severity; more improvement for hCVA; significant improvement on all items of K-WAB; better results in fluent PWA within 1 m after stroke + severe aphasia	None
Kang et al. (2011)	Online naming therapy (nouns) + word-picture matching	Picture naming (accuracy + reaction time)	Improvement in naming accuracy	None
Vines et al. (2011)	Online MIT random	Picture naming, verbal fluency, and picture description	A sign>s; in fluency of speech	None
Saidmanesh et al. (2012)	Online naming therapy (nouns)	Picture naming, working memory + aphasia quotient	atDCS enhances WM + functional recovery in PWA	
Cherney et al. (2013)	Online oral reading	WAB	Improvement in AQ + auditory comprehension	None

Fiori et al. (2013)	Online naming therapy (nouns + verbs)	Picture naming	Improvement in noun naming after atDCS; in verb naming after atDCS IFG	1 week/4 weeks
Lee et al. (2013)	Online naming therapy (nouns) + reading paragraphs	Picture naming (accuracy + reaction time) + picture description	Improvement in naming response time for uni- and bipolar tDCS	None
Marangolo, Fiori, Cipollari et al. (2013)	Online random SLT	Picture naming (reaction time)	A sign>s; 2× follow-up	2 × 1 week
Marangolo, Fiori, Di Paola et al. (2013)	Online syllables/word repetition	Repetition	Improvement in repetition accuracy after bihemispheric tDCS	1 weeks
Marangolo, Fiori, Calpagnano et al. (2013)	Online conversational therapy	Spontaneous speech	Improvement in content units, verbs, and sentence production after atDCS	1 month
Santos et al. (2013)	Online language production (naming + verbal fluency)	Comprehension	Improvement of speech and comprehension	None
Volpato et al. (2013)	Offline SLT	Picture naming (accuracy + reaction time)	Improvement in accuracy and response time for 1 patient	None
Marangolo, Fiori, Gelfo et al. (2014)	Online conversational therapy		Improvement in cohesive devices after atDCS	None
Rosso et al. (2014)	Online naming therapy (nouns)	Picture naming (accuracy)	High interindividual variability in naming ability improvement after ctDCS	None
Vestito et al. (2014)	Online naming therapy (nouns)	Picture naming (noun + verb accuracy)	Improved naming after atDCS	16 weeks
Campana et al. (2015)	Online conversational therapy	Picture description + verb/noun naming	Improvement in picture description, noun + verb naming	None
Cipollari et al. (2015)	Online MIT	Comprehensive language battery	Improvement in repetition accuracy after atDCS	1 week
de Aguiar, Bastiaanse et al. (2015)	Online ACTION therapy	Language battery + cognitive screening	Improvement in verb production	None
Galletta and Vogel-Eyny (2015)	Online sentence completion	Sentence completion of nouns and verbs	Improvement of verb retrieval after atDCS	None

(continued)

Table B3 (continued)

Article	Intervention	Outcome measures	Outcome	Follow-up
Richardson et al. (2015)	Online auditory picture matching task (nouns) + naming therapy	Picture naming (accuracy + response time)	Improvement of naming accuracy and response time	1 week
Shah-Basak et al. (2015)	Online naming therapy (nouns)	WAB	Trend toward improvement after atDCS L DLPFC	2 months
Wu et al. (2015)	Online naming therapy + auditory comprehension (nouns)	BDAE—Chinese version PACA	Improvement after atDCS	None
Meinzer, Darkow et al. (2016)	Online naming therapy (nouns)	Picture naming (60 trained; 284 untrained items (=transfer); everyday communication (CETI + PCQ) (=generalization)	Post-intervention, naming> after a/stDCS; transfer in both groups; generalization> after atDCS; follow-up, treatment gains maintained → effectiveness of intervention; follow-up, effects for trained items superior after atDCS; follow-up, transfer effects only maintained after atDCS; follow-up, generalization effect superior after atDCS; all patients believed that they had received atDCS	6 months
Darkow et al. (2017)	Online naming therapy	AAT + picture naming	Enhanced activity and connectivity within naming network after a-tDCS	None
Marangolo et al. (2017)	Online verb generation/ verb naming		Improvement in verb generation accuracy	1 week
Norise et al. (2017)	Online SLT	Picture naming	Improvement in fluency after real tDCS at 2-week follow-up only for PWA with severe baseline	2 weeks

AAT Aakense Aphasia Test, *atDCS* anodal transcranial direct current stimulation, *AQ* aphasia quotient, *BDAE* Boston Diagnostic Aphasia Examination, *CETI* communicative effectiveness index, *ctDCS* cathodal transcranial direct current stimulation, *DLPFC* dorsolateral prefrontal cortex, *hCVA* hemorrhagic cerebrovascular accident, *IFG* inferior frontal gyrus, *L* left, *MIT* melodic intonation therapy, *n* number, *PACA* Psycholinguistic Assessment in Chinese Aphasia, *PCQ* partner communication questionnaire, *PWT* patients with aphasia, *sign* statistically significant, *SLT* speech-language therapy, *stDCS* sham transcranial direct current stimulation, *WAB* Western Aphasia Battery

Appendix C: Clinical fMRI Scan History Form

Name: _____ Date: _____

• What language do you speak most in daily life? _____

• What language did you speak most before age 8? _____

• Any complications at your birth/delivery? _____

E.g., anything require a stay in the Neonatal Intensive Care unit

• Have you ever been diagnosed with Reading Disability or Dyslexia? _____

• At what age was your first seizure? _____

Have you had neurosurgery before? Yes No

Do you know what side of the brain your seizures are coming from?

