Hippocampal Pathology in Schizophrenia

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Abstract The hippocampus is abnormal in schizophrenia. Smaller hippocampal volume is the most consistent finding and is present already in the early stages of the illness. The underlying cellular substrate is a subtle, yet functionally significant reduction of hippocampal interneurons. Neuroimaging studies have revealed a pattern of increased hippocampal activity at baseline and decreased recruitment during the performance of memory tasks. Hippocampal lesion models in rodents have replicated some of the pharmacological, anatomical and behavioral phenotype of schizophrenia. Taken together, this pattern of findings points to a disinhibition of

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hippocampal pyramidal cells and abnormal cortico-hippocampal interactions in schizophrenia.

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1 Introduction

Over the course of the last 20 years, there has been a growing interest in the hippocampus of patients with schizophrenia. The evidence accumulated so far indicates subtle, yet reproducible abnormalities and has given rise to several models of hippocampal dysfunction in schizophrenia. We will provide a brief review of the human hippocampus, including an outline of three neuropsychiatric conditions with known hippocampal pathology. Then, we will review the major models of hippocampal dysfunction in schizophrenia and provide a summary of the main lines of evidence. We will conclude with a critical review of the evidence and a set of recommendations for further studies of the hippocampus in schizophrenia.

2 The Human Hippocampus

The hippocampus is an elongated structure in the ventromedial region of the human temporal lobe. With a volume of 3–5 cm$^3$ per hemisphere, it occupies less than 1% of the brain. The hippocampus borders the amygdala anteriorly, is covered by the parahippocampal gyrus medially, and extends posteriorly to the pulvinar nucleus of the thalamus. Perpendicular to the anterior–posterior axis, the hippocampus can be divided into five regions: the cornu ammonis (CA) sectors 1–4 and the dentate gyrus (DG) (Fig. 1).

The human hippocampus plays a crucial role in the processing of information (Eichenbaum 2004). Sensory information (e.g., visual, auditory, somatosensory) is relayed from the primary sensory cortices to the multimodal cortices of the prefrontal, parietal, and lateral temporal cortices. These higher-order cortical areas send projections to the entorhinal cortex, a region of the anterior parahippocampal gyrus. The entorhinal cortex sends this highly processed, multimodal sensory information to the hippocampus via two inputs: the direct pathway (to sector CA1) and the indirect pathway (to DG → CA2/3 → CA1) (Witter et al. 2000) (Fig. 1). After processing of the sensory information, the hippocampus sends information back to the entorhinal cortex via the subiculum.

The direct and indirect pathways converge on pyramidal cells in sector CA1 (Fig. 1). The CA1 neurons integrate new sensory information (arriving via the direct pathway) with previously experienced sensory data (retrieved from cortical regions via the entorhinal cortex and the indirect pathway). If these two signals
coincide, the CA1 neurons send a “match” signal to the cerebral cortex, limbic structures, and the brainstem (Lisman and Grace 2005; Lisman and Otmakhova 2001). The detection of novelty is then followed by the evaluation of valence and salience of new sensory information, through a neural circuit that includes the hippocampus, ventral tegmental area, and nucleus accumbens (Lisman and Grace 2005). The electrophysiological correlates of this information processing are oscillatory rhythms of hippocampal neurons (θ-oscillation at a frequency of 4–8 Hz and γ-oscillation at a frequency of 30–100 Hz) (Tsien 2000). These oscillations are generated by the coordinated firing of excitatory and inhibitory neurons in the hippocampus (Somogyi and Klausberger 2005).

The cellular organization, connections, and electrophysiological properties of the hippocampus as outlined here are crucial for memory function (Eichenbaum 2004) and for the integration of emotion and cognition (Bannerman et al. 2004; McNaughton et al. 2007).

### 3 The Hippocampus in Neuropsychiatric Disorders

Neuroscientists did not appreciate the crucial role of the hippocampus until the case report of patient H.M., who underwent bilateral medial temporal lobe surgery for intractable seizures in 1953 and subsequently developed amnesia (Corkin 2002;
Scoville and Milner 1957). There is now extensive literature linking three neuropsychiatric conditions, that is, amnesia, dementia, and seizures, to hippocampal pathology.

The most compelling evidence for the importance of the hippocampus comes from case reports of patients with selective hippocampal lesions (Cohen and Eichenbaum 1993). More recently, amnesia patients have provided the foundation for models of hippocampal-specific memory processes. For example, the recollection of entire episodes and the ability to relate individual items to each other has been associated specifically with the hippocampus (Konkel et al. 2008).

