Animal Models for Brain Research

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Abstract

Animal models are important experimental tools in neuroscience research since they allow appraisal of selected and specific brain pathogenesis-related questions – often not easily accessible in human patients – in a temporal and spatial pattern. Translational research based on valid animal models may aid in alleviating some of the unmet needs in the current pharmaceutical market. Of primary concern to a neuroscience researcher is the selection of the most relevant animal model to achieve pursued research goals. Researchers are challenged to develop models that recapitulate the disorder in question, but are quite often confronted with the choice between models that reproduce cardinal pathological features of the disorders caused by mechanisms that may not necessarily occur in the patients versus models that are based on known aetiological mechanisms that may not reproduce all clinical features. Besides offering some general concepts concerning the relevance, validity and generalisation of animal models for brain disorders, this chapter focuses in detail on animal models of brain disease, in particular schizophrenia models as examples of animal models of psychiatric disorders and Alzheimer's disease models as examples of animal models of neurological/neurodegenerative disorders.

Abbreviations

AChE	Acetylcholinesterase
AD	Alzheimer's disease
APP	Amyloid precursor protein
Aβ	Amyloid β
BPSD	Behavioural and psychological signs and symptoms of dementia
ChAT	Choline O-acetyltransferase
DISC1	Disrupted in schizophrenia-1 gene
DSM-IVTR	Diagnostic and Statistical Manual of Mental Disorders 4th edition
DTNBP1	Dysbindin gene
ERBB4	Neuregulin 1 receptor gene
FRL	Flinders resistant line
FSL	Flinders sensitive line
HAB	High-anxiety-related behaviour Wistar rat line
LAB	Low-anxiety-related behaviour Wistar rat line
LI	Latent inhibition
NFT	Neurofibrillary tangle
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NRG1	Neuregulin 1 gene
PCP	Phencyclidine
PDAPP	Platelet-derived growth factor promoter-driven APP
PPI	Prepulse inhibition
PSEN	Presenilin

RELN	Reelin gene
SAM	Senescence-accelerated mouse
SAMP	SAM-prone substrain
SNP	Single nucleotide polymorphism
TDP-43	TAR DNA-binding protein 43

1.1 Introduction to Animal Modelling for Human Brain Disease

Animal models aiming at studying human disorders emerged in the 1800s and experienced a major boost over the last decades. The value of animal experimentation in the advances of human health is exemplified by the list of Nobel Prizes awarded for Physiology or Medicine. Since the beginning of the twentieth century, these prizes have chronicled the world's greatest medical advances. Of the 102 Nobel Prizes awarded for Physiology or Medicine up to 2011, 82 were directly dependent on animal-based research or the discovery relied on crucial data obtained from animal studies by other research groups.

Basic neuroscience research on animal models is essential to understand the nature of brain disorders that afflict humans and develop purposeful therapies. In the mid-1960s, the neural circuits containing and utilising the neurotransmitters dopamine and norepinephrine were visualised for the first time in rodent brain (Glowinski et al. 1966; Glowinski and Iversen 1966a, b; Iversen and Glowinski 1966). Further development of other (antibody-based) methods allowed neuroscientists to link synaptic molecules to neural circuits in rodent and nonhuman primate brains, thereby coordinating neuroanatomy, neuropharmacology and neurophysiology into a cohesive view of biochemically coded brain circuitry. Application of these techniques in human brain aided in elucidating the neurotransmitter-based nature of specific brain circuits affected in disease, e.g. the degeneration of cholinergic neurons in the basal forebrain of Alzheimer's disease (AD) patients (Whitehouse et al. 1982). The concept of synaptic communication between nerve cells as the key level of interaction in the brain further culminated with the work of E. Kandel and colleagues, who were awarded the Nobel Prize in 2000. The synapse has become a key target for pharmaceutical intervention in many brain disorders that are now understood at the level of synaptic circuitry and functional brain organisation, including multiple psychiatric disorders (e.g. schizophrenia, depression), as well as neurodegenerative disorders (e.g. AD, amyotrophic lateral sclerosis, Parkinson's disease).

The starting point for the development of a new animal model for a specific brain disease is mostly the current dominant theory about the disorder. Although a logical first approach, it is essential to broaden the focus of animal models under development based on the increasing knowledge of underlying disease mechanisms.

Animal models of human disease can be classified into spontaneous, induced, negative and orphan models, of which the two latter types are in general not relevant for psychiatric and neurological disorders. Negative models after all are models in which

a specific human disorder does not develop, while orphan models display a condition which has never been described in man or other target species. Spontaneous models are presumed to develop their condition without experimental manipulation, but selective breeding is often compulsory to establish and maintain the desired line. Especially for psychiatric and neurological conditions, few spontaneous models exist, and experimentally induced pathology is often required. Such artificial manipulations include surgical procedures, administration or withdrawal of biologically active substances, application of physical or physicochemical stimuli and genetic manipulations.

1.1.1 Relevance of Animal Models

Relevance reflects the meaningfulness and usefulness of results obtained with an animal model for a particular scientific and/or clinical purpose (van der Staay 2006). The two most important clinically inspired applications of animal models in neuroscience research are (1) the development and evaluation of mechanistic hypotheses about neurological and psychiatric disorders in general and their neural substrates in particular (i.e. brain–behaviour relation) and (2) the identification and screening of novel therapeutic approaches, most frequently drugs.

Opponents of animal research often question the relevance of animal models to understanding diseases and disease processes in humans. The disputed similarities between human and other species at the structural and functional level of the CNS are often considered a major hurdle for the use of animal models in studies of human neurological and psychiatric conditions.

Neuroscientists are far from reaching consensus about the level of similarity between the brains and 'minds' of humans and other species. Comparative neuroscience can provide essential information for the adequate comparison of both structural and functional aspects of human and nonhuman brain and thereby identify research areas in which animal models are likely to be useful, as well as the appropriate species for such studies. Specifically when considering models of psychiatric disease, the issue of similarities between the mental lives of animals and humans is fundamental. Animal consciousness or unconsciousness is difficult, if not impossible, to corroborate. On the other hand, one could argue whether it is necessary for the animal mind to be as complex as the human mind. Behavioural responses and brain mechanisms associated with anxiety, fear, aggression and coping serve such a crucial adaptive function that they must have evolved very early in the development of mammalian species and are probably highly conserved (Steimer 2011). Other classes of vertebrates and even lower invertebrates may display some form of anxiety and have the capacity to detect danger and react to threat, i.e. display a fight-or-flight response. Components of emotional processes, as well as the biological and neuronal logistic systems essential for their realisation, gain in complexity higher up in the phylum. Species located higher in the phylogenetic tree gain additional capabilities (e.g. autonoetic consciousness in humans, orang-utans, chimpanzees and bonobos) but never lose the more primitive abilities shared with lower invertebrates (Belzung and Philippot 2007), thereby opening perspectives for the

use of lower species like zebrafish (Gerlai 2010) or even fruit flies (Iliadi 2009) in the studies of emotional responses and specific psychiatric disorders. The further focus of this chapter will be, however, on rodent models given their widespread use and applicability of microimaging techniques in these species.

Although some attributes still appear to be rather unique to the human brain, other aspects seem to be shared with more species than originally believed. Also at the neuroanatomical level, major species differences should be taken into consideration. The complex pattern of human cortical sulci and gyri, as well the extent of the prefrontal cortex, the neural substrate of many higher functions, is beyond compare in the rest of the animal kingdom (Fuster 1980). The prefrontal cortex may be present, however, in more species than initially thought, and the prefrontal to nonprefrontal cortical surface ratio in itself may not be an optimal index of evolution. Improved knowledge of rat prefrontal cortex anatomy has modified strategies to manipulate specific cortical areas to model prefrontal involvement, although reports delineating boundaries between prefrontal cortical subareas of the rat in comparison with the primate homologues show some dissimilarities. Nevertheless, current anatomical and functional data indicate that rats do have a prefrontal cortex, although not as differentiated as the primate prefrontal cortex. Rats have a functionally divided prefrontal cortex that includes not only features of the medial and orbital areas in primates, but also some features of the primate dorsolateral prefrontal cortex (Uylings et al. 2003).

1.1.2 Validity of Animal Models

The conclusions drawn from animal models largely depend on the validity of the model in representing the human condition. The more levels of validity a model satisfies, the greater its value, utility and relevance to the human condition. The validity of a model can only be determined in a multidisciplinary approach. A 'perfect' model would account for aetiology, symptomatology, treatment response and physiological basis, as originally proposed by McKinney and Bunney in 1969. Animal models in general do not meet all of these criteria. Moreover, in developing and assessing an animal model, it is critical to consider the explicit purpose intended for the model, because the intended purpose determines the criteria that the model must satisfy to establish its validity. The following perspectives are commonly used in the characterisation of a model's validity (Van Dam and De Deyn 2006, 2011b).

1.1.2.1 Face Validity

Face validity refers to the resemblance between the animal model and the situation or process being modelled. It refers to the phenomenological similarity between the model and the human condition. Similarity of symptoms is most commonly used to assess face validity in animal models of behavioural dysfunction. Throughout this chapter, several behavioural paradigms will be mentioned. Writing a complete 'how-to manual' for the behavioural phenotyping of a new brain disease model would go beyond the scope of this chapter. For further reading, we would like to

refer the readers to excellent manuals on behavioural neuroscience as, e.g. 'What's wrong with my mouse?' (Crawley 2000) and 'Methods of Behavior Analysis in Neuroscience' (Buccafusco 2008).

1.1.2.2 Construct Validity

Construct validity refers to the theoretical clarification of what a test measures or a model is supposed to mimic. Because a given condition may manifest itself in different ways in different species, the behaviour used in the animal model may not match that of humans, yet the test or model may still be valid. Construct validation is useful in the incessant process of further developing and refining an animal model.

1.1.2.3 Aetiological Validity

Aetiological validity is closely related to construct validity and refers to identical aetiologies or phenomena in the model and the human condition. Models with high aetiological validity are most valuable in drug development and discovery.

1.1.2.4 Predictive Validity

Predictive validity represents the extent to which the performance of the animal model in a test predicts the performance in the condition being modelled. This level of validation necessitates parallel development of clinical measures for meaningful comparisons between model and man. In a more narrow sense, this term is sometimes used to indicate pharmacological isomorphism, i.e. the model's ability to identify compounds with potential therapeutic effects in the human condition.

1.1.3 Homology, Analogy and Isomorphism

As a consequence of the different validation levels, validity is highest in the so-called homologous models, where the symptoms displayed and the cause of the condition in the animal are identical to those of the human condition. Especially in neurosciences, homologous models are very rare and mostly limited to well-defined lesion syndromes. Analogous or isomorphic models are more common, but, although they display similar symptoms, the condition is not provoked by the same events as the human condition. In reality, most animal models are partial models, focusing only on restricted aspects of a disease, and modelling the complete condition is often not pursued. Of primary concern to neuroscientists is the selection of the most relevant animal model to achieve his/her research goals. Researchers are challenged to develop models that recapitulate the disorder in question, which is often not as straightforward as it may seem. Quite often they are confronted with the choice between models that reproduce cardinal pathological features of the disorders caused by mechanisms that may not necessarily occur in the patients versus models that are based on known etiological mechanisms that may not reproduce all clinical features. Although animal models cannot replicate human pathophysiology or psychopathology in every detail, we should envisage them as experimental systems in which selected and specific CNS pathogenesis-related questions – often not

easily accessible in human patients – can be studied in a temporal and spatial pattern. Partial models may be of substantial value in the gradual process of building a more complete image of the disease and underlying pathophysiological mechanisms, whereas more complete and complex models are only possible in case of better understood diseases (De Deyn and Van Dam 2011).

