REVIEW

USING HUMAN BRAIN IMAGING STUDIES AS A GUIDE TOWARD ANIMAL MODELS OF SCHIZOPHRENIA

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Abstract—Schizophrenia is a heterogeneous and poorly understood mental disorder that is presently defined solely by its behavioral symptoms. Advances in genetic, epidemiological and brain imaging techniques in the past half century, however, have significantly advanced our understanding of the underlying biology of the disorder. In spite of these advances clinical research remains limited in its power to establish the causal relationships that link etiology with pathophysiology and symptoms. In this context, animal models provide an important tool for causally testing hypotheses about biological processes postulated to be disrupted in the disorder. While animal models can exploit a variety of entry points toward the study of schizophrenia, here we describe an approach that seeks to closely approximate functional alterations observed with brain imaging techniques in patients. By modeling these intermediate pathophysiological alterations in animals, this approach offers an opportunity to (1) tightly link a single functional brain abnormality with its behavioral consequences, and (2) to determine whether a single pathophysiology can causally produce alterations in other brain areas that have been described in patients. In this review we first summarize a selection of well-replicated biological abnormalities described in the schizophrenia literature. We then provide examples of animal models that were studied in the context of patient imaging findings describing enhanced striatal dopamine D2 receptor function, alterations in thalamo-prefrontal circuit function, and metabolic hyperfunction of the hippocampus. Lastly, we discuss the implications of findings from these animal models for our present understanding of schizophrenia, and consider key unanswered questions for future research in animal models and human patients.

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Key words: schizophrenia, brain imaging, dopamine, striatum, thalamo-cortical circuit, hippocampus.

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SCHIZOPHRENIA IS A MENTAL DISORDER DEFINED BY ITS SYMPTOMS

Schizophrenia is a highly heterogeneous disorder that is characterized by so-called positive, negative and cognitive symptoms. The positive symptoms – also known as psychotic symptoms – include hallucinations, delusions and disordered thought processes. The presence of positive symptoms is a prerequisite for diagnosis and as such, positive symptoms are most often the dominant characteristic generally associated with schizophrenia. However, most patients also exhibit impairments in a number of social, emotional and cognitive behaviors (Tandon et al., 2009). Such deficits are categorized as either negative symptoms (e.g. social withdrawal, anhedonia and deficits in incentive motivation), or cognitive symptoms (e.g. impairments in working memory, behavioral flexibility, verbal memory, reference memory and cognitive processing speed). Although negative and cognitive symptoms are not required elements of the diagnostic criteria, they are present in a high proportion of patients and can be particularly insidious for patient outcomes (Fenton and McGlashan, 1991; Green et al., 2000). While many patients respond to dopamine D2 receptor (D2R) blockers as a treatment for positive symptoms – albeit with the risk of profound side effects – negative and cognitive symptoms remain largely untreatable (Miyamoto et al., 2012). Moreover, normal social, emotional and cognitive processing are essential requirements for everyday functioning and success in society. These two realities largely explain the finding that the severity of cognitive and negative symptoms is more predictive of the long-term prognosis of patients than the severity of positive symptoms (Green, 1996; Green et al., 2000).

At present, the symptom-based diagnosis of schizophrenia lacks biological meaning due to limited knowledge of the underlying disease pathology. Yet understanding how schizophrenia pathology manifests itself in the symptoms of patients is essential for the development of both novel biomarkers for aiding diagnosis and for new or improved therapeutics that limit side effects. In the last 30 years, technical developments in human genetics, epidemiology, and brain imaging have provided significant advances in our knowledge of the biological processes that are affected in the disorder. In the following, we summarize the biological findings from schizophrenia patients that we found to be most reliable; propose a role for and discuss findings from translational animal models based on intermediate pathophysiological phenotypes observed in schizophrenia; and discuss the utility and future directions of such translational animal modeling approaches in illuminating the biological basis of schizophrenia.

BEYOND SYMPTOMS: THE BIOLOGY OF SCHIZOPHRENIA

Genetic studies have revealed a significant genetic component in schizophrenia

Twin studies had long been pointing to the importance of genetic factors in schizophrenia (Kallmann, 1946; Slater, 1953; Fischer et al., 1969), with findings suggesting a heritability of about 70% (Kendler and Diehl, 1993; Gottesman and Erlenmeyer-Kimling, 2001). Early behavioral genetic studies were followed up by gene association studies, which identified a variety of common allelic variants that associated with the disorder, although with very low penetrance (Rees et al., 2015). However, many of these associations could not be replicated due to low sample sizes (Tosato et al., 2005). The advent of whole genome studies using significantly larger sample sizes changed the picture by adding statistical power to some of the common variants and, in addition, by isolating rare variants with high penetrance (Stefansson et al., 2008; Schizophrenia Working Group of the Psychiatric Consortium, 2014). One well-replicated example of a rare mutation with high penetrance is the 22q11 deletion, which increases the risk for schizophrenia by about 30-fold (Karayiorgou et al., 1995). However, it is important to note that many high penetrance rare variants are not specific to schizophrenia and are also associated with phenotypes that go beyond the diagnostic symptoms of the disorder (Watson et al., 2014). The recent identification of *de novo* mutations that were isolated by studying family triads adds another level of complexity since they are genetic in origin but not inherited – although there may be a predisposition affecting the rates of *de novo* mutations (Xu et al., 2011, 2012). Nevertheless, these studies have clearly confirmed the existence of a strong genetic component to schizophrenia, and ongoing work aimed at uncovering novel gene associations and understanding the biological consequences of highly penetrant genetic mutations is an important and powerful avenue for future research.

Epidemiological studies have revealed that environmental factors also contribute to schizophrenia

Epidemiological studies have identified a number of environmental risk factors for schizophrenia, including prenatal infection, malnutrition, hypoxia, and exposure to stress or cannabis during early adolescence (Dean and Murray, 2005). Interestingly, many of these risk factors occur during development years before schizophrenia is diagnosed. These observations support the hypothesis that schizophrenia has a neurodevelopmental origin (Weinberger, 1987). One well-replicated example of a developmental risk factor is prenatal infection. Because a variety of pathogens – including influenza virus, toxoplasmosis, herpes simplex virus-2 and rubella – are capable of conferring risk, it is thought that the core risk factor is an activation of the maternal immune system (Brown, 2012; Canetta and Brown, 2012). Like other risk factors, however, prenatal infection is not specific for schizophrenia but increases risk for several other disorders, including autism, bipolar disorder and depression (Machon et al., 1997; Brown et al., 2014). In addition – as is the case with common genetic alleles – environmental risk factors only moderately increase the risk for developing schizophrenia. It is therefore thought that a combination of environmental and genetic factors is required for developing the disorder. Exploring the biological consequences

of prenatal infection and other identified environmental risk factors, and how they may interact with genetic susceptibility, are promising and important avenues for future research (Meyer, 2014).

Structural brain imaging findings have revealed abnormalities that converge on key brain areas

An understanding that etiological risk factors produce the symptoms of schizophrenia by causing brain pathology dates back nearly 100 years to the pioneering work of Emil Kraepelin (Kraepelin, 1919). However, very few reliable pathological discoveries emerged until the advent of superior stereological post-mortem analyses, computer tomography (CT) and magnetic resonance imaging (MRI). The imaging techniques in particular allowed for the first assessment of the brains of patients with schizophrenia during life, thus providing the opportunity to measure structural abnormalities at various clinical stages – including in at-risk individuals, first-episode patients, and patients with chronic schizophrenia. As such, structural imaging studies have been important for bringing attention to the brain areas most robustly observed to be abnormal in patients and in revealing the progression of pathology through prodromal, early-onset and chronic phases of the disorder.

The first and most striking structural finding to emerge was the presence of ventricular enlargement in chronic schizophrenia compared to healthy controls (Johnstone et al., 1976). Well over a hundred subsequent studies of gross brain structure in a variety of patient populations have reliably established the existence of ventricular enlargement in schizophrenia and that this effect is not an artifact of chronicity or treatment (Reveley et al., 1982; Suddath et al., 1990). The observation of ventricular enlargement, however, provides little insight into the brain areas that contribute to the pathological or behavioral manifestations of schizophrenia. Yet at the same time, researchers quickly intuited that enlarged ventricles imply a reduction in brain tissue volume. Subsequent studies both confirmed the hypothesis of globally reduced brain volume (Andreasen et al., 1994; Zipursky et al., 1994; Noga et al., 1996) and began to uncover a differential involvement of particular brain structures. Whole brain meta-analyses of over a decade of structural MRI research in schizophrenia have revealed that volumetric brain reductions in patients are most frequently reported in a network of frontal, temporal, limbic and subcortical regions (Ellison-Wright et al., 2008; Glahn et al., 2008; Fornito et al., 2009).

One of the earliest individual observations to emerge was a reduction in tissue volume in temporal limbic structures (Bogerts et al., 1990; Shenton et al., 1992), including the hippocampal formation (Nelson et al., 1998; McCarley et al., 1999). A subsequent whole brain meta-analysis reported that reduced brain volume in patients is most frequently observed (> 50% of the studies assessed) in the medial temporal lobe, which in this analysis included the hippocampus, amygdala and entorhinal cortex (Honea et al., 2005). A more recent meta-analysis focusing exclusively on the hippocampus

corroborates the presence of reduced hippocampal volume in both first-episode and chronic patients, an indication that this pathology may occur early on in the disease process (Adriano et al., 2012). However, it is important to note that structural imaging studies based on a priori regions of interest can be subject to bias in the manual outlining or stereological procedures used to obtain volumetric measurements and may therefore overlook differences in unspecified brain regions. Indeed, two more recent whole brain meta-analyses suggest that, while frequently present, hippocampal gray matter reductions may be less robust compared to other brain areas (Ellison-Wright et al., 2008; Fornito et al., 2009). For a more in depth discussion of hippocampal pathology in schizophrenia we refer readers to the reviews of Harrison (2004) and Heckers and Konradi (2010).