Left | Right | Both | Don't Know

Edinburgh Handedness Inventory - Short Form

Please indicate your preferences in the use of hands in the following activities or objects:

	Always right	Usually right	Both equally	Usually left	Always left
Writing	☐	☐	☐	☐	☐
Throwing	☐	☐	☐	☐	☐
Toothbrush	☐	☐	☐	☐	☐
Spoon	☐	☐	☐	☐	☐

Notes

_____

_____

_____

_____

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Scoring: Edinburgh Handedness Inventory: Short Form

Source: Veale, S. (2014). Edinburgh Handedness Inventory – Short Form: a revised version based on confirmatory factor analysis. *Laterality, 19*(2), 164–77.

www.jaimieveale.com/wp-content/uploads/2014/04/Edinburgh-Handedness-Inventory-short-form.pdf

Scoring:

For each item: Always right = 100; Usually right = 50; Both equally = 0; Usually left = -50; Always left = -100

To calculate the Laterality Quotient add the scores for the four items in the scale and divide this by four:

Writing score	
Throwing score	
Toothbrush score	
Spoon score	
Total	
Total ÷ 4 (Laterality Quotient)	

Classification:	Laterality Quotient score:
Left handers	-100 to -61
Mixed handers	-60 to 60
Right handers	61 to 100

Appendix D: Example Clinical Report

Patient:	PATIENT	Handedness:	Left
DOB, Age:	–.–.– (42 years)	Primary language:	English
Sz onset:	30 years	Years of education:	12 years
Sz focus:	Left temporal	Research fMRI Date:	–.–.–
Report date:	–.–.–		

Referrer: X MD

Neuropsychologist: Y PhD

Background. PATIENT 1 is a 35 year-old woman who developed seizures aged 30. Her seizures are consistently left temporal per vEEG. MRI was unremarkable with the exception of subcortical white matter hyperintensities. The possibility of a left temporal encephalocele was raised but is uncertain. She has average overall cognitive functioning (FSIQ = 103, VCI = 98, PRI = 105), verbal memory (RAVLT LD $Z = -0.5$), and naming skill (BNT $Z = -0.3$). PATIENT is strongly left-handed (Edinburgh Handedness Inventory—Short Form laterality quotient = −100).

Question: Language lateralization.

Technical (see also final page):

- Tasks: (1) Object naming [OBJ], (2) verbal naming (VRN), and (3) auditory naming [ARN]. Language: English. Speed: typical (3 s/item).
- Movement: Average. Excluding images with >1 mm movement or >3SD of signal variation effectively removes 1% (OBJ), 9% (VRN), and 6% (ARN) of images. In an average scan, < =5% of scans are impacted by motion.

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https://doi.org/10.1007/978-3-030-35687-3

- Registration: Average, very slight misalignment in some regions.
- Model: Based on the above, reported data use models that are artifact corrected.

Summary: Overall, this language mapping (Map 1) suggests:

- Broca's: Left.
- Wernicke's: Left.

This is a good-quality and clearly left-dominant language map.

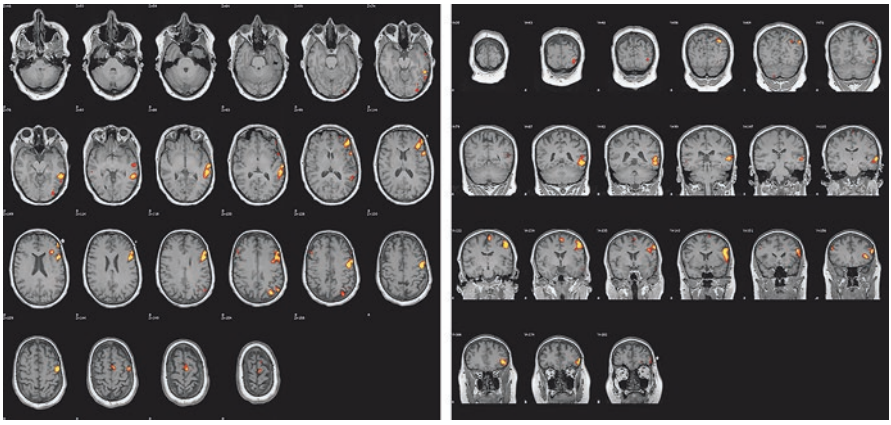
In reviewing individual tasks, PATIENT did not engage Wernicke's area on the object naming task. As a result, a conjunction of two tasks—verbal naming (reading, eyes open) and auditory naming (listening, with eyes closed)—is reviewed (see images). All areas—Broca's, Wernicke's, Exner's, basal temporal language area, SMA, and the angular gyrus—appear left-dominant.

