Working Memory-Related Prefrontal Activity Measured with Magnetoencephalography: Abnormalities in Schizophrenia and Relationship to Dopamine

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Preface

The motivation for this project arises from the severe cognitive impairments suffered by individuals with schizophrenia, which often prevent them from functioning in society and living as fulfilling a life as they would hope for. Much evidence has been accumulated to implicate various dysfunctional neural systems, particularly in terms of brain regional activation during cognitive tasks such as working memory. However, the electrophysiological underpinnings of this dysfunctional activation, and its relationship to other neurophysiological dimensions implicated in schizophrenia, has not yet been fully defined, and thus serves as the focus of my thesis.

In my introduction I discuss the dorsolateral prefrontal cortical (DLPFC) activity underlying working memory-related (dys)functions in health and schizophrenia, and in turn, receptor-specific aspects of dopaminergic signaling that modulate this working memory-related DLPFC activity. I also provide background on magnetoencephalography (MEG), a more specialized neuroimaging modality that nevertheless offers unique potential for revealing and understanding human brain function in health and disease states.

In Chapter 2 I describe my work characterizing working memory-related prefrontal activity using MEG in a large sample of healthy individuals. I found that in the pre-response period of the working memory (WM) task, the DLPFC exhibited an extremely robust event-related desynchronization (ERD) of beta band activity.

Based on the results discussed in Chapter 2, I then hypothesized that patients with schizophrenia would show altered DLPFC beta band ERD. As I discuss in Chapter 3, indeed beta desynchronization was reduced in patients: utilizing a unique medication withdrawal study to control for, and examine the anti-dopaminergic effects of antipsychotics, I found that patients, while off antipsychotic medication, exhibited significantly reduced DLPFC beta band ERD. In the same study I showed that while on antipsychotic medication, these patients experienced a time-specific "normalization" of beta band ERD, a result that I discuss further in my conclusions (Chapter 5).

In Chapter 4 I present my work using both PET and genetic variation in the dopamine D_1 receptor gene *DRD1* to parse the contributions of dopamine D_1 and D_2 receptor function to DLPFC activity, in healthy volunteers. Both PET and genetic analyses revealed associations between beta band ERD and D_1 receptor function, converging on the importance of the D_1 receptor in healthy WM function.

In Chapter 5 I summarize my findings and how they advance the current understanding of WM-related DLPFC activity in health and in schizophrenia, particularly regarding its relationship to the dopamine system. I also discuss preliminary results relating to future directions, for example, that medication-related "normalization" of beta band ERD in patients was strongly correlated with dopamine D_2 receptor availability in the striatum. Additional patient-specific results will help clarify possible abnormalities in dopaminergic regulation of WM function, and how these abnormalities may contribute to the observed clinical

phenotype. Ultimately, this work will lead to a greater understanding of the underlying neurophysiology of cognitive deficits in schizophrenia, and how to better treat them.

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CHAPTER 1 INTRODUCTION

1.1 Schizophrenia

Schizophrenia, or perhaps more accurately schizophrenias (Bleuler, 1911), is a family of highly debilitating mental disorders that affect up to 1% of the population worldwide, disabling in its sufferers the highly complex cognitive and social behaviors necessary to function in society (Schultz & Andreasen, 1999). Impaired cognitive functions vary widely, from working memory (WM) and goal execution, to attention and processing speed (Fatouros-Bergman et al., 2014; Andreasen & Carpenter, 1993). Diminished social functions include social withdrawal, avolition, and other 'negative' symptoms. Frustratingly, current pharmacological treatments primarily target the 'positive' symptoms such as hallucinations and delusions but not the cognitive and negative symptoms. The task, therefore, for researchers of this devastating disorder is to identify the neurophysiological substrates of these cognitive and negative symptoms, which can then be used as targets for new treatments.

Much work has been done to uncover these substrates, with etiological hypotheses ranging across nearly all neural systems and dimensions (Fallon et al., 2003), as well as subcellular genetic networks and environmental milieus both internal and external (Howes et al., 2017). At the neural circuits level, the

dorsolateral prefrontal cortex (DLPFC) sits at a central locus in these hypotheses, as the brain region most involved in planning and executing complex behaviors. Some of the many neural circuits involving the DLPFC implicated in schizophrenia include the thalamo-prefrontal circuit connecting the mediodorsal nucleus of the thalamus to the DLPFC (Marenco et al., 2012; Anticevic et al., 2013), the hippocampal-prefrontal circuit (Meyer-Lindenberg et al., 2005; Godsil et al., 2013), and the cortico-cerebellar-thalamo-cortical circuit (Andreasen, 2014). At a more microscopic level, another well-established hypothesis is based on a single cell type: the fast-spiking parvalbumin-positive interneuron (Lewis et al., 2005; Nakazawa et al., 2012). These cells are fundamental in the generation of gamma oscillations (Cardin et al., 2009; Carlén et al., 2012), and underlie other etiological hypotheses of schizophrenia based on aberrant gamma activity (Uhlhaas & Singer, 2010; Lewis et al., 2012). The fast-spiking interneuron hypothesis dovetails with the GABA hypothesis, based on the well-replicated finding of reduced GABA expression in patients (Akbarian & Huang, 2006). However, other neurotransmitter theories abound, including a serotonin hypothesis (Eggers, 2013), the glutamate hypothesis (Moghaddam & Javitt, 2012), and most importantly the dopamine hypothesis (Howes & Kapur, 2009), discussed in section 1.5.1, which also closely relates to hypotheses at other levels of analysis such as the fronto-striato-thalamic circuit (Robbins, 1990; Dandash et al., 2016) and the DLPFC in general (Weinberger et al., 2001).

Mirroring this etiological complexity is the clinical complexity of highly variable presentation of schizophrenia. While the diagnostic definition according to the DSM-V (American Psychiatric Association, 2013) consists of symptoms such as hallucinations, delusions, disorganization, and social dysfunction, many patients may only show subsets of these, and between any given two individuals with schizophrenia there may be only few, core overlapping symptoms.

The immense scientific challenge to unravel the connections between some of the mental domains implicated in schizophrenia serves as the motivation for my project, which focuses on one of the most impaired cognitive domains, working memory (Fatouros-Bergman et al., 2014), and attempts to clarify its physiological underpinnings, specifically as they relate to prefrontal and dopaminergic function.

WM impairment is among the more devastating deficits in schizophrenia, hindering goal maintenance and short-term memory, and has even been proposed to lead to entirely other symptoms (Goldman-Rakic, 1994). It is long known that prefrontal damage can lead to schizophrenia-like behavioral disorders (Freeman & Watts, 1939), and that working memory relies on intact prefrontal circuitry (see section 1.3). How is the network activity of the prefrontal cortex disrupted in patients? Much evidence points to abnormal neural oscillatory activity, as described in section 1.4.3, and which I measure with magnetoencephalography (MEG), discussed below.

1.2 Magnetoencephalography

1.2.1 Background and history

MEG is unique among neuroimaging techniques in its ability to both measure electrophysiological activity at sub-millisecond timescales (like electroencephalography [EEG]), and localize cortical neural activity with near-millimeter resolution (like functional magnetic resonance imaging [fMRI]). A short overview of the technique is provided due to the relative rarity of its use, compared to more well-known modalities such as fMRI and EEG.

MEG began with David Cohen (1968), who like Hans Berger (1929), the first to record EEG activity, measured alpha waves from occipital cortex during eyes closed resting state. Similar to EEG, MEG measures changes in electrical activity of the brain, which manifest as changes in the magnetic field outside the head, which MEG sensors detect. More specifically, magnetic dipoles are generated by intracellular dendritic currents associated with excitatory post-synaptic potentials (EPSPs), which summate to produce a measurable signal if aligned in parallel in great enough number (~100,000 cells) (Hämäläinen et al., 1993). While EPSPs are believed to dominate the MEG signal, some simulation studies have suggested that under certain circumstances, highly synchronous action potentials may also be measurable (Murakami & Okada, 2006). Unlike EEG, which is more sensitive to currents projecting along the radial axis from the center of the head out, MEG is more sensitive to the tangential (parallel to the brain surface) component of currents, due the perpendicular orientation of the magnetic field to its underlying

direction of current flow. Importantly, the changes in magnetic field measured by MEG are not distorted by the skull and scalp, in contrast to the changes in electrical activity measured by EEG, thus allowing for more accurate localization of neural source activity.

This enhanced spatial acuity is what differentiates MEG most from EEG, and manifests in the different analysis techniques used in the two modalities. Whereas the evoked potential, calculated from the average signal of specific sensors across many trials, is the preferred method of analysis in EEG, localization methods such as dipole fitting and beamformers are more popular with MEG. In this thesis, I use a localization technique based on the linearly constrained multivariate beamformer (Vrba & Robinson, 2001), which independently localizes frequency-specific activity via adaptive spatial filters for specified points in the brain. These filters are calculated to maximize signal from a given point, while suppressing signals from all others, thus localizing activity and removing artifacts. Methods like this one have been shown to achieve localization accuracy of ~5mm (Sekihara et al., 2005), and may thus enable a more spatially-precise indexing of WM-related prefrontal function compared to EEG (and more temporally-precise than fMRI), which can then be probed in patients.

1.2.2 Neural oscillations

Both EEG and MEG measure neural activity at the millisecond time scale, allowing for better characterization of precise event-related activity, or oscillatory activity throughout a cognitive task, compared to fMRI. Event-related

potentials/fields (ERPs/ERFs) are calculated by averaging the signals across the entire frequency spectrum from many trials. In contrast, oscillations are analyzed by filtering the neural signal into its different frequency components. Oscillations at different frequencies throughout a wide spectrum from 1Hz to >200Hz have long been shown to relate to various aspects of cognition, including perception (Gray et al., 1989), working memory (von Stein & Sarnthein, 2000), and selective attention (Fries et al., 2001). More specifically, different oscillations reflect different organized patterns of activity within and between specific brain regions, cortical layers, or specific neuron types, and have thus been associated with specific cognitive functions (Uhlhaas & Singer, 2010). For example: theta band (~6Hz) activity is the dominant oscillatory rhythm of the hippocampus, and has been associated with memory function (Buzsáki, 2002); alpha (~10Hz) activity is associated with thalamo-cortical connections and often reflects attentional gating (Lopes da Silva et al., 1973; Feige et al., 2005); beta band (~20Hz) oscillations are still less understood but partly rely on the synchronous input to supragranular and infragranular layers (Sherman et al., 2016) and seem to be involved in cortical inhibition and often in motor control (Jensen et al., 2005); gamma (~40Hz) oscillations can be generated by the rhythmic interplay of inhibitory interneurons and pyramidal cells generally underlying sensory perception (Cardin et al., 2009). Although these frequency bands are not restricted to those particular systems, oscillations can thus provide additional inferred functional information, besides simply being measures of activation (Siegel et al., 2012). In summary, neural oscillations reflect distinct modes of activity in

neural circuits and are thus indispensable for a complete explanation of how neural phenomena give rise to behaviors such as working memory, and its dysfunctions (Lopes da Silva, 2013).

1.3 Dorsolateral prefrontal cortex and working memory

Baddeley & Hitch (1974) helped to develop the concept of working memory, which is based mainly on the function of immediate, or short-term memory (STM). Both short-term and working memory refer not just to the maintenance of information during a delay period, but also the more complex system underlying the manipulation and use of this information for subsequent action (Baddeley & Hitch, 1974). While working memory is associated with cortical and sub-cortical networks (including parietal cortex and striatum [Jonides et al., 1993; Baier et al., 2010 Darki & Klingberg, 2015]), this section briefly discusses the dependence on one particular cerebral region – the prefrontal cortex, which is an especially important node in WM networks.

1.3.1 Early lesion studies

The association of WM function to the prefrontal cortex was not established until after similar cognitive functions had already begun to be ascribed to this brain region in the early 20th century (Bianchi, 1922; Ackerly, 1935; Jacobsen 1936), along with the recognition that even non-motor related behaviors could be partially localized to specific cerebral regions (Ferrier, 1873). Perhaps the most famous individual case of psychiatry – the case of Phineas Gage (Harlow, 1868) – also promoted interest in the frontal lobe and its possible relationship to schizophrenia (Mesulam, 1986). Jacobsen (1936) however was first to show that monkeys with bilateral prefrontal lesions were severely impaired specifically in delayed-response tasks, which probed short-term, or "immediate memory". In humans the affected

function was predictably more complex: a relatively large sample of patients was assessed by Freeman & Watts (1939), who concluded that the role of the frontal lobe was to "assemble the available data, synthesize them, plan a course of action with the ideal in mind, and … direct him toward his goal".

While such studies implicated the frontal lobe in a general manner as being important for working memory, the questions remained as to which specific part of the frontal cortex is most important for WM function and how do neurons in that region organize to execute this important function. These questions motivated the seminal work of Patricia Goldman-Rakic and others (Arnsten, 2013).

1.3.2 Delayed response activity in non-human primates

Studies of non-human primates probed short-term memory using variations of delayed-response tasks, for example a delayed-alternation paradigm in which a monkey is baited to choose a food reward from one of two containers. The containers are then shielded from view for several seconds, and the monkey is prompted to choose the alternate container. Goldman & Rosvold (1970) utilized this paradigm, along with experimental lesions, to specifically implicate the dorsolateral prefrontal cortex (DLPFC) as the crucial area for maintaining information over the delay period. The use of single-cell recordings within the awake behaving monkey revealed that DLPFC neurons continued firing during the delay, and helped further define how this region may maintain information (Fuster & Alexander, 1971).

Later studies employed the oculomotor delayed-response (ODR) task, which benefited from its control of the monkey's memory-guided movement until the

appropriate time, ensuring a more purely mental encoding of information over the delay (Funahashi et al., 1989). In this paradigm, which would become the standard WM paradigm for monkeys, a cue was provided to saccade to a specific location, after which the monkey was trained to withhold eye movements for the duration of a delay period. A second cue then prompted the saccade to the appropriate target.

More recent studies in non-human primates have investigated oscillatory dynamics of prefrontal WM-related activity. For example, Lundqvist et al. (2016) recorded prefrontal local field potentials from monkeys performing both delayed-response saccade task and delayed match-to-sample task (described in section 1.3.3) to demonstrate the existence and characteristics of beta and gamma band activity underlying WM function, providing validation for the human imaging studies discussed below.

While these studies confirmed the centrality of the DLPFC for WM maintenance, the advent of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) finally enabled non-invasive localization of WM function in humans (Jonides et al., 1993).