1.1.4 Generalisation and Extrapolation

The ultimate goal of animal modelling is the generalisation of results and insights to the target species, which in most occasions of course is man. The term extrapolation is also often used to describe how data obtained from animal studies can be reliably used to apply to the human condition. Extrapolation is therefore not performed in its mathematical sense, in which data fit a certain function that may be described graphically and the graph extends beyond the highest or lowest sets of data to describe a situation outside the window of observation. Generalisation across species is intrinsically based on the Darwinian evolutionary concept. Phylogenetic similarity in morphology and physiology between different species allows observations made in animals to be translated to the human condition based on homology. Related to animal models for psychiatric and neurological disorders, this cross-species comparison may focus or be based on the biological, genetic or environmental basis of personality traits (Gosling 2001) or neuroanatomical structures and their function (Striedter 1998). Uncritical generalisation or extrapolation of animal findings to the human condition may lead to unreliable or even dangerous conclusions. As a general rule, extrapolation tends to be most reliable when a plurispecies approach is taken and the condition is studied in a variety of relatively unrelated laboratory animals. Differences in metabolic patterns and speed, as well as several other confounding variables (e.g. age, sex, distress, diet, housing condition, route of administration, rhythmic variations), need to be taken into account, particularly when quantitative extrapolation is intended (De Deyn and Van Dam 2011).

Generalisation may be advanced by the development of translatable preclinical biomarkers, including small animal imaging (Kaimal and McConville 2009; Sakoğlu et al. 2011), and biochemical assays on biological fluids such as plasma and cerebrospinal fluid (Liu and Duff 2008). These biomarkers could be used to characterise the translatability of animal models, determine the translatability of a novel therapeutic intervention if the same biomarker can be used in a clinical trial, assess target engagement of investigational treatments and monitor biological responses to treatment in real time.

1.2 Animal Models of Psychiatric Disorders

Psychiatric disorders represent a diverse set of conditions, variously affecting all domains of mental function and affecting the most fundamental human attributes, namely, language, thought, perception, mood and sense of self. Many psychiatric

symptoms, e.g. hallucinations, delusions, sadness, guilt and suicidal thoughts, are probably uniquely human and cannot be convincingly ascertained in animals. Researchers should also refrain from uncritical anthropomorphising of emotional behaviour in general. Feeling anxious or depressed arev subjective emotional experiences that may require a certain minimal level of consciousness that may well be uniquely human.

The evaluation of animal models of neuropsychiatric disorders is further challenged by the use of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IVTR) criteria in the clinical diagnosis, combined with the lack of knowledge of pathophysiological mechanisms and objective diagnostic tests. DSM-IVTR diagnosis is based on phenomenology (i.e. signs, symptoms, course of illness), and mostly, a minimal number of symptoms should be present for at least a specified period of time. In the case of schizophrenia, two (or more) of the following symptoms should be present for a significant portion of time during a 1-month period (or less if successfully treated): delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour and negative symptoms, i.e. affective flattening, alogia, or avolition, in addition to social/occupational dysfunction (4th ed., text rev.; *DSM–IV–TR*; American Psychiatric Association 2000). Two individuals with the same DSM-IVTR diagnosis of schizophrenia may therefore present with extremely heterogeneous symptom combinations. Similar problems exist for most DSM-IVTR-based diagnoses, thereby further complicating the evaluation and validation process of newly developed mouse models for psychiatric illnesses (Nestler and Hyman 2010).

1.2.1 The Endophenotype Concept in Psychiatry

The concept of endophenotypes appears to be unique to the broad field of psychiatry. An endophenotype is a biomarker associated with genetic components, as well as the clinical symptoms of neuropsychiatric disorders. It plays an important role to bridge the gap between the microscopic and macroscopic level of neuropsychiatric disorders. It is per definition any hereditary characteristic that is normally associated with some condition but is not a direct symptom of that condition. Criteria useful for the identification of endophenotypes of diseases that display complex inheritance patterns have been suggested (Gottesman and Gould 2003):

1. The endophenotype is associated with illness in the population.
2. The endophenotype is heritable.
3. The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).
4. Within families, endophenotypes and illness co-segregate.
5. The endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population.

Endophenotype analysis can be based on neuroanatomical, neurophysiological, biochemical, endocrinological, cognitive and neuropsychological/behavioural measures (Leboyer et al. 1998). Advanced neuroimaging techniques, including PET and SPECT, have left little doubt that specific structural CNS anomalies can be linked

to particular neurological and psychiatric diseases. Neuroimaging endophenotypes are vitally important to the identification of genetic determinants of complex brain-related disorders (Glahn et al. 2007).

The study of endophenotypes is particularly useful to understanding underlying disease mechanisms in neuropsychiatric disorders, essential for the accurate diagnosis, classification, early detection purposes, the development and evaluation of valid animal models and accelerating the drug discovery pipeline concerned.

1.2.2 Approaches to Modelling Psychiatric Disease

1.2.2.1 Behavioural Approach

In the absence of knowledge of underlying genetic causes, the first attempts to model psychiatric disturbances in animals consisted of the behavioural approach that defined behavioural assays thought to mimic particular psychiatric symptoms. Animals with specific behavioural deficits were generated through pharmacological, surgical or genetic (e.g. comparison of inbred strains) procedures. Well-known examples are the learned helplessness model of depression, spontaneous alternation indexing working memory in schizophrenia, decreased social interaction linked to autism spectrum disorder and approach–avoidance conflict behaviours associated with anxiety disorders (Crawley 2000; Mitchell et al. 2011). The development of valid behavioural models and paradigms is currently still ongoing, but with more attention for the neurobiological and clinical relevance (Baker 2011). A rodent behavioural paradigm has neurobiological construct validity if it isolates and measures a behavioural process with similar environmental regulators and neural mediators as the human process of interest. However, many behavioural assays lack sufficient construct validity, and their use in the development of rodent models for psychiatric disorder is mainly based on face validity (Moore 2010).

Although brain–behaviour relationships are assumed to be conserved across evolution for many aspects of normal motor and sensory functions, this may not be translated as easily to abnormal behaviour, let alone psychiatric disease. Animal brain circuitry and neurochemical systems involved may differ from the complex human (disease) system. A mental disorder is not characterised by an aberration in one single feature, but is a syndrome with a myriad of deviations in behaviour, cognition and/or emotion. Behavioural models of psychiatric disease, like the learned helplessness model of depression, are of course partial models that mimic only one single isolated feature of the human condition (Insel 2007).

1.2.2.2 Pharmacological Models

The administration of certain chemicals may induce behavioural changes reminiscent of specific psychiatric symptoms based on interference with central neurotransmission pathways. Understanding the mechanisms of these actions might contribute to our fundamental understanding of the illness. Drug-based models include the reserpine model of depression (Hendley and Welch 1975) and N-methyl-D-aspartate (NMDA) receptor antagonist-based models of psychosis (Andiné et al. 1999).

1.2.2.3 Genetic Models

Genetic models of psychiatric disorders were initially dominated by inbred strains, often after selection for a relevant psychiatric-like phenotype. Examples include the selectively bred Flinders Sensitive Line and the Flinders Resistant Line of rats (FSL versus FRL), a genetic animal model of depression (Overstreet et al. 1989); selectively bred Wistar rat lines with high- versus low-anxiety-related behaviour (HAB versus LAB) (Liebsch et al. 1998); and the continuous distribution of PPI (see section "Sensory Discrimination") response amongst mouse inbred strains, which indicates PPI to be a polygenetic trait (Willott et al. 1994; Bullock et al. 1997; Paylor and Crawley 1997). The success of inbred and selectively bred strains was closely followed by single-gene models developed through homologous recombination in embryonic stem cells, as illustrated by neurokinin-1 receptor knockout mice that display significantly reduced anxiety and stress-related responses (Santarelli et al. 2001) and the glutathione S-transferase M1-knockout mouse model for autism (Yochum et al. 2010). Based on information obtained from genome-wide association studies, single-gene knockout or mutation models will undoubtedly maintain a stable position in the field of psychiatry models. They aid in assessing the putative link between gene and disorder using increasingly powerful and sophisticated tools to elucidate underlying neurobiology and disease mechanisms from the level of synapses over brain circuitry to behavioural outcome (Mitchell et al. 2011). With the advancement of genetic engineering techniques, the number of genetic mouse – and even rat – models is strongly increasing. The development of genetic rat models is of specific value for the study of psychiatric disorders, since they display more complex and sociable behaviour compared to mice. Genetic possibilities in rodents include full knockouts, spatial and/or temporal knockouts, knock-in of human alleles, and precisely engineered chromosomal rearrangements (e.g. inversions, deletions, translocations or duplications) into syntenic animal genes (van der Weyden and Bradley 2006). The theory that genes and environment combine to confer susceptibility to the development of diseases surfaced in the early half of the last century, but the use of such a framework for exploring the aetiology of psychiatric disorders is more recent. Given the fact that many – if not all – psychiatric disorders are multifactorial, sophisticated genetically engineered animal models can of course also be used to disentangle complex aetiological mechanisms with the appraisal of gene–environment interactions. Laviola et al. (2009), for example, studied the effect of repeated maternal separation or exposure to pesticides early in ontogeny on the reelin-deficient mouse, i.e. the reeler model that has been linked to autism and schizophrenia.

1.2.3 Animal Models of Schizophrenia

1.2.3.1 Aetiology and Symptomatology of Schizophrenia

Schizophrenia is a devastating and common psychiatric disorder that is associated with a high degree of medical morbidity and reduced life span. Both incidence and prevalence estimates vary across the world, and even within countries, and at the

local and neighbourhood level. The median lifetime prevalence was estimated at 4/1,000 and the lifetime morbid risk at 7.2/1,000, while the median incidence was estimated at 15.2/100,000 individuals. Incidence rates differ between sexes with a male to female ratio of 1.4:1 (for review, see McGrath et al. 2008). These variations are supportive of the assumption that schizophrenia is a clinical syndrome, perhaps comprising several disease entities.

Symptoms cluster into three categories: positive symptoms (including hallucinations, delusions, thought disorder and conceptual disorganisation), negative symptoms (including emotional blunting, social withdrawal, anhedonia, avolition, poverty of thought and content of speech) and cognitive dysfunction (including impaired executive functioning, working memory and attention) (Andreasen 1995). The onset of some aspects of the disease may be observed from birth onward, but psychotic symptoms generally become manifest in late adolescence and early adulthood in males, with an extended onset period in females (Carpenter and Koenig 2008; McGrath et al. 2008).