Another notable and frequently reported structural observation in patients has been a reduction in gray matter in the cortex, or cortical thinning. This has been observed in the frontal (Andreasen et al., 1994), parietal (Schlaepfer et al., 1994), and temporal (Kuperberg et al., 2003) cortices of patients, although it is perhaps not exclusive to these cortical areas. Cortical thinning has been observed in childhood-onset cases (White et al., 2003), first-episode cases (Narr et al., 2005b) and chronic cases (Kuperberg et al., 2003). These results suggest that thinning of the cortex potentially occurs early in the disease process, an idea supported by observations of cortical thinning in individuals at high risk for developing schizophrenia (Job et al., 2003; Pantelis et al., 2003). However, other studies have suggested a link to disease progression, with more pronounced thinning in elderly patients (Narr et al., 2005a) that is independent of antipsychotic treatment (Nesvag et al., 2008). While not mutually exclusive ideas – thinning may occur early in development and progressively worsen after onset (Pantelis et al., 2005) – such conflicting reports and interpretations reflect the difficulty of disentangling disease pathology from clinical hetereogenity, patient lifestyle, outcome and treatment history in human patient studies.

Reduced cortical volume in patients is intriguing to consider in the context of observations of reduced thalamic volume in patients (Andreasen et al., 1990; Konick and Friedman, 2001; Honea et al., 2005), a structure that shares dense, reciprocal connections with the cortex. While negative findings exist (Portas et al., 1998; Arciniegas et al., 1999), approximately half of structural MRI studies report significant decreases in thalamic volume in patients (Byne et al., 2009), with observations also emerging from analyses of post-mortem brain tissue (Byne et al., 2002). Interestingly, decreases in the volume of the thalamus do not appear to be distributed uniformly, but rather affect particular regions, including the anterior, pulvinar, centromedial and mediodorsal subnuclei (Kemether et al., 2003; Ellison-Wright et al., 2008; Shimizu et al., 2008; Pergola et al., 2015). These thalamic subnuclei share extensive connectivity with prefrontal and temporal cortices, areas where gray matter reductions have been found to be particularly robust (Fornito et al., 2009). Reductions in gray matter volume in the

medidorsal thalamus (MD) – a subnucleus sharing reciprocal connectivity with the PFC – were even observed in a population of first-episode patients (Chen et al., 2014a).

The advent of diffusion tensor imaging (DTI) of white matter tracts has recently provided suggestive bridges between the structural abnormalities observed in distributed brain areas of schizophrenia patients and the anatomical connections among them. Strikingly, a recent meta-analysis of DTI findings revealed significant reductions in two white matter tracts: one associated with anatomical connections interconnecting the frontal lobe, thalamus and cingulate, and a second with interconnections with the frontal lobe, insula, hippocampus-amygdala and temporal lobe (Ellison-Wright and Bullmore, 2009). While such findings provide enticing pathological links between the brain-wide structural abnormalities most frequently observed in patients, the cause-or-consequence relationship between brain area volume reductions, the cellular mechanism behind volumetric changes, and the direct connection between brain volume reductions and patient symptoms remain largely unknown.

While structural MRI findings from schizophrenia patients have frequently implicated abnormalities in temporal limbic, cortical and thalamic structures, such observations have not been limited to these areas alone. For excellent and comprehensive reviews on structural abnormalities in other brain areas observed in schizophrenia patients, we refer readers to the reviews of Andreasen and Pierson (2008) and Shepherd et al. (2012).

Functional brain imaging studies have provided a link between schizophrenia pathophysiology and symptoms and shifted emphasis from single structures to distributed neuronal circuits

While structural imaging studies have implicated individual brain areas in schizophrenia, they have limited power for linking brain function to symptoms. The ascent of functional MRI (fMRI) in the 1990s, which allowed brain activity to be measured in patients performing behavioral tasks, has provided an important bridge to this gap. While early fMRI studies focused on single brain structures, recent findings – in part aided by the emergence of resting state fMRI (rsfMRI) studies of brain region "functional connectivity" – have begun to shift focus from abnormalities in single structures to dysfunction in distributed neuronal circuits.

Among the earliest proposed links between brain function and behavioral deficits in schizophrenia patients was the observation of hypofunction in the prefrontal cortex during the performance of various executive function tasks, especially those assessing working memory. Although the precise relationship between global PFC activation and working memory has since been revealed to be more complex than a simple PFC hypofunction (Callicott et al., 2000; Manoach, 2003; Karlsgodt et al., 2009), the association between deficits in working memory and altered activation, or "inefficient" engagement, of the dorsolateral PFC (dlPFC) is one of the best replicated findings in

schizophrenia research (Weinberger et al., 1988; Weinberger and Berman, 1996; Barch et al., 2001; Perlstein et al., 2001). Interestingly, several studies suggest decreased working memory evoked activation of the PFC may be present early on in the disease process. A meta-analysis of fMRI studies in patients at clinical high risk for psychosis reported a robust decrease in activation of several prefrontal areas, including the dlPFC, during cognitive and emotional processing, although it is unknown whether these subjects progressed to clinical diagnosis (Fusar-Poli, 2012). In a separate high-risk population, Wolf et al. (2015) found decreased activation of the dlPFC in at-risk subjects performing a working memory task. Moreover, this study observed that dlPFC activation was negatively correlated with cognitive deficits but not with positive symptom severity. Task-activated functional imaging findings, however, are complicated by the fact that working memory impairments are a core cognitive symptom of patients, thus making it difficult to determine whether abnormal PFC activity is a cause of impaired working memory behavior or a consequence of the inability to engage in the assessed behavioral task.

Functional abnormalities related to impaired cognition in schizophrenia are moreover not restricted to the PFC (Minzenberg et al., 2009) and may potentially derive from aberrant neural circuitry rather than a primary prefrontal pathology (Andreasen et al., 1997). Due to the above-described observations of structural thalamic abnormalities in schizophrenia and the anatomical connectivity between cortex and thalamus, the thalamo-cortical circuit in particular has garnered significant attention. Indeed, the main thalamic partner of the PFC – the MD thalamus – is activated during cognitive testing in tasks assessing both working memory and attention in healthy subjects (Burgess et al., 2003; Krasnow et al., 2003), and patients with schizophrenia show a decrease in MD activation in tasks addressing executive function, including working memory (Hazlett et al., 1999, 2004; Andrews et al., 2006; Minzenberg et al., 2009). It is therefore possible that working memory and other cognitive symptoms of the disorder may derive from abnormal circuitry, at least in part, between the MD and PFC (Fig. 1). In support of this idea, several studies have reported a decreased correlation in activity between the MD and the PFC during cognitive testing in patients (Katz et al., 1996; Mitelman et al., 2005; Minzenberg et al., 2009). Decreased communication between the MD and PFC is also supported by rsfMRI functional connectivity studies under resting conditions (Woodward et al., 2012; Anticevic et al., 2014). Interestingly, these studies have observed *increased* functional connectivity in sensory thalamo-cortical circuits, potentially suggesting the existence of an underlying pathology that differentially impacts distinct thalamo-cortical circuits. However, the functional relationship between these contrasting thalamo-cortical abnormalities, their relation to discrete symptoms, and their causal origin remain unknown.

Supporting a functional consequence of structural abnormalities in the hippocampus of schizophrenia patients, both hyper-activation of this structure and
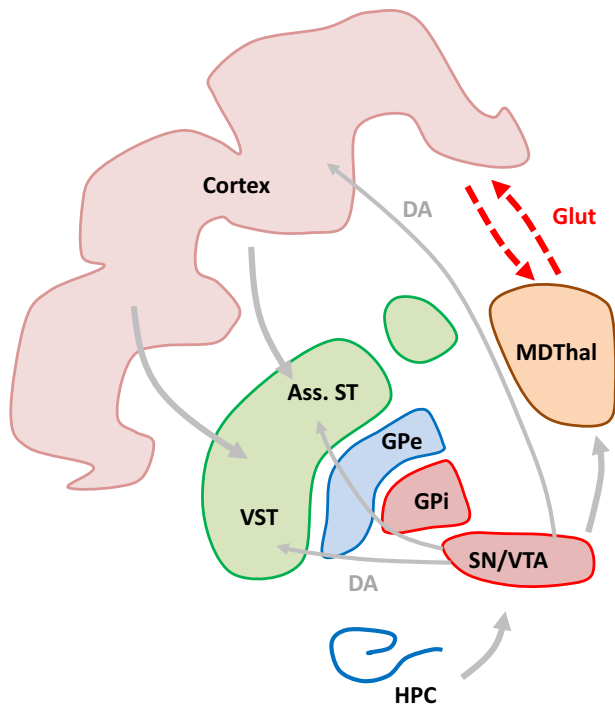
Fig. 1. Functional brain imaging studies have found decreased functional connectivity between the medio-dorsal thalamus (MDThal) and the prefrontal cortex in patients with schizophrenia. Decreased communication between MDThal and the cortex may cause cognitive symptoms including deficits in working memory. Ass. ST: associative striatum, VST: ventral striatum, GPe, GPi: external and internal segments of globus pallidus, SN/VTA: dopaminergic neurons in substantia nigra and ventral tegmental area, HPC: hippocampus.
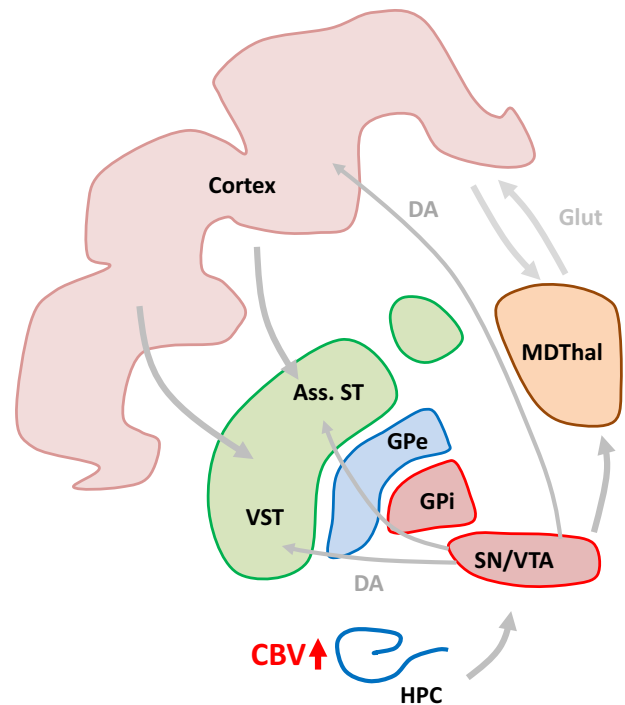
Fig. 2. Functional imaging studies have found increased cerebral blood volume (CBV) in patients with schizophrenia. Hypermetabolism is first observed in the CA1 region of the hippocampus in subjects at high risk for schizophrenia before it spreads to other regions of the hippocampus. Hippocampal hypermetabolism is proposed to be a biomarker that predicts conversion to schizophrenia. MDThal: medio-dorsal thalamus, Ass. ST: associative striatum, VST: ventral striatum, GPe, GPi: external and internal segments of globus pallidus, SN/VTA: dopaminergic neurons in substantia nigra and ventral tegmental area, HPC: hippocampus.