1.3.3 Human neuroimaging studies

In addition to Jonides (1993), who used a spatial WM task similar to the ODR task described above, other PET studies have utilized additional WM paradigms to show that these tasks elicit increased blood flow (which is closely related to neural activity [Attwell et al., 2010]) to the DLPFC, further establishing the importance of this particular area in humans as well as primates. Such paradigms include a verbal

WM task in which subjects are instructed to speak the numbers 1-10 in a random order with no repeats (Petrides et al., 1993), a visual n-back task where subjects continually respond "Yes" or "No" to whether a stimulus is the same as the one seen previously, either 1- or 2-back (Cohen et al., 1997), and an n-back task designed to be a more complete probe of *working* memory in which memory contents need to be continuously updated (Glabus et al., 2003). With the arrival of fMRI, researchers were now able to examine cerebral activity with greater resolution than with PET. Cohen et al. (1997) confirmed that WM-related DLPFC activity was sustained throughout the task, in agreement with the recordings from monkeys showing sustained firing throughout the maintenance period (Fuster, 1973). With the ability to examine neural activity in humans during cognitive tasks, the modulation of DLPFC activity with more nuanced variations in task difficult and complexity was now possible. For example in studies using two variations of the n-back task, the DLPFC was not only activated during these WM tasks, but its activity level also increased with memory load and correlated with performance (Cohen et al., 1997; Callicott et al., 1999). Additional research demonstrated that the DLPFC is further activated by additional manipulation demands of WM contents, and not solely to the maintenance of this information (D'Esposito et al., 2000).

While the above studies helped define the types of cognitive domains that the DLPFC is and is not involved in, as well as its connections with other regions in support of WM function, including the ventrolateral PFC and parietal cortex, as well as numerous subcortical regions (Gazzaley et al., 2004), none clarified the finer-

grained temporal characteristics of WM-related DLPFC neurophysiology. Specifically, it is known that neuronal networks can be characterized in part by their oscillations (Buzsáki, 2009). Is WM-related DLPFC network activity likewise concentrated in specific frequency bands? Electrophysiological studies offer answers to this question.

1.3.4 Human electrophysiological characterizations of WM-related prefrontal activity

Correlates of WM activity in frontal cortex have been reported in nearly all frequency ranges, from theta through gamma (Roux & Uhlhaas, 2014), even among more invasive studies that have used intracranial EEG (iEEG) to measure more directly from the prefrontal cortex. For example, Raghavachari et al. (2001) focus on the role of prefrontal theta band oscillations as a "gating" mechanism for multi-item working memory, due to its immediate and sustained increase in oscillatory power following stimulus presentation. Prefrontal alpha has also been associated with WM processing, being found to increase parametrically with greater WM loads (Leiberg et al., 2006; Pesonen et al., 2006). Other studies expanded on this finding, demonstrating that lateral frontal alpha power decreased during stimulus encoding, and then increased during maintenance (Bashivan et al., 2014), supporting the notion that alpha power suppression correlates with a region's receptiveness to external stimuli. However, a greater number of studies have implicated beta and gamma band activity in relation to WM-processing in the DLPFC.

1.3.4.1 Beta band

Event-related desynchronization (ERD) in beta band has long been observed in relation to motor activity (Stancák & Pfurtscheller 1995), but also during working memory in both delayed match-to-sample and n-back tasks (Pesonen et al., 2006; Brookes et al., 2011). Prefrontal beta band activity was also associated with specific stimulus properties (Spitzer et al., 2014), suggesting this type of activity may be more involved in specific representation of WM contents, rather than imposing a general readiness state on the cortex, like alpha activity. Furthermore, recent MEG work has utilized an adaptive beamformer technique to localize this beta band ERD more specifically to the DLPFC (Altamura et al., 2010; Heinrichs-Graham & Wilson, 2015). In both of those studies a delayed match-to-sample task was used to show beta ERD from encoding to execution. While the precise neural mechanisms underlying this rhythm are still being clarified, data and models suggest an association with cortical inhibition (Jensen et al., 2005; Lee et al., 2013) and a decrease in cortico-cortical or thalamo-cortical information transfer (Sherman et al., 2016). As discussed in section 1.6, the cellular evidence for cortical inhibition supporting WM is well established (Rao et al., 2000). Thus, beta band ERD may be interpreted as a release of this inhibitory mechanism, allowing increased information transfer and processing.

1.3.4.2 Gamma band

In contrast to the desynchronization observed in prefrontal beta band activity, many studies have focused on the relationship between working memory and increased gamma oscillations (for review see Jensen et al., 2007). This focus

draws in part from early studies demonstrating a close relationship between gamma band activity and selective attention as well as stimulus feature binding (Fries et al., 2001; Singer & Gray, 1995). For example, increased post-stimulus gamma (>30Hz) activity during a delayed match-to-sample memory condition was found, relative to a control condition, in prefrontal electrodes (Tallon-Baudry et al., 1998), supporting the idea that gamma activity may underlie WM maintenance of visual information. Using magnetoencephalography (MEG) to better localize oscillatory activity again during delayed match-to-sample tasks, recent studies show that prefrontal gamma activity is positively correlated with memory load during spatial working memory (Palva et al., 2011; Roux et al., 2012). More direct neural recordings using intracranial EEG with a delayed match-to-sample and letter-based WM task show similar results (Howard et al., 2003; Mainy et al., 2007). Specifically, prefrontal gamma increased during the stimulus-encoding period, and increased more with greater memory load, demonstrating significant modulation by working memory during memory retention as well. Interestingly, similar to beta band oscillations, WM-related gamma activity has also been associated with cortical inhibition. Evidence for this association comes not only from the association of interneurons with the generation of gamma oscillations (Cardin et al., 2009), but was also suggested by Barr et al. (2009) who used the inhibition-enhancing potential of repetitive transcranial magnetic stimulation (rTMS) to increase WM-related prefrontal gamma activity during an n-back task.

These electrophysiological studies complement fMRI/PET to further define the type of prefrontal network activity underlying working memory in terms of more direct electrophysiological correlates. This allows for more direct bridging to modeling (Sherman et al., 2016) and non-human primate studies (Lundqvist et al., 2016) where more direct neural recordings implicated beta and gamma bursting in WM-related prefrontal activity, and where neurostimulation and neurochemical interventions can be tested. In Chapter 2 I present my original work replicating many of these findings in a large sample of healthy controls.

1.4 Working memory and prefrontal dysfunction in schizophrenia

1.4.1 Behavioral findings

Cognitive impairments in schizophrenia have long been recognized and indeed, this key observation contributed to localizing WM function (at least in part) to the prefrontal cortex. While Smith (1969) was the first in modern times to confirm short-term memory difficulties in patients for both verbal and visual information, similar difficulties were noted in the work of Kraepelin (1919) who helped define the symptomatology of the disorder. Kraepelin described the impairment of "mental efficiency", noting that "patients are distracted, inattentive … they cannot keep the thought in mind" (p. 23). Similar WM impairments are increasingly considered a core aspect of the disorder (Elvevåg & Goldberg, 2000): they begin early in childhood, long before clinically significant symptoms appear (van Oel et al., 2002; Woodberry et al., 2008), with performance in neurocognitive batteries, and working memory in particular, emerging as a strong predictor of future functional outcome (Green et al., 1996; Nuechterlein et al., 2011). In these cognitive tests, the term "working memory" can refer to either pure short-term memory tests involving replaying a string of digits or words for example, or tests that involve a greater degree of manipulation of information held online, such as the n-back tasks described in section 1.3.3 (Gur et al., 2007). A recent meta-analysis revealed that patients tend to show a WM performance decrease of about one standard deviation below the mean (Fatouros-Bergman et al., 2014), which made

working memory among the most affected cognitive domains, along with verbal memory and processing speed where performance was comparably impaired.

While working memory is generally treated as a separate cognitive domain, the above studies suggest it has special importance relative to other domains, especially with regard to schizophrenia. Goldman-Rakic (1994) hypothesized the centrality of working memory to thought disorder, defining working memory as "the basic psychological process that allows active mental operations and prevents the tyranny of external stimuli". In this way, WM impairments would lead to distractibility and thus attention difficulties. Furthermore, the inability to cohesively string together mental concepts would prohibit the formation of complex goals, manifesting as lack of initiative and goal-directed action. These behavioral impairments once again lead back to prefrontal dysfunction as their underlying physical cause, given the similar loss of function in patients with frontal lobe injuries (Freeman & Watts, 1939; Pantelis et al., 1997). Some have also suggested a specifically spatial (as opposed to verbal) WM deficit in patients, which would seem to further implicate the DLPFC (Park & Holzman, 1992). This hypothesis was partly supported by a meta-analysis finding slightly more consistent deficits in visuo-spatial compared to verbal working memory (Lee & Park, 2005). But the evidence for prefrontal dysfunction in schizophrenia is not solely based on their shared connection to working memory. Even aside from WM deficits, many differences in prefrontal structure have also been reported in people with schizophrenia, as discussed below.

1.4.2 Prefrontal structural findings

As discussed in section 1.1, the DLPFC sits at the junction of many hypotheses of schizophrenia etiology. While the original source of evidence came from uncontrolled brain injury (see section 1.3.1), more recent studies have investigated the details of prefrontal abnormalities at every level, starting with the genetic. For example, neuregulin-1, a candidate gene associated with schizophrenia (Stefansson, 2002) was found to have altered expression of one of its specific isoforms in the DLPFC of individuals with schizophrenia (Hashimoto et al., 2004). Similar results were found for proteins involved in GABA synthesis (Hashimoto et al., 2003) and GABA function (Hyde et al 2011; Tao et al., 2012), although levels of GABA itself in the DLPFC may not necessarily be altered (Kegeles et al., 2012). DARPP-32, a key protein involved in dopaminergic and glutamatergic signaling, has also been found to be reduced in postmortem DLPFC tissue of people with schizophrenia (Albert et al., 2002). Likewise, while dopaminergic findings are generally concentrated in subcortical regions such as the striatum, cortical dopaminergic abnormalities have also been found in patients (Weinstein et al., 2017). Specifically alterations were found in patients in both dopamine D_1 receptor availability (Abi-Dargham et al., 2002) and dopamine release (Slifstein et al., 2015) in the DLPFC, measured with PET ligands [^{11}C]NNC112 and [^{11}C]FLB457. Incidentally, the effect of dopamine on inhibition in the DLPFC was found to be mediated specifically by D_1 receptors (Kröner et al., 2007), suggesting a relationship to the GABA-related inhibitory findings discussed above.

At the more mesoscopic level of cellular structure, Goldman-Rakic & Selemon (1997) found altered neuronal density in the DLPFC of patients, leading them to conclude that the DLPFC in patients exhibits reduced neuropil, since neuronal density was also correlated with cortical thinning. As they point out, this coincides with MRI findings of reduced prefrontal volume in patients (Andreasen et al., 1986; Andreasen et al., 2011; Hajima et al., 2012). Furthermore, both Goldman-Rakic et al. (1997) and Lewis et al. (2001) posit the involvement of the medio-dorsal nucleus (MDN) of the thalamus, based on the laminar specificity of the cellular findings and the known connections between this thalamic nucleus and the DLPFC. This would coincide with the known involvement of MDN neurons in WM maintenance (Fuster & Alexander, 1971).

Alterations in this more macroscopic level of thalamo-prefrontal connectivity has found considerable evidence from related volumetric changes (Knöchel et al., 2016) and findings of diminished white matter integrity (Marenco et al., 2012; Wagner et al., 2015). The question though is how these findings of aberrant prefrontal structure at the protein, cellular, and network levels, translate into dysfunctional brain activity and/or behavior in patients. This question has begun to be answered with more recent multimodal imaging. And indeed, WM-related activation in the DLPFC and cognitive impairment (specifically in working memory or executive function) were both associated with alterations in GABA concentration (Chen et al., 2014), dopamine function (Abi-Dargham et al., 2002; Slifstein et al.,

2015), gray matter volume (Andreasen et al., 2011; Knöchel et al., 2016), and thalamo-prefrontal anatomical connectivity (Marenco et al., 2012).

1.4.3 Prefrontal functional findings

Franzen & Ingvar (1975) were the first to report abnormally decreased frontal activation in schizophrenia, using ^{133}Xenon clearance techniques to measure regional cerebral blood flow (rCBF), a proxy for neural activation, at rest. Later studies using similar techniques to measure task-related rCBF during a simple picture-naming task and spatial reasoning test, observed decreased activation in frontal regions in medication-free patients relative to the controls, further supporting the notion of "hypofrontality" (Berman et al., 1988). This abnormal activation was further localized to the DLPFC, and was importantly shown to be more specific to tasks that relied on this area. Hypofrontality was also observed during a non-spatial n-back task, using PET to measure rCBF (Carter et al., 1998). As expected, they demonstrated reduced WM-related DLPFC activation in patients, even when performance did not differ from controls. Additionally, fMRI studies have likewise shown reduced DLPFC activation during n-back paradigms (Glahn et al., 2005) however others have also shown hyper- rather than hypo-activation of DLPFC in patients (Manoach et al., 1999; Callicott et al., 2000). This discrepancy has led many to shift focus from hypo- vs. hyperfrontality, to inefficiency (Potkin et al., 2009), interestingly reviving the original Kraepelinian nomenclature of "mental efficiency" (Kraepelin, 1919). Accordingly, cortical deficits in patients would necessitate either greater energy demands for the same functional output, or

alternatively force the use of less efficient networks that require greater energy usage to perform the same function as networks used by controls (Callicott et al., 2003). More temporally-precise analyses have attempted to better uncover the neurophysiological underpinnings of this well-corroborated inefficiency (Potkin et al., 2009).

While earlier imaging studies above grappled with the "what" of WM-related DLPFC dysfunction, later studies began to examine the "when", by dividing the WM task into separate encoding, maintenance, and execution periods. Using fMRI, Driesen et al. (2008) showed that during the maintenance and execution phases of a spatial delayed match-to-sample task, patients exhibited reduced prefrontal activation even with comparable WM performance. Mirroring the above-noted discrepancies between hypo- and hyper-activation, a large multi-site study found instead increased fMRI BOLD activation during the execution of a verbal WM task (but not during the encoding epoch), again even with matched performance between groups (Potkin et al., 2009). Yet others have shown a more complicated profile of both hypo- and hyper-frontality, as well as diminished lateralization of WM-related activity (Lee et al., 2008), perhaps reflecting compensatory activation in patients. Thus, dissecting individual WM components of encoding, maintenance, and execution, as well as matching for group performance, while slightly emphasizing dysfunctional executive function in patients, nevertheless leaves open the question of what underlies prefrontal inefficiency.