The dopamine hypothesis of schizophrenia proposes that dysfunction in dopaminergic neurotransmission, specifically hyperactivity of dopaminergic neurons in the limbic system and striatum, produces the positive symptoms, while underactive mesocortical dopaminergic neurons cause the negative, cognitive and affective symptoms of schizophrenia (Seeman 1987). Besides the dopaminergic hypothesis, dysfunction of the glutamatergic system has been implicated in schizophrenia (Olney and Farber 1995; Tsai and Coyle 2002). Glutamate is the major excitatory neurotransmitter in the CNS. The glutamate hypothesis posits that the function of the NMDA receptor is compromised in this disease. NMDA receptors mediate slow excitatory postsynaptic potentials, which are considered critical for the proper expression of complex behaviours, such as associative learning, working memory, behavioural flexibility and attention, many of which are impaired in schizophrenia.

1.2.3.2 Validating Animal Models of Schizophrenia

When validating animal models of schizophrenia, behavioural and electrophysiological endophenotypes are most commonly employed. Currently, still less commonly used endophenotypes focus on neurochemical alterations, e.g. brain dopamine levels (Winter et al. 2009; Ayhan et al. 2011), or on neuroanatomical changes, e.g. reduction of brain (region) volume (Ayhan et al. 2011; Drew et al. 2011), ventricular enlargement (Li et al. 2009; Ayhan et al. 2011) and dendritic spine density (Ayhan et al. 2011; Berlanga et al. 2011).

Electrophysiological Endophenotypes

Electroencephalography recordings have been widely used to assess sensory processing deficits in schizophrenia. Analogous human and rodent auditory-evoked event-related potentials that are similarly affected by pharmacological interventions and stimulus manipulations were described. The human auditory-evoked potential waveform shows characteristic positive deflections 50, 200 and 300 ms poststimulus (respectively, P50, P200 and P300) and a negative deflection 100 ms poststimulus (N100). The rodent analogues are P20, N40, P80 and P120 in order of occurrence.

When exposed to a paired-click paradigm (S1 – 500 ms interval – S2), the waveform amplitudes are lower after S2 than after S1. Schizophrenia patients display a gating deficit based on a decreased response to S1 and/or a failure to inhibit S2 that results in similar amplitudes after S1 and S2. Useful endophenotypes with acknowledged heritability include decreased P50 (P20), N100 (N40) and P200 (P80) amplitude and gating, as well as decreased P300 (P120) amplitude. Schizophrenia patients also show a reduced ability to detect changes in the auditory environment, which is measured with a mismatch negativity paradigm, an exaggerated negative voltage deflection following N100 (N40), elicited when the qualitative features of a novel tone fail to match the pattern of a previous series of repetitive tones (for review, see Amann et al. 2010).

Cognitive Endophenotypes

The cognitive phenotype can be evaluated using various protocols and paradigms (Crawley 2000), including a wide range of dry land (e.g. radial arm maze) and water mazes (e.g. Morris water maze) to specifically assess working memory. Contextual and fear conditioning are based on learning the association of a nonaversive context or cue with an aversive stimulus and the evaluation of freezing responses. The novel object recognition task is based on the rodents' tendency to focus attention on novel objects in their surroundings and the evaluation of exploration of a familiar versus a new object. Impairments in different forms of behavioural flexibility are commonly associated with schizophrenia. A number of behavioural paradigms using different sensory modalities and classes of stimuli have been developed to assess behavioural flexibility, in particular reversal learning, in rodents (Floresco et al. 2009).

Locomotor Activity

The majority of early tests for schizophrenia-related behaviours in rodents were based on the antipsychotic activity of dopamine D2 receptor antagonists (Ellenbroek and Cools 1990), with behavioural outcome parameters including locomotor hyperactivity and stereotyped sniffing and/or grooming. Locomotor activity can be scored in an open-field arena equipped with a video tracking system or infrared sensors to detect spontaneous exploration and ambulatory horizontal locomotion over a specific time frame (Crawley 2000). Motor stereotypy is mostly scored in rodents employing the Creese–Iversen stereotypy scale ranging from 0 (mouse either sleeping or inactive) to 6 (mouse engaged in continuous and nonstop route-tracing stereotypic behaviours) (Creese and Iversen 1973). Repeated administration of psychostimulants, including amphetamine, causes sensitisation to the motor-activating properties, as exemplified by enhanced hyperlocomotion and increased neuronal release of dopamine after the second or third administration. Behavioural sensitisation is quantified by repeatedly testing spontaneous ambulatory locomotion in an open-field arena (Crawley 2000).

Sensory Discrimination

Abnormalities in the automatic processes of sensory discrimination, orienting and reorienting of attention are evident in the early phases of schizophrenia. Two

attentional tasks were developed to be used both in humans and rodents: latent inhibition (LI) and PPI of the startle reflex. LI is the retarded conditioning to a stimulus that is repeatedly presented without reinforcement. In other words, the prior experience that a stimulus does not have a consequence makes it less likely that the brain will form an association with that stimulus later. LI is widely considered to relate to the cognitive abnormalities that characterise schizophrenia because it reflects an organism's ability to ignore irrelevant stimuli. One major strength of the LI task is that it can be applied across (mammalian) species (Lubow and Gewirtz 1995; for review, see Amann et al. 2010).

PPI of the startle reflex is a neurophysiological and behavioural measure of sensorimotor gating. One of its primary advantages is its ability to translate between mice and humans, as it is one of the few tests that is largely conserved across all vertebrate species. In rodents, the startle response is typically evoked using either acoustic or tactile stimuli and is characterised by contractions of the major muscles of the body, generally leading to extension of the forepaws and hind paws followed by muscle flexion into a hunched position. PPI is evoked when a weak stimulus (e.g. a 70- to 80-dB tone or a puff of air) inhibits the subsequent startle response to a strong stimulus (e.g. a 120-dB tone or a second puff of air) if presented within 100 ms. The whole-body startle from the rodent, restrained in a cylindrical holder, is quantified with piezoelectric motion sensors. Abnormal sensory inhibition may reflect a deficit in processing and prioritising incoming sensory information (Crawley 2000; for review, see Amann et al. 2010). A genetic component underlying PPI was suggested based on inbred mouse strain differences (Paylor and Crawley 1997).

Negative Symptoms

Certain negative symptoms, like poverty of speech, may be uniquely human, but other negative symptoms can be assessed in rodents using relatively simple behavioural paradigms. Anhedonia is studied with the sucrose preference test, which measures reduction in reward function in rodents (Crawley 2000). Deficits in social functioning is best scrutinised in rodents using a range of behavioural protocols, which may include a social choice paradigm for spontaneous affiliative behaviour, assessments of social recognition–discrimination, play-soliciting behaviour, social grooming, dominance, aggression and social defeat. Other negative symptoms, including avolition and blunted affect, have been studied in rodents using respectively behavioural despair tests (forced swim test and tail suspension test) and general anxiety tests, but interpretation is rather controversial (O'Tuathaigh et al. 2010).

1.2.3.3 Neurodevelopmental Schizophrenia Models

Epidemiological evidence indicates gestational or perinatal exposure to adverse environmental events, like maternal stress, malnutrition and infection, and obstetric complication (e.g. hypoxia) increases the risk of developing schizophrenia (Lewis and Levitt 2002). Exposure to early-life adverse events combined with genetic predisposition is hypothesised to trigger deviating neuronal development and connectivity leading to the development of schizophrenia. When developing animal models

based on this neurodevelopmental hypothesis, the timing of the exposure to a certain adverse event during the sensitive perinatal period is critical. Various adverse events have been applied, including postweaning social isolation (Fone and Porkess 2008), gestational exposure to the DNA-alkylating agent methylazoxymethanol acetate (Lodge and Grace 2008), exposure to bacterial or viral infection of pregnant rats (Gayle et al. 2004; Buka et al. 2008) or maternal exposure to stress (Martínez-Téllez et al. 2009; Markham et al. 2010). Depending on the chosen procedure and timing, these models may display, amongst others, disrupted sensory gating, decreased social interaction, cognitive deficits and enhanced drug-induced locomotion.

1.2.3.4 Drug-Induced Schizophrenia Models

The development of an animal model is often based on the observation that certain drugs produce abnormal behaviour in healthy people. Usually the following steps are included in the process of developing an animal model based on pharmacological compounds: (1) the drug in question induces behavioural effects in healthy people that resemble human psychiatric pathology; (2) the drug induces specific biochemical alterations in animals; (3) the drug produces similar behavioural effects in animals, allowing for any species differences in behaviour; (4) the biochemical observations in animals provide insight into the behavioural effects of the drug in humans; and (5) if the behavioural effect of the drug in humans has the same characteristics as pathological behaviour, then the biochemical changes produced by the drug in animals may also provide data relevant for the understanding of the abnormal human behaviour. The vast majority of schizophrenia-related models have been based on the induction of abnormal behaviour by psychotomimetics, including both psychostimulants and hallucinogens. These drug-induced states, however, resemble the early stages of a range of psychotic disorders, and not necessarily the diagnostic syndrome of schizophrenia.

Psychostimulant Models

The most widely studied class of drug-induced animal models of schizophrenia is based on behavioural effects of psychostimulant drugs, such as amphetamine. Amphetamine-induced psychosis has been used as a model to support the dopaminergic hypothesis of schizophrenia (Seeman 1987). A hypodopaminergic state in the frontal-cortical terminal fields of mesocortical dopaminergic neurons has also been proposed to be the basis of negative symptoms (Dworkin and Opler 1992), but these are relatively rare in amphetamine-induced psychosis, due to the hyperdopaminergic nature of this model. One of the primary consequences of amphetamine treatment is the release of catecholamines from nerve terminals. In addition to its effects on release, amphetamine also blocks the reuptake of catecholamines from the synaptic cleft, and in high dosages, it is a potent monoamine oxidase inhibitor (Kokkinidis and Anisman 1981).

In rodents, chronic amphetamine administration induces a persistent sensitisation that, both behaviourally and neurochemically, mirrors several features linked to the positive symptoms of schizophrenia. Behavioural alterations include locomotor

hyperactive and/or stereotypy or perseverative behaviours, reduced PPI and disrupted LI (for review, see Featherstone et al. 2007). While amphetamine sensitisation does not produce memory impairments similar to those seen in schizophrenia, it does produce strong impairments in set-shifting, suggesting schizophrenia-like changes in prefrontal functioning (Featherstone et al. 2007, 2008). Interestingly, rhesus monkeys displayed behavioural alterations reminiscent of schizophrenia-like hallucination, including tracking, grasping 'at thin air', manipulating nonapparent stimuli (e.g. picking at imaginary parasites) and hypervigilance after amphetamine administration (Castner and Goldman-Rakic 1999, 2003).