abnormal hippocampal-PFC coupling have been observed during the performance of cognitive and working memory tasks (Goldberg et al., 1994; Meyer-Lindenberg et al., 2005). However, many functional imaging findings of the hippocampus in patients have reported hyperactivity during tasks requiring minimal or no cognitive load. Indeed, hippocampal hyperactivity has been observed during visual fixation on a point (Malaspina et al., 2004), passive listening to an urban noise stimulus (Tregellas et al., 2009), and passive viewing of fearful faces (Holt et al., 2005). Supporting this body of research, Scott Small and colleagues have reported an increase in hippocampal blood volume – a correlate of oxygen consumption or metabolic state – in a group of at-risk individuals during baseline conditions (Schobel et al., 2009). Interestingly, the degree of hippocampal hyper-metabolism correlated with both positive and negative symptoms in the prodromal state and predicted conversion to psychosis. Hyper-metabolism is first restricted to the CA1 region of the hippocampus and spreads to the subiculum following onset of psychosis (Schobel et al., 2013). Increased CA1 hyper-metabolism has recently been replicated by an independent group (Talati et al., 2014). This body of work suggests the hippocampus may be a particularly sensitive circuit node that is close to the etiological and mechanistic origin of a number of schizophrenia symptoms, and perhaps most strikingly, the onset of psychotic symptoms (Fig. 2).

Evidence for functional alterations in neurotransmitter systems have provided mechanistic insights to the structural and functional abnormalities of schizophrenia

Genetic and post-mortem findings and findings from brain imaging studies – in particular those using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) – have been critical in illuminating the common neurotransmitter systems that are abnormal in schizophrenia patients. Such findings have aided the development of hypotheses regarding the molecular and circuit mechanisms potentially causing the structural and functional abnormalities observed in the disorder.

The dopamine system. The dopaminergic system is the neurotransmitter system most robustly implicated in schizophrenia pathology, with disruptions in subcortical dopamine systems linked to the positive symptoms and disruptions in cortical dopamine transmission linked to cognitive impairment. The former idea refers to the long-standing dopamine hypothesis originally formulated by van Rossum in the 1960s, which posits that dopamine *hyperactivity* is central to psychosis in schizophrenia (Baumeister and Francis, 2002). In the 1950s, the dopamine antagonist chlorpromazine was accidently

discovered as an antipsychotic medication. Later in the 1970s Philipp Seeman, Solomon Snyder and colleagues found that the therapeutic dose of antipsychotic medication is inversely proportional to their binding affinity for dopamine receptors (Creese et al., 1976; Seeman et al., 1976). Despite many efforts by the pharmaceutical industry, all antipsychotic medications used to treat patients with schizophrenia still target D2Rs – the main site of action of chlorpromazine.

Using post-mortem analyses, direct evidence for alterations in the dopamine system were also uncovered early on. These studies consistently showed increased levels of D2Rs in the brains of patients with schizophrenia (Mita et al., 1986; Hess et al., 1987), and particularly in the striatum (Joyce et al., 1988; Marzella and Copolov, 1997). Numerous imaging studies have also pointed to increased density of D2Rs in the striatum of patients with schizophrenia, with Laruelle calculating a 12% increase in striatal D2R density in drug-naïve or drug-free patients after comparing 13 imaging studies (Laruelle, 1998). However, a more recent meta-analysis suggests it is still unclear whether the increase in D2R density is truly present early in the disorder or if it is due to subsequent antipsychotic treatment (Howes et al., 2012). Dopamine depletion experiments have additionally reported increased basal occupancy of striatal D2Rs in drug-free patients that not only correlates with positive symptoms but predicts their response to antipsychotics, thus suggesting a tight relationship between D2R hyperfunction in the striatum and psychosis (Abi-Dargham et al., 2000).

A concomitant decrease in D2R occupancy has also been reported in extra-striatal brain structures. Such findings have been less common, however, potentially due to the lower density of D2Rs outside of the striatum and the need for high-affinity radio-ligands. Nevertheless, at least six studies using highly selective D2R radio-ligands have revealed a decrease in D2R occupancy averaging about 9.4% in the thalamus of patients, (Seeman, 2013). This finding remains controversial, however, and it has been argued that the effect can be accounted for by the significant decrease in thalamic volume frequently observed in schizophrenia patient populations (Kegeles et al., 2010b).

Impairments in the striatal dopamine system have also been observed at the presynaptic level. Increased striatal uptake of ^{18}F-fluorodopa (or L-β-^{11}C-DOPA) and increased amphetamine-induced dopamine release have been repeatedly measured in patients as an indication of presynaptic dopamine hyperfunction (Howes et al., 2012). These alterations appear to occur early on in the disease process as they are observed in prodromal subjects that are at high risk for conversion (Howes et al., 2009). Surprisingly, newer imaging tools with higher spatial resolution have revealed that the largest effect size of these abnormalities is not in the limbic striatum, as has been postulated for many years, but rather in the associative striatum – a striatal area that receives dense input from several prefrontal cortical areas, including the dlPFC (Kegeles et al., 2010a; Howes et al., 2012) (Fig. 3). Given that structural and
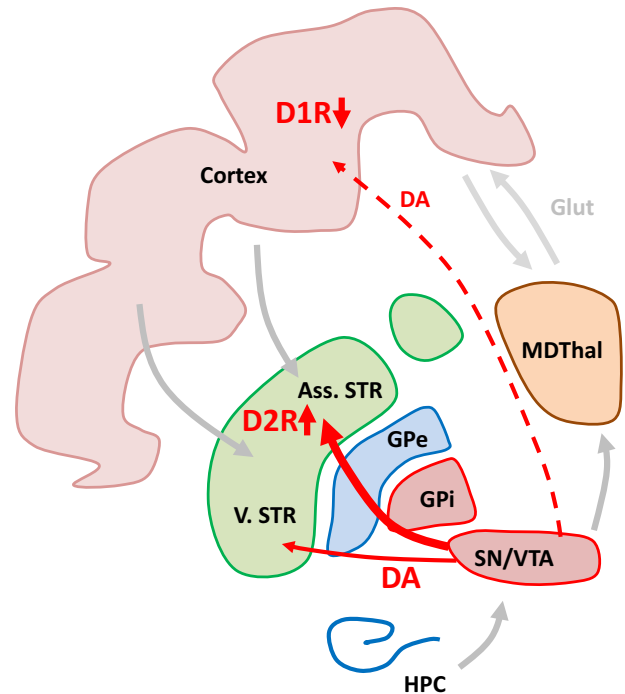
Fig. 3. PET and SPECT imaging studies suggest a hyperactive subcortical and hypoactive mesocortical dopamine system in patients with schizophrenia. The effect size of increased F-Dopa uptake and enhanced amphetamine induced dopamine release is highest in the associative striatum. MDThal: medio-dorsal thalamus, Ass. ST: associative striatum, VST: ventral striatum, GPe, Gpi: external and internal segments of globus pallidus, SN/VTA: dopaminergic neurons in substantia nigra and ventral tegmental area, HPC: hippocampus, D1R, D2R: D1 and D2 receptors.

functional abnormalities in the cortex are also observed early on in schizophrenia, this finding raises important questions about the pathophysiological origins and relationship between the cortical and meso-striatal pathologies observed in patients. Reduced PFC activity in patients has been linked to increased striatal dopaminergic function, supporting the idea that both abnormalities in cortical and subcortical regions share a common origin (Meyer-Lindenberg et al., 2002). Whether a primary pathology arises first in the meso-striatal dopaminergic system or is secondary to cortical abnormalities is an intriguing question that is difficult to causally establish in patient populations.