While amnesia is typically caused by an acquired lesion of the hippocampus, dementia is associated with a degenerative pathology of the hippocampus. The stages of Alzheimer’s disease are defined by the anatomical pattern and severity of neuritic plaque and neurofibrillary tangle depositions and subsequent cell loss in the entorhinal cortex, DG, CA sectors, and subiculum (Braak and Braak 1991; Duyckaerts et al. 2009). Even before autopsy, structural and functional neuroimaging studies can demonstrate smaller hippocampal volume, increased (i.e., inefficient) BOLD signal change, and increased cerebral blood volume (CBV) of the hippocampus in Alzheimer’s disease (Bookheimer et al. 2000; Reitz et al. 2009).

Temporal lobe epilepsy is often associated with selective lesions of the hippocampus. A typical scenario is an ischemic lesion of hippocampal neurons, leading to cell loss and a focus of electrical hyperexcitability (Dichter 2009). In addition to acquired seizure syndromes, mouse mutants with selective lesions of hippocampal interneurons display the behavioral, histological, and electrophysiological signs of epilepsy (Cobos et al. 2005).

The evidence for hippocampal pathology in amnesia, dementia, and epilepsy is compelling. In contrast, the emerging literature on hippocampal pathology in schizophrenia is intriguing, but has not provided the basis for an objective test or a neuropathological confirmation of the clinical diagnosis.

4 Models of Hippocampal Dysfunction in Schizophrenia

The rapidly growing evidence for abnormalities of hippocampal structure and function in schizophrenia has given rise to several models of hippocampal dysfunction. In contrast to models of cortical (preliminary prefrontal) dysfunction (Heckers 1997), hippocampal models did not attract serious interest in the schizophrenia research community until the early 1990s (Heckers 2001; Heckers and Konradi 2002). Each hippocampal model emphasizes different aspects of the schizophrenia phenotype (e.g., psychosis vs. memory deficit) and different lines of evidence (e.g., neural circuits vs. neurotransmitters and receptors). For the purpose of this review, we are highlighting five models of hippocampal dysfunction in schizophrenia:
1. Hippocampal pathology drives psychosis. This hypothesis predates any data collected in patients with schizophrenia (Adler and Waldo 1991; Bickford-Winer et al. 1990; Hemsley 1993; Kriechhaus et al. 1992; Port and Seybold 1995; Roberts 1963; Venables 1992), but has received support from neuroimaging and neural network modeling studies that have linked hippocampal dysfunction to the degree of psychosis in schizophrenia (Friston et al. 1992; Liddle 1992; Siekmeier et al. 2007; Talamini et al. 2005).

2. Hippocampal pathology leads to memory deficits in schizophrenia. While the evidence for memory deficits in schizophrenia is definite (Aleman et al. 1999), it has been surprisingly difficult to find strong clinicopathological correlations of memory deficits and hippocampal abnormalities (Weiss and Heckers 2001). For example, episodic memory deficits in schizophrenia may be due to hippocampal or prefrontal cortex dysfunction and the available literature cannot disambiguate between these two hypotheses (Leavitt and Goldberg 2009; Preston et al. 2005; Reichenberg and Harvey 2007).

3. Disconnection of the hippocampus from multimodal association cortices leads to schizophrenia. This is the anatomical correlate of the psychosis (#1) and memory deficit (#2) models and may serve as the overarching theory of all the hippocampal models of schizophrenia. Since it is unlikely that schizophrenia is a selective lesion of the hippocampus (such as hippocampal amnesia), it is compelling to conceptualize schizophrenia as a perturbation of the reciprocal corticohippocampal pathways (Fletcher 1998). This notion has served as a guide for many neuroimaging studies, which can test the hypothesis of a hippocampal-cortical network dysfunction (Ellison-Wright and Bullmore 2009). Several neural network models have embraced this model as well.

4. Impaired function of glutamatergic (primarily N-methyl-D-aspartate – NMDA) receptors in the hippocampus leads to psychosis. While the glutamate hypothesis of schizophrenia does not make any a priori prediction of localized pathology, the prominent role of hippocampal NMDA receptors in the creation of oscillatory activity and the encoding/retrieval of information has led to several models of hippocampal dysfunction in schizophrenia (Greene 2001; Grunze et al. 1996; Harrison 2004; Harrison et al. 2003; Lisman and Otmakhova 2001; Medoff et al. 2001). These models focus particularly on the integration of the direct and indirect pathways via the NMDA receptor on CA1 pyramidal cells (Greene 2001; Lisman et al. 2008) and the modulation of these neurons by dopamine (Lisman et al. 2008; Lisman and Otmakhova 2001).

5. Insufficient γ-aminobutyric acid (GABA)ergic inhibition of hippocampal neurons leads to schizophrenia (Benes 1999; Benes and Berretta 2001). The abnormal expression of GABAergic genes and proteins and the abnormal activity of the hippocampus observed in studies of glucose metabolism and blood flow have provided compelling evidence for this model (Heckers et al. 1998; Schobel et al. 2009b). Some have proposed that GABAergic dysfunction of the hippocampus is secondary to NMDA receptor hypofunction in schizophrenia (Benes 2009; Lisman et al. 2008; Olney and Farber 1995).
While the models of hippocampal dysfunction in schizophrenia are supported by preliminary evidence, they are still in need of data. This will allow us to decide which model has the greatest explanatory power and how it relates to other models of schizophrenia (e.g., dopamine hypothesis, prefrontal cortex model, thalamic model).