Hallucinogen Models

NMDA receptor antagonists, such as phencyclidine (PCP, 'angel dust') and ketamine, produce psychotic symptoms and cognitive disturbances reminiscent of schizophrenia (Cohen et al. 1962; Krystal et al. 1994), findings that have contributed to the hypoglutamatergic hypothesis of schizophrenia. As opposed to amphetamine-induced psychosis, hallucinogen-induced psychosis encompasses negative symptoms (e.g. emotional withdrawal) as well. Positive schizophrenia-like symptoms induced in laboratory animals include hyperlocomotion, stereotyped movements, circling and ataxia, while deficits in social behaviour are reminiscent of negative symptoms typical for schizophrenia. PCP and PCP-like drugs impair sensorimotor discrimination (LI and PPI) and affect performance in several cognitive paradigms, both in rats and monkeys (Javitt and Zukin 1991; Jentsch and Roth 1999).

1.2.3.5 Lesion-Induced Schizophrenia Models

To address some of the issues surrounding progressive neurodevelopmental or neurodegenerative changes in schizophrenia, a number of targeted lesion animal models have been developed. Besides electrolytic and aspiration lesions, the majority of models is based on the application of excitotoxic agents (Marcotte et al. 2001). Three major sites of actions were chosen based on their presumed involvement in schizophrenia, i.e. the prefrontal cortex, hippocampus and thalamus. The prefrontal cortex is involved in higher cognitive functions, including attention, working memory, emotional expression and social interaction. Executive function allows us to interact with the world in a purposive, goal-directed manner. It relies on several cognitive control operations that are mediated by different regions of the prefrontal cortex. The hippocampus modulates activity of the prefrontal cortex and thus exerts direct control over the schizophrenia-linked mesolimbic dopaminergic system. The thalamus is the brain's relay station that filters and gates sensory information and is therefore involved in PPI. Despite reasonable claims of predictive and face validity for many adult lesion models, the required size and temporal nature of these lesions limits their construct validity as animal models of schizophrenia. The neonatal ventral hippocampus lesion model is the best characterised model to test neurodevelopmental hypotheses of schizophrenia. This excitotoxicity model leads to dopamine-related behavioural alterations in adolescence or early adulthood, which include hyperlocomotion in response to stress, sensory gating deficits (PPI and LI),

disturbed working memory and reduced social contacts, as well as psychotomimetic-induced hyperactivity, apomorphine-induced stereotypies and reduced catalepsy in response to haloperidol. Aberrant development of the prefrontal cortex, illustrated by molecular changes in this region, in response to neonatal hippocampal damage may be a critical factor in the onset of symptoms (for review, see Lipska and Weinberger 2000). The neonatal rat excitotoxic brain lesion model was also adapted to the ventral thalamus (Wolf et al. 2010) and the prefrontal cortex (Klein et al. 2008; Lazar et al. 2008).

1.2.3.6 Genetic Schizophrenia Models

As exemplified by twin studies, schizophrenia has a substantial genetic compound (Cardno et al. 1999). An important shift can be observed in the way animal models are being used for the genetic dissection of psychiatric disease. Initially, inbred strains, often selectively bred for a disease-specific trait, dominated the literature, followed by single-gene knockout or mutation models developed with homologous recombination in embryonic stem cells. Whole-genome association studies are presently expected to provide strong evidence for the involvement of susceptibility genes that will lead to attempts to model multiple susceptibility genes. In addition, the development of microarray and proteomic technology has enabled global description of gene expression in schizophrenia, although it may be difficult to distinguish between primary aetiology and secondary pathology, confounding influences or compensatory mechanisms. Changes in gene expression with a primary etiopathological role may arise from sequence variants in regulatory regions of genomic DNA, epigenetic/stochastic variation or environmental influences, while secondary changes may reflect points of convergence in the action of individual susceptibility genes (for review, see Bray 2008). Given the complex aetiological nature of schizophrenia, genetic models expressing risk genes may form the basis to study the effect of environmental manipulation on such mutant phenotypes at specific developmental stages and may help in defining the trajectory, relative contribution of and interaction between genes and environmental factors in the emergence of the schizophrenia phenotype (Desbonnet et al. 2009).

Inbred and Selectively Bred Rodent Strains

Remarkable variability in outcome of specific cognitive and behavioural tasks is evident in different rodent strains (van der Staay and Blokland 1996; Crawley et al. 1997; Crawley 2000). Genetic factors determine sensory and sensorimotor gating in rodents, and consequently, strain differences in baseline startle response and PPI have been described (Paylor and Crawley 1997; Palmer et al. 2000; Willott et al. 2003; Pietropaolo and Crusio 2009). Moreover, strain and substrain differences for pharmacological (e.g. amphetamine-based) disruption of sensorimotor gating were observed (Kinney et al. 1999; Swerdlow et al. 2000, 2012; Varty et al. 2001). Interestingly, strain-dependent changes across adolescence have been observed, indicating that genetic factors and the early adolescent phase are critically important considerations in the design of animal models of neuropsychiatric disturbances (Pietropaolo and Crusio 2009). Variations between strains and substrains, whether

or not accomplished through selective breeding, form a good basis to study the underlying biological mechanisms and hence, therapeutic strategies in schizophrenia (Swerdlow et al. 2005, 2012; Dieckmann et al. 2007; Gogos et al. 2008; Flood et al. 2011).

Genetically Modified Models

Promising candidate genes for schizophrenia are dysbindin (*DTNBP1*, for review, see Williams et al. 2005); neuregulin 1 (*NRG1*) and its receptor *ERBB4* (for review, see Banerjee et al. 2010); *DISC1* (i.e. disrupted in schizophrenia-1; for review, see Muir et al. 2008); reelin (*RELN*; for review, see Grayson et al. 2006); components of the Akt-GSK3β signalling pathway, including AKT1 (Freyberg et al. 2010); and genes located in chromosomal region Δ22q11.2, which has been implicated in schizophrenia based on the 22q11.2 deletion syndrome (for review, see Paylor and Lindsay 2006). For an updated list of published genetic association, studies for schizophrenia readers are referred to the SzGene database (Allen et al. 2008).

Several spontaneous mutant rodent models have been studied as presumed phenocopies of schizophrenia. The *sandy* mouse has a deletion of two of the exons of the dysbindin gene and is therefore a naturally occurring dysbindin-knockout model. *Sandy* mice display some behavioural phenotypes with relevance to schizophrenia, including increased anxiety and deficits in social interaction (Hattori et al. 2008). After the discovery of *DISC1* as a potential schizophrenia candidate gene, some of the earliest animal studies on its potential role included the detection of natural mutations in different mouse strains. All 129 mouse substrains carry a 25-bp deletion in the *mDISC1*, which modulates working memory (Clapcote and Roder 2006; Koike et al. 2006). Reeler is an autosomal recessive mutant mouse with reduced cerebellar size, disruption of the laminar organisation in several brain regions and inversion of neocortical cellular layers (Falconer 1951; Caviness 1976). The reelin-haploinsufficient heterozygous reeler mouse has been used as an animal model for schizophrenia based on several neuropathological and behavioural abnormalities homologous to schizophrenia. Heterozygous reeler mice exhibit alterations in sensorimotor gating (Barr et al. 2008), deficits in working memory (Brigman et al. 2006) and impaired social interaction (Podhorna and Didriksen 2004).

DNA variation that affects expression of candidate disease genes can take various forms, including single nucleotide polymorphisms (SNPs), deletions, insertions, variable repeat sequences, rearrangements or duplications (copy number variations). Downregulation of individual susceptibility genes can be mimicked via gene knockout or via RNA interference, while upregulation can be achieved with gene knock-in techniques or RNA activation.

Multiple genes (perhaps thousands) of small effect are thought to exist for the illness, given its status as a complex genetic illness (Gejman et al. 2011). Nonetheless, tissue effects in animals with risk mutations are presumed to be associated in some way with schizophrenia pathophysiology. The biological characterisation of animals with risk genes is highly relevant to ultimately discovering disease pathophysiology, even though every aspect of the biology may not be critical. For the currently most promising risk genes, few transgenic mouse models will be briefly discussed.

Many mouse models with manipulated expression levels of the different NRG1 isoforms have been created. Mutants with heterozygous deletion of the transmembrane domain exhibit hyperactivity, a deficit in PPI, selective impairment in social novelty preference and altered patterns of social interaction. Studies focusing on deletion of specific NRG1 isoforms have shown that type III NRG1 mutant mice display even more pronounced PPI deficits in addition to working memory dysfunction (for review, see Desbonnet et al. 2009). Homozygous knockout of *NRG1* is developmentally lethal in mice, but viable heterozygous, hypomorphic/conditional knockouts that can modulate neuregulin–ErbB4 signalling have been developed, all with distinct 'schizophrenia-like' alterations, including – depending on the genetic models studied – hyperactivity, PPI, LI and social interaction deficits, impairment in contextual fear conditioning and mismatch negativity (Harrison and Law 2006; Mei and Xiong 2008; for review, see Jones et al. 2011). Seven different strains of transgenic mice containing inducible and/or partial *DISC1* gene mutations resulting in a (partial) loss of DISC-1 function have been created (for review, see Jaaro-Peled 2009). These mice exhibit enlarged lateral ventricles and reduced cortical thickness and brain volume, mimicking some characteristics of schizophrenia. Some mutants display reductions in hippocampal dendritic complexity, structure and density. Some *DISC1* mice display PPI deficits that are attenuated with antipsychotics, while hyperactivity, reduced sociability, working memory and executive function impairments have been described as well.

Discussing all currently developed genetic models of schizophrenia would go beyond the scope of this chapter. Readers are referred to some of the recent review papers referred to in the preceding paragraphs or the Schizophrenia Research Forum website for more in-depth information (http://www.schizophreniaforum.org/).

1.3 Animal Models of Neurological Disorders

The discovery of new therapies for neurological disorders is predicated on the use of animal models both to identify new therapeutic targets and to perform preclinical trials of drugs prior to clinical application. In both cases, the challenge is to develop models that recapitulate the disorder. The starting point for the development of a new animal model for a specific neurological condition is often the current dominant theory about the disease. Although a logical first approach, it is essential to broaden the focus of animal models under development based on the increasing knowledge of underlying disease mechanisms. The development of animal models for Alzheimer's disease (AD) serves an excellent example of such a strategy.

Advances in biochemical pathology and human genetics have yielded striking progress in our understanding of molecular mechanisms underlying nervous system diseases such as AD, Parkinson's and Huntington's disease. Of great importance is the pivotal concept that certain normally soluble neuronal proteins can misfold and aggregate into oligomers and fibrils, which can confer profound cytotoxicity. Perhaps the foremost example, both in terms of its societal impact and how far knowledge has moved toward the clinic, is that of AD, hence the focus of the following paragraphs.

1.3.1 Approaches to Modelling Neurological Disorders

In contrast with psychiatric disorders, approaches to model neurological conditions are not easily categorised. The approach largely depends on the aetiology of the human neurological condition, which may be acquired or degenerative. Specific approaches when developing new animal models should be applied depending on the aetiology, which may be amongst others infectious (e.g. Creutzfeldt–Jakob disease, HIV dementia), immune-related (e.g. multiple sclerosis), genetic (e.g. Charcot–Marie–Tooth disease; leukodystrophies), lesion-based (e.g. head trauma), and environmental/toxicity-related (e.g. alcohol-related dementia, toxic-metabolic encephalopathy).