Another link between the dopamine system and cortical function in patients comes from the observation of cortical dopaminergic *hypofunction* (Fig. 3). This observation has been posited to explain the decreased activation of the PFC during cognitive testing in schizophrenia patients. Indeed, the degree of dlPFC activation in patients performing a working memory task is correlated with decreased cerebrospinal concentrations of dopamine metabolites (Weinberger et al., 1988), and a nonselective dopamine agonist can increase frontal activity in the brains of patients performing similar tasks (Daniel et al., 1989; Dolan et al., 1995). However, in these original studies it was unclear whether the decreased metabolites were indeed originating from

the cortex or from other brain structures. More direct evidence comes from a recent imaging study using a newly developed high affinity tracer showing that amphetamine-induced dopamine release is indeed decreased in the cortex of patients (Slifstein et al., 2015). Given the relationship between D1R activation in the PFC and working memory, this finding raises the possibility that a decrease in cortical dopamine release could be contributing to the cognitive deficits observed in patients with schizophrenia (Goldman-Rakic, 1994; Arnsten et al., 2012). However, evidence for this hypothesis in patients to date remains largely correlational.

Lastly, there is growing evidence from human imaging studies for a link between mesolimbic dopamine hypofunction and negative symptoms including deficits in motivation. In one study using fMRI, patients with psychosis were imaged while being tested in an instrumental reward conditioning paradigm, and results showed that patients have abnormal physiological responses related to a reward prediction error in the dopaminergic midbrain and striatum (Murray et al., 2008). Moreover, Wolf and colleagues recently reported that hypofunction in the ventral striatum of patients with schizophrenia is associated with poor performance in a behavioral test for motivation that correlates closely with clinical assessments for negative symptoms (Wolf et al., 2014). Consistent with a function of ventral striatal dopamine in negative symptoms, the severity of negative symptoms in patients has been found to be correlated with low dopamine release selectively in the limbic striatum (Kegeles et al., 2010a).

The GABA system. In addition to decreased dopaminergic function in the cortex, decreased GABAergic neurotransmission has also been hypothesized to cause PFC dysfunction and cognitive impairment. Early findings in post-mortem studies of patients revealed evidence for decreased GABA synthesis (Bird et al., 1977), GABA uptake (Simpson et al., 1989), and increased binding to GABA-A receptors in the neocortex (Hanada et al., 1987; Benes et al., 1996). Using various techniques, additional studies have observed reduced gene expression of the enzyme responsible for most GABA synthesis, GAD67 (Akbarian et al., 1995; Vawter et al., 2002; Hashimoto et al., 2008); reductions in the expression of the GABA reuptake transporter, GAT1 (Volk et al., 2001); and altered expression of GABA receptor subunits in the dlPFC of patients (Hashimoto et al., 2003; Maldonado-Aviles et al., 2009; Beneyto et al., 2011; Hoftman et al., 2015). GABAergic interneurons that express the calcium-binding protein parvalbumin (PV) appear to be particularly affected. Decreased PV interneuron function has been hypothesized to contribute to the working memory deficits of schizophrenia due to their putative role in coordinating synchronous neural activity in local and brain-wide circuits (Conde et al., 1994; Cho et al., 2006; Lewis and Hashimoto, 2007; Uhlhaas et al., 2008; Uhlhaas and Singer, 2010). While an intriguing hypothesis, studies directly assessing GABA levels, altered neuronal oscillations, and working memory impairment in single patients are rare and, moreover, can only provide correlational

evidence (Chen et al., 2014a). Additionally, as is true of most pathological findings in schizophrenia, it is difficult to tease out whether cortical GABAergic abnormalities in patients are a cause of, consequence, or compensation for the pathophysiological findings observed in other brain structures of schizophrenia patients.

Interestingly, GABAergic abnormalities – including in PV-positive interneurons – are not restricted to the cortex but have also been observed in the hippocampus (Benes, 1999; Heckers et al., 2002; Zhang and Reynolds, 2002; Konradi et al., 2011). These observations are particularly intriguing to consider in the context of the hippocampal hyper-activity that is observed during baseline conditions in at-risk patients and which is exacerbated at the onset of psychosis (Schobel et al., 2009, 2013; Talati et al., 2014) (Fig. 2). Does GABAergic dysfunction in the hippocampus cause hippocampal hyperactivity or is it a compensation for glutamatergic hyperactivity? The observation of multiple brain region abnormalities in the GABA system and linkages between GABAergic dysfunction in specific brain areas to disparate clinical phenotypes strongly implies this cell type is close to the causal origins of the disorder. However, whether these effects are due to intrinsic abnormalities in GABAergic cells or if this cell type is simply a sensitive target of more proximal causes of the disorder remains to be determined.

The Glutamate system. Perhaps secondary only to the dopamine theory of schizophrenia, the "glutamate hypothesis" posits that dysfunction in glutamatergic neurotransmission may be central to the pathogenesis of schizophrenia (Javitt and Zukin, 1990). This hypothesis has its origins in observations of the similarity between psychosis in schizophrenia and psychosis induced by drugs like ketamine and phencyclidine hydrochloride (PCP), both of which antagonize the NMDA glutamate receptor. A growing body of research has subsequently provided evidence for morphological alterations in the dendrites and synapses of glutamatergic neurons in post-mortem studies, particularly in the cerebral cortex (Hu et al., 2015), as well as genetic links to glutamatergic signaling, plasticity and neurotransmission (Harrison and Weinberger, 2005). Interestingly, functional imaging studies of glutamatergic indices in medication-naïve or medication free patients have most consistently reported elevated, not reduced, tissue levels of glutamate and its precursor glutamine, particularly in the medial PFC, basal ganglia and hippocampus (Moghaddam and Javitt, 2012). Consistent with this observation however, healthy subjects treated with ketamine also exhibit elevated cortical activity (Breier et al., 1997), thus revealing the complex pharmacology underlying NMDA receptor antagonism. Evidence suggests, however, that this seemingly paradoxical effect of ketamine on glutamate levels and cortical activity derives from a disinhibition of pyramidal neurons due to a relatively stronger NMDA receptor antagonism at excitatory-to-inhibitory synapses (Homayoun and Moghaddam, 2007; Seamans, 2008). As such, the most promising novel pharmacological therapeutic based on the glutamate hypothesis of schizophrenia to date has

been a G_i-linked metabotropic mGlu2/3 agonist (Patil et al., 2007; Kinon et al., 2011; Adams et al., 2013), which is postulated to work by reducing the presynaptic release of glutamate (Moghaddam and Adams, 1998). Although Phase II clinical trials of an mGlu2/3 agonist have failed to reveal improvements in the symptoms of chronic schizophrenia patients (Adams et al., 2013), this result may potentially be due to the fact that the treatment was given too late in the progression of the disease. For reasons of space, we refer readers to excellent and more comprehensive reviews of glutamatergic dysfunction in schizophrenia (Moghaddam and Javitt, 2012; Merritt et al., 2013; Poels et al., 2014; Hu et al., 2015).

ANIMAL MODELS ALLOW FOR STUDYING CAUSAL RELATIONSHIPS BETWEEN PATHOPHYSIOLOGY AND BEHAVIOR

As intimated in the above sections, the main limitation of studying patient populations is that they allow for identifying associations, but have limited power for establishing causality. As a result, the current clinical picture of schizophrenia is increasingly rich with data on proximal genetic and early environmental factors and intermediate molecular and pathophysiological waypoints, yet lacks the conclusive causal evidence necessary to link this myriad of pathological observations to one another and to discrete symptoms observed in the disorder. Consequently, and despite significant progress, our present biological understanding of schizophrenia remains hazy, novel and more effective treatments have been slow to emerge, and a sub-optimal, symptom-based characterization of the disorder continues to provide the best basis for diagnosis.

Animal models provide an important avenue for addressing these problems by providing insights into the causal relationships between biological manipulations and behavioral consequences. Obviously, no animal model can fully recapitulate a human disorder such as schizophrenia. This limitation is especially the case with the positive symptoms, such as hallucinations and delusions, which lack a translationally valid behavioral readout in animals. However, we argue that it is not necessary to produce a perfect animal model of schizophrenia but that research efforts using various "entry points" for studying aspects of the disorder are immensely valuable for fleshing out the causal biological pathways and interactions that exist between discrete causal factors, pathophysiologies and behavioral outcomes – especially the cognitive and negative symptoms that can be assessed with high translational validity.

One entry point that offers powerful insight into the pathophysiology and behavioral outcomes that derive from proximal genetic factors is to create mouse models of rare mutations with high penetrance. For example, the orthologous region of the above-described 22q11 deletion in schizophrenia patients has been deleted in the mouse, and many groups are studying the consequences of this manipulation on behavior and brain physiology (Paylor and Lindsay, 2006; Sigurdsson et al., 2010; Chun et al., 2014). Although the human phenotype of this mutation is broader than that of schizophrenia, the fact that this mutation has high penetrance provides this mouse model with a high degree of construct validity. For an in-depth discussion of this approach and findings from it, we refer readers to the excellent review of Joseph Gogos and collogues in this issue of Neuroscience.

Another entry point is to model proximal environmental risk factors, such as maternal immune activation (MIA) during pregnancy. Although MIA is not a risk factor for schizophrenia exclusively, this widely used animal model also has good construct validity and offers opportunities to link a proximal causal factor to subsequent brain pathophysiology and behavior (for reviews of this approach see: Canetta and Brown (2012) and Meyer (2014)).

A third entry point is to model the neurochemical conditions that produce psychoses in humans. Amphetamine-induced dopamine release and NMDA antagonism via ketamine are both capable of inducing psychosis in healthy subjects and, in lower doses, can exacerbate the psychotic symptoms in schizophrenia patients (Lahti et al., 2001). Treatments of either amphetamine or ketamine in rodents can produce a variety of behavioral phenomena potentially relevant to schizophrenia symptomatology, including hyperlocomotion, and deficits in latent inhibition and sensorimotor gating. Despite debatable face validity due to the difficulty of directly translating these behaviors to the psychotic symptoms of schizophrenia, the fact that these deficits can be rescued with antipsychotic treatments provides these models with good predicative validity. As such, these models have been extensively used by the pharmaceutical industry as an entry point for modeling the neurochemical conditions that approximate psychosis across species, and for screening novel antipsychotic medications that act to normalize the abnormal brain states elicited by these drugs.