Electrophysiological EEG/MEG studies have likewise documented differential oscillatory activity in patients across many frequency bands (Uhlhaas & Singer, 2010), and may thus help elucidate the neurophysiology underlying prefrontal inefficiency. While few of these studies have localized differences to the DLPFC per se, they are better-suited than fMRI and PET studies to investigate the temporal aspect of prefrontal dysfunction in schizophrenia. Their findings have been varied though. Using a verbal delayed match-to-sample task, Ince et al. (2009) found that frontal delta band event-related synchronization (ERS) and beta band ERD were reduced during encoding and maintenance periods. Other studies employing different WM tasks, such as the n-back, have also found decreased activation during encoding and maintenance periods, manifested as reduced beta and gamma band activity (Barr et al., 2010; Cho et al., 2006; Chen et al., 2014). However, Barr et al. (2010) also note increased gamma activity in patients; this discrepancy may be similarly explained by the inefficiency argument proposed above from fMRI studies. Yet others have found that in patients with early-onset schizophrenia, frontal gamma activity during the maintenance period peaks at lower WM loads compared to controls (Haenschel et al., 2009). Thus, while such electrophysiological studies have not converged on one specific task epoch most significantly altered in patients, they tentatively suggest that prefrontal inefficiency may at least partly rely on dysfunctional task-modulated beta and gamma oscillations.

However, the results of these studies were confined to sensor-based analyses, which prevents a direct anatomic comparison to the fMRI and PET studies of DLPFC

function. Furthermore, at least two major confounds complicate the interpretation of these studies and may partly contribute to the observed differences in patients. First, task performance in patients is generally significantly different, not just in reduced accuracy but also in altered response times, which is important in such temporally sensitive measures as EEG and MEG (Cho et al., 2006; Barr et al., 2010; Haenschel et al., 2009). Second, the presence of antipsychotic medication poses a significant and complicated confound, especially considering the relationship between dopamine and schizophrenia, as discussed in section 1.5.2. In Chapter 3 I present original work that accounts for and examines the effects these confounds.

1.5 Dopamine and schizophrenia

The discovery in the 1950s of D_2 antagonists as antipsychotic treatment ushered in the dominance of dopamine in etiological theories of schizophrenia, and motivated the intense research into the brain's dopamine signaling system, and how alterations in this system in patients may give rise to their symptoms.

1.5.1 The dopamine system

Dopamine-producing neurons are located primarily in two mesencephalic regions of the brain, the ventral tegmental area (VTA) and the substantia nigra (SN), but also further out both rostrally to the hypothalamus and caudally to the medulla (Björklund & Dunnett, 2007). Primate studies demonstrate that dopaminergic neurons project topographically from midbrain regions to regions throughout the brain, such that to an approximation, among midbrain neurons in the VTA/SN that project to the prefrontal cortex (the mesocortical pathway), more medial neurons project to more medial PFC, and more dorso-lateral neurons project to more dorso-lateral PFC. An analogous topographical organization is found in midbrain projections to the striatum, where more medial VTA neurons project to more medial striatal areas such as the ventral striatum (the mesolimbic pathway) and more dorso-lateral midbrain neurons in the SN project to more dorso-lateral subcortical regions such as the sensorimotor and associate striatum (the nigrostriatal pathway) (Williams & Goldman-Rakic, 1998; Weinstein et al, 2017).

With respect to working memory, the mesocortical projections are most important, supplying dopamine to the DLPFC in a tonic as well as phasic manner

(Grace, 1991). Feedback from the frontal cortex to the midbrain is relayed via glutamatergic corticomesencephalic projections, which close the loop of this mesofrontal dopaminergic control system (Tanaka, 2006). Additionally, frontostriatal projections underlie prefrontal control of the basal ganglia, which then loop back to frontal cortex via the thalamus, making the overall mesocorticolimbic dopamine system highly dynamic and complex (Alexander et al., 1986).

Besides the dense connectivity between regions of the dopaminergic system, difference among dopamine receptors add to the dopamine system's dynamic and complex interrelationships. There are five types of dopamine receptors (D_1 – D_5), which are grouped into two families (D_1-type: D_1 and D_5; D_2-type: D_2, D_3, D_4) with D_1 and D_2 receptors being the most widespread compared to the other subtypes. Both families are G-protein coupled receptors, but activation of dopamine D_1-type receptors leads to activation of adenylyl cyclase, generally resulting in increased neuronal activity, whereas activation of D_2-type receptors inhibits neuronal activity (Sokoloff & Schwartz, 1995). Their effect on network activity is less straightforward, due to their localization to both excitatory and inhibitory neurons. Laminar localization also differs: while both D_1 and D_2 receptors are expressed more abundantly in the striatum than in other regions, D_1 receptors dominate in the cortex specifically in superficial layers, compared to D_2 receptors which occur in much less abundance and in deeper layers (Meador-Woodruff et al., 1996; Goldman-Rakic et al., 1990). Nevertheless, the functional significance of the smaller number

of cortical D_2 receptors may still be instrumental for the pathology underlying schizophrenia, as well as the effect of antipsychotics discussed below (Lidow et al., 1989).

1.5.2 The discovery of antipsychotics and the dopamine hypothesis

The first evidence supporting dopamine's important role in the etiology of schizophrenia came from the observation that chlorpromazine, a D_2 receptor antagonist, greatly reduced positive symptoms, while amphetamines, which stimulate dopamine release, exacerbated them (Snyder et al., 1974). Chlorpromazine quickly rose in psychiatric use during this time from the 1950s (Ban, 2007), and it soon became apparent that its therapeutic effect, and that of other antipsychotics, was due to their action on dopamine receptors (Creese et al., 1976; Seeman et al., 1976). The dopamine hypothesis was thus born, although it was cautioned that evidence at the time was indirect, based only on the therapeutic effect of the drugs (Snyder, 1976). Nevertheless, since this discovery, dopamine antagonists have remained the standard of treatment. This discovery also revolutionized the science of schizophrenia, in its providence of a concrete anchor for other hypotheses of schizophrenia etiology, for example based on prefrontal dysfunction. This motivated investigations of the relationship between the prefrontal cortex and dopamine, by Goldman-Rakic and others, as discussed in section 1.6.

Although the dopamine hypothesis began as little more than a serendipitous connection, the mechanisms by which dopamine may induce the symptoms of

schizophrenia were eventually fleshed out in greater detail, resulting in a new theory of subcortical hyperdopaminergia (accounting for the positive symptoms) combined with prefrontal hypodopaminergia (accounting for the "deficit" symptoms) (Davis et al., 1991). These two facets were conceptualized as two sides of the same coin, as increasing prefrontal dopaminergic function through apomorphine injections resulted in reduced striatal dopaminergic activity, and prefrontal dopaminergic lesions resulted in increased striatal dopaminergic activity (Pycock et al., 1980). Since this updated version of the dopamine hypothesis was based largely on studies in rats, and since the mesocortical dopaminergic system is known to differ greatly in primates (Berger et al., 1988; Björklund & Dunnett, 2007), a new instantiation was warranted, that would also incorporate the different receptor functions in the dopaminergic system, and how it all relates not just to the chronic state of schizophrenia, but the prodrome as well (Howes & Kapur, 2009).

In the latest version of the dopamine hypothesis, many different risk factors for schizophrenia converge specifically on the striatal dopaminergic system to produce the final clinical state of psychosis. Some risk factors include those highlighted in Davis' hypothesis, of increased presynaptic striatal dopaminergic function, transmitted via postsynaptic D_2 receptors, combined with decreased prefrontal dopamine function, specifically at the D_1 receptor. Evidence of modestly greater $D_{2/3}$ receptor density has been reported (Kestler & Vega, 2001), as has evidence of reduced prefrontal dopamine levels (Abi-Dargham et al., 2002). From a genetic standpoint, many of the strongest associated genes are associated with

dopaminergic function, although GABAergic and glutamatergic related genes are also highly associated (Howes & Kapur, 2009). Environmental stress factors are also more recently becoming recognized as instrumental mediators of the genetic risk for psychosis (Howes et al., 2017), as they have been found to lead to over-sensitive dopaminergic function specifically in the striatum (Mizrahi et al., 2011).

Seamans and others (Seamans et al., 2001; Rolls et al., 2008) have extended this dopamine theory to the information processing performed by prefrontal cortex to explain how abnormal dopamine signaling, and the differential dysfunction of D_1 versus D_2 receptors, can lead to the host of cognitive symptoms observed in patients (see section 1.6.2). However, one of the obstacles to understanding these mechanisms is the confound of medication present in most studies, discussed below.

1.5.3 Effect of antipsychotic medications on WM activity

It has been common knowledge that antipsychotic medications fail to improve cognitive deficits, and may even exacerbate them given the hypothesized state of prefrontal hypodopaminergia in patients (Reilly et al., 2006). Newer, second-generation 'atypical' antipsychotics, which have reduced D_2 receptor affinity but greater serotoninergic affinity, may break with this trend, however. For example, when substituted for haloperidol, risperidone treatment improved verbal working memory in a randomized, double-blind study of 59 patients (Green et al., 1997). A meta-analysis likewise found similar results in other studies (Meltzer & McGurk, 1999), finding additionally that olanzapine, another atypical antipsychotic,

improved verbal memory but not working memory. Consistent with this lack of improvement on working memory with olanzapine treatment, Schlagenhauf et al. (2008) found no changes in fMRI-measured DLPFC activation during a WM task after patients switched from typical antipsychotics to olanzapine. In further agreement with Meltzer & McGurk (1999), Honey et al. (1999) found that patients who were switched to risperidone from typical antipsychotics had increased activation in the right DLPFC during a verbal WM task, as well as increased performance. However, a more recent large multi-site study examining the potential cognitive benefits of second-generation antipsychotics found no difference when compared to perphenazine, a typical antipsychotic, although both did minimally improve cognitive performance (Keefe et al., 2007). The presence or absence of neuroleptic effect on cognition thus remains controversial.

Whether effects on performance or activation are due to reduced D_2 receptor antagonism, increased serotoninergic action, or some interaction, is not known. Some have argued that the fMRI BOLD effects are related to the D_2 affinities of antipsychotics (Röder et al., 2013; Abbott et al., 2013), in part due to dopamine's effect on cerebral vasculature (Krimer et al., 1998), but only found evidence for a general, inconsistent effect of atypical antipsychotics on BOLD activity. Similarly, Murphy et al. (2016) demonstrated differential effects of aripiprazole and risperidone versus placebo on WM-related DLPFC activation in healthy individuals: DLPFC activation increased following aripiprazole treatment, but exhibited a trend for reduction following risperidone treatment. While they interpreted this result as

a demonstration of the D_2 partial agonist effect of aripiprazole, the complex binding profile of this drug with respect to serotonin receptors still cannot be ruled out as a possibility (Farah, 2005). Thus, in Chapter 3 I present my original work that examines the effects of antipsychotic medication on WM activity, using MEG, which does not have the additional confound of potential neurovascular effects.

1.6 Mechanisms of dopaminergic modulation of dorsolateral prefrontal cortical activity via D_1 and D_2 receptors

How does dopamine modulate the prefrontal cortex to give rise to the patterns of abnormal activation observed in patients? As alluded to above, much of the evidence points to the differential effects dopamine exerts on neuronal activity via D_1 versus D_2 receptors.

1.6.1 Non-human primate and in vitro studies

Motivated by the association of prefrontal dysfunction to schizophrenia (see section 1.4.2), and dopamine to schizophrenia (see section 1.5.2), researchers attempted to clarify the relationship between dopamine and prefrontal activity, especially during WM-dependent behaviors. The first concrete evidence for such a relationship came from the work of Brown & Goldman (1977) who reported the presence of relatively high concentrations of dopamine in the prefrontal cortex, compared to other neuromodulators such as epinephrine. This relationship was further clarified with the extremely thorough studies during the 1990s detailing the meso-frontal dopaminergic projections in monkeys (e.g. Goldman-Rakic et al., 1990; Williams & Goldman-Rakic, 1998). Key findings to emerge from this work revolve around the D_1 receptor, including its greater concentration in the DLPFC compared to D_2, its differential laminar profile compared to D_2 receptors, which was heavily weighted towards the superficial cortical layers, and its localization to inhibitory interneurons in addition to excitatory pyramidal cells (Muly III et al., 1998). This led to the now well-established hypothesis that D_1 receptors are instrumental in

supporting recurrent DLPFC network activity that underlies WM function, via its control of prefrontal inhibition (Kröner et al., 2007).

In addition to the anatomical evidence linking dopamine to the prefrontal cortex, early functional studies confirmed the influence of prefrontal dopamine on working memory via dopamine depletion, which resulted in spatial WM deficits in monkeys nearly as severe as ablation of prefrontal tissue (Brozoski et al., 1979). These behavioral deficits, which were not observed in a simple visual discrimination task, were reversed with dopaminergic treatment and specific to dopamine, compared to norepinephrine and serotonin, depletion of which did not result in WM impairments. The link between dopamine and the DLPFC was further examined with respect to the post-synaptic effects of dopamine. Consistent with the relative abundance of prefrontal D_1 versus D_2 receptors, Sawaguchi & Goldman-Rakic (1991) demonstrated a privileged role of D_1 receptors in the modulation of WM activity in the DLPFC. Specifically, they found that D_1 receptor antagonists impaired short-term memory, while D_2 antagonists injected into the same DLPFC sites did not. Similarly, D_1 receptor antagonist fluphenazine and non-specific dopamine antagonist haloperidol suppressed WM-related DLPFC neural firing, while D_2 antagonist sulpiride did not (Sawaguchi et al., 1988). Much subsequent research has sought to further differentiate the roles of D_1 versus D_2 receptors in modulating WM-related activity, and has painted a more nuanced picture. Specifically, Wang et al. (2004) found that D_2 receptor (ant)agonists do in fact modulate WM-related DLPFC neurons, but only those that were associated with memory-guided behavior

as opposed to those associated with delay-related activity. This led to the distinction between D_1 receptor-associated supragranular delay cells, and D_2 receptor-associated infragranular response cells (Arnsten et al., 2015).

Seamans et al. (2001) further demonstrated the differential, and in many ways oppositional, effects of D_1 and D_2 receptor activation on prefrontal network activity, specifically via cortical inhibition. While D_1 receptor activation enhanced inhibition by increasing interneuron excitability, D_2 receptor activation depressed inhibition by decreasing GABA release. They therefore proposed the existence of two states of working memory, one dominated by D_2 receptor activation in which multiple representations would be activated simultaneously but weakly, and another D_1-dominated state, in which only one or few representations would be strongly represented and protected from interference (Seamans et al., 2001; Jacob et al., 2016). Vijayraghavan and others (2007) support this idea by demonstrating that D_1 receptor agonists sharpen the spatial tuning curve of prefrontal neurons, suggesting a more "focused" state less susceptible to distractors.

These results help to explain the "inverted-U" relationship of dopamine to prefrontal cortical function, which is another nuance of dopaminergic modulation of WM-related DLPFC activity. This phenomenon refers to the observation that delay activity in the DLPFC is reduced at low and high concentrations of D_1 receptor stimulation, but increased at intermediate levels (Williams & Goldman-Rakic, 1995; Vijayraghavan et al., 2007). Thus, depending on the endogenous level of dopamine and D_1 receptor activation, low concentrations of both D_1 agonists (Vijayraghavan et

al., 2007) or antagonists (Williams & Goldman-Rakic, 1995) may enhance DLPFC neuronal activity, and higher concentrations of either would suppress it (for reviews see Cools & D'Esposito, 2011; Arnsten et al., 2015).