1.3.2 Animal Models of Alzheimer's Disease

1.3.2.1 Aetiology and Symptomatology of Alzheimer's Disease

As the prototype of cortical dementias, AD is characterised by prominent cognitive deficits. Patients initially exhibit limited forgetfulness with disturbance of memory imprinting, which further evolves to short-term memory disruption and, ultimately, to long-term memory deficits. At more advanced stages, patients display executive dysfunctioning leading to advanced helplessness (Selkoe 2000). Besides cognitive deterioration, patients demonstrate behavioural and psychological signs and symptoms of dementia (BPSD), including paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, anxieties and phobias (Reisberg et al. 1987). The histopathological hallmarks of AD brain are extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFT), accompanied by decreased synaptic density, which eventually leads to widespread neurodegeneration and failure of neurotransmitter pathways, particularly those of the basal forebrain cholinergic system (Selkoe 2001). The number of affected individuals is likely to grow in the decades to come as a result of demographic changes and rising life expectancy. It is forecast that the worldwide number of elderly people suffering from dementia will rise to 63 million in 2030 and to 114 million in 2050 (Wimo et al. 2003).

1.3.2.2 Validating Animal Models of Alzheimer's Disease

Cognitive Symptoms

A variety of paradigms and protocols has been developed to assess cognitive functions in rodents (for review, see Crawley 2000 and Buccafusco 2008). Ideally, several paradigms requiring distinct sensory and motor abilities are chosen when phenotyping a new dementia model. Protocols distinguishing explicit versus implicit memory can be chosen, as well as designs assessing short-term versus long-term memory (Tulving 1987). The Morris water maze is presently the most widely used paradigm for the evaluation of hippocampus-dependent visual-spatial learning and memory skills in rodents, which represents the highest cognitive level appreciable in rodents (for review, see; D'Hooge and De Deyn 2001). Besides the Morris

water maze, several other mazes could be employed, which are all based on the same principle; successfully passing through the maze is rewarded by escaping from the water in wet mazes or by food as a positive reinforcer in dry-land mazes. Examples include the plus-shaped water maze, radial arm mazes, multiple Y mazes and the Barnes maze. Complex nonspatial hippocampus-dependent tasks like the odour paired-associates task (Bunsey and Eichenbaum 1996) are analogous to the verbal paired-association task for humans, but the long duration of the protocol, which requires several months, makes it unsuitable for the assessment for memory in progressing phenotypes (Van Dijck et al. 2008). The same disadvantage may arise when using schedule-induced operant tasks employing operant conditioning or Skinner boxes. Both active and passive avoidance learning protocols are widely used to assess cognitive function in a short time frame. However, procedural components of the task are not easily distinguishable from declarative memory components as is the case in the Morris water maze or in cued and contextual learning (Crawley 2000). Associative learning (cued and contextual conditioning) requires a different set of sensory and motor functions, so that the procedural components of associative tasks do not overlap. Other potentially useful learning and memory tasks include novel object recognition, conditioned taste aversion, social recognition and discrimination learning.

BPSD-Related Symptoms

In accordance with the increased clinical focus on BPSD, major efforts have been made to mimic specific behavioural alterations in animal models and to develop useful tools (for review, see Crawley 2000 and Buccafusco 2008) to evaluate new psychopharmacological strategies to replace atypical antipsychotics or classic neuroleptics, which display only modest effect size and are frequently associated with significant side effects (De Deyn et al. 2005).

Activity and circadian rhythm disturbances can be easily screened using infrared sensors surrounding the animal's home cage. The number of beam interruptions over a specific time interval is recorded as a measure of activity comparable to actigraphic measurements in the clinical setting (Vloeberghs et al. 2004). Aggressive behaviour in male rodents can be provoked using a variety of behavioural protocols based on dominance hierarchy, as is the case in the commonly used isolation-induced resident–intruder protocol (Valzelli 1973). Anxiety and fear-related behaviours can be assessed using both conditioned (i.e. conflict tests like the Vogel's lick-suppression test) and unconditioned response tests, which are based on the quantification of fear-related responses like freezing, defecation and thigmotaxis, and the conflict between the innate trait of nocturnal animal like mice and rats to prefer narrow, dark enclosures and the tendency to explore new environments (Crawley 2000). Appraisal of depression-related symptoms in rodents is based on learned helplessness and behavioural despair phenomena, in which animals are exposed to uncontrollable and inescapable stress, e.g. the Porsolt forced swim test, the tail suspension test and inescapable shock paradigms. Failure to try to escape from this type of aversive stimulus in rodents is considered to model a depression-like state (Chourbaji et al. 2005). Anhedonia, a core symptom of clinical depression, which is defined as the

loss of sensitivity to reward, can be assessed in rodents with a sucrose preference test during which the consumption of a 0.8 % sucrose solution is compared to the simultaneous consumption of tap water (Sanchis-Segura et al. 2005). Phenotyping can also focus on ingestive behaviour. The intake of food and water can be screened using metabolic cages. More detailed analysis of food intake is possible in operant conditioning boxes equipped with pellet dispensers and optical lick-o-meters that allow appraisal of the circadian rhythm of ingestive behaviour (Vloeberghs et al. 2008).

Pathological Alterations

Amyloid structure is most commonly stained using congo red, thioflavin S or Aβ-specific antibodies (for review, see Castellani et al. 2007; Vidal and Ghetti 2011). Amyloid plaque burden can be evaluated by employing stereological methods, which allow a three-dimensional geometrical interpretation of structures based on observations made on two-dimensional sections. Levels of Aβ peptides and other APP-derived molecules can be quantified using ELISA or Western blotting techniques. While ELISA is a very sensitive method to detect and quantify total Aβ levels, commercially available kits provide no or very little information on the possible aggregation state and structure of Aβ. Western blotting, on the other hand, is less suited for quantification but makes it possible to detect aggregates and roughly estimate their size. However, it still only provides very limited information about the structure and composition of the aggregates. Researchers more interested in the molecular structure, composition and formation of the oligomers turned to mass spectrometry techniques, which allow very accurate determination of protein identity, amino acid sequence and presence of modifications, or even – when using nondenaturating approaches – the macromolecular structure (Ashcroft 2010; Bleiholder et al. 2011). Tau pathology can be assessed at various levels, including a quantitative assessment using Western blot, biochemical and immunohistochemical determination of different phosphorylation states and sites, as well as the immunohistochemical assessment (e.g. with the ALZ-50 monoclonal antibody) of the spatiotemporal progression of tau pathology (Rankin and Gamblin 2008). Monitoring inflammatory processes can be based on the use of histopathological and immunohistochemical markers of astrocyte and microglia activation, as well as on various biochemical assays of inflammatory markers in body fluids (McGeer and McGeer 2003). Potential biomarkers of oxidative stress, including an imbalance between free radicals (reactive oxygen and nitrogen species) and the antioxidant response (free radical scavengers and antioxidant enzymes), as well as the subsequent damage to macromolecules (lipids, proteins, nucleic acids and sugars), can be determined in body fluids or brain using a wide range of biochemical techniques, including spectrophotometric, fluorometric, chromatographic and immunohistochemical assays (Migliore et al. 2005). Degenerative processes (e.g. neuritic spheroids) can be visualised by silver impregnation, neurofilament or ubiquitin immunostaining (Castellani et al. 2007).

Neurochemical Alterations

The cholinergic hypothesis of AD is based on the fact that degeneration of cholinergic neurons in the nucleus basalis of Meynert, situated in the basal forebrain and

primarily projecting to the neocortex, occurs early in the course of the disease and leads to a marked decline in the activities of choline O-acetyltransferase (ChAT) and acetylcholinesterase (AChE) (for review, see Contestabile 2011). In rodent models, the presence of cholinergic deficits can be scrutinised with the determination of ChAT or AChE enzyme activities based on, respectively, a radiochemical (Fonnum 1975) and a spectrophotometric (Ellman et al. 1961) protocol. Microdialysis extraneuronal sampling coupled with a high-sensitivity HPLC detection and quantification method has been often used for assessing the cholinergic impairment and its recovery in many AD models (Pepeu and Giovannini 2007). Moreover, immunohistochemical visualisation and quantification of ChAT- or AChE-positive neurons and fibres has been employed, as well as determination of high-affinity choline uptake, considered a biochemical marker of the localisation and integrity of the cholinergic nerve endings and a measure of the activity of the cholinergic neurons (for review, see Pepeu and Rosi 2011).

Neurochemical alterations observed in AD brain, however, are not confined to the cholinergic system. Moreover, many data indicate that the neurochemical alterations underlying cognitive deterioration and related disturbances in cortical processing implicate more widespread neurodegeneration that cannot be attributed solely to the cholinergic system (for review, see Dringenberg 2000). Neuronal loss and, inherently, alterations in the concentration of neurotransmitters and metabolites of the noradrenergic, adrenergic, dopaminergic and serotonergic system, as well as neurotransmitter amino acids, have been described in AD (for review, see Gsell et al. 2004). In rodent models, chromatography-based determination of neurotransmitter (and metabolite) levels in microdialysis samples or brain (region) homogenates can be employed to assess neurotransmitter alterations. Deficits in peptidergic neurotransmission (or co-transmission) have been implicated in AD. Classically, neuropeptides are mainly studied by radioimmunoassay and immunohistochemistry, but recently researchers have shifted to mass spectrometry-based methodologies (for review, see Van Dam et al. Accepted for publication *Current Alzheimer Research* 2013).

1.3.2.3 Spontaneous and Selectively Bred Alzheimer's Disease Models

Some species, including dogs (Cummings et al. 1993, 1996; Rofina et al. 2006), cats (Head et al. 2005; Gunn-Moore et al. 2006), bears (Cork et al. 1988; Tekirian et al. 1996; Uchida et al. 1995), goats and sheep (Braak et al. 1994), wolverine (Roertgen et al. 1996), as well as several nonhuman primate species (Bons et al. 1994; Gearing et al. 1994, 1997; Lane 2000; Geula et al. 2002; Kimura et al. 2003; Sani et al. 2003; Lemere et al. 2004, 2008), spontaneously develop plaque pathology and some species even display tauopathies. These histopathological changes can be accompanied by cognitive decline (Cummings et al. 1996; Voytko and Tinkler 2004; Rofina et al. 2006; Gunn-Moore et al. 2006). The use of these species for experimental research is however limited by availability, economical (based on long lifespan) and/or ethical reasons.

Ageing rodents do not spontaneously develop histopathological AD-like hallmarks, but do display senescence-related cognitive decline and behavioural alterations associated with neurochemical and morphological alterations (Erickson and

Barnes 2003), including age-associated cholinergic hypofunction (Sherman and Friedman 1990). In addition, they aid in uncovering the boundary between normal and pathological ageing, allowing in-depth investigation of basic neural mechanisms underlying brain ageing.