5 Evidence of Hippocampal Dysfunction in Schizophrenia

Several lines of evidence support hippocampal abnormalities in schizophrenia: smaller hippocampal volume, abnormal hippocampal neuron number, abnormal function of genes expressed at high levels in the hippocampus, and abnormal hippocampal activity. While they support some of the models of hippocampal dysfunction in schizophrenia, the studies reviewed below have progressed more or less independently and an integration of their findings is still at an early stage.

5.1 Hippocampal Volume Change in Schizophrenia

The hippocampus is smaller in schizophrenia compared to matched healthy control subjects. This is a very robust finding, supported by many neuroimaging studies and confirmed by several meta-analyses (Honea et al. 2005; Nelson et al. 1998; Steen et al. 2006; Vita et al. 2006; Wright et al. 2000). The effect sizes for smaller hippocampal volume in schizophrenia are 0.8 for all patients and about 0.4 for first-episode patients, putting them at the top of morphometric studies in schizophrenia (Wright et al. 2000). There are, however, several unresolved questions.

The anatomical pattern of hippocampal volume change is not clear. There is some evidence that the volume of the anterior but not the posterior hippocampus is smaller in schizophrenia (Csernansky et al. 1998; Goldman et al. 2007; Rossi et al. 1994; Schobel et al. 2009a; Suddath et al. 1990; Wang et al. 2001), but this anterior/posterior gradient has not been found in all studies (Velakouli et al. 2001; Weiss et al. 2005). Several high-resolution structural imaging methods have been developed to subdivide the hippocampus into the four CA sectors, which provides another approach to test the hypothesis of regionally selective hippocampal pathology in schizophrenia (Malykhin et al. 2009; Zeineh et al. 1998).

The timing of hippocampal volume change is unknown. Hippocampal volume is already reduced at the time of the first psychotic episode (Steen et al. 2006; Vita et al. 2006). But it is not clear whether hippocampal volume is already reduced in subsyndromal at-risk subjects (Pantelis et al. 2003; Velakouli et al. 2006; Witthaus et al. 2009).

The quantification of hippocampal volume is not diagnostic for schizophrenia, since it is within the normal range for most patients. Reduced hippocampal volume
is also not specific for schizophrenia, since several other psychiatric disorders, such as depression (Campbell and Macqueen 2004; Koolschijn et al. 2009), alcoholism (Geuze et al. 2005), and PTSD (Smith 2005; Woon and Hedges 2008), show a similar pathology. This limits the use of structural imaging as a diagnostic test for schizophrenia, an approach with great promise in the early diagnosis of dementia (Teipel et al. 2008). Complicating the picture even more is the finding that hippocampal volume is also smaller in first-degree relatives of schizophrenia subjects (although not to the same degree as in patients) (Boos et al. 2007; Smith 2005). If this finding holds up in future studies (for concerns, see McDonald et al. 2008), then volume studies need to explore a slope of hippocampal volume from healthy subjects at low genetic risk, through asymptomatic subjects at risk for schizophrenia, to patients with prodromal schizophrenia and ultimately chronic schizophrenia.

5.2 Hippocampal Neurons in Schizophrenia

Each human hippocampus contains approximately 10 million neurons (West and Gundersen 1990). The majority of hippocampal neurons (about 90%) are large, pyramidal-shaped, glutamatergic neurons (principal cells). The remaining 10% of hippocampal neurons are smaller, nonpyramidal, GABAergic neurons (nonprincipal cells) (Freund and Buzsaki 1996; Olbrich and Braak 1985). Despite the relatively small total number of interneurons, they have developed into a highly specialized group of neurons, which differ in their anatomical, biochemical, and electrophysiological properties (Freund and Buzsaki 1996). The two types of hippocampal neurons give rise to an intricate balance of excitation (principal cells) and inhibition (nonprincipal cells). Most hippocampal neurons are located in the pyramidal cell layer (Fig. 1), whereas the two other layers of the hippocampus (i.e., the stratum oriens and the stratum radiatum/lacunosum/moleculare) contain few neurons. Subtle differences in the cellular architecture of the three-layered hippocampus give rise to the four sectors of the cornu ammonis (CA1–4) and the dentate gyrus (Fig. 1).