In the following sections, we would like to describe an alternative approach that uses functional alterations observed with brain imaging as an entry point for the animal model. While agnostic to the proximal etiological origin of such functional abnormalities, we believe this approach offers an opportunity to (1) tightly link a single functional brain abnormality with its behavioral consequences, and to (2) more fully describe the potential causal pathophysiological outcomes that derive from functional abnormalities in single structures. In the subsequent sections we provide three examples of this approach. The first example describes a model based on the above-mentioned enhancement in striatal D2R function observed in schizophrenia patients using PET imaging. The second example describes an approach for studying alterations in neuronal circuit function based on fMRI imaging studies revealing alterations in thalamo-cortical activity in schizophrenia. Lastly, we describe animal models that address hippocampal metabolic hyperactivity in patients as measured with CBV.

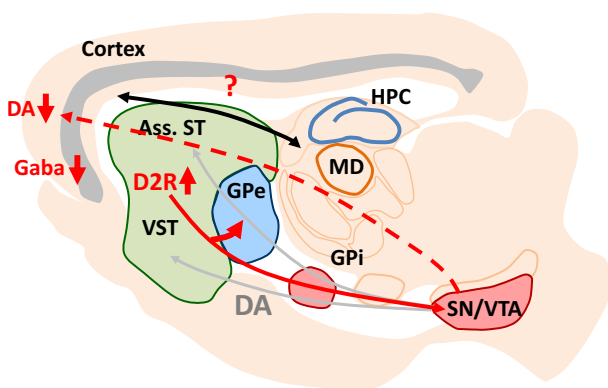## Modeling increased striatal D2R function in mice

Based on the above-described observations of increased D2R occupancy and density in the striatum of patients, we chose to closely model this pathophysiology in the mouse by overexpressing D2Rs selectively in the striatum. This approach allows for an assessment of the causal consequences on brain function and on behaviors relevant to the cognitive or negative symptoms that are downstream of striatal D2R hyperfunction. Specifically, we used the bi-transgenic tetracycline-sensitive expression system to selectively overexpress D2Rs in the striatum in a temporally controlled, reversible manner (D2R-OE mice) (Kellendonk et al., 2006). Over time D2R-OE mice have been analyzed in a battery of behavioral tasks (Kellendonk et al., 2006; Drew et al., 2007; Bach et al., 2008; Ward et al., 2009, 2012; Ben Abdallah et al., 2011; Simpson et al., 2011). Interestingly, D2R-OE mice have been shown to exhibit particular impairments in cognitive tasks that are dependent on the PFC, including deficits in working memory and conditioned associative learning – two cognitive abilities that are sensitive to frontal lobe lesions in humans and are impaired in patients with schizophrenia.

The finding that up-regulation of D2Rs in the striatum would lead to deficits in behaviors that are usually attributed to prefrontal function was surprising. Nevertheless, D2R up-regulation in the striatum of mice was found to be associated with decreased dopamine turnover and increased D1R sensitivity in the prefrontal cortex (Kellendonk et al., 2006) (Fig. 4). Due to the tight relationship between D1R activation in the cortex and cognition, especially working memory (Goldman-Rakic, 1994; Arnsten et al., 2012), these results suggested that disrupted cortical D1 receptor activation may be at the origin of the cognitive phenotype in the mouse. Recently,

Fig. 4. Overexpression of dopamine D2 receptors in the striatum of mice decreases VTA dopamine neuron activity as well as dopamine turnover and inhibitory transmission in the prefrontal cortex. It further alters the balance of the direct and indirect pathways within the basal ganglia by enhancing the density of bridging collaterals to the GPe. Striatal D2R overexpression may affect thalamo-cortical activation via basal ganglia output, and the decrease in cortical dopamine may affect synchronization between the MDThal and the prefrontal cortex. MDThal: medio-dorsal thalamus, Ass. ST: associative striatum, VST: ventral striatum, GPe, Gpi: external and internal segments of globus pallidus, SN/VTA: dopaminergic neurons in substantia nigra and ventral tegmental area, HPC: hippocampus.

Simpson and colleagues have discovered a decrease in burst firing in dopaminergic neurons of the ventral tegmental area (VTA) in D2R-OE mice that cannot be reversed by normalizing striatal D2R expression (Krabbe et al., 2015) (Fig. 4). This finding suggests that abnormal VTA activity may also contribute to impaired cognition in D2R-OE mice, potentially compounding decreased cortical D1 receptor activation to produce a dopaminergic-dependent hypofunction of the cortex. Finally, D2R-OE mice additionally display decreased GABAergic transmission in the cortex (Li et al., 2011), a second cortical abnormality commonly postulated to be present in patients. Together, these results demonstrate that both a dopaminergic and a GABAergic hypofunction in the cortex – two abnormalities proposed to contribute to cognitive impairments in patients – can be causally induced by a primary dopaminergic hyperfunction in the striatum.

Strikingly, the cognitive deficits in D2R-OE mice, as well as the decrease in VTA burst firing, are not reversed by switching off striatal D2R up-regulation in the adult animal, thus suggesting that these changes have a developmental origin (Kellendonk et al., 2006; Bach et al., 2008; Krabbe et al., 2015). This observation is intriguing as it suggests that one reason antipsychotic medication is not effective for treating cognitive deficits is because it is given too late in the progression of the disorder. At the time patients are diagnosed with schizophrenia in late adolescence, increased striatal D2R activity may have already altered brain circuitry and function in a persistent, irreversible way – perhaps via decreased VTA burst firing – and these abnormalities cannot be reversed by normalizing or blocking the primary pathophysiological cause of these brain-wide alterations: D2R levels and dopaminergic function in the striatum. This observation stresses the importance of early diagnosis of the disorder and suggests that cognitive outcomes may be significantly improved with early pharmacological interventions.

In addition to PFC-dependent cognitive deficits, D2R-OE mice also display deficits in motivation, a prominent negative symptom of schizophrenia. Rigorous behavioral testing of D2R-OE mice has revealed that this motivational deficit cannot be explained by anhedonia, motor dysfunction or decreased appetite (Drew et al., 2007; Ward et al., 2009; Simpson et al., 2011, 2012); but is rather associated with an inability to adapt behavior to reward and reflects a deficit in incentive motivation similar to what has been observed in patients with schizophrenia (Fervaha et al., 2013; Gold et al., 2013; Wolf et al., 2014). In a striking contrast to the cognitive deficits of D2R-OE mice, the motivational phenotype can be rescued when transgenic D2R expression is turned off in the adult animal, thus suggesting that concurrent up-regulation of D2Rs in the striatum is contributing to this deficit (Drew et al., 2007). In an attempt to more precisely and mechanistically understand how this pathophysiology may contribute to the motivational deficit, we examined how up-regulation of D2Rs in medium spiny neurons (MSNs) of the striatum affects the physiological function and anatomical connectivity of these neurons.

We discovered that up-regulation of D2Rs increases the excitability of MSNs by down-regulating the protein levels and currents of inward-rectifying potassium (Kir2) channels (Cazorla et al., 2012). Moreover, we found that up-regulation of D2Rs not only increases MSN excitability but also alters the anatomical and functional balance of the dorsal striatal output pathways (Cazorla et al., 2014) (Fig. 4). Striatal MSNs are organized into the canonical direct and indirect projection pathways. The direct pathway predominantly expresses D1Rs and projects monosynaptically to the basal ganglia output nuclei, the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). In contrast, the indirect pathway predominantly expresses D2Rs and modulates GPi/SNr output through a polysynaptic circuit via the external segment of the globus pallidus (GPe) (Gerfen and Surmeier, 2011). Both pathways are functionally opposing with regard to thalamo-cortical activation in the broader cortico-striato-thalamo-cortical circuit and are therefore often referred to as "Go" and "NoGo" pathways. Generally, the direct and indirect pathways are discussed as anatomically segregated. However, single-cell tracing studies in rats and monkeys have shown that over 90% of direct pathway MSNs possess collaterals in the GPe where indirect pathway MSNs terminate (Kawaguchi et al., 1990; Wu et al., 2000; Levesque and Parent, 2005; Fujiyama et al., 2011). We observed that these collaterals, which "bridge" the direct with the indirect pathway, are extremely plastic in the adult animal and that their density is directly regulated by D2R expression (Cazorla et al., 2014). Indeed, genetic up-regulation of striatal D2Rs enhances the density of bridging collaterals, whereas genetic down-regulation leads to a gene dosage-dependent decrease (Cazorla et al., 2014). Moreover, increasing excitability specifically in the indirect pathway of wild-type mice using the trans-dominant negative Kir2 channel is sufficient to induce bridging collaterals, while the increased bridging collaterals of D2R-OE mice are reversed by re-expression of wild-type Kir2 channels (Cazorla et al., 2014). We confirmed the functional importance of these bridging collaterals using *in vivo* direct pathway stimulation during anesthetized recordings of GPe activity and also using *in vivo* direct pathway stimulation in behaving animals. *In vivo* recordings during direct pathway stimulation in D2R-OE mice revealed enhanced inhibition of GPe activity, and *in vivo* direct pathway stimulation in D2R-OE mice impaired the behavioral activation that is normally observed after stimulation of the direct "Go" pathway (Kravitz et al., 2010; Cazorla et al., 2014).