In short, it is hypothesized that the complementary actions of dopamine D_1 and D_2 receptors together sculpt prefrontal network activity to maintain a balance between cognitive stability and flexibility, depending on task demands. A shift in this delicate balance may lead to the cognitive impairment seen in schizophrenia (Winterer & Weinberger, 2004; Rolls et al., 2008). The details of how this would occur have been tackled using computational models (see section 1.6.3), and have begun to be confirmed in human studies as discussed below.

1.6.2 Human studies

Due to the difficulty of DLPFC-specific dopaminergic interventions in humans, human studies are forced to rely on more indirect methods to verify the predictions generated by primate studies and computational models. Such methods include genetic association analyses, the use of systemic dopaminergic agents, and PET to measure different receptor availabilities, as discussed in the following sections, respectively.

1.6.2.1 Genetic associations of dopamine with WM activity

Human genetic associations of dopamine function with prefrontal WM activity generally rely on single nucleotide polymorphisms (SNPs) in genes related to dopamine function, as well as to dopamine receptors in particular.

Perhaps the most widely cited dopamine-related gene in relation to schizophrenia is *COMT*, precisely because of its effect on prefrontal dopamine levels. The gene codes for the protein catechol-O-methyltransferase, which catabolizes dopamine, thus reducing its concentration, especially in the prefrontal cortex. Here, COMT is the main constraint on synaptic dopamine concentrations (Egan et al., 2001). A common mutation in *COMT* gene is the Val108/158Met polymorphism (rs4680) in which the minor Met allele results in a 75% reduction of COMT enzymatic activity, thus increasing synaptic dopamine concentrations (Egan et al., 2001). Numerous studies have associated variation in this genotype with prefrontal activation during working memory, using fMRI (Egan et al., 2001; Winterer et al., 2006a), EEG (Winterer et al., 2006b), and MEG (Altamura et al., 2016), which all consistently demonstrated greater prefrontal inefficiency in Val carriers. Furthermore, the effect of decreasing dopamine levels with COMT inhibitors had the predicted differential effect on Val/Val versus Met/Met individuals, such that reducing dopamine levels improved WM performance in Val/Val individuals, who typically have higher levels of prefrontal dopamine, but impaired performance in Met/Met individuals, who typically have lower levels of prefrontal dopamine (Apud et al., 2007).

Less is known about the neurophysiological effects of *DRD1* and *DRD2* SNPs, whose associations with WM-related prefrontal function have only more recently been examined. One of the most widely-studied SNPs in *DRD1* for example, is rs4532, which occurs in the 5' untranslated region of the *DRD1* gene, 48 base pairs

upstream of the protein coding start site (Cichon et al., 1994), and has thus been hypothesized to be involved in regulation of *DRD1* expression (Huang et al., 2008). Via haplotype association with rs686, another SNP of *DRD1*, the C minor allele of rs4532 was indirectly associated with reduced *DRD1* expression (Huang et al., 2008). Despite this indirect evidence, the C allele of rs4532 has been associated with differential treatment response to clozapine (Potkin et al., 2003), who found that C allele homozygotes exhibited significantly less DLPFC response to clozapine treatment. Furthermore, rs4532 has been strongly associated with schizophrenia in a large meta-analysis (Allen et al., 2008), which found the C allele to be the risk allele. However, findings with rs4532 vary greatly. While a more recent study also found associations between the C allele and treatment-resistant schizophrenia (Ota et al., 2012), a greater number have found weak or no effects on schizophrenia risk (Cichon et al., 1994; Kojima et al., 1999; Zhang et al., 2010; Dmitrzak-Weglarz et al., 2006), as have meta-analyses (Yao et al., 2014; Pan et al., 2014). In particular, recent very large genome-wide association (GWA) studies have also failed to show a significant effect of rs4532 (or other loci in the *DRD1* gene) on risk for schizophrenia (Ripke et al., 2014). While this does not rule out an effect of rs4532 or *DRD1* variance, it suggests that whatever contribution may exist is perhaps filtered in a complex way through interactions with other genes.

The large degree of individual variation in symptomatology of patients may also contribute to the discrepancies between these findings, by masking its potentially increased association with only specific subsets of the clinical phenotype.

In particular, this SNP may have greater impact in patients with greater negative symptoms (Zhang et al., 2011, Gurvich et al., 2016), which may partly underlie their treatment resistance. In further support of the functional significance of rs4532, Rybakowski et al. (2005) found that C allele homozygous individuals with schizophrenia performed worse on the Wisconsin Cart Sort Test, a measure of working memory and rule-updating. Additional associations between rs4532, specifically its C allele, and other clinical phenotypes have also been reported, including alcohol dependence (Batel et al., 2008) and inattentive symptomatology in ADHD (Luca et al., 2007). These associations with negative symptoms of schizophrenia and other behavioral phenotypes may reflect the modulation of prefrontal function by rs4532, given the potential relationship between negative symptoms and prefrontal circuitry (Okubo et al., 1997).

Genetic polymorphisms in the *DRD2* gene, perhaps because of their greater association with schizophrenia based on the mechanism of antipsychotics, have recently been examined more closely. Despite the association with schizophrenia (Kaalund et al., 2014), few studies have shown modest effects of *DRD2* genetic variance on prefrontal function during working memory. Specifically, WM-related DLPFC activity was related to both individual SNPs (Zhang et al., 2007) and a *DRD2* polygenic co-expression network, such that greater *DRD2* expression scores predicted prefrontal inefficiency and treatment response in people with schizophrenia (Pergola et al., 2017). While more investigation is needed into these

associations, the lack of strong effects would be consistent with the privileged role of D_1 receptors previously discussed.

1.6.2.2 Modulation by dopaminergic agents

More direct interventions using dopaminergic agents have provided greater evidence of dopaminergic modulation of WM activity in humans. While many of these studies have involved individuals with schizophrenia who were prescribed such agents (see section 1.5.3), some studies were also performed with healthy volunteers. Regarding the differential effect of D_1 versus D_2 stimulation, results are mixed: Müller et al. (1998) found that pergolide, a D_1/D_2 agonist, improved performance on a delayed matching WM task in healthy adults, whereas D_2 agonist bromocriptine did not, suggesting a preferential role for D_1 receptors. Similarly, Kimberg et al. (2001) found that bromocriptine did not affect task performance, and while it did modestly reduce activation of WM-related regions, those did not include the DLPFC. However, aripiprazole, a D_2 partial agonist, was found to significantly increase WM-related DLPFC activation as measured by fMRI (Murphy et al., 2016). Results regarding the D_1 agonist dihydrexidine are also mixed: it was found to improve WM performance in a group of patients with schizotypal personality disorder (Rosell et al., 2015), as well as resting-state DLPFC perfusion in people with schizophrenia (Mu et al., 2007), but affected neither performance nor DLPFC activation in a separate group of individuals with schizophrenia (Girgis et al., 2014).

One explanation for this discrepancy, and a complication in relating these results to pre-clinical studies, is that in humans the dopaminergic agents are

administered systemically (orally), rather than directly into DLPFC as they are in monkeys. Thus, in human experiments D_2 (and D_1) modulation may affect working memory primarily through other circuits, such as the basal ganglia (Nyberg et al., 2016). This would indeed be consistent with the higher concentration of dopamine receptors in the striatum versus other regions, as well as with the localization of D_2 receptors to deeper cortical layers, which synapse with subcortical regions (Goldman-Rakic et al., 1990).

A second source of discrepancy between human and monkey studies is the modality of measurement of neural activity: in monkeys, electrophysiological activity is measured directly, often in the form of neuronal spiking, while in humans, neural activity is assessed indirectly via blood flow-related changes measured with PET and fMRI BOLD, which may be more associated with neural input rather than output activity (Logothetis et al., 2001). These two important differences impede the effort to relate modeling and non-human primate research to human studies, the bridging of which is crucial to the development of more targeted therapies for cognitive disorders related to abnormal dopaminergic function, such as schizophrenia.

1.6.2.3 Association of dopamine receptor specific function to WM-related DLPFC activity in humans using PET

A more specific intervention involves the administration of radioactive tracer ligands that bind specifically to either D_1- or D_2-like receptors. This is the underlying strategy of PET studies, which can use such radioligands to image the binding

potentials of tracers in specific brain regions, and thus infer receptor availabilities. The few studies to use such methods have generally corroborated the existing literature from non-human primates. Specifically, D_1 receptor availability was found to be increased in drug-naïve patients (Abi-Dargham et al., 2012) and strongly predicted WM performance in patients with schizophrenia (but not controls) (Abi-Dargham et al., 2002). While not specific to the DLPFC, a separate study investigated D_1 receptor availability across the whole cortex, and found an association with prefrontal-related network dynamics during working memory (Roffman et al., 2016).

A separate study of healthy individuals found that the change in D_2 receptor availability in the DLPFC following amphetamine-induced dopamine release predicted WM-related DLPFC activation, supporting the important role of dopaminergic function within the DLPFC specifically (Slifstein et al., 2015). No studies have yet examined the differential relationship between D_1 and D_2 receptors as they relate to DLPFC activation, especially in electrophysiological terms that can be directly related to non-human primate studies. In Chapter 4 I present my original work investigating this relationship using MEG to measure electrophysiology, and PET to measure D_1 and D_2 receptor availabilities.

1.6.3 Lost in the noise: an integrated model of dopaminergic modulation of the DLPFC and schizophrenia

There are many ways to approach the dopamine hypothesis of schizophrenia and its relation to working memory. Here I summarize the perspective based on the

differential actions of D_1 and D_2 receptors on prefrontal network activity previously discussed. These differential roles have been formalized in computational models by Durstewitz & Seamans (2008) among others (Rolls et al., 2008). Building off of non-human animal studies discussed in section 1.6.1, the models differentiate between a D_1 receptor-dominated state ("D_1 state") and a D_2 receptor-dominated state ("D_2 state"). In the D_1 state, memory fields, and neural network states in a more general sense, are robust, while in a D_2 state they are more easily disrupted. From a computational point of view, one may regard a memory state as an attractor state of the DLPFC network. In this model, an attractor has variable stability, reflecting how much energy it takes to move the network from that attractor to a different state. One may therefore imagine a robust memory to be a very stable attractor that requires relatively greater energy to degrade, whereas a less robust memory will require less energy to degrade and is thus more susceptible to random noise or incoming stimuli (Rolls et al., 2008).

This conceptualization relates to WM deficits in schizophrenia in that the deficits can be characterized by a shift from the D_1 to the D_2 network state leading to a combination of increased excitation mediated by D_2 receptor hyperfunction (Ott & Nieder, 2016) and decreased inhibition mediated by D_1 receptor hypofunction (Kröner et al., 2007), leading to excessive prefrontal noise. This noisiness and instability of the network leads to poor WM maintenance, increased distractibility, and the "loosening of associations" which Bleuler posited as a core deficit (Moskowitz & Heim, 2011). And since it is a combination of D_1 and D_2 receptor

dysfunction that leads to this inefficient network state, this model hypothesizes that both D_2 antagonists and D_1 agonists are needed to shift the balance back towards an optimal level (Rolls et al., 2008).

Many of the details of these interactions have not been verified in humans. To help answer the question of how dopamine gives rise to prefrontal dysfunction and the accompanying WM deficits in schizophrenia I present three major pieces of work. First: a replication and clarification of the electrophysiological characterization of WM-related prefrontal activity in healthy individuals, to provide quantitative measures by which to assess the impact of dopamine (Chapter 2); second: an examination of how these particular WM-related neurophysiological measures are abnormal in patients with schizophrenia while controlling for (and examining) the effects of medication (Chapter 3); third: an examination of the relationship between these WM indices and prefrontal-specific aspects of dopamine signaling (Chapter 4). Future work will further examine dopamine dysfunction in patients themselves, to test how different abnormalities in this system are related to their WM-related neurophysiological inefficiencies.

CHAPTER 2 SPATIOTEMPORAL CHARACTERIZATION OF WORKING MEMORY ACTIVITY IN HEALTHY INDIVIDUALS

2.1 Introduction

In the project presented in this chapter I investigated the electrophysiological underpinnings of WM-related prefrontal activation in healthy individuals, to provide quantitative measures by which to assess the association with dopamine, which I report in Chapters 3 and 4. I hypothesized that across multiple frequency bands, widespread WM-related cortical activity would be observed. Specific to the prefrontal cortex I expected to see primarily beta and gamma band power modulations. I hypothesized that prefrontal power modulations would be concentrated around the time of the response, which would be consistent with previous findings and also the structure of the task, in which demands of memory manipulation are greatest at this task epoch (Glahn et al., 2002). One of the limitations with the structure of this n-back task with respect to MEG analysis is its continuous nature, which may impede efforts to find a single event to anchor average neural responses. This may contribute to the potential for lack of observed prefrontal power modulations. A lack of response-related activation may also indicate that prefrontal activation is mainly related to stimulus encoding. This would be evident by anchoring event-related averages to the stimuli instead of

responses. The findings in this chapter will help guide subsequent analyses presented in Chapters 3 and 4.

The n-back task is a classic WM paradigm that has been consistently shown to activate the dorsolateral prefrontal cortex (DLPFC), whether using PET or fMRI. The robustness with which the task elicits DLPFC activity enables it to be used as an effective "reflex hammer" in the study of neurophysiological dysfunction in psychiatric conditions with known DLPFC deficits, such as schizophrenia. However, one major impediment to its use in the study of prefrontal dysfunction is the poor electrophysiologically-based precision with which activity during the task is defined, which complicates attempts to relate human neuroimaging findings to those from in vitro and non-human primate studies. MEG allows for the measure of such electrophysiological activity, as well as sufficient spatial resolution to confidently localize DLPFC-specific activity, especially as compared with EEG.

I therefore used MEG to record neural activity during an n-back task from a large set of carefully screened healthy individuals to attempt to further define the frequency-specific and spatiotemporal activation of the DLPFC during WM performance.

I found that DLPFC activation during working memory manifested as a desynchronization of beta band power, and an enhancement of gamma band power in the pre-response period of the task. There were weak correlations between behavioral measures and measures of neural activity, especially in regions and times overlapping with task-related prefrontal activation. With this more resolved

definition of the WM-related DLPFC response, both in frequency band and time, it may be easier to reveal the deeper neurophysiological underpinnings of this potentially abnormal activity in schizophrenia (discussed in Chapter 3) as well as the dopaminergic underpinnings of WM activity in healthy individuals (Chapter 4).