Selective breeding from a genetic pool of AKR/J mice has led to the development of the senescence-accelerated mouse (SAM) model, which includes nine major SAM-prone (SAMP) substrains and three major SAM-resistant substrains. The SAMP8 substrain is of particular interest given the development of age-associated learning and memory deficits in association with Aβ deposition (Butterfield and Poon 2005; for review, see Renã and Butterfield 2011).

Pharmacological, Chemical and Lesion-Induced Rodent Models of Alzheimer's Disease

Disruption of multiple neurotransmitter systems underlies the cognitive and behavioural disturbances associated with AD. The majority of animal models that fall within this category are based on the cholinergic hypothesis of AD, which states that degeneration of cholinergic neurons in the nucleus basalis of Meynert, located in the basal forebrain and projecting to the neocortex, occurs early in the course of the disease (Davies and Maloney 1976; Whitehouse et al. 1982). The most widely used pharmacological model is scopolamine-induced amnesia (Sunderland et al. 1986; Ebert and Kirch 1998). The application of this muscarinic antagonist has increased our knowledge of the role of the cholinergic system in cognition and allows preclinical evaluation of symptomatic efficacy of cholinomimetics. The applicability of this model is however limited by the fact that cholinergic hypofunction is not associated with the development of AD-typical pathology, and the lack of disease progression both at the cholinergic and cognitive level. Blockade of nicotinic receptors by mecamylamine also induces learning impairment (Moran 1993; Estapé and Steckler 2002). Since AD brain shows both reduced muscarinic and nicotinic acetylcholine receptor densities (Whitehouse and Au 1986; Nordberg et al. 1989), blockade of both receptors may offer a better animal model for AD-related amnesia (Levin et al. 1990; Riekkinen et al. 1990).

In addition to scopolamine-induced amnesia, cortical cholinergic involution has been replicated in lesion models that focus on specific cholinergic centres of the basal forebrain, as well as more general lesions of all basal forebrain cholinergic neurons. Focal lesions are most often directed at the nucleus basalis magnocellularis (Lescaudron and Stein 1999; Vale-Martínez et al. 2002), the rodent analogue of the nucleus basalis of Meynert, the septal area (Mulder et al. 2005), or include fimbria/fornix transection leading to septo-hippocampal cholinergic denervation (He et al. 1992; Alonso et al. 1996). Lesions can be induced by mechanical, i.e. knife cut, or electrolytic procedures and intraparenchymal or intracerebroventricular microinjections of neurotoxic substances, such as quinolic, kainic, ibotenic and quisqualic acids, NMDA, the cholinotoxin AF64, and the immunotoxin 192 IgG-saporin (for review, see Toledana and Alvarez 2011). Such lesion models increase our understanding of the role of cholinergic innervations in the aetiology and treatment of cognitive disorders.

AD-related memory deficits can also be (partially) reproduced by lesioning brain structures or pathways essential for different aspects of learning and memory, such as the hippocampus, striatal or cortical regions (Gray and McNaughton 1983; Glenn et al. 2003; Sloan et al. 2006; Castañé et al. 2010). These models increase our knowledge of the neural mechanisms underlying memory dysfunction, but of course lack disease progression and do not develop AD-like pathological hallmarks. Moreover, selected lesions are compared with the more global disease process of AD.

Certain chemically induced models focus on one specific pathophysiological pathway thought to underlie AD, such as neuroinflammation or glucose/energy metabolism impairment, and their effects on neurodegeneration. Neuroinflammation develops upon the infusion of endotoxins, like lipopolysaccharide (Hauss-Wegrzyniak et al. 1998), or proinflammatory cytokines (Wenk et al. 2003). Brain metabolism can be disrupted through interference with mitochondrial metabolic pathways (Szabados et al. 2004) or neuronal insulin signal transduction (Ishrat et al. 2009).

1.3.2.4 Amyloid-β Infusion Rodent Models of Alzheimer's Disease

The amyloid cascade hypothesis states that cerebral accumulation and aggregation of Aβ peptides into amyloid plaques is the primary culprit in AD (Selkoe 2000; Hardy and Selkoe 2002). More recently, a key role was assigned to soluble Aβ oligomers (Gong et al. 2003; Lacor et al. 2004; Walsh and Selkoe 2007; Selkoe 2008) (Fig. 1.1).

Aspects of AD can be modelled by acute or repetitive intracerebral or intracerebroventricular infusion of Aβ peptides in rodent brain (for review, see Lawlor and Young 2011). To better mimic the progressive nature of AD, chronic and continuous administration is accomplished by connecting an implanted cannula to an osmotic mini-pump (Nakamura et al. 2001; Olariu et al. 2002) or a micro-infusion pump (Nag et al. 1999), or with microdialysis (Harkany et al. 2000). In addition to measurable adverse effects on memory and behaviour (Harkany et al. 1998; Yamada et al. 2005; Sipos et al. 2007), exogenous administration of Aβ peptides can lead to AD-like neuropathological alterations (Frautschy et al. 1996; Sipos et al. 2007), although the full complexity of the human pathology is not reproduced and pathology is not widespread as in patients. Accumulation of Aβ deposits can be associated with, e.g. inflammation and microglial activation, oxidative stress and local cell loss (Weldon et al. 1998). More specifically, disruption of cholinergic function was reported (Harkany et al. 1998; Yamada et al. 2005).

CNS Aβ infusion animal models provide insight into the mechanisms and secondary effects of Aβ toxicity and allow preclinical evaluation of drugs targeting Aβ, as well as evaluation of protective efficacy of pharmacological modulation of microglial signalling. Rodent infusion models have some advantages over transgenic amyloid-related models. Infusion models can deliver the desired (pathological) outcome within a time frame of a few weeks (Frautschy et al. 1996) versus several months in transgenic models. Moreover, they allow researchers to administer defined amounts of a specific Aβ species of known sequence and length or to introduce controlled cofactors related to plaque development, while transgenic overexpression of APP results not only in increased production of Aβ1-40 and/or Aβ1-42, but in elevated

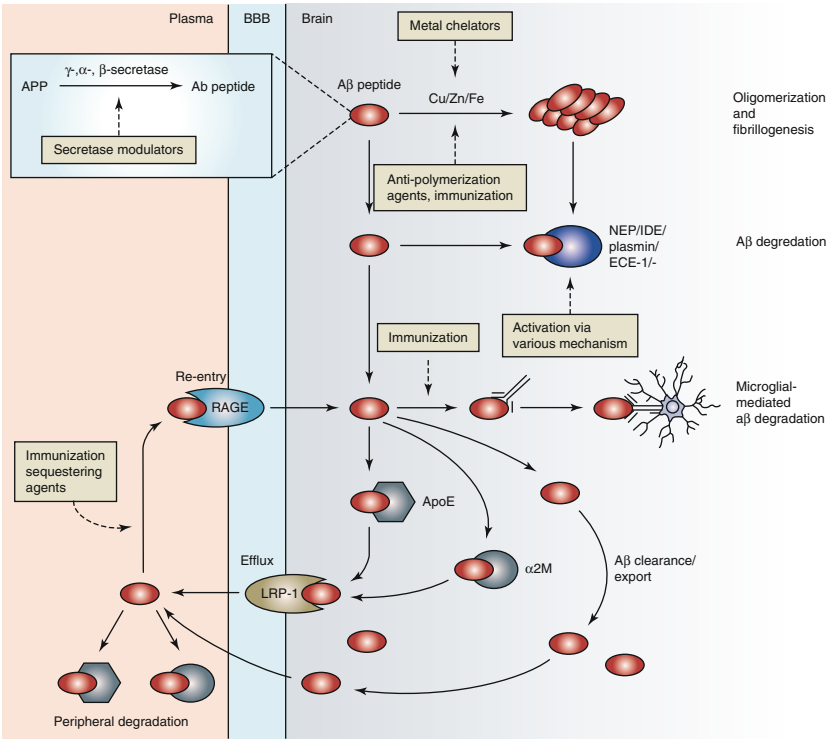

Fig. 1.1 This figure represents the major processing pathways of amyloid precursor protein (APP) and amyloid β (Aβ) peptides, including the potential therapeutic targets and therapeutic interventions. *APP* amyloid precursor protein, *CTF* C-terminal fragment, *NTF* N-terminal fragment, *Aβ* amyloid β peptide, *ApoE* apolipoprotein E, *BBB* blood–brain barrier, *CSF* cerebrospinal fluid, *ECE-1* endothelin-converting enzyme-1, *IDE* insulin-degrading enzyme, *LRP-1* low-density lipoprotein receptor-related protein-1, *NEP* neprilysin, *RAGE* receptor for advanced glycation end products, *α2M* α-2-macroglobulin

levels of other APP fragments, which can have neuroprotective, neurotoxic or signalling functions and influence learning and memory. On the other hand, major caveats of infusion models are the fact that administered Aβ concentrations are much higher than Aβ levels found in the brain or cerebrospinal fluid of AD patients (Vickers et al. 2000) and that effects of ageing on AD progression are lacking. Moreover, the invasive nature of Aβ infusion inevitably brings about brain injury, which – in addition to the potential neurotoxic effects of vehicles used – may contribute to the induction of inflammation observed in these models. These potentially confounding effects should be controlled for by including proper sham and/or scrambled peptide groups.

1.3.2.5 Genetically Modified Alzheimer's Disease Mouse Models

Modelling of AD in transgenic mouse models became reality in the mid-1990s with the development of the platelet-derived growth factor promoter-driven APP (PDAPP) model (Games et al. 1995; for review, see Basak and Holtzman 2011), followed in

subsequent years by the Tg2576 (Hsiao et al. 1996; for review, see Deacon 2011) and the APP23 mouse model (Sturchler-Pierrat et al. 1997; for review, see Van Dam and De Deyn 2011a), currently the most widely used amyloidosis models in AD-related research. The choice of *APP* as the incorporated transgene was based on two lines of evidence: APP is the precursor of Aβ and it is the target of the first described early-onset AD mutations. The PDAPP model expresses human *APP* carrying the Indiana familial AD mutation driven by the platelet-derived growth factor-β promoter, whereas both the Tg2576 and APP23 model express human APP with the Swedish mutation driven by the hamster prion protein and murine Thy-1 promoter, respectively. The discovery of familial AD mutations in the presenilin (PSEN) genes, which influence APP processing, opened the path for PSEN1 and PSEN2 transgenic mouse models and double-cross APP/PSEN models. Although early-onset AD accounts for only a small proportion of AD cases, models expressing pathogenic mutations of human genes have become crucial tools in unravelling disease processes and have boosted drug discovery and development.

Apolipoprotein E (ApoE) has been identified as a major genetic risk factor for developing late-onset AD. Mice expressing a human ApoE isoform, such as Apoε4 (Huber et al. 2000), have been developed to study the pathophysiological link between ApoE and AD.