Together, these results strongly suggest that the reversible anatomical changes observed in the bridging collaterals of the dorsal striatum in D2R-OE mice are a consequence of the alteration in neuronal excitability that result from decreased Kir2 expression in MSNs. The parallel reversibility of motivational deficits, MSN excitability and bridging collateral density when switching off D2R up-regulation offers an enticing link between pathophysiology and behavior. At the same time, the function of the direct and indirect pathways of the dorsal striatum have most frequently been studied in the context of motor regulation, and their contribution to motivated behavior is at present much less clear. A key limitation of the D2R-OE model is that over-expression occurs in multiple striatal areas and in both output pathways, thus making it unclear which precise striatal sub-region and pathway potentially contribute to the motivation deficits. For example, the motivational impairment in D2R-OE mice may arise from alterations in ventral striatal functioning, where the presence of bridging collaterals whose density is regulated by D2Rs is likely, yet presently unknown. As such, future work using increasingly restricted manipulations to address these questions promise to provide a more complete understanding of the causal mechanisms that explain the motivational deficits observed in D2R-OE mice.

Our present findings to date in D2R-OE mice provide interesting parallels to schizophrenia pathophysiology and symptomology and offer insight on potential causal relationships involved in the disease process. Perhaps most strikingly is the fact that cortical abnormalities and subcortical dopaminergic abnormalities can arise secondarily from D2R up-regulation in the striatum (Fig. 4), and that the irreversible nature of these changes when normalizing striatal D2R expression mirrors the fact that D2R antagonists treat the psychotic, but not cognitive, symptoms of patients. Although our data suggest a link between anatomical and functional striatal abnormalities and negative symptom-like motivation deficits, these physiological abnormalities may also be relevant to the positive symptoms of patients, despite the fact that we cannot reliably or fully measure psychotic behaviors in mice with a high degree of validity. Although, unlike patients, D2R-OE do not exhibit a deficit in sensorimotor gating or an enhanced motor response to amphetamine (C.K., unpublished data) – two measures often used as a behavioral readout of positive-like symptoms in rodent models – the reversibility of striatal abnormalities in D2R-OE mice has several interesting parallels to the reversibility of positive symptoms in patients. As discussed above, striatal D2R occupancy in the striatum and amphetamine-induced dopamine release correlate with positive symptom severity and predict treatment response to antipsychotic medication, thereby demonstrating a tight relationship between meso-striatal dopamine hyperfunction and psychosis. Based on the reversible anatomical and functional observations of striatal circuitry in D2R-OE mice, we hypothesize that drug-naïve patients that exhibit striatal D2R hyperfunction also have an increase in bridging collaterals in direct pathway striatal neurons and that this increase potentially contributes to the generation of positive symptoms. Moreover, our results suggest that decreased expression of Kir2 channels in striatal neurons may be the molecular mechanism underlying this phenomenon in patients. We further hypothesize that in patients treated with D2R blockers, such as haloperidol, bridging collateral density and Kir2 expression in MSNs will be normalized and that this normalization may be key for treatment response. Consistent with this idea, full efficacy with antipsychotic

medication is achieved after days to weeks of treatment (Sherwood et al., 2006), a duration that is comparable with haloperidol-induced retraction of bridging collaterals in mice (Cazorla et al., 2012).

Modeling MD hypofunction in mice

As stated above, the MD is the main thalamic partner of the PFC – both providing significant excitatory drive to the PFC and receiving driving glutamatergic input from the PFC. Indeed, early comparative neuroanatomy work defined the PFC across species as the area of cortex that receives anatomical input from the MD (Rose and Woolsey, 1948; Akert, 1964). Despite several distinguishing features, a general consensus has emerged regarding the existence of significant homologies in both MD and PFC anatomy and function across humans, primates and rodents (Preuss, 1995; Uylings et al., 2003). One anatomical homology of note is the cross-species presence of MD projections to cingulate, medial (mPFC), and orbitofrontal (OFC) cortical areas, each of which has been linked to discrete cognitive processes. Given the association of both PFC and MD dysfunction in the cognitive deficits of schizophrenia, this observation raises important causal questions regarding how the decreased activity observed in one structure relates to the other, and how mechanistically these functional abnormalities contribute to the cognitive deficits observed in patients.

Taking advantage of the ability to both elicit reversible physiological alterations and measure their physiological outcomes in behaving animals, we recently sought to address this question in a mouse model. Specially, we tested the hypothesis that a primary decrease in MD activity could impair PFC-dependent cognitive behaviors. To avoid the limitations of classical lesion approaches that irreversibly inactivate entire structures and to better mimic the alterations observed in imaging studies in patients, we employed a recently developed pharmacogenetic tool, the Designer Receptor Exclusively Activated by a Designer Drug (DREADD) (Armbruster et al., 2007). Using a viral vector approach to express the mutated muscarinic receptor hM4D in the MD of mice, we induced a mild and reversible 30% decrease in neuronal activity in about one third of MD neurons following systemic injection of Clozapine-N-Oxide (CNO) (Parnaudeau et al., 2013). Importantly, CNO is a biologically inert compound that is metabolized within the order of hours (Ray et al., 2011; Dymecki et al., 2012). Therefore, restricted viral delivery of hM4D to the MD provides refined spatial control of neural activity, while timing of CNO delivery provides reversible temporal control.

Using this approach we found that acute and reversible induction of MD hypofunction was sufficient to produce cognitive impairments in PFC-dependent spatial working memory and flexible goal-directed behavior tasks while sparing more general mnemonic, anxiety and fear-related behaviors (Parnaudeau et al., 2013, 2015). These results demonstrate that global MD hypofunction can cause a wide variety of cognitive deficits, many of which have been previously linked to distinct PFC subnuclei. Indeed, while working memory has been linked to mPFC and dlPFC function in rodent and primate studies respectively (Funahashi et al., 1993; Floresco et al., 1997; Bechara et al., 1998), the OFC of both rodents and primates has frequently been linked to flexible goal-directed behaviors, such as reversal learning (Chudasama and Robbins, 2003; Schoenbaum et al., 2003; Izquierdo et al., 2004; Morrison et al., 2011).

In order to more tightly link a primary MD hypofunction with subsequent PFC dysfunction, we carried out multi-site *in vivo* physiological recordings in mice while they performed a spatial working memory task. When simultaneously recording MD and mPFC activity in mice learning to perform the task we observed that synchronous MD-mPFC activity in the 13–30-Hz beta-frequency range increased hand-in-hand with task performance and that MD hypofunction delayed both behavioral performance and synchronous MD-mPFC activity (Parnaudeau et al., 2013). In a separate cohort of mice that were trained to reach criterion performance we found that control animals exhibited an increase in MD-mPFC beta-synchrony during a task phase when working memory demand is at its peak and animals must select an action based on previously held information. Acute induction of MD hypofunction in experimental animals abolished this increase in MD-mPFC beta-synchrony (Parnaudeau et al., 2013). These results demonstrate a tight link between MD and mPFC activity in working memory behaviors and supports the idea that the alterations in PFC activity in schizophrenia classically linked to cognitive impairment could also arise secondarily from deficits in MD function (Fig. 1).

These findings additionally provide a framework for further elucidating the precise thalamo-prefrontal circuit abnormalities that potentially underlie particular cognitive deficits in schizophrenia. While our results suggest a strong link between activity in direct MD projections to the mPFC and proper working memory performance, the causal relationship between activity in reciprocal mPFC-to-MD projections and working memory remain to be explored (Fig. 1). Moreover, although an increase in MD-mPFC synchrony during peak working memory demand suggests a role for this circuit in the maintenance of working memory, a causal test of this hypothesis requires a manipulation of activity on an even finer timescale than that of hours. The emergence of optogenetic tools for manipulating neural activity in a projection-specific and temporally precise manner in animal models provides an important new tool for addressing these questions (Bernstein and Boyden, 2011; Fenno et al., 2011). Projection-specific approaches offer a level of precision in analyzing the function of brain circuits that is impossible to achieve in humans. Future efforts to tease apart the precise functional importance of distinct connections in the thalamo-prefrontal circuit for the performance of discrete cognitive tasks, such as working memory and reversal learning, promise to provide important insight into how abnormalities in this circuit may contribute to the cognitive deficits of schizophrenia.
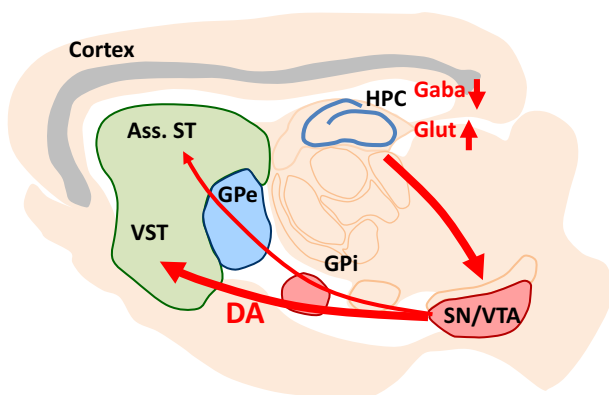
Modeling hippocampal hyper-activity in mice

As mentioned previously, non-competitive NMDA receptor antagonists, such as ketamine and PCP, induce psychosis in healthy human subjects that can be indistinguishable from psychosis in schizophrenia. While behavioral readouts for psychosis in animal models are perhaps impossible to achieve, the fact that NMDA antagonists have similar action on conserved molecular and circuit structures across species endows a powerful role for animal models in illuminating the brain-wide physiological consequences of NMDA antagonism and how these phenomena relate to pathophysiological observations in patients suffering from psychoses.