2.2 Methods

2.2.1 Subjects

Three-hundred forty-two healthy volunteers (HVs) between the ages of 18 and 60 (M = 31.17, SD = 9.51; 195F) were screened as part of the NIMH Genetic Study of Schizophrenia (National Institutes of Health Protocol 95-M-6150) – an ongoing observational study of individuals with schizophrenia, their siblings, and healthy controls. They were screened and excluded for history of alcohol or drug abuse, psychiatric illness, family history of schizophrenia, or injury-induced loss of consciousness.

2.2.2 Data acquisition

Neuromagnetic activity was recorded with a 275-channel SQUID magnetoencephalography (MEG) system (CTF systems), with radial first-order gradiometers uniformly distributed in a helmet, providing whole-brain coverage. Head position was determined by attaching three reference coils at the nasion and preauricular points to each participant, which were used to align the MEG recording to an anatomical MRI. These reference coils were used to record head movement during the recording; data from individuals with overall movement exceeding 5mm were excluded.

Participants were seated in a well-lit magnetically shielded room lined with mu-metal and aluminum to reduce the effect of environmental magnetic noise. The

MEG operators communicated with the participant via an intercom system, and visually monitored them via camera.

Participants completed an n-back WM task consisting of a 0-back sensorimotor control condition, and 1-back and 2-back WM conditions. Each of the three conditions was presented six times in blocks of approximately 30s. Blocks rotated from 0- to 1- to 2-back, and consisted of 11 stimuli, each presented for 160ms, with an inter-stimulus interval of 1.8s. Participants held, in their dominant hand, a response pad with four colored buttons arranged in a diamond formation. While they all had been previously trained on the task to maximal performance prior to the MEG, task instructions were repeated immediately preceding the MEG recording, as follows: for the 0-back, press the button corresponding to the number currently seen; for the 1-back, press the button corresponding to the number seen one number previous; for the 2-back press the number corresponding to the number seen two numbers previous. This task was performed as the last task of a neurocognitive battery including eyes-closed resting state, a passive auditory clicks paradigm, and an auditory oddball task. Only the 0-back and 2-back data was used in the present study. The task was adapted from Callicott et al. (1999) (Figure 2.1).

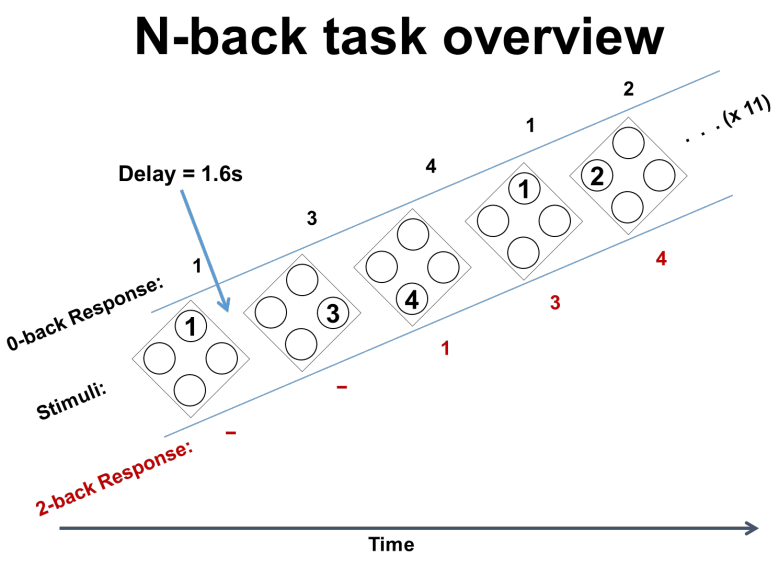

Figure 2.1. N-back working memory task design (adapted from Callicott et al., 1999)

2.2.3 Data preprocessing

MEG signals were digitized at a sampling rate of 600Hz or 1200Hz, and filtered using synthetic 3rd gradient online noise cancellation. Datasets sampled at 1200Hz were down-sampled to 600Hz. Each channel's signal was mean-centered and high-pass filtered at 0.6Hz, as well as notch-filtered at 60Hz (and higher harmonics) to remove power line-related noise. Data quality was evaluated via visual inspection for excessive eye blinks or high frequency activity, which was exclusionary. Stimuli and responses were automatically marked, manually inspected for accuracy, and adjusted as needed.

2.2.4 Data analysis

Anatomical MRIs of each individual were tagged at the nasion and preauricular fiducial points, and then transformed into standard MNI space using

AFNI (Cox, 1996). The MRIs were used to create 3-dimensional brain models, which were used in subsequent source localization. Source localization was achieved using synthetic aperture magnetometry (SAM) (Vrba & Robinson, 2001), a minimum-variance adaptive beamforming algorithm. In short, the algorithm estimates source power by simultaneously maximizing signal from a given point, while suppressing signals from others. Task-related power modulation was estimated as the log power ratio of the active condition (2-back) to the control condition (0-back), at 5mm-spaced grid points throughout the brain. This process additionally removes artifactual activity correlated to task-related activity.

WM-related modulation of source power was first estimated by using a single time window of the 500ms surrounding the last 9 correct responses of each condition (2-back conditions had a maximum of 9 responses). In the case of there being a greater number of correct responses in the 0-back condition compared to the 2-back, a subset of the 0-back correct responses was randomly selected to match in number to the number of correct responses in the 2-back condition. This "block" analysis was performed for theta (4-8Hz), alpha (8-14Hz), beta (14-30Hz), and gamma (40-150Hz).

In addition to the block analysis, a sliding window analysis was performed as follows: for each frequency range, power was estimated in nine sliding windows of 400ms (overlapping by 200ms) from 800ms before to 800ms after correct responses, thus covering the full length of time from one response to the next. In light of the continuous nature of the n-back task (encoding, maintenance,

manipulation/updating and execution are intermixed) time-locking to responses ensured alignment of WM updating and executive processes across trials. For each time window the contrast (log ratio of 2-back power to 0-back power) image was transformed into standard MNI space, and then normalized by subtracting the whole-brain mean and dividing by the whole-brain standard deviation. This process was performed independently for each individual.

2.3 Results

2.3.1 Behavioral performance

Subjects performed the 0-back and 2-back tasks with high accuracy: average 0-back score was 99.1% (*SD* = 2.4%) and average 2-back score was 89.5% (*SD* = 13.9%), with response times of 506ms (*SD* = 87ms) and 363ms (*SD* = 208ms), respectively.

2.3.2 Frequency-specific power modulations

Examining the 500ms window around responses first, all frequency bands exhibited robust WM-related modulation in various regions, especially in beta band, which exhibited particularly strong fronto-parietal activation (Table 2.1).

Table 2.1. Significant clusters of WM-related beta band modulation in the 500ms window spanning correct button press responses. Threshold at 10% most significant voxels.

Cluster region	Cluster size (cm^3)	MNI coordinate (LPI)			Log power ratio	*t* stat
		x	y	z		
R inferior parietal lobule	50.5	42.5	-57.5	42.5	-1.09	-17.57
L inferior parietal lobule	33.38	-37.5	-57.5	37.5	-0.99	-16.60
R superior frontal gyrus	13.75	32.5	17.5	42.5	-0.72	-11.84
L superior frontal gyrus	11.5	-32.5	17.5	52.5	-0.71	-11.53
R and L orbital gyrus	8.13	-12.5	-102.5	2.5	0.75	12.95
Thalamus	13.38	2.5	-17.5	7.5	0.52	12.49

In theta band, the medial prefrontal cortex showed enhanced power in the 2-back relative to 0-back condition, and decreased power in bilateral superior temporal and inferior parietal regions. Alpha band exhibited a predominantly inferior parietal desynchronization. Beta band revealed an extremely robust bilateral fronto-parietal desynchronization. Gamma band revealed

desynchronizations in left motor and medial prefrontal cortex, as well as power enhancements in right prefrontal and right parietal cortex (Figure 2.2).

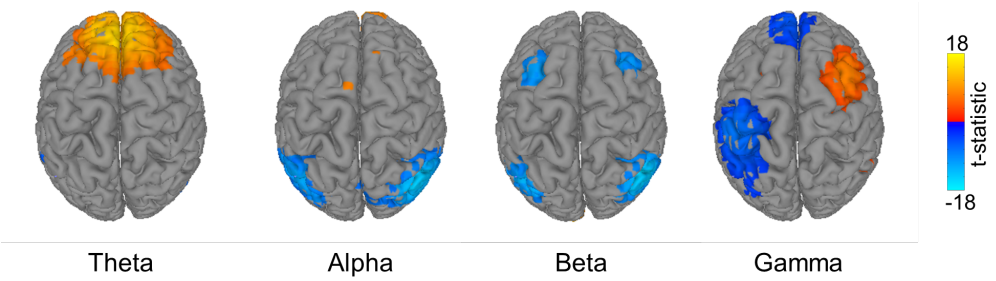

Figure 2.2. Surface renderings showing 10% most significantly modulated regions by WM task in the 500ms window surrounding correct responses. Orange indicates increases in power in 2-back compared to 0-back (event-related synchronization [ERS]); blue denotes event-related desynchronization (ERD).

Sliding window time series analysis (Figure 2.3) revealed few time-dependent changes in the most significantly activated regions in the slower frequency bands (theta and alpha). Increased theta power in medial prefrontal cortex was sustained throughout the time period, as was decreased parietal cortex power in both theta and alpha bands. In contrast, decreased fronto-parietal power in beta band was concentrated before and around the time of the response, as were prefrontal increases in gamma power. The right prefrontal cortex peaked in beta band desynchronization during the pre-response time window centered at 200ms before the button press response (M = -0.74, SD = 1.03; $t(341)$ = -13.36, $p < .001$). At times farther away from the response, motor activity was more evident in both beta and

gamma bands, likely reflecting the increased motor preparatory demands in the 2-back condition compared to 0-back.

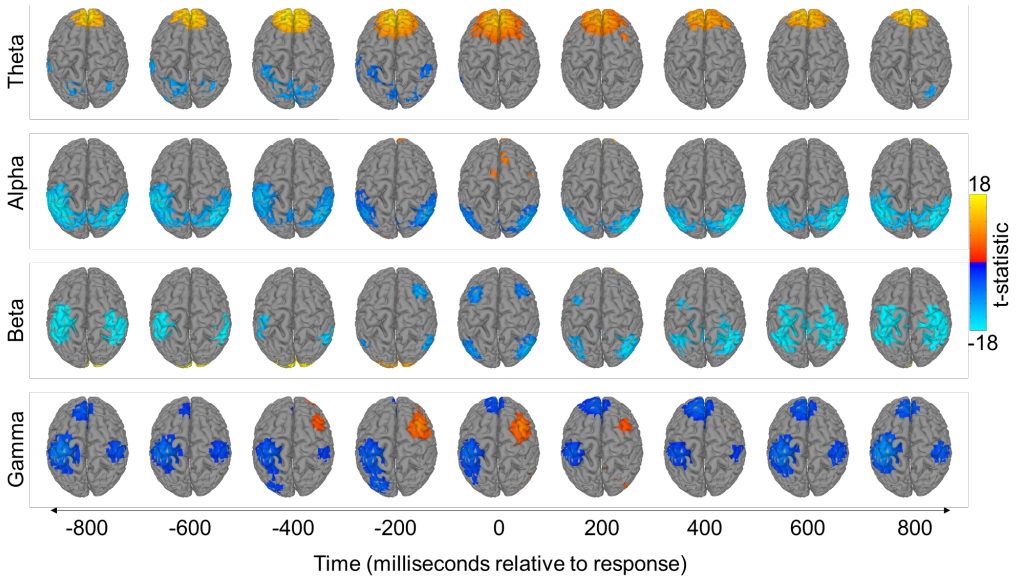

Figure 2.3. WM-related ERD/ERS across time, relative time of button press response. Times indicate in milliseconds the center of the 400ms window. For each time point the images display the 10% most significant voxels.

2.4 Discussion

I demonstrate here that activation of the prefrontal cortex during working memory manifests predominantly as a desynchronization of beta band activity and enhancement of gamma band power in the pre-response period of the task. The beta band prefrontal desynchronization occurs in the context of the desynchronization of a bilateral fronto-parietal network, a network that has been consistently shown to be activated by WM studies (Owen et al., 2005). Furthermore, activation observed here is especially strong on the right side, which is consistent with previous findings indicating right-prefrontal dominance of both manipulation-related demands (Glahn et al., 2002), which are increased during this WM updating epoch of the task, and the right laterality effect observed in location-based spatial WM tasks (McCarthy et al., 1996; Owen et al., 2005).

The demonstration of beta band desynchronization of the near identical fronto-parietal network shown using fMRI is consistent with previous studies comparing the two modalities (Singh et al., 2002; Stevenson et al., 2011), although WM-related gamma activity has also been found to correlate with fMRI BOLD (Khursheed et al., 2011). While prefrontal gamma is also observed here on the right side, the rest of the WM network is not apparent in this frequency band. This may be due to the nature of the n-back task I used. While other studies use tasks that more clearly differentiate between periods of stimulus encoding and response, responses are more continuous here, which may make it more difficult to see the potentially more rapidly-changing faster frequency gamma modulations.

The results further replicate and clarify previous studies showing modulations of beta and gamma band (Altamura et al., 2010; Palva et al., 2011), particularly in the prefrontal cortex. Using a delayed match-to-sample paradigm, Palva et al. (2011) found suppressed prefrontal (and parietal) oscillatory power in beta and gamma bands, which occurred most strongly during the executive period of the task. However, they combined prefrontal cortex with other WM-related regions, making it difficult to isolate the time course of prefrontal activation alone. Nevertheless, they suggest the presence of beta band desynchronization during pre-response period as well. Similar beta band desynchronization of the fronto-parietal WM network has been shown during the execution period (Altamura et al., 2010). Thus, both the spatial extent and the timing of my findings are consistent with previous findings.

To conclude, the current study achieves two primary goals. First, it specifically identifies the pre-response, or execution period in beta and gamma frequency ranges, as the temporal and frequency-specific loci of WM-related prefrontal "activation"; second, it demonstrates the utility of the n-back task as an elicitor of prefrontal neurophysiological response. This "reflex hammer" and knowledge of the expected response in healthy individuals can be used to evaluate prefrontal neural dysfunction in patients with schizophrenia, as demonstrated in the following chapter.

CHAPTER 3 SPATIOTEMPORAL ALTERATIONS OF WORKING MEMORY-RELATED ACTIVITY IN SCHIZOPHRENIA AND ITS MODULATION BY ANTIPSYCHOTIC MEDICATIONS

3.1 Introduction

In this chapter I examined whether and how the particular WM-related neurophysiological measures described above were abnormal in patients with schizophrenia, while controlling for, and examining, the effects of antipsychotic medication. Based on the previously discussed findings of WM-related prefrontal dysfunction in schizophrenia, I hypothesized that this WM task would expose the prefrontal dysfunction in patients at the specific spectro-temporal locus documented above.

