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The dynamics of disordered dialogue: Prefrontal, hippocampal and thalamic miscommunication underlying working memory deficits in schizophrenia

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Abstract

The prefrontal cortex is central to the orchestrated brain network communication that gives rise to working memory and other cognitive functions. Accordingly, working memory deficits in schizophrenia are increasingly thought to derive from prefrontal cortex dysfunction coupled with broader network disconnectivity. How the prefrontal cortex dynamically communicates with its distal network partners to support working memory and how this communication is disrupted in individuals with schizophrenia remain unclear. Here we review recent evidence that prefrontal cortex communication with the hippocampus and thalamus is essential for normal spatial working memory, and that miscommunication between these structures underlies spatial working memory deficits in schizophrenia. We focus on studies using normal rodents and rodent models designed to probe schizophrenia-related pathology to assess the dynamics of neural interaction between these brain regions. We also highlight recent preclinical work parsing roles for long-range prefrontal cortex connections with the hippocampus and thalamus in normal and disordered spatial working memory. Finally, we discuss how emerging rodent endophenotypes of hippocampal- and thalamo-prefrontal cortex dynamics in spatial working memory could translate into richer understanding of the neural bases of cognitive function and dysfunction in humans.

Keywords

Connectivity, hippocampus, oscillations, prefrontal cortex, schizophrenia, synchrony, thalamus, working memory

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Working memory, or the ability to store and manipulate information to guide behaviour on a timescale of seconds, is a central cognitive function (Baddeley, 2012, 1974). Working memory processes are critical for adaptive decision-making and goal-directed action, and their impairment is core to many neuropsychiatric disorders, including schizophrenia (Barch and Ceaser, 2012; Forbes et al., 2009). Although not among the diagnostic criteria for schizophrenia, deficits in working memory and other cognitive functions are predictive of long-term disease prognosis (Fett et al., 2011; Green, 1996; Hofer et al., 2005) and essentially resistant to currently available treatments (Buoli and Altamura, 2015; Lett et al., 2014). As such, the neural bases of normal and disordered working memory remain impactful areas of research.

Spatial working memory (SWM), or the active encoding, maintenance and retrieval of spatial information to direct behaviour in the short term, is a cognitive domain particularly amenable to bridging the preclinical and clinical neuroscience of schizophrenia. SWM is widely studied in humans, non-human primates and rodents using an array of laboratory assays (Bahner and Meyer-Lindenberg, 2017; Dudchenko, 2004; Funahashi, 2017), including spatial delayed-response tasks. In the simple 'delayed non-match-to-sample' (DNMS) task, subjects must maintain a memory trace of a recently sampled spatial cue or maze location across an ensuing delay period in order to correctly choose the opposite cue or location to receive a reward (Wikmark et al., 1973). Using these and related tasks, researchers have demonstrated that SWM is markedly impaired in individuals with schizophrenia (Fleming et al., 1997; Glahn et al., 2003; Park and Holzman, 1992; Piskulic et al., 2007). Similar deficits are seen in healthy relatives of those with schizophrenia (Cannon et al., 2000; Park et al., 1995), indicating that these deficits may reflect an underlying genetic predisposition to the disease. Importantly, deficits in SWM are recapitulated in many rodent models for the scientific study of schizophrenia (Gourevitch et al., 2004; Kellendonk et al., 2006; Lipska et al., 2002; Meyer and Feldon, 2009; Verma and Moghaddam, 1996), including mouse models

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engineered to carry schizophrenia susceptibility genes (Budel et al., 2008; Mukai et al., 2015; Stark et al., 2008).

Since Jacobsen's (1936) seminal finding that lesions of dorsolateral regions of the prefrontal cortex (PFC) in monkeys impaired their ability to remember the location of a concealed food reward after a brief delay, the PFC has remained the principal known neural substrate of SWM (Funahashi, 2017). From rodents to primates, damage to regions comprising the PFC impairs SWM (Curtis and D'Esposito, 2004; Dias and Aggleton, 2000; Funahashi et al., 1993; Goldman and Rosvold, 1970; Ptito et al., 1995; Rogers et al., 1992; Yoon et al., 2008), despite considerable differences in tasks commonly used to study the cognitive process (e.g. maze-based navigation in rodents vs egocentric visuospatial tasks in primates; Funahashi, 2017) and controversy regarding interspecies homology of the PFC regions most commonly implicated (e.g. medial vs dorsolateral PFC in rodents and primates; Seamans et al., 2008; Uylings and van Eden, 1990). Rodents and primates further show PFC activity patterns during SWM that encode a variety of SWM task–related information and correlate with performance (Bolkan et al., 2017; Driesen et al., 2008; Horst and Laubach, 2012; Jung et al., 1998; Onos et al., 2016; Spellman et al., 2015). For example, sustained activity of individual PFC neurons during the delay period of SWM tasks that encodes spatial information, among other features, has provided an alluring and intuitive neural correlate of a mnemonic trace necessary for SWM maintenance (Funahashi, 2017; Funahashi et al., 1989; Fuster and Alexander, 1971; Goldman-Rakic, 1995; Haller et al., 2017; Kubota and Niki, 1971). Notably, however, refined analyses and modelling of PFC activity during the delay and other SWM task periods suggest that highly dynamic neuronal population coding and trial-by-trial assignment of PFC neuron selectivity shaped by short-term synaptic plasticity better encapsulate SWM processing in the PFC (Bolkan et al., 2017; Lundqvist et al., 2016; Shafi et al., 2007; Stokes, 2015).