5.2.1 Hippocampal Neuron Number

The total number of hippocampal neurons in schizophrenia is not reduced to the degree seen in Alzheimer’s disease or temporal lobe epilepsy (Falkai and Bogerts 1986; Heckers et al. 1991; Schmitt et al. 2009; Walker et al. 2002). Furthermore, the volume of the pyramidal cell layer and the packing density of cells in the pyramidal cell layer (see Fig. 1) are not decreased in schizophrenia (Heckers et al. 1991; Hurlemann et al. 2005). These studies provide compelling evidence that hippocampal pathology in schizophrenia is distinctly different from that of dementia and epilepsy, both of which are characterized by hippocampal volume reduction due to a significant loss of neurons. It is surprising that the postmortem studies have not
corroborated the finding of decreased hippocampal volume in schizophrenia, reported by the large majority of neuroimaging studies (Heckers et al. 1990, 1991; Schmitt et al. 2009; Walker et al. 2002). While postmortem brain volume estimates are prone to substantial bias due to tissue processing, and therefore are of limited value (Braendgaard and Gundersen 1986), we do not have a simple explanation for the discrepancy between the in vivo and ex vivo hippocampal volume estimates in schizophrenia.

### 5.2.2 Glutamatergic Neurotransmission

Most studies of glutamatergic neurotransmission in schizophrenia have focused on the expression of glutamate receptor complexes, including ionotropic (NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid – AMPA, and kainate) and G protein-coupled (metabotropic) receptors (Kristiansen et al. 2009; Meador-Woodruff and Healy 2000).

Several studies have reported a decreased expression of the AMPA subunits GluR1 and GluR2 in the hippocampus and the parahippocampal gyrus (Eastwood et al. 1995, 1997; Harrison et al. 1991). In concordance, ligand binding to AMPA receptors was decreased (Kerwin et al. 1990). The kainate receptor subtypes GluR6 and KA2 were also significantly reduced in the hippocampus (Porter et al. 1997). Studies on kainate receptor density, conducted with radiolabeled kainate, demonstrated a decrease in the hippocampus (Deakin et al. 1989; Kerwin et al. 1990).

Initial studies of the NMDA receptor, which focused on the PCP-binding site located inside the ion channel, found no marked changes in the hippocampus in schizophrenia (Kornhuber et al. 1989; Meador-Woodruff and Healy 2000). A study of the NMDA receptor subunits NR1, NR2A, and NR2B found an increase of NR2B mRNA and a decrease of NR1 mRNA in the hippocampus in schizophrenia (Gao et al. 2000), but this has not been replicated in subsequent studies (Kristiansen et al. 2009).

The balance of GABAergic and glutamatergic neurotransmission in the hippocampus in schizophrenia was explored in studies of the expression of the two modulatory proteins: complexin I (presumably reflecting the integrity of GABAergic neurons) and complexin II (presumably reflecting the integrity of glutamatergic neurons). While complexin II expression was found to be more reduced in schizophrenia than complexin I (Eastwood and Harrison 2000; Harrison and Eastwood 1998), this did not correlate with similar changes of the vesicular GABA transporter (vGAT) and vesicular glutamate transporter (vGluT1) (Sawada et al. 2005). However, the complexin II/I ratio correlated inversely with the degree of cognitive impairment antemortem (Sawada et al. 2005), providing intriguing evidence that glutamatergic dysfunction in the hippocampus will lead to cognitive deficits in schizophrenia.
5.2.3 GABAergic Neurons

A growing body of literature deals with abnormalities of GABAergic hippocampal neurons in schizophrenia. Initial studies focused on postsynaptic GABAergic receptors, located on pyramidal and nonpyramidal cells, and revealed a regionally specific upregulation of GABA-A receptor binding in sectors CA2–4, but not CA1 (Benes et al. 1996, 1997). The marked increase of the GABA-A receptor in CA2/3 was found primarily on interneurons, indicating a decreased GABAergic regulation by other interneurons (Benes 1999).

The first evidence for an abnormality of hippocampal interneurons in schizophrenia came from a study of neuron density. Using the shape and staining pattern of pyramidal and nonpyramidal cells as the distinguishing pattern, Benes et al. reported a decrease in the number of nonpyramidal cells, but no changes in the density of pyramidal cells, in schizophrenia and bipolar disorder (Benes et al. 1998). More recent studies have focused on the defining marker of GABAergic neurons, that is, glutamic acid decarboxylase (GAD), the enzyme that converts glutamate to GABA. Two isoforms of GAD are known: the gene GAD1 codes for GAD67 and the gene GAD2 codes for GAD65. An initial in situ hybridization study of GAD mRNA expression in the hippocampus in normal controls, patients with schizophrenia, and patients with bipolar disorder revealed significant decreases of GAD2 (and to a lesser degree GAD1) mRNA expression in bipolar disorder and less significant changes in schizophrenia (Heckers et al. 2002). A subsequent gene expression microarray study confirmed the decreased expression of GAD1 and GAD2 in bipolar disorder, but did not find any changes in schizophrenia (Konradi et al. 2004). Finally, a large-scale postmortem study of GAD1 mRNA expression in 32 patients with schizophrenia and 76 normal control subjects revealed decreased expression in schizophrenia in the dorsolateral prefrontal cortex, but no changes in the hippocampus (Straub et al. 2007). These studies of hippocampal GAD mRNA expression in schizophrenia have to be reevaluated in light of a recent study using laser-capture microdissection and microarray profiling, which revealed that changes of hippocampal GAD67 expression in schizophrenia are regionally specific: While the expression was normal in the large sector CA1, it was significantly decreased in sector CA2/3 (Benes et al. 2007).