Interestingly, recent work in animals reveals that acute and chronic ketamine exposures in adolescent mice increases hippocampal CBV, or metabolic rate, in a manner that is similar to what is observed in prodromal patients with schizophrenia using identical measurements (Schobel et al., 2013). As detailed above, although an elevation in activity or metabolic rate following NMDA receptor antagonism appears paradoxical, previous work suggests this outcome is explained by a stronger antagonism of NMDA receptors expressed on inhibitory interneurons, thus resulting in decreased inhibitory tone and a disinhibition of pyramidal neuron activity (Homayoun and Moghaddam, 2007; Seamans, 2008). Interestingly, increased hippocampal CBV after chronic treatment of ketamine in mice subsequently results in atrophy of the hippocampus (Fig. 5) – a finding that parallels the observation of decreased hippocampal volume reported by structural imaging studies in patients. These results are consistent with the idea that ketamine induces hippocampal hyperactivity via elevated release of glutamate, a key hypothesis of the glutamate theory of schizophrenia. Indeed, when mice are pretreated with an agonist for the G_i-linked metabotropic glutamate receptor mGluR2/3, which inhibits pre-synaptic glutamate

release (Moghaddam and Adams, 1998), hippocampal hyper-metabolism and atrophy can be prevented (Schobel et al., 2013).

These results provide causal evidence for the idea that hippocampal hyperactivity and subsequent atrophy can derive from enhanced glutamate release, substantiating the hypothesis that a similar mechanism may occur in patients with schizophrenia. In this context, animal studies on heterozygous glutaminase knock-out mice reveal interesting parallel findings (Gaisler-Salomon et al., 2009b). These mice express reduced levels of the enzyme that converts glutamine into glutamate and have been observed to have a concurrent reduction of glutamate levels in the hippocampus (Gaisler-Salomon et al., 2009a, 2012). Strikingly, these mice display the inverse imaging phenotype of both ketamine-treated mice and patients with schizophrenia: a hippocampal *hypo*-metabolism that is also associated with reduced ketamine-induced frontal activation and amphetamine-induced dopamine release. Findings from these two animal models suggest that glutamate down-regulation may be protective for psychosis, potentially via regulating hippocampal hyper-activity or by down-regulating the striatal dopamine system. These results also support the idea that attenuation of the glutamate system may be a promising pharmacological strategy for novel therapeutics seeking to prevent conversion to schizophrenia. While attempts to reduce glutamate release with an mGluR2/3 agonist have failed in clinical trials (Kinon et al., 2011; Adams et al., 2013), these studies were conducted on chronic schizophrenia patients. It remains possible that treatment may need to occur earlier on in the disease process, perhaps prior to the onset of gross morphological brain abnormalities, in order to achieve beneficial outcomes.

Interestingly, chronic ketamine treatment in mice additionally results in a decrease in the number of hippocampal PV interneurons, another observation frequently reported in schizophrenia patients (Schobel et al., 2013) (Fig. 5). While this result suggests that PV abnormalities may arise subsequent to hippocampal hyperactivity in patients, findings from the cyclin D2 knock-out mouse model reveals a more complicated picture of the potential causal interactions between these two pathophysiologies. A chief phenotype of cyclin D2 knock-out mice is a reduction in cortical PV interneurons, most prominently in the hippocampus (Glickstein et al., 2007). Interestingly, this primary deficit in PV interneurons is sufficient to cause increased *in vivo* spiking in hippocampal projection neurons and increased fMRI-measured basal metabolic activity (Gilani et al., 2014), thus revealing that hippocampal hyperactivity can be causally derived from either a primary elevation in glutamate release or a primary reduction in GABAergic function. Cyclin D2 knock-outs additionally exhibit increased VTA activity and amphetamine-induced hyperactivity (Gilani et al., 2014), two phenotypes with associations to psychosis in schizophrenia patients and drug-induced psychosis in healthy subjects, respectively. Strikingly, transplanting interneuron precursors into the adult hippocampus of cyclin D2 knock-out mice can reverse both

Fig. 5. Chronic ketamine exposure in mice induces hippocampal hypermetabolism, hippocampal atrophy and decreases parvalbumin interneuron density, all of which are ameliorated by inhibitors of glutamate release. Hippocampal hyperactivity in turn is thought to enhance ventral striatal dopamine release via disinhibition of dopamine neuron activity in the VTA. MDThal: medio-dorsal thalamus, Ass. ST: associative striatum, VST: ventral striatum, GPe, Gpi: external and internal segments of globus pallidus, SN/VTA: dopaminergic neurons in substantia nigra and ventral tegmental area, HPC: hippocampus.

of these phenotypes as well as hippocampal hyper-activity (Gilani et al., 2014).

The combined results from these three animal models reveal a tight link between glutamatergic and GABAergic function in the hippocampus. While a primary deficit in one system can result in impairment of the other, these studies suggest that the chief downstream outcome of either causal pathway is hyper-activation of the hippocampus. Given the relationship between hippocampal hyperactivity and subsequent conversion to psychosis in schizophrenia, these animal findings indicate the possibility for multiple pathophysiological pathways toward this outcome in patients.

SYNTHESIZING THE FINDINGS AND INTERACTIONS BETWEEN PATIENT AND ANIMAL MODEL RESEARCH

In the previous sections we have detailed several genetic, epidemiological and pathological brain abnormalities associated with schizophrenia. We then described a number of findings from animal studies seeking to model three abnormalities that had been observed in patients using brain imaging techniques. While we have made efforts to emphasize the relevance of findings from these models to various patient observations, a core challenge of translational approaches is the need to synthesize individual findings into meaningful frameworks such that fruitful hypotheses capable of guiding future research in patients and animals alike may be developed.

In this context, we believe that one key question – posed by both clinical observations in patients and findings from animal models – is the degree to which distributed brain abnormalities co-exist within individual patients. Indeed, the symptomatology of schizophrenia exhibits a high degree of heterogeneity and patients usually share some, but not all, of the symptoms of the disorder. Moreover, the complex genetic architecture of the disorder and the large variety of environmental risk factors suggests the potential for multiple etiological origins in the progression to schizophrenia. As a result, it appears increasingly likely that the divergence in symptoms across patients must be explained by divergent etiological factors that result in distinct pathophysiological outcomes. Yet understanding how these causal factors converge to produce psychosis – the diagnostic anchor of schizophrenia – and how they diverge to produce distinct symptom outcomes requires a fuller charting of the causal pathways linking etiology to pathophysiology, and pathophysiology to behavioral outcome within single patients. While the animal models we have discussed here do not directly test hypotheses regarding the most proximal etiological origins of schizophrenia, they do provide important insight into the potential causal relationships and interactions between brain abnormalities frequently observed in patients. By anchoring the causal chain to a single brain abnormality and mapping the subsequent pathophysiological and behavioral consequences, we believe these studies provide important causal evidence for potential areas of

convergence and divergence in the pathophysiologies and symptoms exhibited by schizophrenia patients. We hope these findings can serve as guideposts for future research in both patients and animal models.

Potential areas for pathophysiological and symptom convergence in schizophrenia

Imaging studies have occasionally described physiological abnormalities that co-occur in the same population of patients. For example, reduced prefrontal activation during cognitive testing has been found to co-exist with increased striatal F-dopa uptake (Meyer-Lindenberg et al., 2002; Fusar-Poli et al., 2010). Interestingly, the relationship between these two pathophysiologies is inversely correlated, thus suggesting a possible functional link between them. This correlation, however, does not reveal whether this group of patients exhibited cortical hypofunction due to abnormalities in the dopamine system or due to, for example, the cortical GABAergic abnormalities that have been extensively reported in other cohorts of patients (Lewis et al., 2014; Schmidt and Mirnics, 2015). The existing studies that have observed dopaminergic cortical hypofunction and striatal hyperfunction also fail to bridge this causal gap as they have been done using different ligands and in different patient cohorts (Howes et al., 2012; Slifstein et al., 2015). As such, cross-sectional human imaging studies are unable to answer whether cortical hypofunction causally leads to striatal hyperfunction or vice versa. Although the application of novel tools for direct manipulation of human brain activity in patients (e.g. transmagnetic cranial stimulation) is a powerful new way to address such questions (Luber et al., 2007; Stanford et al., 2008; McClintock et al., 2011), animal models provide the opportunity to manipulate and measure brain function with a mechanistic precision not presently possible in humans.

In this light, the animal models described above offer an interesting perspective on potential causal interactions between these patient pathophysiologies by suggesting a surprising degree of convergence between them. As detailed above, striatal D2R-OE mice demonstrate that a single subcortical dopaminergic abnormality can produce decreased VTA activity, decreased dopamine turnover in the PFC, and deficits in PFC-dependent cognitive behaviors (Kellendonk et al., 2006; Krabbe et al., 2015) (Fig. 4). Strikingly, a classical lesion study in rats reported the converse causal relationship: lesioning of dopaminergic terminals in the PFC results in both increased dopamine binding and D2R levels in the striatum (Pycock et al., 1980). These animal findings reveal that a primary disturbance in dopaminergic activity in either a single subcortical or cortical structure can have widespread consequences on brain-wide activity patterns. As such, these results suggest that any etiological risk factors in schizophrenia patients that affect dopaminergic function are likely to lead to a variety of subcortical and cortical abnormalities, each of which may differentially contribute to the positive, negative and cognitive symptoms of the disorder.

Interestingly, D2R-OE mice additionally display impaired GABAergic function in the mPFC and, as described above, decreased GABA function is postulated in schizophrenia based on observations of molecular and structural abnormalities in GABAergic neurons. The most prevalent view of GABAergic abnormalities in schizophrenia is that it occurs early in the pathogenesis of the disorder and originates in GABA neurons potentially as a consequence of chronic inflammation, oxidative stress or deficits in interneuron development (O'Donnell, 2011; Nakazawa et al., 2012; Siegel et al., 2014). While the elegant studies described above using the cyclin D2 knock-out mouse provide causal support for this hypothesis (Glickstein et al., 2007; Gilani et al., 2014), the presence of cortical GABAergic abnormalities in D2R-OE mice indicates that multiple pathophysiological pathways to decreased cortical GABA function are possible and that GABAergic abnormalities in schizophrenia may be secondary to dopaminergic abnormalities. While future work in animal models may causally demonstrate that cortical GABAergic function is tightly linked to cognitive behavior, understanding whether GABAergic abnormalities in schizophrenia are both primary to disease progression and causally involved in cognitive symptoms requires both improved early clinical detection of schizophrenia and an increase in longitudinal studies following the disorder's pathophysiological progression in the broadest manner possible.