In recent decades, it has become clear that SWM, like other high-level cognitive processes, manifests out of orchestrated communication across expansive brain networks (Cohen and D'Esposito, 2016; Dehaene et al., 1998; Fries, 2005). The PFC has been proposed to function as a critical hub in these networks, wherein SWM task–relevant information is dynamically gated and integrated to guide activity in distal brain regions and support contextually tuned behaviour (Cole et al., 2012; Miller and Cohen, 2001). Of the many network partners of the PFC, two with robust long-range anatomical connectivity and functional interactions with the PFC during SWM are the hippocampus (Bahner et al., 2015; Colgin, 2011; Goldman-Rakic et al., 1984; Hoover and Vertes, 2007; Jones and Wilson, 2005) and thalamus (Bolkan et al., 2017; Jones, 2007; Saalmann, 2014). But what is the dynamic nature of their communication with the PFC during SWM? And what information do long-range projections between the PFC and these brain regions convey to support SWM?

PFC dysfunction is central to many theories of schizophrenia pathogenesis (Kraepelin and Robertson, 1919; Lewis et al., 2012; Weinberger and Berman, 1996) and correlates with cognitive deficits of the disorder (Minzenberg et al., 2009; Perlstein et al., 2001). Modern clinical and preclinical imaging and electrophysiology also continue to validate the view that schizophrenia and its cognitive symptoms stem from broad patterns of aberrant neural synchrony and long-range circuit disconnectivity (Barr et al., 2010, 2017; Colgin, 2011; Friston, 1999; Senkowski and Gallinat, 2015; Skatun et al., 2016; Stephan et al., 2009; Uhlhaas, 2013; Zhou et al., 2015). Two brain regions with abnormal connectivity with the PFC in individuals with schizophrenia are the hippocampus (Bahner and Meyer-Lindenberg, 2017) and thalamus (Anticevic et al., 2014; Dawson et al., 2013; Woodward et al., 2012); similar disconnectivity has also been seen in etiologically relevant rodent models (Dickerson et al., 2010; Phillips et al., 2012; Sigurdsson et al., 2010). The physiological dynamics that underlie this abnormal connectivity, and how these dynamics distort the content of hippocampal- and thalamo-PFC communication to impair SWM, remain unknown.

Here we review recent evidence that PFC communication with the hippocampus and thalamus is essential for normal SWM, and that miscommunication between these structures underlies SWM deficits in schizophrenia. We focus on studies using normal rodents and rodent models designed to investigate schizophrenia-related cognitive dysfunction, with emphasis on studies assessing the dynamics of neural communication between these brain regions. We also highlight recent preclinical work parsing roles for long-range PFC connections with the hippocampus and thalamus in normal and disordered SWM.

Hippocampal-PFC communication in SWM

The hippocampus, a brain region with famous roles in spatial navigation, learning and memory (Buzsaki and Moser, 2013; Eichenbaum and Cohen, 2014), is anatomically poised to interact with the PFC via a variety of direct and indirect pathways. Direct hippocampal-PFC connectivity in the rodent derives primarily from unidirectional, monosynaptic projections from the CA1/subiculum subfields of the ventral-most two-thirds of the hippocampus (Hoover and Vertes, 2007; Jay and Witter, 1991; Oh et al., 2014; Swanson, 1981) that innervate both pyramidal cells and interneurons in the medial prefrontal cortex (mPFC; Gabbott et al., 2002; Thierry et al., 2000). The dorsal hippocampus also receives a monosynaptic projection from the anterior cingulate subregion of the mPFC (Rajasethupathy et al., 2015). Many indirect hippocampal-PFC connections exist, most notably via the nucleus reuniens of the thalamus and lateral entorhinal cortex, both of which reciprocally connect to the hippocampus and mPFC (Cassel et al., 2013; Hoover and Vertes, 2012; Moser and Moser, 2010).

Early lesion and inactivation studies in rodents revealed that SWM performance is disrupted by bilaterally interfering with either the hippocampus or the mPFC (Aggleton et al., 1986; Dias and Aggleton, 2000; Hallock et al., 2013; Izaki et al., 2001). 'Disconnection' studies impairing the hippocampal function in one hemisphere and PFC function in the other provided early causal evidence of hippocampal-PFC interactions in SWM (Churchwell et al., 2010; Floresco et al., 1997; Lee and Kesner, 2003; Wang and Cai, 2006). Interestingly, such manipulations have implicated various rodent hippocampal and mPFC subregions in these interactions, despite well-documented anatomical and functional demarcations and gradients across the two structures (Barker et al., 2017; Heidbreder and Groenewegen, 2003; Hoover and Vertes, 2007; Strange et al., 2014; Takita et al., 2013).

Insight into the dynamics of hippocampal-PFC interactions in SWM has come from rodent electrophysiological studies assessing how neural activity in the two structures correlates in time during SWM tasks (Sigurdsson and Duvarci, 2015). Many such studies indicate a critical role for long-range coordinated oscillations of neural activity in the theta-frequency band (4–12 Hz), which are known to be generated (in part) within the hippocampus (Buzsaki, 2002; Colgin, 2011). Theta-frequency oscillations in the hippocampus have been shown to entrain the activity of mPFC neurons (Siapas et al., 2005) and to correlate with spatial navigation and cognition (Kahana et al., 1999; Lee et al., 2005; Raghavachari et al., 2001; Vanderwolf, 1969). Recording simultaneously from the rat hippocampus and mPFC, Jones and Wilson (2005) found that correlated neuronal firing in the two structures was enhanced in the 'choice' period of an SWM task, when the memory trace is retrieved to guide action execution. Two additional measures of hippocampal-PFC synchrony, the 'phase-locking' of mPFC neuron firing to theta oscillations of hippocampal local field potentials and theta-phase coherence of mPFC and hippocampal local field potentials, were preferentially enhanced during correct, but not incorrect, choices (see also Hallock et al., 2016; Hyman et al., 2010; Liu et al., 2018; Sigurdsson et al., 2010). Choice period–related increases in hippocampal-PFC theta synchrony have since been reported in both the dorsal and ventral hippocampus of mice (O'Neill et al., 2013) and found to increase with improved performance across training on an SWM task (Sigurdsson et al., 2010; Benchenane et al., 2010). Theta-frequency interactions between the hippocampus and PFC have also been implicated in the delay (maintenance) periods of SWM tasks. Analysis of the lag between mPFC unit firing and dorsal hippocampal theta-frequency oscillations in rats performing a delayed-alternation task revealed that the hippocampal activity preceded the mPFC activity during the delay, suggesting a predominance of hippocampus-to-mPFC information flow and influence in the theta range during this period (Hallock et al., 2016; Liu et al., 2018). Furthermore, a recent study using rats trained on an 8-arm radial maze DNMS task showed that theta power and synchrony between the hippocampus and mPFC peaked towards the end of the delay period, and mPFC neurons that showed a ramp-like increase in firing rate across the delay period showed higher firing rates on good performance trials (Myroshnychenko et al., 2017).