Additional evidence for selective changes in hippocampal interneurons in schizophrenia comes from the study of calcium-binding proteins, which are differentially expressed in subpopulations of hippocampal interneurons (Freund and Buzsaki 1996; Seress et al. 1993) (Fig. 2). These subpopulations of neurons create a dynamic, spatiotemporal control of hippocampal cell firing, which gives rise to several brain states crucial for normal cognition (Somogyi and Klausberger 2005). An initial study of neuronal density revealed a significantly decreased density of parvalbumin-positive neurons in all hippocampal regions, while the density of calretinin-positive cells was normal (Zhang and Reynolds 2000). The finding of decreased parvalbumin expression has now been corroborated by further studies.
and provides evidence for a subtype-specific abnormality of interneurons in schizophrenia (Eyles et al. 2002; Torrey et al. 2005).

5.2.4 Other Neurotransmitters

While most studies have explored abnormalities of GABAergic and glutamatergic neurotransmission, additional evidence suggests abnormalities of serotonergic, cholinergic, and dopaminergic neurotransmission in the hippocampus in schizophrenia (Kristiansen et al. 2009). Arguably, the most compelling evidence is the decreased expression of and binding to the α7 nicotinic receptor and the M1/M4 muscarinic receptors (Kristiansen et al. 2009). In addition, a recent line of evidence has implicated abnormalities of mitochondrial function in both schizophrenia and bipolar disorder. While some have reported abnormal expression of nuclear genes coding for proteins involved in mitochondrial energy metabolism in bipolar disorder but not schizophrenia (Konradi et al. 2004), others have provided evidence for mitochondrial pathology in both disorders (Altar et al. 2005).

Taken together, there is evidence for cellular and molecular abnormalities of the hippocampus in schizophrenia. These changes lead neither to an overall decrease in the number of neurons nor to an overall decrease of either GABAergic or glutamatergic neurotransmission. Rather, hippocampal pathology in schizophrenia seems to be selective for subtypes of neurons and for regions within the CA. Such a pattern of cell- and region-specific pathology could be related to some of the recently identified genetic mechanisms of schizophrenia and could give rise to selective deficits of hippocampal function in patients with schizophrenia.

5.3 Genetic Mechanisms of Hippocampal Pathology in Schizophrenia

The genetic basis of schizophrenia is now firmly established (Owen et al. 2005). However, it is less clear which regions of the brain are affected by changes of DNA sequence or RNA expression (Harrison and Weinberger 2005). Several genes of interest are expressed at high levels in the hippocampus, which makes them sensible targets for the exploration of genetic mechanisms of hippocampal pathology in schizophrenia. Here, we will briefly review the evidence for four genes associated with a risk for schizophrenia, that is, neuregulin-1 (NRG1), disrupted in schizophrenia-1 (DISC1), dystrobrevin-binding protein-1 (DTNBP1), and brain-derived neurotrophic factor (BDNF).

The NRG1 gene (located on chromosome 8p22) and the gene for one of its receptors, ErbB4 (located on chromosome 2q34), have both been associated with schizophrenia (Harrison and Law 2006; Owen et al. 2005). NRG1 and ErbB4 are expressed in the hippocampus (Law et al. 2004; Mechawar et al. 2007) and regulate GABAergic neurotransmission (Woo et al. 2007). They also affect the function of
α7 nicotinic receptors (Chang and Fischbach 2006), located on hippocampal interneurons. NRG1 is known to affect long-term potentiation of hippocampal synapses and to modulate dendritic growth and plasticity (Li et al. 2007a). ErbB4 receptors are expressed primarily on hippocampal interneurons and ErbB4 knockout models lead to selective dysfunction of some but not all hippocampal interneurons (Neddens and Buonanno 2009; Vullhorst et al. 2009).