Genetically modified mouse models based on other aetiological hypotheses that are considered relevant to the preclinical AD field include, e.g. mutated human α-synuclein models (Freichel et al. 2007), TAR DNA-binding protein 43 (TDP-43)-related models (Wu et al. 2010; Wils et al. 2012), mutated human cyclooxygenase-2 overexpression models (Andreasson et al. 2001), anti-nerve growth factor (NGF) mice (in which NGF activity is neutralised using antibodies) (Capsoni et al. 2000), neprilysin (Iwata et al. 2001), insulin-degrading enzyme knockout mice (Farris et al. 2003) and recent crosses between mutated human APP overexpression strains and nitric oxide synthase 2 knockouts (Colton et al. 2008). For more in-depth information and latest updates, readers are referred to the Alzheimer Research Forum website (http://www.alzforum.org), which includes an online compendium of relevant mouse models for AD and related disorders. Most of these models robustly mimic a subset of AD features, including Aβ deposition, plaque formation and cerebral amyloid angiopathy, as well as neurodegeneration, synaptic dysfunction and inflammation, in addition to cognitive decline.

The major limitation of the above-mentioned models, i.e. the lack of NFT formation, was partially counterbalanced with the development of several (mutated) tau models, and the crossing of tau and amyloidosis models, which featured enhanced amyloid deposition accompanied by tau phosphorylation, NFT-like formation and overt neuronal loss (Götz et al. 2004; Ribé et al. 2005). It has proven challenging to develop mice in which both histopathological hallmarks occur in AD-relevant brain regions, such as the hippocampus and cortex. However, the development of triple transgenic (3×Tg) mice seems to have overcome this hurdle (Oddo et al. 2003; for review, see Sy et al. 2011). Rather than crossing independent mutant mouse lines, two transgenes (mutant APP and tau) were microinjected into single-cell embryos from homozygous mutant PSEN1 mice. The major advantages of this approach are

the integration of APP and tau at the same genetic locus (which prevents segregation in subsequent generations), more cost-effective breeding requirements and the fact that there is no mixing or altering of the genetic background. In accordance with the amyloid cascade theory, these 3×Tg mice develop Aβ plaques prior to NFT pathology with a temporal and spatial profile equivalent to AD. Studies using the 3×Tg-AD mice have revealed a strong interaction between Aβ and tau, which synergistically drive the pathogenesis in the brain. The first signs of cognitive decline manifest at age 4 months as a deficit in long-term retention and correlate with accumulation of intraneuronal Aβ in the hippocampus and amygdala (Billings et al. 2005).

For an updated list of genetically modified AD-related models, readers are referred to the website of the Alzheimer Research Forum (http://www.alzforum.org/res/com/tra/default.asp).

More recently, the use of viral vector gene transfer technology has allowed the development of 'somatic transgenic' models, whereby genes putatively involved in AD pathogenesis can be selectively overexpressed in specific brain regions involved in AD (for review, see Jaworski et al. 2010; Lawlor and Young 2011). Although this promising strategy has been shown to result in the development of both cognitive deficits and Aβ deposits, these genetic models require further characterisation to show reproducible development of behavioural deficits and neuropathology prior to their widespread adoption as a reliable and useful model of AD.

1.4 Imaging in Rodent Models of Brain Disease

This chapter does not aim at giving an overview of neuroimaging involving PET and SPECT in models of brain disease, but rather serves as an introduction to models of brain disorders with a selected overview of modelling approaches and methodological aspects with regard to phenotyping. We will briefly describe some relevant imaging techniques and show a couple of examples related to schizophrenia and AD.

With the development of more sophisticated techniques, neuroimaging has become an essential component of studying brain structure and function in the diseased state. In drug development research, utilising methodology and results that can easily be translated from preclinical to clinical platforms will facilitate the identification and the assessment of efficacy of neuroprotective therapeutic compounds to treat CNS diseases. Translational neuroimaging can provide quantitative information on brain morphology and function in preclinical models of CNS diseases, healthy human subjects and patients. Amongst the variety of imaging methods used for understanding and treating brain diseases are PET, SPECT, X-ray/computed tomography, near-infrared optical imaging and magnetic resonance imaging.

Normal laboratory rodents may be used for in vivo biodistribution experiments focussing on CNS penetration and washout of radiotracers, while (transgenic) disease models may form the basis for ex vivo autoradiography to assess binding of probes to the targeted molecule on brain slices, or of course the in vivo evaluation of tracer retention in brain.

1.4.1 Imaging in Schizophrenia

Recent advances in the development and applications of neurochemical brain imaging have improved the ability to study the neurochemistry of the living brain in psychiatric disorders. In particular, PET and SPECT have been used to determine neurochemical substrates of schizophrenia and to uncover the mechanism of action of antipsychotic medications. The growing availability of radiotracers for monoaminergic neurotransmitter synthesis, transporters and receptors has enabled the evaluation of hypotheses regarding neurotransmitter function in schizophrenia derived from preclinical and clinical observations. Ongoing clinical schizophrenia PET-/SPECT-based trials study (1) abnormalities in indices of neurotransmitter systems with an established role in schizophrenia in patients versus controls, (2) new tools to study other neurotransmitter systems or potential biomarkers (e.g. inflammation markers) (Doorduin et al. 2009) (Figs. 1.2 and 1.3) and (3) characterisation of target occupancy by antipsychotic drugs, as well as its relationship to efficacy and side effects (for review, see Urban and Abi-Dargham 2010; http://www.clinicaltrials.gov).

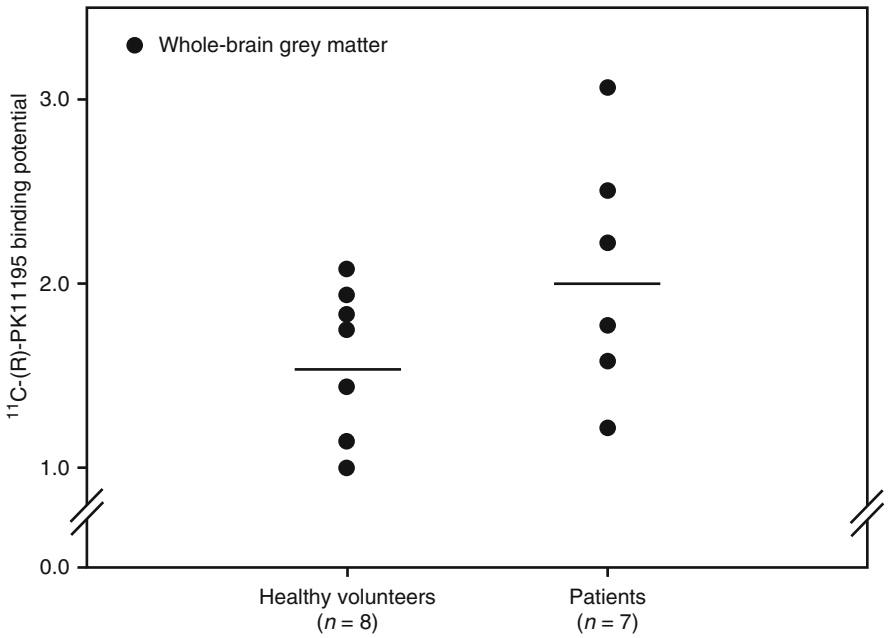

Fig. 1.2 Binding potential of the PET marker [^{11}C]-PK11195 that binds to translocator protein (TSPO), a biomarker to study activated microglia cells, in healthy volunteers and schizophrenia patients. All schizophrenia patients met the DSM-IV criteria of schizophrenia spectrum disorders. Each dot represents an individual subject, and *horizontal lines* represent mean values. Whole-brain grey matter binding potential was 30 % higher in patients versus healthy controls, although this difference did not reach statistical significance (Reprinted from Doorduin et al. (2009) with permission. Copyright@2009 Society of Nuclear Medicine and Molecular Imaging)

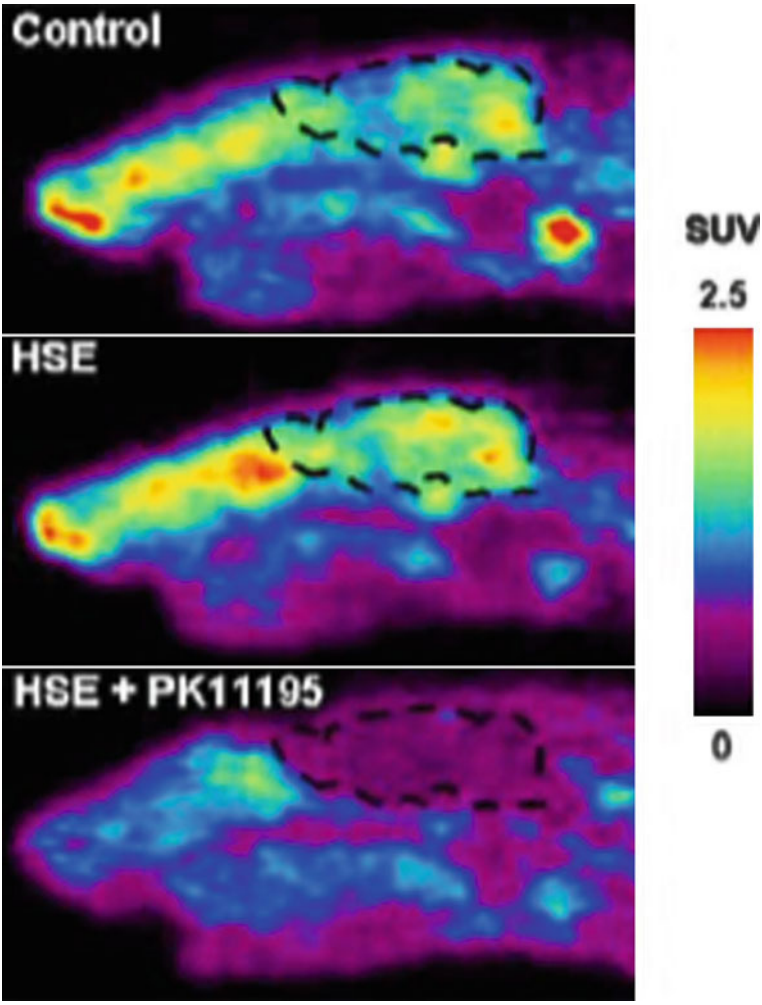

Fig. 1.3 Many neurological and psychiatric disorders are associated with neuroinflammation, which can be studied using PET markers like [^{11}C]-PK11195 that binds to translocator protein (TSPO), a biomarker to study activated microglia cells. The sensitivity of [^{11}C]-PK11195 may however be insufficient to visualise mild neuroinflammation. [^{11}C]-N-(2,5-dimethoxybenzyl)-N-(4-fluoro-2-phenoxyphenyl)-acetamide, [^{11}C]-DAA1106, proposed as a potentially more sensitive neuroinflammation tracer, was evaluated in a rat model of herpes encephalitis (*HSE*). Sagittal view of the head of a control rat (*control*), a rat with HSE and a HSE rat pretreated with 5 mg/kg of unlabeled PK11195 (*HSE + PK11195*), in which the brain is delineated by a *dashed line*. The images represent tracer uptake between 30 and 60 min after injection of [^{11}C]-DAA1106 (44 ± 14 MBq). Images show a high uptake of [^{11}C]-DAA1106 in the brainstem. Pretreatment with unlabeled PK11195 resulted in effective blocking of [^{11}C]-DAA1106 uptake. In vivo uptake, however, did not significantly differ between control and HSE rats. [^{11}C]-DAA1106 may not be an ideal tracer to perform longitudinal PET studies in small animals to study the role of neuroinflammation in neurological and psychiatric disorders (Reprinted from Doorduin et al. (2010) with permission. Copyright@2010 Elsevier)

A variety of PET tracers, including ^{11}C, ^{15}O-water, ^{18}F-fallypride and L-3, 4-dihydroxy-6-^{18}F-fluorophenylalanine (^{18}F-FDOPA), has been used to identify brain abnormalities in schizophrenia based on kinetic modelling. The most consistent findings show a difference in the dopamine content in the prefrontal cortex, anterior cingulate gyrus and hippocampus between healthy controls and schizophrenia patients. In addition, a higher density of D2 receptors in the striatum and neural brain dysconnectivity was observed (for review, see Patel et al. 2010), while [^{11}C]PET to map D1/D2 receptors identified reduced D1R densities in the prefrontal cortex (Okubo et al 1997).