Like theta oscillations, gamma oscillations (30–120 Hz) have also been linked to spatial learning and memory (Carr et al., 2012; Yamamoto et al., 2014), coordinate activity in distal brain regions (Engel et al., 1991; Spellman et al., 2015; Steinmann et al., 2017) and contribute to hippocampal-PFC synchrony and SWM performance. Indeed, Spellman et al. (2015) reported heightened phase-locking of mPFC neuron firing to gamma oscillations in the mouse ventral hippocampus during the sample (encoding) period of DNMS trials that was particularly robust on correct trials and implied a hippocampal-to-PFC information flow. Interestingly, gamma synchrony that was consistent with an mPFC-to-dorsal hippocampus directionality of influence and predictive of choice accuracy has been reported in rats at the choice (retrieval) point of a delayed-alternation task (Hallock et al., 2016). These and other findings indicate that the hippocampus and PFC communicate via frequency band–specific and task period–specific synchrony that may support the encoding, maintenance and retrieval of SWM.

Hierarchical relationships between co-occurring theta and gamma oscillations, known as cross-frequency coupling, exist within and between the hippocampus and PFC (Belluscio et al., 2012; Canolty and Knight, 2010; Hyafil et al., 2015; Lisman and Jensen, 2013; Sirota et al., 2008). Local and long-range coupling of the phase and/or power of these oscillations is thought to coordinate activity in neuronal circuits and ensembles important for SWM and other cognitive processes (Axmacher et al., 2010; Canolty et al., 2006; Chaieb et al., 2015; Daume et al., 2017; Li et al., 2012; Lisman and Idiart, 1995; Park et al., 2013; Pastoll et al., 2013; Rajji et al., 2017; Roux and Uhlhaas, 2014; Shirvalkar et al., 2010; Tort et al., 2009). For example, Hallock et al. (2016) showed in rats that the coupling of hippocampal theta phase with PFC gamma power at the choice point of a T-maze significantly correlated with performance on a delayed-alternation task. Increasing the difficulty of a DNMS task also enhanced the phase–power coupling of theta and low gamma oscillations in the mouse hippocampus and PFC selectively during correct trials (Tamura et al., 2017). Interestingly, recent clinical work by Alekseichuk et al., (2016) provides unique support for the contribution of cross-frequency coupling to SWM ability by showing that co-applying theta- and gamma-wave transcranial stimulation to the human PFC boosts SWM only when gamma bursts were phase-locked to peaks of the theta cycle (see also Bilek et al., 2013; Polania et al., 2012).

Emerging evidence also indicates that hippocampal sharp-wave ripples, or characteristic bursts of high-frequency neuronal activity in the hippocampal area CA1 (Buzsaki, 2015), serve as an important conduit for hippocampal-PFC interactions supporting spatial learning and memory processes (Tang and Jadhav, 2018; Yu and Frank, 2015). Often studied as mediators of memory replay and consolidation during slow-wave sleep (Girardeau et al., 2009; Khodagholy et al., 2017; Maingret et al., 2016; Peyrache et al., 2009; Wilson and McNaughton, 1994), sharp-wave ripples can occur during awake immobility and slow movement to coordinate reactivation and stabilisation of ensembles that encode recent spatial experience (Davidson et al., 2009; Diba and Buzsaki, 2007; Foster and Wilson, 2006; Jadhav et al., 2012; Roux et al., 2017) and predict upcoming choices of spatial navigation (Pfeiffer and Foster, 2013; Singer et al., 2013). Awake hippocampal ripples can also profoundly modulate PFC neuron firing and hippocampal-PFC ensembles in a behaviour- and experience-dependent manner (Jadhav et al., 2016; Tang et al., 2017; Yu et al., 2017). Direct tests of the contribution of ripple-induced hippocampal-PFC interactions in explicit tasks of SWM (e.g. delayed-alternation, DNMS) remain to be conducted.

Although hippocampal-PFC synchrony and oscillatory coupling are presumed to optimise information transfer between the two regions (Canolty and Knight, 2010; Colgin, 2011; Gordon, 2011), the exact nature of the information being communicated and the neural substrates supporting this communication remain unclear. Temporally precise causal manipulations of neural activity, enabled by modern optogenetic tools, have refined our understanding of these issues (Kim et al., 2016; Roux et al., 2017; Yamamoto et al., 2014). For example, pathway-specific optogenetic inhibition of inputs from the ventral hippocampus to the mPFC selectively during the sample period, but not the delay or choice periods, impaired performance on a mouse DNMS task (Bolkan et al., 2017; Spellman et al., 2015). This inhibition disrupted the spatial tuning of a subset of mPFC neurons (i.e.