In addition to testing for specific dysfunction of beta and gamma activity in patients, I tested for the effects of antipsychotic medication on WM-related activity. I hypothesized based on the importance of D_1 compared to D_2 receptors in WM-related DLPFC activity (see section 1.6.1), and the small effect of antipsychotics on cognitive impairments (Keefe et al., 2007), that medications would not significantly "normalize" prefrontal activity. This would affirm the importance of D_1 receptors and the need for developing D_1-related treatments for WM impairment. Alternatively, a significant effect of medication may support the hypothesis that the

effect of dopamine receptor modulation on prefrontal activity depends on baseline levels of receptor function and WM performance (Gibbs & D'Esposito, 2005), both of which differ between patients and healthy individuals. A medication effect may also reflect the involvement of receptors besides dopamine, such as serotonin receptors, which are among those targeted by antipsychotic medications (Bymaster et al., 1996). This may be partially resolved by examining correlations between medication effects and other dopamine receptor-specific measures, using positron emission tomography (PET).

To determine the nature of abnormal WM-related neural activity in schizophrenia, and its modulation by antipsychotic medication, I used magnetoencephalography to measure spatiotemporally-specific neural activity of the same patients on and off medication (N=25), as well as performance-matched healthy controls (N=100), while they performed an n-back WM task. During the medication-free condition, patients showed abnormalities in WM-related activation in the beta frequency band, primarily during the 400 milliseconds before correct responses – the time period associated with WM updating and action preparation. The locations of these abnormalities in activation included prefrontal, parietal, and visual cortices. Antipsychotic medication "normalized" the patients' neural responses such that the time-courses of activation in medicated patients more closely resembled those of controls. These findings demonstrate that the neural activation abnormalities in schizophrenia during working memory are frequency

band-dependent and time-specific, and that they are closely associated with neural systems targeted by antipsychotic medication.

3.2 Methods

The main difference in the methods of this study compared to those of Chapter 2 is the addition of the coded medication protocol, an extremely unique and delicate study. The 'coded' study involves slowly and carefully removing patients from their medication for several weeks at a time, and then gradually resuming antipsychotic treatment – a process that relies on the highly trained nursing staff of the NIMH inpatient unit, and takes advantage of the stable and attentive environment they provide. The two arms of this study – the medicated and placebo – were blinded and counterbalanced. This allowed for examination of the effects of atypical antipsychotic medications (D_2 receptor antagonists) on WM-related activity – a significant confound present in many other studies, especially those seeking to understand the dopaminergic underpinnings of prefrontal dysfunction.

3.2.1 Subjects

Twenty-five inpatients with schizophrenia (n=21) or psychosis NOS (n=4), and 100 healthy controls were included in the current study. Written informed consent was provided by each participant in accordance with the NIH Combined Neuroscience Institutional Review Board. All participants were evaluated by physical examination, medical history, routine laboratory studies, urine toxicology, and clinical brain MRIs to confirm the absence of confounding major medical, neurological, or substance-related illness at the time of study. Both patients and controls were also assessed with a clinician-administered structured clinical

interview for diagnosis (SCID) (First et al., 1996) to determine psychiatric diagnosis according to DSM-IV criteria or lack thereof for controls.

Patients were recruited to the NIMH Intramural Research Program to participate in research studies related to schizophrenia, and diagnosis was further confirmed with longitudinal psychiatric evaluation on the NIMH inpatient schizophrenia ward. Patients were also assessed by clinical EEG to further rule out confounding neurological problems. Patients participated in a blinded, placebo-controlled cross-over design study, in which after stabilization on standard antipsychotic monotherapy, they underwent two 4-6 week phases in counter-balanced order: a placebo phase and an active, atypical antipsychotic monotherapy treatment phase (aripiprazole [n=4], olanzapine [n=9], quetiapine [n=3], risperidone [n=8], or ziprasidone [n=1]). Doses across different medications were standardized using chlorpromazine equivalents (Andreasen et al., 2010). Medication was administered by inpatient nursing staff under direct observation to ensure study medication adherence.

Healthy control subjects were recruited as part of an ongoing observational study of schizophrenia (as described in Chapter 2, Methods). The subset of controls included in the current analysis (n=100) was chosen to be group-matched to the set of patients on demographic measures (age, sex, and handedness; Table 3.1), as well as on task-related variables (accuracy, response time, and response time variance).

Table 3.1. Participant demographics

	Controls (N=100)	Medicated (N=25)	Unmedicated
Age±SD (range)	30.22±10.26 (18-54)	27.82±9.02 (18-59)	
Sex (%M)	71	72	
Handedness (%R)	88	88	
Years of Illness	--	6.1±6.5	
Chlorpromazine Equivalent Dose	--	308.6±96.7	0
PANSS Total Score	--	61.0±9.4	61.4±8.9

Patients were studied twice: once during each arm, an average of 25.2 days (SD = 5.4) after treatment with either placebo or antipsychotic medication. Controls were studied once.

3.2.2 Data processing and analysis

Within-group analyses were identical to those described in Chapter 2. Voxel-wise t-tests were then carried out using AFNI (Cox, 1996) to compare unmedicated patients and controls, at each time window in each frequency. A significance threshold of $p < .05$, voxel-wise FDR $q < .05$ across all 9 time windows, was used to determine significantly different regional activation between groups.

Next, to determine which of these regional activations were affected by antipsychotic medication, regions-of-interest (ROIs) containing all voxels significant at $p < .05$, FDR-corrected in the between-groups comparison were delineated. Data from the placebo and active medication arms in the patients were averaged over these ROIs and analyzed with paired t-tests using R (R Core Team, 2013). R was also used to perform correlations between ROI activations and other variables of interest: chlorpromazine equivalent medication dose, 2-back percent

accuracy, and Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), of which I used the five-factor consensus model developed by Wallwork et al. (2012) consisting of positive, negative, disorganized, excited, and depressed factors. Statistical significance was determined by Bonferroni correction for multiple comparisons. Plots were generated using MATLAB (2015).

3.3 Results

Healthy controls and patients (both during the medicated and unmedicated arms) performed comparably on the 2-back and the 0-back conditions, as defined by numbers correct, incorrect, and omissions, response time, and variation in response time (Figure 3.1).

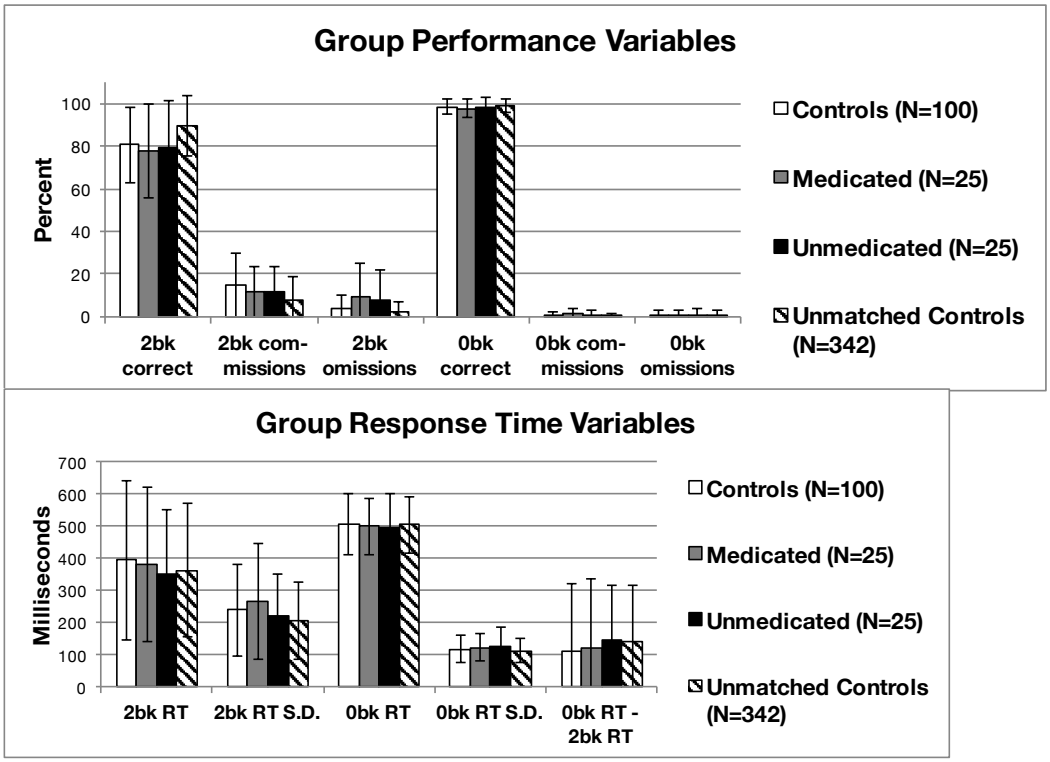

Figure 3.1. Behavioral performance variables for healthy controls and patients while on and off medication. Error bars indicate standard deviations.

In theta, alpha, and gamma bands, the patterns of WM-related power increases and decreases were grossly similar in healthy controls as in people with schizophrenia. While between-group differences appeared in these frequency bands in cortical regions including frontal, temporal, motor, and parietal at thresholds of $p < .005$, uncorrected, they failed to reach the stringent statistical significance threshold employed here of $p < .05$, FDR $q < .05$. Only the group

differences in beta band were significant at this threshold and are described in more detail below.

Healthy controls exhibited a fronto-parietal network of beta band desynchronization, which was strongest during the response period, similar to results shown in Chapter 2. This network consisted of bilateral prefrontal and parietal cortex. The time course of beta band desynchronization is shown for a representative axial brain slice through the dorsolateral prefrontal cortex (DLPFC) (z=+32) for visualization purposes in Figure 3.2. The concentration of WM-related power decreases in beta band in particular is consistent with previous WM studies and those correlating such power decreases with neural activation as measured with other imaging modalities (Singh et al., 2002; Altamura et al., 2010). Patients exhibited similar WM-related parietal desynchronization, but with frontal increases in synchronization (i.e. neural deactivation) rather than the decreases in beta band power corresponding to neural activation in the controls (Figure 3.2).

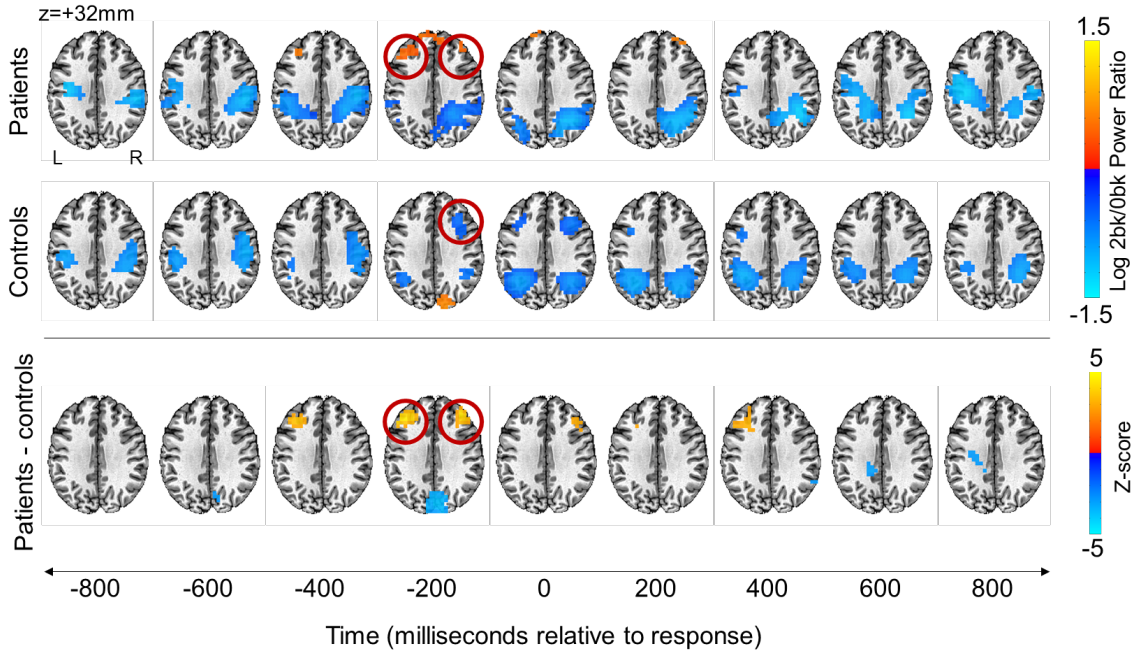

Figure 3.2. Regional localization and time course of WM-related beta band ERD/ERS for unmedicated patients and controls (threshold at 10% most modulated voxels) and their difference ($p < .005$, uncorrected) in a slice through the DLPFC.

In direct statistical comparison with healthy controls, WM-related activation in unmedicated patients differed at $p < .05$, FDR $q < .05$, in 11 spatio-temporally distinct clusters in the beta band (Table 3.2).

Table 3.2. Abnormal beta band activations in unmedicated patients compared to controls and effects of medication in patients. Clusters were identified by comparison of unmedicated patients to controls, and are shown in temporal order relative to the button press response. Statistical assessment of medication effects (on versus off) are indicated for each cluster in the right-hand columns.

Cluster region	Cluster size (mm^3)	MNI coordinate			Peak time (ms rel. to response)	Direction of effect	Peak z score	Peak *p* value (2-tailed)	On vs. off *t* statistic	On vs. off *p* value (2-tailed)
		x	y	z						
R lingual gyrus	875	12.5	-62.5	-7.5	-600	Patients > Controls	-4.34	1.4e-5	3.32	2.88e-3
R cerebellum	6375	7.5	-87.5	-22.5	-200	Patients > Controls	-5.38	7.5e-8	0.880	NS, 0.387
L middle occipital gyrus	1750	-17.5	-92.5	12.5	-200	Patients > Controls	-4.49	7.0e-6	3.74	1.00e-3
R cuneus	1125	7.5	-82.5	27.5	-200	Patients > Controls	-4.72	2.3e-6	1.73	NS, 0.097

L inferior frontal gyrus	1750	-42.5	32.5	27.5	-200	Controls > Patients	4.77	1.8e-6	-2.94	7.18e-3
R middle frontal gyrus	375	37.5	37.5	32.5	-200	Controls > Patients	4.39	1.1e-6	-2.30	0.031
R insula	375	37.5	12.5	7.5	-200	Controls > Patients	4.10	4.1e-5	-1.99	NS, 0.058
L superior frontal gyrus	875	-32.5	32.5	47.5	0	Controls > Patients	4.79	1.6e-6	-3.66	1.25e-3
L cerebellum	375	-27.5	-37.5	-42.5	400	Patients > Controls	4.17	3.1e-5	-4.13	3.78e-4
L superior parietal lobe	250	-17.5	-52.5	72.5	400	Patients > Controls	-4.18	3.0e-5	0.066	NS, 0.948
L postcentral gyrus	1000	-52.5	-12.5	47.5	600	Patients > Controls	-4.42	9.9e-6	0.436	NS, 0.667

Beta band abnormalities were spatially distributed across several cortical regions, but were temporally concentrated in the 400-millisecond pre-response period. Patients generally showed attenuated WM-related beta desynchronization in frontal regions, and greater desynchronization (increased activation) in posterior regions (Figure 3.2).