The above-described work by Scott Small and colleagues (Schobel et al., 2009, 2013) offers a powerful example of how longitudinal clinical research can be tightly linked to translational animal models in the effort to pinpoint core pathophysiological abnormalities and guide research on novel therapeutic targets. One important unanswered question that derives from this work is whether hippocampal hypermetabolism in patients contributes to psychosis via a disinhibition of the subcortical dopamine system. Indeed, cyclin D2 knock-out mice reveal that hippocampal hypermetabolism can cause an increase in VTA activity that can be reversed by normalizing hippocampal activity (Gilani et al., 2014). Studies performed by Tony Grace and colleagues in rats further support the hypothesis that hippocampal activity regulates subcortical dopamine release via a disinhibitory mechanism (Grace, 2012). However, in these studies hippocampal hyperactivity has been found to disinhibit the mesolimbic dopamine system, whereas, in humans, increased dopamine release is highest in the associative striatum and D2R occupancy in this area correlates with positive symptoms. In order to test the relevance of this mechanism for schizophrenia, future clinical studies could simultaneously measure striatal F-Dopa uptake and hippocampal CBV within the same patient populations. In general, future patient imaging studies that track multiple structural, resting-state or task-evoked functional abnormalities within single patients promise to provide important insight into disease progression, how one pathophysiological abnormality may be related to another and how each of these relates to symptomatology. Large scale, collaborative initiatives of this type – such as the North American Prodrome Longitudinal Study and the Philadelphia

Neurodevelopmental Cohort – have already begun to yield important findings and publicly available data from such longitudinal cohorts will undoubtedly prove to be a significant resource for future research (Addington et al., 2007; Woods et al., 2009; Satterthwaite et al., 2014, 2015). In a similar manner, ongoing work in animals seeking to model aspects of schizophrenia will best aid this effort by examining brain-wide abnormalities with the highest degree of mechanistic detail.

Potential areas for pathophysiological and symptom divergence in schizophrenia

In an effort to improve both diagnosis and our biological understanding of symptom heterogeneity in schizophrenia, several research groups have employed and advocated for approaches that link genetic risk factors to discrete patient populations exhibiting distinct phenotypes (Hallmayer et al., 2005; Allen et al., 2009; Ivleva et al., 2012; Arnedo et al., 2015). Although it requires replication, a recent study observed that 42 single nucleotide polymorphisms associated with schizophrenia could be segregated into eight populations of interacting gene clusters, each of which mapped onto distinct phenotypic outcomes (Arnedo et al., 2015). Historically, a major gap in such gene linkage studies has been an overreliance on symptoms and a lack of objective measurements for the intermediate pathophysiologies that causally bridge the connection between gene and phenotype. While recent large scale NIH-funded initiatives, such as the Bipolar-Schizophrenia Network for Intermediate Phenotypes and the Consortium on Genetics of Schizophrenia, have begun to address this limitation by seeking to associate discrete genetic risk profiles to both clinical phenotype and brain structural and functional abnormalities (Greenwood et al., 2011; Meda et al., 2012; Keshavan et al., 2013), the causal linkages between gene, pathophysiology and symptom remain largely unknown at present. If schizophrenia can be divided into sub-types, what are the brain areas directly affected by genes? What are the causal physiological mechanisms that produce distinct phenotypic outcomes?

Ultimately, only patient imaging studies that track multiple structural, resting-state or task-evoked functional abnormalities within single patients and relate these observations to symptomatology can provide direct answers to these questions. However, the above-described findings from a mouse model of MD hypofunction may offer potential illumination for such efforts. Indeed, the rather selective deficits in cognitive tasks that are observed in mice with MD hypofunction demonstrate a tight link between proper cognitive performance and normal functioning of this structure. The thalamic structural abnormalities reported in schizophrenia patients potentially suggest that the thalamus is a sensitive target for particular etiological risk factors, with MD abnormalities, in particular, likely contributing to cognitive impairment. It is further interesting to conjecture that inconsistencies in replicating structural observations in the thalamus may reflect phenotypic differences in the degree of cognitive

impairment in patient populations. Once more, ongoing research efforts aimed at integrating structural imaging with task-activated functional imaging and detailed clinical phenotyping within single patients provide the most promising avenue for addressing such hypotheses. Future work in animal models will also benefit from testing hypotheses on MD dysfunction that approximate more causal, etiological origins. For example, in light of the strong neurodevelopmental component in the disorder and the observation of thalamic abnormalities in first-episode patients (Chen et al., 2014b), it would be interesting to understand the potential downstream brain abnormalities that can causally derive from a primary decrease in MD activity during development.

Results from the MD hypofunction mouse model also provide a broader picture of the brain-wide physiological alterations that derive from primary deficits in the MD and how they underlie deficits in discrete cognitive behaviors. Indeed, we observed that MD hypofunction induces deficits in PFC-dependent tasks that have been linked to discrete PFC subnuclei; and that MD hypofunction impairs synchronous thalamo-mPFC activity during the performance of a working memory task. These findings are reminiscent of the decreased correlation in activity between the MD and PFC during cognitive testing in patients (Katz et al., 1996; Mitelman et al., 2005; Minzenberg et al., 2009) and suggest that a tight link may exist between thalamo-prefrontal activity and cognitive impairment in schizophrenia. However, while MD hypo-function is sufficient to impair thalamo-prefrontal activity and PFC-dependent cognition, it is important to consider the fact that PFC-dependent cognitive deficits are also present in other models, including in striatal D2R-OE mice. This observation perhaps exposes the difficulty of tightly linking complex cognitive tasks to brain areas that are highly interconnected. Nevertheless, the development of new techniques for simultaneous large-scale imaging and manipulation of neural activity in cell-type and projection-specific manners is rapidly providing the tools necessary to address such difficulties in behaving animals with remarkable levels of precision (Grosenick et al., 2015; Madisen et al., 2015). The existence of PFC-dependent cognitive deficits in MD hypofunction and striatal D2R-OE mice may also suggest, as discussed above, a certain level of convergence between causal pathophysiological pathways – although not toward shared pathophysiologies but rather toward shared phenotypic outcomes. At the same time, the complete causal relationships that bridge these observations have yet to be fully explored in these animal models. For example, simultaneous physiological recordings of MD and PFC activity in D2R-OE mice may reveal disruptions in synchronous thalamo-prefrontal activity during working memory performance, thus tightening the link between the thalamo-prefrontal circuit and cognition despite revealing multiple pathways to this abnormality.

CONCLUSION

Patients with schizophrenia display a heterogeneous set of symptoms and clinical research has implicated a broad range of brain abnormalities that may underlie various aspects of the disorder. Several brain areas that have been consistently implicated in the disease process include the meso-striatal dopamine system, the thalamo-prefrontal circuit and the hippocampal formation. However, because causal relationships are extremely difficult to establish in patients, animal models provide an important avenue for illuminating the potential biological mechanisms that trigger particular brain abnormalities and how they relate to behavioral outcomes.

While there exist multiple entry points through which animal studies can model this complex human disorder, we believe one fruitful entry point uses patient brain imaging studies as a guide. A major strength of this approach is that it dramatically simplifies a complex and hetereogenous human disorder with few known highly penetrant genetic or environmental causes. As such, animal studies of commonly observed intermediate pathophysiologies of the disorder have increased power for offering mechanistic insight into the links between single brain pathophysiologies and behavioral outcomes, and they can additionally reveal potential brain-wide pathophysiological interactions that derive from a single brain manipulation.

One key issue for future research on schizophrenia is the need to resolve the reasons behind the disorder's immense heterogeneity in genetic and environmental risk factors, intermediate pathophysiologies, and patient symptoms. While many of the findings from the animal models presented here reveal that multiple primary pathophysiologies can lead to convergent brain-wide abnormalities with overlapping sets of symptoms, this evidence is not fully conclusive. Ultimately, a final resolution to this issue will require direct clinical evidence in patient populations. Toward this effort, new and ongoing longitudinal studies that follow at-risk populations while measuring the broadest possible spectrum of genetic, pathophysiological and behavioral readouts promise to provide the greatest insight into the biological processes underlying schizophrenia. For example, simultaneous tracking of hippocampal hyperactivity using CBV, subcortical dopamine release using PET, and phenotypic assessments of prodromal patient cohorts will provide an improved picture of how these pathophysiologies evolve prior to and following psychosis onset. Another possible example that could provide insight into the relationship between thalamo-cortical abnormalities and cognitive symptoms would be a simultaneous tracking of thalamic and cortical structural abnormalities using MRI, resting state functional and structural connectivity abnormalities using rsfMRI and DTI, and task-activated functional abnormalities using fMRI. Findings from such studies would provide clear guideposts for future animal modeling work capable of testing causal relationships and further illuminating biological mechanisms with increasing precision.

Finally, a major limitation of such animal modeling approaches is that they cannot provide links between translationally valid proximal etiological causes and subsequent pathophysiological and behavioral

outcomes—a link that can only be filled by translational animal models of known genetic and epidemiological risk factors for the disorder. Together, however, the combination of findings derived from animal models of causal etiological factors and findings from approaches modeling intermediate pathophysiologies based on human imaging studies promise to provide the fullest possible insight into the biological mechanisms that link schizophrenia etiologies to brain pathophysiologies, how individual pathophysiologies interact in brain-wide networks, and how these biological processes produce the disorder's heterogeneous set of symptoms.

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