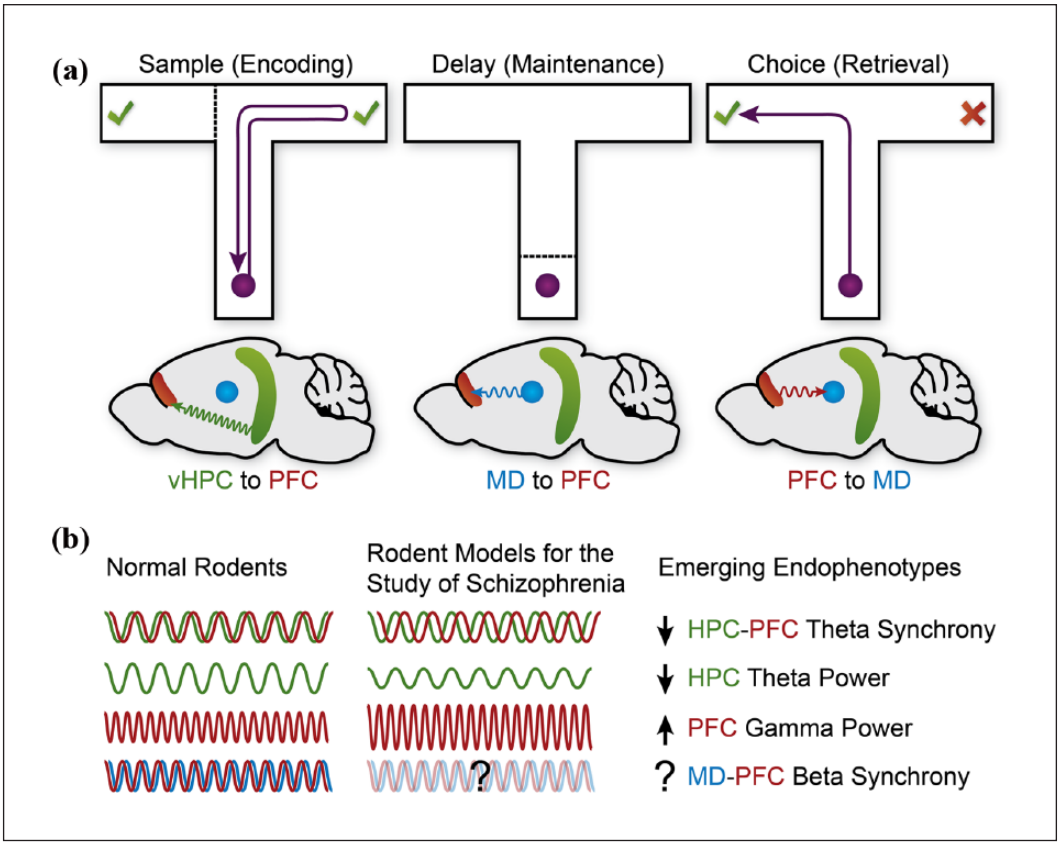

Figure 1. (a) Neural pathway–specific roles in distinct periods of a delayed non-match-to-sample T-maze spatial working memory task. Performance on this task is impaired by optogenetic inhibition of ventral hippocampus (vHPC) inputs to the prefrontal cortex (PFC) during the sample period, mediodorsal thalamus (MD) inputs to the PFC during the delay period, and PFC inputs to the MD during the choice period (Bolkan et al., 2017; Spellman et al., 2015). (b) Schematic noting some emerging electrophysiological endophenotypes of PFC miscommunication with the HPC and MD during spatial working memory in rodent models for the study of schizophrenia (e.g. Dickerson et al., 2010; Hunt and Kasicki, 2013; Sigurdsson et al., 2010).

preferential firing to one maze location during both the sample and choice periods; Bolkan et al., 2017; Spellman et al., 2015) and reduced the overall strength of sample-period gamma synchrony between the ventral hippocampus and mPFC (Spellman et al., 2015). These findings support a causal role for direct hippocampal-PFC inputs in the frequency-specific communication and spatial cue encoding that guides SWM performance (Figure 1(a)).

Thalamo-PFC communication in SWM

The thalamus, a heterogeneous collection of brain nuclei long regarded as a relay between different cortical areas (Jones, 2007; Saalmann, 2014), has a privileged anatomical relationship with the PFC. The mediodorsal thalamus (MD) in particular, among the higher-order thalamic nuclei (Mitchell, 2015), shares dense, direct and reciprocal excitatory projections with various PFC subregions (Groenewegen, 1988; Krettek and Price, 1977; Uylings and van Eden, 1990). This reciprocal connectivity is also notably selective as the MD receives its main cortical input from the PFC, and the PFC receives its main thalamic input from the MD (Jones, 2007; Mitchell, 2015). In addition, the nucleus reuniens of the thalamus reciprocally connects to the PFC and hippocampus (Cassel et al., 2013; Hoover and Vertes, 2012), making it well positioned to influence or mediate the thalamo- and hippocampal-PFC interactions during cognitive functions like SWM (Griffin, 2015; Hallock et al., 2016; Ito et al., 2015).

Reminiscent of the cognitive deficits seen following damage to the mPFC, lesions of the rodent thalamus that include the MD can impair performance in SWM tasks (Alexinsky, 2001; Hunt and Aggleton, 1991, 1998a, 1998b; M'Harzi et al., 1991; Mitchell and Chakraborty, 2013; Stokes and Best, 1990). Functional disconnection of the MD and mPFC by asymmetric pharmacological inhibition similarly impaired performance in a delayed-response radial arm maze task (Floresco et al., 1999). Reversible inactivation of the nucleus reuniens can also impair SWM (Davoodi et al., 2009; Griffin, 2015; Hallock et al., 2016; Hembrook et al., 2012; Layfield et al., 2015; Viena et al., 2018). Interestingly, this manipulation was shown to abolish SWM-related increases in dorsal hippocampal-PFC theta synchrony, underscoring the contribution of this synchrony and its regulation by thalamic structures to normal SWM (Griffin, 2015; Hallock et al., 2016).