The DISC1 gene was originally identified in a single pedigree with prominent psychiatric history and has subsequently been associated with several aspects of the schizophrenia phenotype (Roberts 2007). In adult mouse brain, the highest levels of DISC1 mRNA were found in the DG, followed by lower expression in sectors CA1–CA3 (Ma et al. 2002). In a transgenic mouse model, early postnatal induction of mutant C-terminal DISC1 resulted in a cluster of schizophrenia-related phenotypes, including reduced hippocampal dendritic complexity, decreased hippocampal synaptic transmission, and abnormal spatial working memory. This led to the postulation that alterations in DISC1 function during brain development may contribute to the pathogenesis of schizophrenia (Li et al. 2007b). Mice carrying a deletion in the DISC1 gene that model the schizophrenia-associated translocation showed alterations in the organization of DG neurons, a deficit in short-term plasticity and a selective working memory impairment (Kvajo et al. 2008). Although in schizophrenia the expression of DISC1 mRNA was not found to be abundant, the expression of several molecules in the DISC1 pathway was decreased (Lipska et al. 2006). While the exact mechanisms of DISC1 in schizophrenia remain unclear, hippocampal volume and function are under considerable control by the DISC1 gene (Callicott et al. 2005) and there is tentative evidence that some polymorphisms of the DISC1 gene contribute to smaller hippocampal volume in schizophrenia (Cannon et al. 2005).

The dystrobrevin-binding protein-1, also known as dysbindin-1, has been associated with schizophrenia in several studies (Harrison and Weinberger 2005). DTNBP1 mRNA is expressed in principal cells of the hippocampus (Talbot et al. 2004). Presynaptic dysbindin-1 expression was reduced in glutamatergic terminals of the hippocampus in schizophrenia. This has been interpreted as contributing to glutamatergic dysfunction in the polysynaptic pathway of the hippocampus and receives support from a mutant mouse model of dysbindin-1 (Talbot 2009).

BDNF plays a major role in brain development and reduced concentrations of the protein have been reported in schizophrenia. In rats, it has been demonstrated that BDNF is vital for hippocampal memory consolidation (Lee et al. 2004). While the association of the BDNF gene with schizophrenia is not very strong, several studies have reported that hippocampal volume is larger in individuals with the Val/Val than the Val/Met allele of the most frequently studied single nucleotide, rs6265 (van Haren et al. 2008). Moreover, the Met allele was associated with poorer episodic memory, abnormal hippocampal activation, and lower levels of hippocampal N-acetylaspartate in MRI spectroscopy (Egan et al. 2003).

Taken together, it is likely that genetic variations of NRG1, DISC1, DTNBP1, and BDNF in schizophrenia affect hippocampal function. This emerging literature on hippocampal effects of schizophrenia risk genes is complemented by the
literature on hippocampal pathology in first-degree relatives of patients with schizophrenia. Adult relatives of schizophrenia patients who do not develop schizophrenia (but might show more subtle signs of psychopathology) have smaller hippocampal volumes (Boos et al. 2007; Honea et al. 2005; Seidman et al. 1999, 2002). This indicates that hippocampal pathology in schizophrenia is, at least in part, under the control of genetic factors.

5.4 Hippocampal Function and Schizophrenia

The hippocampus serves a unique role in the encoding and retrieval of memory. It allows the brain to disambiguate relationships between items and to record the sequences of events, making it essential for the creation of relational, episodic, and autobiographical memory (Eichenbaum 2004). Most investigators studying hippocampal function in schizophrenia using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have looked at the role of the hippocampus in the encoding and retrieval of memory (Achim and Lepage 2005; Boyer et al. 2007). However, other functions of the hippocampus have also been explored (Bannerman et al. 2004; Bast and Feldon 2003), ranging from sensory gating (Tregellas et al. 2007) to decisional capacity (Eyler et al. 2007).

5.4.1 Hippocampal Activity at Rest in Schizophrenia

Studies of hippocampal activity at rest have found two different patterns in schizophrenia: lower regional cerebral glucose metabolic rates (rCMRglc) (Buchsbaum et al. 1992; Nordahl et al. 1996; Tamminga et al. 1992) and increased regional cerebral blood flow (rCBF) (Friston et al. 1992; Kawasaki et al. 1992, 1996; Lahti et al. 2003; Liddle et al. 1992; Malaspina et al. 2004; Medoff et al. 2001). It is not easy to reconcile these findings. But several studies have demonstrated that increased hippocampal rCBF in schizophrenia is normalized in patients treated with dopamine D2 antagonists (Lahti et al. 2003; Malaspina et al. 2004; Medoff et al. 2001), potentially obscuring abnormal patterns of resting activity. Furthermore, increased left temporal brain metabolism is more prominent in patients with negative symptoms and those with severe delusions and hallucinations (Gur et al. 1995) and resting rCBF values are positively correlated with more severe psychopathology in general (Friston et al. 1992) or with more prominent positive symptoms (delusions and hallucinations) (Liddle et al. 1992). These findings are supported by the few neuroimaging studies that have documented an activation of the hippocampus during auditory hallucinations (Dierks et al. 1999; Silbersweig et al. 1995). Taken together, hippocampal activity has been linked to psychosis, but it remains unclear whether hippocampal activation generates the hallucinatory experience or whether it is involved in the processing, for example, monitoring the source of an auditory representation (Weiss and Heckers 1999).
The studies of hippocampal glucose metabolism and cerebral blood flow in schizophrenia have been complemented by a recent study of CBV (Schobel et al. 2009b). This study of patients with chronic and prodromal schizophrenia revealed increased CBV selectively in hippocampal sector CA1, together with CBV increases in the orbitofrontal cortex and CBV decreases in the dorsolateral prefrontal cortex. The increased CBV in CA1 was interpreted as evidence for a basal hypermetabolic state in the hippocampus in schizophrenia. This was supported by a positive correlation between the degree of CBV and the severity of delusions in the schizophrenia patients.