Note*: fMRI activations are arbitrarily discrete*. Rather than representing islands of language cortex, they represent cortex where blood flow is most strongly associated with a given task. Cortex surrounding these areas is typically also responsive, though to a lesser extent, and the activation here may be overly inclusive. This map will not show all language areas.

These images are available for review in the epilepsy conference.

—Signature—

Map 1: Conjunction of verbal responsive naming and auditory naming. Areas of activity shown were identified separately on each of these two separate tasks. Note: right of image = left of brain. This map was created in two steps: (1) for each task separately, comparing the task with its own control to create contrasts at three thresholds [$p < 0.005$; $p < 0.0005$; $p < 0.00005$] and (2), for each threshold level, taking the overlap of each task contrast. The highest threshold is yellow, the lowest is red.



Comment: This patient completed the practice tasks before scanning without issue. During scanning, she was uncomfortable and moved markedly during the

second run (visual responsive naming) with four large readjustments of her head during the last portion of the run. The other two runs included some occasional, minor movements. The tablet indicating the left hemisphere can be seen on the right of the image in the first few slices of the axial image. Skull stripping was adequate (some residual cerebrospinal fluid left around the perimeter of the skull), while a very slight misalignment in some brain areas was evident when registration of the functional and structural runs was reviewed. When the three separate tasks were reviewed, all three yielded clear maps showing all six language regions with the exception that Wernicke's area was not visible on the object naming task at any threshold, potentially due to a lack of patient engagement during the task. As a result, the latter two tasks were combined in the final conjunction analysis.

Report Addendum

The protocol used is described below after Benjamin et al. (2017), with tasks and parameters modified as follows:

1. Object naming + verb generation > matched baseline (visually scrambled image).

   Standard version (English): blocks of eight objects, 3 s each.

2. Visual naming + verb generation > matched baseline (visually scrambled image).

   Standard version (English): blocks of eight objects, 3 s each.

3. Auditory naming + verb generation > matched baseline (white noise).

   Standard version (English): blocks of eight objects, 3 s each.

The patient was instructed in all tasks in detail pre-scan. They were instructed to sub-vocalize all responses but not talk or move. Instructions were confirmed before and after each run. All tasks used a block design with six pairs of 24 s of task followed by 24 s of rest.

1. Object naming. A black-and-white line drawing of an object was presented. The subject's task was to name the object and something they could do with it. This is a modified version of, e.g., Rutten et al. (2002). In the matched control, the patient was instructed to attend to and watch the same stimuli with parts randomly shuffled (visual white noise).
2. Visual naming. A brief written description of an item was presented (e.g., "tall pink bird"). The task was again to name the item (e.g., answer—flamingo) and something they could do with it (e.g., look at it). This is a modified version of the comprehension task in Gaillard et al. (2004). The control task included the same visual stimuli, scrambled (visual white noise).
3. Auditory responsive naming. An auditory cue (sentences similar to [2]) was presented. The patient's task was again to name the object and something they could do with it. This is a modified version of the comprehension task in

Gaillard et al. (2004). In the control task, the patient listened to the same stimuli, scrambled (auditory white noise).

Acquisition: All T_2* sequences were acquired with parameters TR = 984 ms/TE = 30 ms/FA = 62°, 2.5 mm × 2.5 mm × 2.5 mm, 51 slices, and 387 volumes (2 dropped). Standard T_2 and MPRage acquisitions were also completed.

Analysis is consistent with norms for the field, with adjustments as followed (Benjamin et al., 2018): *Preprocessing*: For all runs, the initial two images were dropped (B0 effects). Structural images were skull-stripped. Within SPM12, the three T_{2*} runs were realigned. The T_2 image was then coregistered with the MPRage. The T_{2*} images were then aligned to the MPRage-coregistered T_2. Images were smoothed (8 mm). Alignment of all images was evaluated visually. *Quality assurance*: Raw data were reviewed (select images and using a cine loop). Analysis with the artifact detection toolbox (ART) was also completed. T maps were reviewed for indication of motion. *Modeling*: Data were analyzed using the GLM. Regressors included task and matched baseline; to allow artifact-correction, additional regressors were included to remove the impact of each outlier image. *Thresholding*: Images were initially thresholded at $p < 0.05$ and then iteratively adjusted to obtain an optimal representation of the language areas noted above. Images were then combined to identify areas of common activation (conjunction analysis). Preference was for a map combining all three images and then for a map with two images from tasks drawing on different modalities.

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Software

SPM12: http://www.fil.ion.ucl.ac.uk/spm/
FSL: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/
ART: http://web.mit.edu/swg/

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G. P. D. Argyropoulos (ed.), *Translational Neuroscience of Speech and Language Disorders*, Contemporary Clinical Neuroscience,
https://doi.org/10.1007/978-3-030-35687-3