Much of what is known about the dynamics of thalamo-PFC communication in SWM comes from electrophysiological studies in non-human primates (Watanabe and Funahashi, 2012). Neurons in the monkey MD, like the dorsolateral prefrontal cortex (DLPFC), show sample-, delay- and choice-period activity,

with the majority of task-related neurons showing sustained activity during the delay period (Fuster and Alexander, 1973; Sommer and Wurtz, 2006; Tanibuchi and Goldman-Rakic, 2003). More recently, analogous rodent studies have revealed notable contributions of MD-PFC communication to working memory maintenance and retrieval (Bolkan et al., 2017; Han et al., 2013; Miller et al., 2017; Parnaudeau et al., 2013).

Strong support for MD-PFC communication in SWM maintenance comes from recent work by Bolkan et al. (2017), who simultaneously recorded single mPFC neurons and MD local field potentials during a T-maze DNMS task. Directionality analysis of neural oscillations in the beta frequency (13–30 Hz) revealed that the MD activity preceded the mPFC activity during the delay period, suggesting a predominance of MD-to-PFC information flow and influence during this period. Consistently, optogenetic inhibition of MD-to-PFC terminal function selectively during the delay period impaired SWM performance. Moreover, a subset of mPFC neurons demonstrated elevated delay-phase spiking that did not encode spatial information (see Onos et al., 2016) but correlated with correct SWM performance. Rather than showing sustained activity across the entire delay, these mPFC neurons showed brief bouts of elevated activity at different temporal offsets such that population activity spanned the entire delay period. This activity pattern parallels the sequential activation of cortical neurons seen across other working memory–guided tasks (Baeg et al., 2003; Fujisawa et al., 2008; Harvey et al., 2012; Lundqvist et al., 2016; Schmitt et al., 2017). Importantly, optogenetic inhibition of MD-to-PFC inputs during the delay period suppressed the elevated firing of mPFC neurons seen in middle and late, but not early, time points in the delay period (Bolkan et al., 2017; Schmitt et al., 2017). Moreover, delay period–selective enhancement of MD neural excitability using a stabilised step function opsin improved SWM performance. Although inconsistent with evidence from Miller et al. (2017) that MD neurons in rats performing an operant DNMS task show no delay period–related firing, these findings strikingly align with recent work by Schmitt et al. (2017) using a working memory–guided attention task in which mice had to maintain a sensory-specific rule representation across a brief delay. Like Bolkan and colleagues, these researchers found that optogenetic suppression of MD activity during the delay impaired both the temporal sequencing of delay-period PFC neuron activity and subsequent choice behaviour, and that the enhancement of delay-period MD neural excitability strengthened task rule encoding by PFC neurons and improved performance (Schmitt et al., 2017). Together, these findings support the view that MD inputs to the PFC sustain PFC representations across the delay period to support SWM maintenance (Figure 1(a); Halassa and Kastner, 2017; Parnaudeau et al., 2017).

Discrete roles for MD-PFC communication in SWM retrieval and action execution have also been identified. In mice trained on a T-maze DNMS task, MD neuron firing showed preferentially enhanced phase-locking to mPFC beta oscillations during the choice period (Parnaudeau et al., 2013). Pharmacogenetic inhibition of MD neurons perturbed this MD-PFC synchrony and impaired task performance (Parnaudeau et al., 2013). In contrast to the MD-to-PFC directionality seen during the delay period of this same task, Bolkan et al. (2017) showed that the mPFC activity led the MD activity during the choice period. Accordingly, optogenetic inhibition of mPFC inputs to the MD during the choice period impaired SWM performance. Complementing the roles for ventral hippocampal and MD inputs to the mPFC in the respective spatial encoding and maintenance of SWM (Bolkan et al., 2017; Spellman et al., 2015), these findings suggest that 'top-down' signals from the mPFC to the MD help guide successful SWM retrieval and/or action execution (Figure 1(a)).

Disordered hippocampal-PFC communication and SWM in models for inquiry into schizophrenia

Brain imaging studies of individuals with schizophrenia reliably reveal abnormal hippocampal-PFC functional connectivity (Bahner and Meyer-Lindenberg, 2017; Benetti et al., 2009; Godsil et al., 2013; Meyer-Lindenberg et al., 2001, 2005; Zhou et al., 2008). The relationship between this connectivity and SWM performance, both in healthy subjects and individuals with schizophrenia, remains understudied and controversial (Bahner and Meyer-Lindenberg, 2017). Unlike rodent studies, the majority of clinical imaging studies of normal and disordered working memory employ non-SWM tasks. In a notable functional imaging study, Bahner et al. (2015) employed a virtual reality version of the radial arm maze, on which patients with schizophrenia are markedly impaired (Spieker et al., 2012), to show in healthy subjects that hippocampal-PFC connectivity is high during SWM encoding and retrieval and correlates with SWM ability (see also Kang et al., 2018). Although the precise functional coupling of hippocampal and PFC regions varies across working memory tasks, populations of patients with schizophrenia and high-risk individuals reliably differ from healthy controls in their task-related hippocampal-PFC functional connectivity (Benetti et al., 2009; Cousijn et al., 2015; Meyer-Lindenberg et al., 2001, 2005; Paulus et al., 2014, 2013; Rasetti et al., 2011; Rissman et al., 2008; Wolf et al., 2009).

Rodent models of the neurobiological underpinnings of schizophrenia, although varied in their aetiology, utility and validity, have been critical for establishing altered hippocampal-PFC communication as a key endophenotype of SWM deficits (Figure 1(b); Bahner and Meyer-Lindenberg, 2017). Mirroring the pathogenic complexity of schizophrenia, genetic, environmental, developmental and pharmacological models have been used to probe the neural basis of these cognitive deficits.