5.4.2 Hippocampal Activity and Cognitive Function in Schizophrenia

The initial evidence for hippocampal dysfunction during cognitive task performance in schizophrenia came from a PET study of word-stem cued recall (Heckers et al. 1998, 1999) (Fig. 2). While normal subjects activated a right frontal–temporal network to retrieve previously studied words, schizophrenia patients failed to recruit the hippocampus, despite robust and even increased activation of prefrontal regions. Compared to the control group, hippocampal baseline activity was continuously increased in schizophrenia and was not modulated by environmental contingencies. The pattern of increased hippocampal activity at baseline and impaired recruitment during episodic memory retrieval was interpreted as the functional

![Fig. 2 Abnormal recruitment of the hippocampus during memory retrieval in schizophrenia. (a) An axial section through the brain shows the location of abnormal brain activation in the right hippocampus in schizophrenia during a word-stem cued recall experiment (for details of the experimental design, see Heckers et al. 1998). (b) Healthy control subjects showed increased regional cerebral blood flow (rCBF) during high accuracy recall when compared with both lexical retrieval at baseline and low accuracy recall. This normal pattern was absent in the schizophrenia group and all three recall conditions were associated with higher rCBF in the hippocampus.](image_url)
correlate of an abnormal corticohippocampal interaction in schizophrenia (in support of the hippocampal model #3 earlier) (Fletcher 1998).

Subsequent studies have extended this initial finding (Hall et al. 2009; Jessen et al. 2003; Leavitt and Goldberg 2009; Ongur et al. 2006; Ragland et al. 2001; Weiss et al. 2003, 2004). First, patients with schizophrenia relied less on the recruitment of the hippocampus and showed more widespread activation of the prefrontal cortex during the retrieval of previously learned information (Weiss et al. 2003). Second, the ability to classify new items as previously not experienced was impaired in schizophrenia (i.e., a higher false alarm rate to new items) and was associated with decreased activation and smaller volume of the hippocampus (Weiss et al. 2004). Third, hippocampal recruitment in schizophrenia was impaired during a relational, but not during a nonrelational memory task (Ongur et al. 2006). In addition to these findings of impaired hippocampal activation during memory retrieval in chronic patients with schizophrenia, a study of first-episode psychosis patients has revealed a selective deficit to engage hippocampal-dependent relational binding, resulting in poorer subsequent recognition performance (Achim et al. 2007).

Abnormal activation of the hippocampus in schizophrenia is not limited to memory function. For example, patients with schizophrenia demonstrate significantly greater activation of the hippocampus while passively viewing facial expressions (Holt et al. 2006). Furthermore, healthy subjects demonstrate significant habituation of hippocampal activity to the repeated presentation of fearful faces, whereas patients with schizophrenia do not demonstrate such habituation (Holt et al. 2005).

In summary, functional neuroimaging studies have reported increased blood flow in the hippocampus in schizophrenia, which is associated with higher levels of psychopathology and psychosis (i.e., delusions and hallucinations). The evidence of abnormal hippocampal activity is particularly strong for the domain of memory, with several studies revealing specific abnormalities of hippocampal recruitment during the performance of memory tasks. Future studies need to explore whether such abnormalities of hippocampal function, demonstrated so far in small samples of subjects, can explain the memory deficits in most patients with schizophrenia and whether they can explain the social dysfunction resulting from memory deficits in schizophrenia (Eyler et al. 2007; Green 1996).

6 Animal Models

Several animal models of hippocampal pathology in schizophrenia have supported the evidence from postmortem and in vivo studies in patients with schizophrenia (Feldon and Weiner 2009; Sawa 2009).

A substantial number of experiments in rodents have shown that a neonatal ventral hippocampal lesion induces several of the pharmacological and behavioral features of schizophrenia (Lipska 2004; Tseng et al. 2009). While the lesion does not provide a good model for the subtle abnormalities of volume and cell number reported for the hippocampus in schizophrenia, it does provide evidence that an
early developmental lesion of the hippocampus perturbs the normal regulation of dopamine release and the proper function of the cerebral cortex.