I then tested to what extent active medication affected the abnormalities in beta band power modulation identified in those 11 spatiotemporal clusters in the same patients. In all 11 of the clusters, active treatment at least nominally shifted neural activation levels toward those of controls. Paired t-tests of these same patients on and off medication showed that in six of the 11 clusters, this "normalization" of activation was significant, and in an additional two, the effect trended towards significance (p's < .1). In all eight of the clusters that showed significant or trending towards significant "normalizations", the effects were time-specific. That is, antipsychotic treatment significantly altered activation in these

regions only for the time windows, or adjacent overlapping time windows, at which they exhibited abnormalities in the unmedicated arm and not for any other non-overlapping time windows.

In the prefrontal cortex specifically, beta band abnormalities were significantly "normalized" by medication (Figure 3.3), although both the abnormality and the "normalization" were stronger on the left side compared to the right (Figure 3.4).

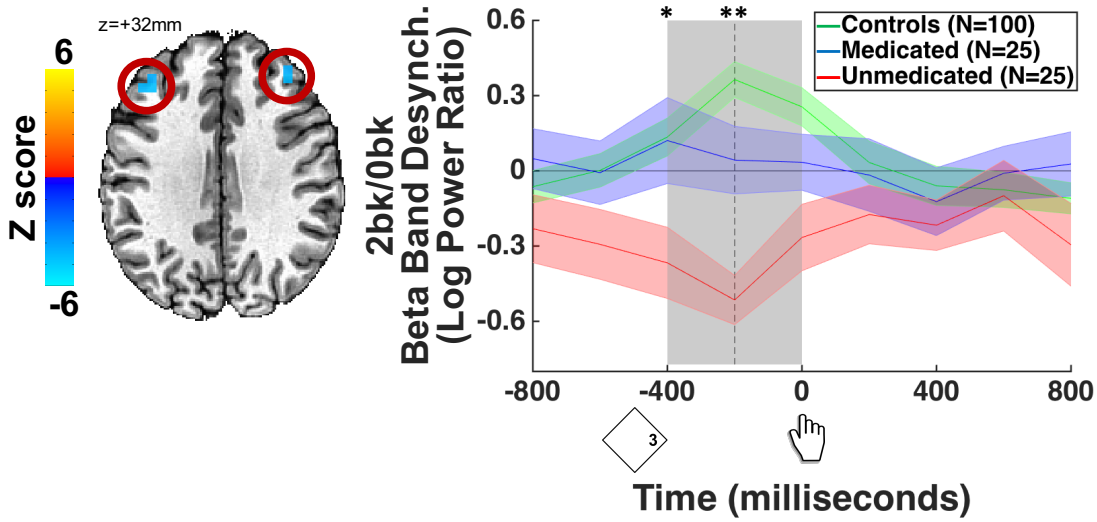

Figure 3.3. Left: axial brain slice showing contrast between unmedicated patients and controls at the time at which the circled cluster has most significant difference (200ms before response). Blue indicates greater ERD in controls. Right: time courses of WM-related activation for the circled clusters, for controls and patients. The gray-shaded rectangle indicates the interval of the time window from which the contrast image on left is generated. The shaded areas around each time series indicate standard errors. Asterisks indicate significance of unmedicated vs. medicated comparison (* = $p < .05$; ** = $p < .01$). Images of the stimulus and hand indicate average relative timing of the stimuli and button press responses, respectively.

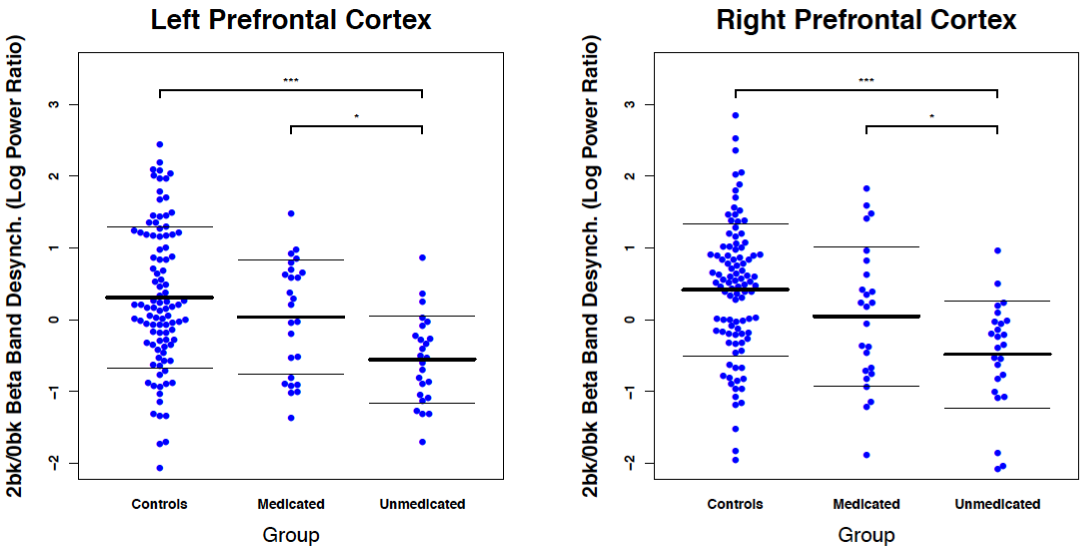

Figure 3.4. Scatterplots showing abnormalities in ERD of left and right prefrontal cortex in patients. Regions defined by clusters indicated in Figure 3.3. Horizontal lines indicate sample means and standard deviations. * = $p < .05$; ** = $p < .01$; *** = $p < .001$.

The degree of "normalization" of these spatiotemporal clusters did not correlate with changes in 2-back score, PANSS (total score and positive, negative, disorganized, excited, and depressed factors), or antipsychotic dose (all p's > .05, corrected). However, the degree of "normalization" in the left superior frontal gyrus was correlated with improvement in the depressed factor of the PANSS at $p < .05$, uncorrected ($r(23) = .40$, $p = .047$), but this correlation was insignificant after Bonferroni correction for multiple comparisons.

3.4 Discussion

My findings reproduced those of many key studies of WM-related abnormalities in schizophrenia, while providing more temporally-refined definitions of regional abnormalities and uniquely shedding light on the important question of medication effects. In summary, I found that unmedicated patients, when compared to healthy control participants group-matched on demographic and task-related behavioral variables, showed WM-related abnormalities that were in general: 1) frontal hypoactivations and posterior hyperactivations temporally focused during WM updating; 2) focused in the beta band; and 3) partially "normalized" by medication in a time-specific manner.

Consistent with established multimodal neuroimaging research on WM-related abnormalities in schizophrenia, I found that unmedicated patients showed widespread alterations in activation, including in the DLPFC. I generally found decreased frontal activation and increased posterior activation, which is also consistent with the first modern neuroimaging studies in people with schizophrenia (Franzen & Ingvar, 1975) as well as more recent WM studies in schizophrenia (Mendrek et al., 2005). However, there is a great deal of variability in whether hypo- or hyper-frontality is observed during working memory in patients with schizophrenia (Berman, 2002; Potkin et al., 2009). This may be due to the specific parameters of the task, its difficulty and the performance of the particular study population, and potentially other unknown factors (Callicott et al., 2003).

Regardless of the direction, the finding of abnormal prefrontal activation fits into the general hypothesis of inefficient prefrontal activity (Potkin et al., 2009).

My examination of the temporal specificity of these abnormalities extends and further refines these results. Specifically, I discovered that patient abnormalities were concentrated in the period of the task associated with WM updating and execution (the few hundred milliseconds preceding a button press), arguably the task period requiring greatest executive demand. Previous studies have observed WM abnormalities in patients throughout all WM phases, from encoding (Haenschel et al., 2009; Basar-Eroglu et al., 2007), through maintenance and execution (Haenschel et al., 2009; Driesen et al., 2008). While the relative lack of prominent abnormalities in my study during the putative maintenance period is consistent with some neurocognitive literature (Lee & Park 2005), it contrasts with several prior delayed match-to-sample type WM neuroimaging studies (Bittner et al., 2015; Driesen et al., 2008; Chen et al., 2014). Whether this is due to the continuous nature of the n-back task and resultant conflation of the maintenance period with other task phases will require further investigation. Nevertheless, the few abnormalities I did see during this period include parietal regions, where a WM buffering role has been proposed (Callicott et al., 1999). Overall, my findings of abnormal activations predominantly in the time window leading up to responses support the large body of work documenting executive impairments in schizophrenia (Eisenberg et al., 2010).

The WM-related abnormalities identified in unmedicated patients occurred most robustly in the beta band. The significance of activity in this oscillatory band is highlighted by previous WM studies of healthy individuals, showing sustained frontal beta desynchronizations associated with WM processing (Brookes et al., 2011) and established correlations between beta band desynchronization and cortical activation measured by fMRI (Singh et al., 2002; Stevenson et al., 2011). These beta band abnormalities are consistent with previous neuro-oscillatory studies of patients (Haenschel et al., 2009; Barr et al., 2010). While the underlying neurophysiological nature of beta band oscillations is still being investigated (Lundqvist et al., 2016; Sherman et al., 2016), some have demonstrated its relation to inhibitory activity (Jensen et al., 2005; Lee et al., 2013). Given the role of inhibition in working memory (Rao et al., 2000) and the link between inhibitory dysfunction in schizophrenia (Liu et al., 2009; Lewis et al., 2012), it is possible that the abnormal beta oscillations observed here in patients may reflect a dysfunction in cortical inhibition.

WM-related abnormalities in schizophrenia are also often found in the lower frequency delta, theta, and alpha bands (Haenschel et al., 2009; Stephane et al., 2008; Canuet et al., 2010), and especially in the higher frequency gamma band (Haenschel et al., 2009; Chen et al., 2014; Barr et al., 2010; Uhlhaas et al., 2010). In light of the preponderance of gamma band-related findings, the lack of gamma abnormalities observed here is surprising. This may be partly due to the strict statistical threshold used in this study, which may obscure weaker results; gamma

activity has especially low signal-to-noise ratio due to lower energy in higher frequencies. Additionally, high individual variability in the timing of certain cognitive functions may further impair the ability of a simple group average to measure them, leading to a lack of group results, especially for shorter-wavelength oscillations. Nevertheless, the robust findings of abnormal beta power modulations reinforce the existing literature documenting abnormal oscillations in schizophrenia, which demonstrate impaired coordination and modulation of cortical activity during cognitive processes (Uhlhaas et al., 2010).

My controlled, within-patient design permitted examination of the effect of medication on WM-related electrophysiological abnormalities in schizophrenia, finding that these neurophysiological abnormalities are significantly reduced by atypical antipsychotic treatment. Previous studies of WM deficits in schizophrenia are often confounded by medication, which my results here suggest may reverse or obscure disease-related abnormalities. Using chlorpromazine equivalents to examine the effect of medication is only a partial solution, which may reveal medication effects (Driesen et al., 2008), and may not (Haenschel et al., 2009); indeed here were found no correlations with chlorpromazine equivalents despite the clear effect of medication overall. FMRI studies that have examined the effect of medication more specifically have also found ameliorations of patient abnormalities in response to antipsychotic treatment, and after switching from typical to atypical antipsychotics (Abbott et al., 2013; Honey et al., 1999; see section 1.5.3). While these previous studies have examined changes in fMRI activation

following antipsychotic treatment, ours is the first to demonstrate similar changes in WM-related neural oscillations, suggesting an intimate relationship between beta oscillations and the neurochemical targets of antipsychotic treatment. This close relationship is further supported by the temporal specificity of the medication effects. Not only did antipsychotic medication largely abolish the observed abnormalities, but also did so in a time-specific way, modulating ROI beta activations only in the time windows during which abnormalities were observed. Due to the varied receptor affinity profiles of atypical antipsychotics and the treatment of patients with different medications, it is difficult to verify which aspect of these medications is most involved in the "normalization" effects observed here. While atypical antipsychotics have high affinities for serotonin receptors (Goldstein, 2000), their clinically relevant mechanism of action has been confirmed to be mainly based on D_2 receptors (Seeman, 2002) (although perhaps in the context of a more complex relationship with serotonin receptors [Richtand et al., 2007]).

Nevertheless, more thorough studies of individual medications are needed to determine the receptor-specific effects of these neuroleptics on neural oscillations. However, it is reasonable to hypothesize that the medication's effect on neural oscillations is due in large part to action at D_2 receptors. Furthermore, the modulation of beta band oscillations by dopamine has already been well established in patients with Parkinson's Disease (Brown et al., 2001). Using positron emission tomography (PET) to assess different dopamine receptor availabilities may help to elucidate the underlying "normalization" effect of medication observed here. A

preliminary investigation utilizing this methodology is presented in Chapter 5. This work thus provides impetus to better understand how this cognitively relevant beta oscillatory signal may be regulated by the dopaminergic system, and how dysfunction in this system impacts cognitive impairments in schizophrenia.

To conclude, my study provides new information regarding the effect of medication on finely resolved time courses of oscillatory activity. Taking advantage of the unique spatiotemporal resolution of MEG, I not only identified prefrontal abnormalities in beta band activity, but also localized them to specific time windows, suggesting they may underlie similar prefrontal abnormalities previously found with PET and fMRI. This work provides evidence that such abnormalities may arise in large part in and around the execution period, rather than the maintenance phases. Future work focused on delineating the circuitry linked to beta oscillations during working memory, its molecular contributors, and particular disruptions in illness will help attain much needed traction on understanding and ultimately combating cognitive deficits in schizophrenia. I present initial examinations into such molecular contributions, in the context of healthy individuals, in the following chapter.