The first identified copy number variant associated with schizophrenia, the 22q11.2 microdeletion, increases the risk for developing the disease by a factor of 20–30 (Bassett and Chow, 2008; Karayiorgou et al., 2010). *Df(16)A*$^{+/-}$ mice carrying a deletion syntenic to the human 22q11.2 locus show impaired SWM (Drew et al., 2011; Stark et al., 2008), phenocopying at least some of the cognitive deficits seen in humans with the deletion (Simon et al., 2005; Sobin et al., 2005). Recording neuronal activity in the hippocampus and PFC during a T-maze DNMS task, Sigurdsson et al. (2010) showed that *Df(16)A*$^{+/-}$ mice have reduced hippocampal-PFC theta-frequency synchrony, measured by phase-locking of PFC neurons to hippocampal theta oscillations and by coherence of local field potentials in the two structures. Moreover, the magnitude of hippocampal-PFC coherence in *Df(16)A*$^{+/-}$ mice at training onset predicted the number of trials required to learn the SWM task and increased more slowly across training (Sigurdsson et al., 2010). Mice deficient for a single gene within

the 22q11.2 locus, *Zdhhc8*, mimicked the *Df(16)A*$^{+/-}$ deficits in hippocampal-PFC synchrony and SWM (Mukai et al., 2015), displayed augmented hippocampal-PFC theta–slow gamma coupling likely to reflect a compensatory mechanism (Tamura et al., 2017) and showed reduced axonal branching of ventral hippocampus inputs to the mPFC (Mukai et al., 2015). Strikingly, developmental inhibition of glycogen synthase kinase-3 (GSK3), which prevented axonal branching deficits in *Zdhhc8*$^{+/-}$ mice (Mukai et al., 2015), rescued impaired hippocampal-PFC synchrony, SWM performance and mPFC neuronal encoding of spatial representations in *Df(16)A*$^{+/-}$ mice (Tamura et al., 2016).

Rodent studies of various other genetic risk factors to schizophrenia have drawn links between disordered SWM and hippocampal-PFC communication. Neuregulin-1, encoded by the schizophrenia susceptibility gene, NRG1 (Harrison and Law, 2006), is a cell adhesion molecule that signals through ErbB4 receptors (Mei and Nave, 2014) found nearly exclusively on parvalbumin (PV)-positive interneurons (Fazzari et al., 2010). Deletion of ErbB4 receptors selectively from PV-positive interneurons, long implicated in schizophrenia and cognition-supporting neural oscillations (Cardin et al., 2009; Gonzalez-Burgos et al., 2015; Lewis et al., 2012; Sohal et al., 2009; Uhlhaas and Singer, 2015), impaired SWM ability, reduced resting hippocampal-PFC theta synchrony and increased hippocampal gamma oscillations during exploration (Carlen et al., 2012; Del Pino et al., 2013; Wen et al., 2010; Yin et al., 2013). Mouse models of the schizophrenia-associated 15q13.3 microdeletion have been reported to have blunted auditory-evoked gamma oscillations in the hippocampus and frontal cortex (Fejgin et al., 2014; Stefansson et al., 2008). These mice also showed increased PFC gamma and reduced PFC and hippocampal theta oscillation power, but spared SWM (Fejgin et al., 2014).

Environmental and developmental models also suggest a role for disordered hippocampal-PFC communication in schizophrenia-related deficits in SWM. For example, rodent maternal immune activation models known to produce deficits in SWM (Meyer and Feldon, 2009; Richetto et al., 2013) display reductions in theta- and low-gamma-frequency hippocampal-PFC synchrony (Dickerson et al., 2014, 2010) that are reversed by acute treatment with the atypical antipsychotic, clozapine (Dickerson et al., 2012). Although no direct link has been established between hippocampal-PFC synchrony and the SWM deficits seen using the neonatal ventral hippocampal lesion model (Lipska et al., 2002, 1993), Lee et al. (2012) found that cognitive training during adolescence that reverses interhippocampal synchrony and cognitive deficits induced by the lesion also enhances hippocampal-prefrontal synchrony across a broad frequency range. Another developmental model that produces schizophrenia-like impairments in SWM (Gourevitch et al., 2004) involves gestational exposure to the teratogen, mitotoxin methylazoxymethanol acetate (MAM; Grace, 1998). Recordings from MAM-treated rats show attenuated delta (<4 Hz) and low gamma oscillations in the mPFC (Goto and Grace, 2006), broadly reduced oscillations in the hippocampus (Perreault et al., 2017), blunted fear-conditioned tone-evoked theta and gamma oscillations in the mPFC and gamma oscillations in the ventral hippocampus (Lodge et al., 2009) and hippocampal-prefrontal decoupling during sleep (Phillips et al., 2012).

A key recent hypothesis regarding schizophrenia pathophysiology proposes that the hypofunction of N-methyl-D-aspartate receptors (NMDARs) underlies aspects of the disorder. Commonly studied using pharmacological receptor blockade (Javitt and Zukin, 1991), NMDAR hypofunction is thought to promote aberrant neural oscillations that contribute to cognitive dysfunction (Homayoun and Moghaddam, 2007; Hunt and Kasicki, 2013; Krystal et al., 1994; Uhlhaas and Singer, 2013). Treatment with NMDAR antagonists, such as ketamine, phencyclidine and MK801, induces SWM deficits (Beraki et al., 2009; Castane et al., 2015; Enomoto and Floresco, 2009; Verma and Moghaddam, 1996) and tends to reduce hippocampal theta oscillations, while enhancing PFC and hippocampal delta-, gamma- and high-frequency oscillations (130–180 Hz; Hinman et al., 2013; Hunt and Kasicki, 2013; Kjaerby et al., 2017; Korotkova et al., 2010; Lazarewicz et al., 2010; Moran et al., 2015; Sapkota et al., 2016). Acute and chronic ketamine treatment in rodents also alters the coupling of hippocampal theta phase with gamma- and high-frequency oscillation power (Caixeta et al., 2013; Michaels et al., 2018), reminiscent of the global and fronto-temporal frequency coupling alterations reported in patients with schizophrenia (Allen et al., 2011; Sun et al., 2013; Won et al., 2017). While the effects of NMDAR antagonists on long-range hippocampal-PFC synchrony are less clear (Lee et al., 2017), reports have shown that sub-anaesthetic doses of ketamine increase hippocampal-PFC functional connectivity measured using functional magnetic resonance imaging (fMRI) in rats (Gass et al., 2014) and humans (Grimm et al., 2015).