The methylazoxymethanol (MAM)-G17 model employs the administration of a mitotoxin, MAM, on gestational day 17 to pregnant rats, to induce a developmental disruption of the hippocampus (Lodge and Grace 2009). The MAM model shows a loss of parvalbumin-containing interneurons (especially in the ventral hippocampus), leading to diminished oscillatory activity (Lodge et al. 2009).

The infusion of picrotoxin, a noncompetitive antagonist of the GABA-A receptor, into the basolateral complex of the amygdala is a model of perturbed amygdala–hippocampal interaction. It leads to an increased flow of excitatory activity into stratum oriens of hippocampal sectors CA2 and CA3, resulting in a selective reduction of GABAergic interneurons containing parvalbumin, calbindin, and calretinin (Berretta et al. 2009).

The blockade of NMDA receptors in the hippocampus (especially in sector CA1) leads to a decreased activity of parvalbumin-positive interneurons, which in turn leads to a disinhibition of hippocampal pyramidal cells (Behrens et al. 2007; Bickel and Javitt 2009; Greene 2001; Kinney et al. 2006; Lisman et al. 2008). In addition, an NR1 knockdown mouse model shows a marked deficit in the phase coupling between θ- and γ-oscillations, indicating abnormal integration of hippocampal–cortical interactions (Ramsey 2009).

Taken together, these rodent models of environmental or genetic lesions of the hippocampus replicate some of the core findings in patients with schizophrenia, that is, loss of parvalbumin-containing interneurons, increased neural activity in the hippocampus, and memory deficits. These models may serve as a crucial bridge between the studies in humans and the study of basic hippocampal mechanisms of schizophrenia, potentially leading to the development of better pharmacological treatments of schizophrenia.

7 Critical Review of Findings and Directions for Future Studies

The literature on hippocampal pathology in schizophrenia is rapidly growing. The main body of literature, that is, studies of hippocampal structure and function in patients with schizophrenia, is supported by postmortem and animal studies of cellular and molecular mechanisms. However, the significance of hippocampal pathology in schizophrenia is still unknown. Here, we will highlight three important aspects that need to be addressed in future studies: regional specificity, timing, and mechanisms of hippocampal pathology.

The anatomical pattern of hippocampal pathology in schizophrenia needs to be studied more thoroughly. Some investigators have proposed regionally specific pathology in sector CA1, others in sectors CA2 and CA3. The two sectors contribute uniquely to different stages of memory formation (e.g., pattern separation, pattern completion, novelty detection) (Cutsuridis et al. 2010; Lisman and Grace 2005; Neves et al. 2008). In addition, some investigators have reported abnormalities
in the anterior but not posterior hippocampus in schizophrenia. The anterior hippocampus is more closely connected with limbic structures and medial prefrontal cortical areas, whereas the posterior hippocampus has prominent reciprocal connections to the dorsolateral prefrontal cortex (Barbas and Blatt 1995; Goldman-Rakic et al. 1984; Lepage et al. 1998; Strange and Dolan 2006; Strange et al. 1999). Regionally specific pathology of the hippocampus should, therefore, predict distinct patterns of hippocampal dysfunction in schizophrenia.

The developmental profile of hippocampal pathology in schizophrenia is unknown. While neuroimaging studies have clearly shown that hippocampal volume changes are present at the time of the first psychotic episode, it is not clear whether hippocampal structure is already abnormal during early stages of development or during the asymptomatic at-risk state (Lawrie 2007; Tebartz van Elst et al. 2007). The issue of vulnerability for smaller hippocampal volume and its progression throughout the illness are an important issue for further study, since the finding of smaller hippocampal volume in first-degree relatives of schizophrenia probands indicates a genetic liability. Similarly, the role of hippocampal dysfunction in the emergence of clinical features, such as psychosis and cognitive deficits, needs to be clarified. Studies of the timing of hippocampal pathology in schizophrenia should include studies of genetic and environmental factors that can affect hippocampal development and postmaturational integrity (Arango et al. 2001; Phillips et al. 2006).

The mechanisms of hippocampal pathology in schizophrenia remain unclear. Several models have been proposed, highlighting abnormalities of interneurons, NMDA receptors, and corticohippocampal connections. To advance our understanding of the hippocampus in schizophrenia, we need to move to strong hypothesis testing, resulting in the exclusion of some of the current hypotheses. This needs to include a test of the specificity of hippocampal pathology. For example, if NMDA receptor hypofunction and a loss of parvalbumin-containing interneurons are at the core of hippocampal pathology in schizophrenia, how is it different from the pathology in the cerebral cortex, where similar changes have been described (Lewis and Hashimoto 2007)?

Ultimately, we want to understand how subtle perturbations in a small, yet crucial region of the medial temporal lobe contribute to schizophrenia. This may include diagnostic tests to predict occurrence (Davatzikos et al. 2005), targets for the development of new drugs (Dhikav and Anand 2007; Newton and Duman 2007), and, eventually, strategies to prevent the development of schizophrenia.

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