There have been some PET studies of the behavioural sensitisation to psychostimulant drugs in dogs (Nakamura et al. 1997), rhesus monkeys (Castner et al. 2000) and rats (Kilbourn and Domino 2011). Given the presumed contribution of excitatory NMDA-linked neurotransmission to schizophrenia, PET/SPECT has scarcely been used for investigations of NMDA perturbations in experimental animals, including rats (Reith et al. 1998), cats (Vollenweider et al. 2000) and monkeys (Tsukada et al. 2000; van Berckel et al. 2006). Albeit the application of microPET/SPECT in schizophrenia is currently still limited, it will most probably advance with the further development of valid genetically modified mouse models.

1.4.2 Imaging in AD

Aβ plaque-bearing mice are obviously a potentially interesting tool for the development of PET/SPECT tracers aiming at the visualisation of amyloid plaques and/or other AD-typical pathological alterations. With the development of a specific tracer that reliably visualises AD pathology in an amyloidosis mouse model, small animal imaging techniques may be used to assess treatment efficacy of anti-Aβ leads in the AD drug discovery pipeline. More in general, the impact of PET/SPECT imaging on drug discovery can also be situated at various levels, including validation of mechanisms of drug localisation, establishing transport efficiency of a drug to the target, establishing drug occupancy of saturable receptor sites and determining half-time of occupancy of the drug (Eckelman 2003).

2-Deoxy-2(^{18}F)fluoro-D-glucose-based PET, [^{18}F]FDG-PET, is a sensitive surrogate marker for AD diagnosis. A typical activity pattern shows decreased metabolism in the posterior cingulate and temporoparietal and prefrontal association cortex, while metabolism is maintained in the primary sensorimotor cortex and basal ganglia. Changes in [^{18}F]FDG-PET are evident prior to the onset of cognitive symptoms in AD-related mutation carriers. Moreover, [^{18}F]FDG-PET has predictive power for conversion of MCI to AD (for review, see Zhang et al. 2012). However, given the lack of specificity of [^{18}F]FDG-PET for AD, much efforts are directed at the development of Aβ-specific radioligands. [N-methyl-11C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, a fluorescent analogue of thioflavin T better known as Pittsburgh compound B, [^{11}C]PiB-PET, emerged as the lead Aβ-specific PET ligand to proceed to clinical development. [^{11}C]PiB-PET studies have demonstrated significant regional retention of radioactive signal in CNS areas with extensive plaque burden in AD brain, including the frontal, parietal and lateral temporal cortex and

the striatum (Klunk et al. 2004; Price et al. 2005). [^{18}F]FDDNP (2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile) is the only currently available PET radiotracer to image neurofibrillary tangles, besides Aβ aggregates, and it is also the only radiotracer to visualise AD pathology in the hippocampal region of living humans (for review, see Shin et al. 2011).

The search for other Aβ-binding radiopharmaceuticals is still ongoing, and also several [^{18}F]-labelled tracers have been developed that are currently undergoing extensive phase II and III clinical trials, e.g. 3′-[^{18}F]F-PiB (Flutemetamol), [^{18}F]-AV-45 (Florbetapir) and [^{18}F]AV-1 (Florbetaben) (for review, see Vallabhajosula 2011). By mid-2012, [^{18}F]AV-45 (Amyvid™) has become the first FDA-approved PET ligand available however only in select US markets. More information concerning current clinical trials in AD with PET and/or SPECT imaging can be obtained at http://www.clinicaltrials.gov.

Based on often disappointing PET imaging results in AD mouse models (Klunk et al. 2005; Toyama et al. 2005; Kuntner et al. 2009; Luo et al. 2012), the usefulness of currently available transgenic mouse models for the identification and optimisation imaging tracers is somewhat controversial. The spatial resolution of PET is often insufficient to allow reliable estimation of Aβ-specific tracer binding. Repeated PET imaging in the same mouse, however, may be applied to study the evolution of plaque burden and may be useful to complement ex vivo autoradiographic radionuclide imaging of brain slices, which provides sufficient spatial resolution for assessment of specific tracer binding but of course lacks the possibility of time-linked observations (Wirths et al. 2009; Teipel et al. 2011). Substantial differences in pharmacokinetics and pharmacodynamics are often observed between animals and humans for CNS targeted molecules (Carpenter et al. 2009). Moreover, the detection of amyloid plaques often depends on the presence of one specific Aβ subtype that may not be present in the same proportion in mouse versus man, or in different transgenic amyloidosis mouse models, as is the case for AβN3-pyroglutamate recognised by [^{11}C]PiB (Maeda et al. 2007). In addition, the presence of high-affinity binding sites may differ between species, as well as between the sources of Aβ even within the same species (Klunk et al. 2005; Rabinovici and Jagust 2009; Rosen et al. 2011). Latter hurdle may be overcome, however, by increasing the specific activity of [^{11}C]PiB to afford an Aβ-specific binding signal in transgenic mouse brain that could be quantified with small animal PET (Maeda et al. 2007; Fig. 1.4).

Despite differences between humans and animals, the development of new radioligands for AD brain lesions still strongly relies on preclinical tests in transgenic amyloidosis mice. For example, the recently developed [^{18}F]AV-45 ligand, which is expected to become a good substitute to [^{11}C]PiB in the coming years, has first been successfully tested in transgenic amyloidosis mice (Choi et al. 2009).

The most important advantage of (micro)PET imaging over (micro)SPECT is that of exhibiting a much higher sensitivity, while (micro)SPECT offers the possibility to widen the observational time window (based on the longer half-life of single-photon emitters) thus allowing the observation of biological processes in vivo several hours or days after administration of the labelled compound. By using different energy radioisotopes conjugated to different molecular targets, (micro)

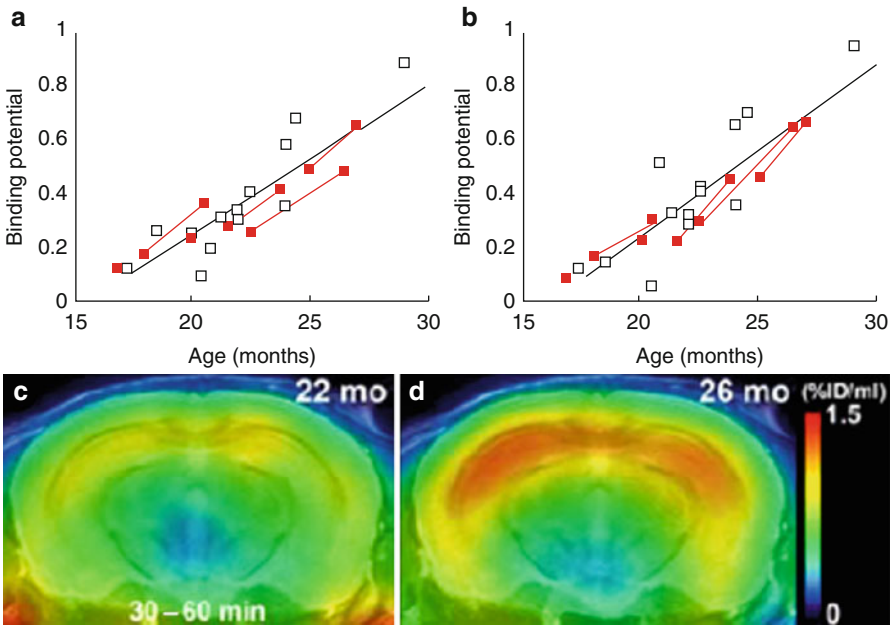

Fig. 1.4 Ability of mouse PET to capture age-dependent evolution of brain amyloidosis. (**a**, **b**) Represent scatter plots of binding potential of N-[^{11}C]methyl-2-(4-methylaminophenyl)-6-hydroxybenzothiazole (or [^{11}C]PIB for 'Pittsburgh compound B') versus age in the hippocampus (**a**) and neocortex (**b**) of Tg2576 mice, with the correlation of the two parameters being statistically significant in both regions. *Black lines* represent regression, and red elements indicate longitudinal analysis of the same individuals ($n=5$). (**c**, **d**) Represent PET images to illustrate [^{11}C]PIB's substantial increase in tracer binding in the hippocampal formations of the same animal at the age of 22 (**c**) and 26 months (**d**), indicating progression of amyloid accumulation. Images were generated by averaging dynamic scan data at 30–60 min after tracer injection and were merged onto an MRI template. *mo* month (Reprinted from Maeda et al. (2007) with permission. Copyright@2007 Society for Neuroscience)

SPECT has the advantage over (micro)PET in being able to image several molecular events simultaneously. Few examples on the application of SPECT in amyloidosis models can be found. Most studies evaluate newly developed SPECT tracers, biodistribution in normal mice and Aβ-specific binding on brain slices of plaque-bearing mice (Cui et al. 2011; Cheng et al. 2012). However, Opazo et al. (2006) assessed radioiodinated clioquinol as an amyloid biomarker in Tg2576 mice, which exhibited higher brain retention of tracer compared to nontransgenic mice.

Conclusion

Patho(physio)logical alterations in rodent models of human disease are usually studied using invasive techniques, requiring sacrificing the animals. This approach implies, amongst other, the use of a large number of animals to reach statistical significance, high associated (labour) costs and follow-up or longitudinal studies is impossible in the same animal. Recent improvements in molecular

imaging technologies employed to image small animal models, at least partially, overcome these limitations. Small animal imaging is increasingly recognised as an important facet of preclinical and translational (neuroscience) research. Perhaps most significant amongst the clear advantages of imaging experimental animals is that physiology, pathology and novel phenotypes can be understood in the most relevant milieu – in an intact, living system. Moreover, longitudinal imaging studies will allow researchers to gain more insight into the (developmental) time course of the modelled endophenotypes. The nuclear imaging modalities PET and SPECT can provide the sensitivities required to obtain the same physiological imaging acuity in small animals as can be obtained in humans, which will greatly facilitate the translation of preclinical studies to applications in the clinic.

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