Unfortunately, few studies using these and other rodent model systems of potential relevance to schizophrenia have assessed the hippocampal-PFC activity dynamics during SWM performance. Moreover, no studies to date have definitively parsed the specific long-range neuronal projections that may mediate, through gain or loss of function, disease-altered hippocampal-prefrontal activity dynamics and SWM.

Disordered thalamo-PFC communication and SWM in models for inquiry into schizophrenia

Classical post-mortem and modern clinical imaging studies indicate that the thalamus, a key hub within cortical–subcortical circuits and an important regulator of cortical activity, is structurally and functionally abnormal in patients with schizophrenia (Buchmann et al., 2014; Glahn et al., 2008; Hazlett et al., 1999; Hazlett et al., 2004; Kemether et al., 2003; Konick and Friedman, 2001; McCarley et al., 1999; Minzenberg et al., 2009; Pakkenberg, 1992). Consistent with their strong reciprocal connectivity, the thalamus and PFC show disordered functional connectivity in patients with the disorder (Anticevic et al., 2015; Cho et al., 2016; Woodward and Heckers, 2016; Woodward et al., 2012). Thalamo-PFC disconnectivity manifests at rest (Anticevic et al., 2014; Giraldo-Chica and Woodward, 2017; Welsh et al., 2010) and during cognitive and working memory testing (Andrews et al., 2006; Bor et al., 2011; Katz et al., 1996; Mitelman et al., 2005; Schneider et al., 2007). Probing the structural basis of this functional disconnectivity, compelling recent work showed in patients with schizophrenia that reductions in thalamo-PFC white matter connectivity correlated with impairments in PFC functional activation and working memory task performance (Giraldo-Chica et al., 2017; Marenco et al., 2012).

Few clinical and rodent studies of genetic predisposition to schizophrenia have shown evidence of altered thalamo-PFC communication, particularly in SWM. Products of the neuregulin-1 gene, NGR1, have been shown in mice to mediate thalamo-cortical axon pathfinding (Lopez-Bendito et al., 2006). This mirrors clinical evidence linking schizophrenia-associated risk variants of the gene with reductions in the structural integrity of the anterior thalamic radiation that connects the MD and anterior thalamic nuclei to the PFC (Barnes et al., 2012; Sprooten et al., 2009). Evidence that neuregulin-1 mutant mice show reduced NMDAR levels in the thalamus (Newell et al., 2013) is particularly intriguing given recent work from Yasuda et al. (2017) showing that the ablation of NMDARs in intralaminar thalamic nuclei attenuates oscillatory power measured by electroencephalography (EEG) in alpha-, beta- and gamma-frequency ranges and induces schizophrenia-like SWM deficits that are rescued by restoring thalamic NMDARs. No preclinical evidence to date indicates disruption in thalamo-PFC communication resulting from the schizophrenia-associated 22q11.2 or 15q13.3 microdeletions, and only mixed evidence of abnormal thalamic structure has been reported in 22q11.2 clinical populations (Bish et al., 2004; Lin et al., 2017). Similarly, environmental and developmental models of potential relevance to schizophrenia have produced limited evidence of disordered thalamo-PFC function or its contribution to SWM deficits, and evidence of altered thalamic volume and neuronal density from these models is modest and mixed (Crum et al., 2017; Matricon et al., 2010; Moore et al., 2006).

Studies using pharmacology to model aspects of schizophrenia, particularly those modelling NDMAR hypofunction, provide the most insight to date into disease-related dynamics of thalamo-PFC communication (Pratt et al., 2017). Acute and chronic administrations of NMDAR antagonists that induce SWM deficits (Enomoto and Floresco, 2009; Verma and Moghaddam, 1996) enhance activity-related gene expression in the thalamus (Castane et al., 2015), but exert mixed effects on the firing of thalamic neurons (Celada et al., 2013; Furth et al., 2017; Santana et al., 2011). Using 2-deoxyglucose imaging in rats, Dawson et al. (2013) showed that acute and chronic (Dawson et al., 2014) ketamine induced respective hypo- and hypermetabolism in the thalamus and PFC, as well as abnormal thalamo-PFC connectivity, paralleling that seen in humans (Langsjo et al., 2004). Interestingly, the same study showed increased functional connectivity between the PFC and thalamic reticular nucleus (Dawson et al., 2013), a structure that inhibits and exerts oscillatory influence over other thalamic nuclei (Mitrofanis and Guillery, 1993; Pratt et al., 2017). Neural oscillations in thalamo-cortical circuits are particularly modulated by NMDAR antagonists, showing preferential increases in power at higher frequency ranges that have been implicated in cognitive functions like SWM (Pratt et al., 2017; Uhlhaas and Singer, 2013; Zhang et al., 2012). For example, recent work by Furth et al. (2017) showed in rats that ketamine increased power within a comparable gamma-frequency range in the mPFC and MD thalamus, but was without effect on thalamo-PFC synchrony. Ketamine also induced contrasting neural activity dynamics in the mPFC and MD, increasing the rate and gamma-phase-locking of neuron firing in the mPFC, but decreasing both measures in MD neurons (Furth et al., 2017). Lower frequency oscillations, including delta oscillations, have also been shown to be altered by NMDAR antagonism (Buzsaki, 1991; Zhang et al., 2009), as they are in schizophrenia (Boutros et al., 2008; Clementz et al., 1994; Fehr et al., 2001). For example, systemic and local NMDAR blockade within the MD (but not the mPFC) increased delta-frequency power in the mPFC (Kiss et al., 2011a, 2011bb), supporting a role for thalamic NMDAR hypofunction in thalamo-PFC activity dynamics. Interestingly, infusion of ketamine into the nucleus reuniens of the thalamus increased delta oscillations locally and in hippocampal CA1, and inhibition of the reuniens prevented this increase in hippocampal delta (but not gamma) oscillations following systemic NMDAR antagonism (Duan et al., 2015; Zhang et al., 2012). Supporting the behavioural relevance of these thalamus-derived delta oscillations, optogenetic activation of inputs from the reuniens to the dorsal hippocampus at a 3 Hz (delta) frequency impaired SWM performance (Duan et al., 2015).

To date, very few studies of schizophrenia-related models have assessed the thalamo-PFC activity during SWM performance and therefore do not inform how disordered thalamo-PFC communication may dynamically vary as the information processing requirements move from encoding to maintenance to retrieval across a given trial (Figure 1; Bolkan et al., 2017; Miller et al., 2017). Fewer studies yet have probed task period–specific and frequency-specific roles for discrete long-range neuronal projections that connect the thalamus and PFC, directly or indirectly, in disordered SWM.

Outstanding questions and future directions

Considerable advances have been made towards an understanding of the dynamic communication of the PFC with its hippocampal and thalamic network partners that supports SWM. Modern preclinical work has revealed that long-range projections between these structures contribute to inter-regional neural synchrony and convey contextually tuned information to facilitate effective SWM (Figure 1(a)). Evidence indicates that the hippocampus and PFC are functionally coupled at various stages of SWM, and the direction of this coupling may transition from a predominantly hippocampus-to-PFC information flow during encoding and maintenance to a ‘top-down’ flow during retrieval (see also Eichenbaum, 2017; Place et al., 2016). Theta-frequency interactions between the hippocampus and PFC may provide a conduit for information pertaining to the maintenance and retrieval of encoded spatial representations in SWM (see also Kang et al., 2018). Gamma-based functional coupling of the hippocampus and PFC may play a privileged role in the encoding of spatial representations, and direct inputs from the ventral hippocampus to the PFC appear to subserve this coupling. Thalamic-PFC communication seems to complement the roles of hippocampal-PFC interactions in SWM. Thalamic influence over PFC activity may be strongest during SWM maintenance, perhaps serving to amplify and sustain cortical representations of the memory trace (Halassa and Kastner, 2017; Parnaudeau et al., 2017), and this influence may reverse during SWM retrieval and action execution. This bidirectional interaction, which may be mediated via oscillations in the beta frequency, requires the function of direct reciprocal thalamo-PFC projections.

Disordered prefrontal connectivity and communication with the hippocampus and thalamus appear to be associated with SWM deficits seen in schizophrenia and its related rodent models (Figure 1(b)). Genetic risk models provide the strongest evidence

that impaired hippocampal-PFC theta synchrony underlies schizophrenia-related impairments in SWM. Other models provide general support for altered oscillatory signatures in the two structures, particularly in the theta- and gamma-frequency ranges. A less clear description of disordered thalamo-PFC communication derives from these models. Indeed, although they show altered functional connectivity and reveal opposing disease-related alterations in neural activity between the thalamus and PFC, few of these models provide evidence of altered thalamo-PFC neural synchrony, particularly in the beta-frequency ranges implicated in normal SWM. Notably, the anatomical and functional heterogeneity of juxtaposed thalamic nuclei, coupled with the regional diversity of PFC and hippocampal cells and circuits, likely contributes to variability in the literature.

More importantly, however, very few studies of schizophrenia-related models involve simultaneous recordings from the PFC, thalamus and hippocampus during SWM performance. Rigorous analysis of dynamic changes in the strength and directionality of inter-regional coherence as animals encode, maintain and retrieve SWM representations stands to reveal more nuanced and predictive electrophysiological endophenotypes of schizophrenia. Furthermore, studies attempting to normalise these endophenotypes with established and emerging treatment strategies will serve as powerful within-subject tests of their validity and help identify those warranting deeper mechanistic study.

Tests of causality are critical to meaningfully advance the understanding of the neural basis of normal and disordered SWM. Loss- and gain-of-function manipulations with the temporal and spatial resolution afforded by modern optogenetics are required to not only parse the discrete cells and projections that mediate SWM function and dysfunction, but also to test the causal relevance of their discrete activity patterns. Open- and closed-loop interventions that replicate, strengthen, weaken or clamp specific oscillatory patterns by the informed and real-time manipulation of discrete cells and projections are beginning to be employed (Grosenick et al., 2015; Jadhav et al., 2012; Padilla-Coreano et al., 2017; Roux et al., 2017; Siegle and Wilson, 2014). Such approaches will help reveal the hippocampal- and thalamo-PFC network dynamics that promote or impair SWM, and advance our understanding of these processes beyond the realm of correlation.

Finally, SWM is a cognitive domain that is ideally suited for translational research, as it is testable in rodents and primates, and its deficits in schizophrenia are recapitulated in many models. Future efforts to parse the neural circuit bases of normal and disordered SWM should prioritise neural synchrony and connectivity phenotypes that are shared between these species, and between the clinical condition and its associated models. Increased clinical application of traditionally preclinical SWM tasks (e.g. Bahner et al., 2015) will aid in identifying phenotypes with the clearest translational utility. Of course, meaningful comparison of these phenotypes requires continued efforts to relate diverse electrical and metabolic measures of neural synchrony and connectivity (Logothetis, 2015), sober consideration of anatomical, functional and behavioural homology across species (Seamans et al., 2008; Uylings and van Eden, 1990) and critical evaluation of the validity of animal models of potential relevance to schizophrenia (Cope et al., 2016; Nestler and Hyman, 2010). Therefore, as rodent systems continue to reveal fundamental neural substrates and principles of network function underlying SWM, concurrent development of non-human primate models of schizophrenia predisposition (Jennings et al., 2016) will enable testing of these findings in animals with brains and behaviours that more closely resemble our own.

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