CHAPTER 4 EFFECTS OF D_1 RECEPTOR FUNCTION ON WORKING MEMORY-RELATED PREFRONTAL ACTIVITY IN HUMANS

4.1 Introduction

In this chapter I examine the relationship between WM-related pre-response beta band desynchronization, and different aspects of dopamine signaling. Specifically, I begin to resolve some of the discrepancies in the relative impact of D_1 versus D_2 function in WM-related DLPFC neural activity. This necessitates the measure of both D_1 and D_2 receptor function, specifically in the DLPFC, in the same individuals, as well as prefrontal-specific neural activation. I attempted this by measuring prefrontal D_1 receptor availability with [^{11}C]NNC112, prefrontal D_2 receptor availability with [^{18}F]fallypride, and prefrontal electrophysiological activity during working memory with MEG. These ligands have been previously shown to be highly sensitive, enabling the measurement of cortical dopamine signaling (Abi-Dargham et al., 2000; Olsson et al., 2004). I hypothesized that D_1 receptor availability would show a significantly greater relationship with WM-related activity than D_2 receptor availability.

Depending on whether D_1 or D_2 receptor availability correlates more with DLPFC beta band activity, the source of this association will be further probed with an examination of receptor-specific genetic polymorphisms, for example the *DRD1*

related SNP, rs4532. While overall associations of this SNP to schizophrenia are mixed (see section 1.6.2.1), more specific associations with negative symptoms may be stronger. This more specific relationship with only a subset of the dysfunctional circuitry underlying schizophrenia would be consistent with the putative neurophysiological basis of this SNP, i.e. its effect on prefrontal D_1 function.

If there is no genetic association, that may reflect multiple possibilities. One would be that the effect of rs4532 on *DRD1* function and subsequent network activity is simply not manifested by changes in beta band desynchronization. Another possibility would be that the true effect of rs4532 on *DRD1* function is negligible or too small to be observed, which would be consistent with negative findings of its association with schizophrenia, but inconsistent with its association with other behavioral phenotypes (see section 1.6.2.1). While one cannot draw firm conclusions from negative findings, such a separation of associations between the NNC and genetic results may also reflect a strong environmental influence on dopaminergic signaling, which may not be mediated by any genetic architecture. This would fit with the highly experience-dependent nature of the dopaminergic system, especially with respect to prefrontal cortex and schizophrenia (Selemon & Zecevic, 2015). If there is a genetic association, this would not preclude developmental influences as well, but it would also suggest that the schizophrenia-related risk conferred by such genetic polymorphisms may be mediated by their effect on prefrontal network function (see section 1.6.2.1). Based on the strong experimental evidence linking D_1

receptors and prefrontal WM-related activity (see section 1.6.1) I hypothesized that there would be an association of D_1-related genetic variation and prefrontal activity.

Despite decades of animal studies examining in detail the complicated relationship between dopamine receptors and prefrontal activity, human studies have been scarce. To examine the relationship between in vivo human dopamine receptor function in the prefrontal cortex, and prefrontal neuronal activity during working memory, I used a combination of PET and MEG. Specifically I used [^{11}C]NNC112 ("NNC") and [^{18}F]fallypride ("fallypride") to index D_1 and D_2 receptor availability, respectively. In a sample of healthy volunteers, D_1 receptor availability significantly and positively correlated with WM-related beta band activation in the DLPFC, while D_2 receptor availability did not. However, their correlations were not significantly different from each other. The relationship between D_1 receptor function and prefrontal activity was further studied by examining the association between the *DRD1* SNP rs4532 and WM-related beta activity. Compared to T allele carriers, C allele homozygotes showed significantly reduced beta band desynchronization of the DLPFC. These findings thus confirm in humans the specific role of the D_1 receptor in WM-related prefrontal function, suggesting further a genetic contribution to this relationship.

4.2 Methods

4.2.1 Subjects

Of the 342 healthy participants studied in Chapter 2, 40 participated additionally in combined NNC and fallypride studies (mean age = 39.3 [*SD* = 10.7], 21M) and 181, all of European ancestry, participated in the genetic study of rs4532 (mean age = 32.1 [*SD* = 10.0], 82M).

4.2.2 PET data processing and correlation with MEG

I used the PET radioligands NNC and fallypride, to assess dopamine D_1 and D_2 receptor availability respectively. Both scans were collected on a Siemens HRRT (CPS Innovations, Knoxville, TN) on separate days. The scanning procedure began with a positioning scan followed by an 8-minute transmission scan to correct for attenuation. An intravenous bolus injection of either NNC or fallypride over 60 or 30 seconds, respectively, initiated the scan. Average doses of NNC and fallypride were 19.76mCi (*SD* = 0.40) and 5.12mCi (*SD* = 0.11), respectively. The PET scan consisted of a 90-minute emission scan for NNC, and three 1-hour emission scans over four hours for fallypride.

Receptor availability was assessed by calculating the non-displaceable binding potential (BP_{ND}) at each voxel in a subject's brain. This was achieved by implementing the simplified reference tissue model (SRTM) in PMOD (PMOD Technologies Ltd., Zurich, Switzerland), using the cerebellar time activity curve as reference region. The resulting brain-wide voxel estimations of BP_{ND} were then

warped with ANTs (Avants et al., 2011) into standard MNI space using the subject's anatomical MRI, and smoothed with an 8mm Gaussian kernel using SPM (Wellcome Department of Cognitive Neurology, University College London, London, UK).

MEG data acquisition and processing procedures were identical to those outlined in previous chapters. Correlations between PET and MEG were performed using R, and Bonferroni-corrected for multiple comparisons.

4.2.3 DRD1 *rs4532 genotyping*

To exclude any ancestry-related confounds, such as variable SNP imputation accuracy (Huang et al., 2009), only individuals of European ancestry were included in this study. Standard techniques were used to extract DNA from blood samples provided by participants. Genotyping of >550,000 SNPs was performed on Illumina QUAD SNP chips. Genotyping completion was >90% and quality was ensured by re-genotyping, which yielded >99% reproducibility. Pre-phasing was first performed using SHAPEIT2 to estimate haplotypes (Delaneau et al., 2014), followed by genotype imputation using IMPUTE2 (Howie et al., 2009) using as a reference panel the phase 3 dataset of 1000 Genomes Project (The 1000 Genomes Project Consortium, 2015). Imputation quality of the SNP genotyping was assessed by the "info" score, which was >0.9. Individual rs4532 genotypes were obtained from this final imputed genome for each subject. Hardy-Weinberg equilibrium was tested using R (Graffelman, 2015).

4.2.4 ROI analysis

DLPFC-specific values for BP_{ND} and beta band desynchronization were calculated by averaging over all voxels within a mask of the DLPFC, constructed based on the cytoarchitectonic definition of BA9/46 by Rajkowska & Goldman-Rakic (1995) (Figure 4.1). Statistical tests were performed in R.

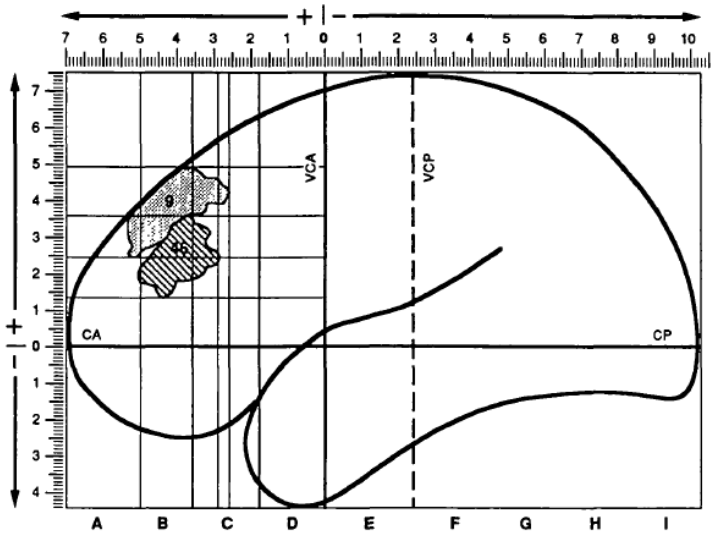

Figure 4.1. Region defined as the DLPFC, from Rajkowska & Goldman-Rakic (1995).

4.3 Results

4.3.1 MEG beta band desynchronization

WM-related beta band desynchronization (i.e. activation) in this group of 40 was similar to that observed in previous control groups (Figure 4.2).

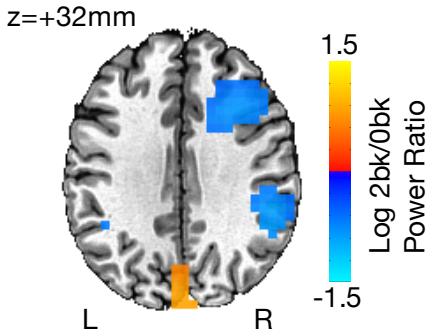

Figure 4.2. Contrast image showing WM-related desynchronization 200ms prior to responses in group of controls who also had PET scans. Threshold at 10% most significant voxels.

The time course of desynchronization was also similar to results reported above, as was the laterality effect (Figure 4.3).

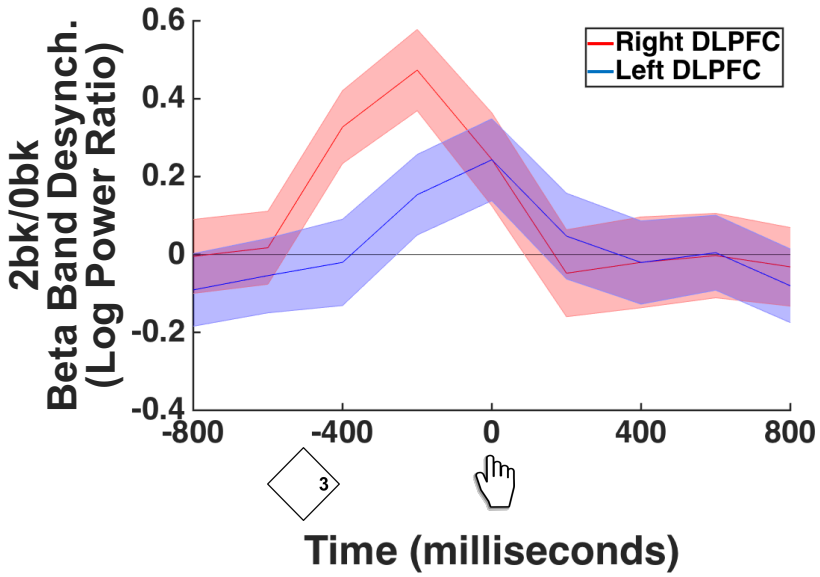

Figure 4.3. Time courses of beta band desynchronization of right and left DLPFC for group of controls who also had PET scans.

While beta desynchronization in the right DLPFC peaked at -200ms (M = -0.47, SD = 0.66; $t(39)$ = -4.54, p < .001), there was not significant desynchronization at this time window in the left DLPFC ($t(39)$ = -1.49, p = .15.), which instead peaked at the time of the response. The right DLPFC was therefore used in subsequent analyses here.

4.3.2 Correlations between MEG and dopamine receptor binding

Mean D_1 receptor BP_{ND} in the right DLPFC was 0.42 (SD = 0.09), and D_2 receptor BP_{ND} in the right DLPFC was 0.32 (SD = 0.15). Both D_1 and D_2 receptor binding potentials were significantly correlated with age (p's < .01). Using linear regression, D_1 and D_2 receptor bindings potentials were therefore modeled at the mean age of the group (39.3 yrs.). In the right DLPFC, D_1 receptor BP_{ND} was significantly correlated with WM-related beta desynchronization ($r(38)$ = .42, p = .0066; Figure 4.4). The correlation between beta desynchronization and D_2 BP_{ND} was not significant ($r(38)$ = .22, p = 0.16). However, there was not a significant difference between these two correlations ($t(37)$ = 1.06, p = 0.15).

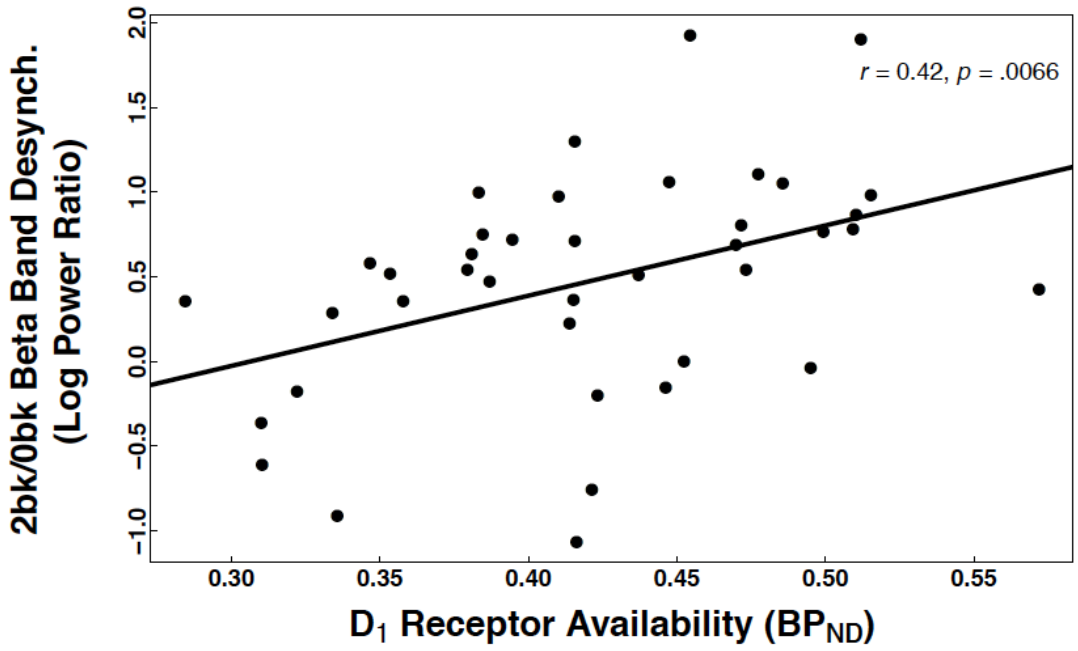

Figure 4.4: Correlation of beta band desynchronization (200ms prior to responses) with D_1 receptor BP_{ND} in the right DLPFC.

While the left DLPFC did not exhibit a significant correlation between D_1 receptor binding and beta desynchronization at this time window (centered at 200ms before response), I hypothesized that this may be influenced by the differential time course of desynchronization of the left DLPFC compared to the right. Indeed, at the time of peak activation of the left DLPFC, which was centered exactly at the time of response, there was a weak correlation ($r(38) = .38$, $p = 0.02$), although it did not survive correction for multiple comparisons.

4.3.3 Effect of rs4532 genotype

Of the 181 individuals included in the genetic study, 22 were minor allele (C) homozygotes, and 76 were major allele (T) homozygotes (Table 4.1). Genotype distribution was found to be in Hardy-Weinberg equilibrium ($\chi^2(1) = .008$, $p = .93$).

There were no significant differences between the genotype groups in age, sex, or 2-back performance.

Table 4.1. Demographic information by genotype

Demographic variable	rs4532 genotype			*p* value
	TT (N=76)	CT (N=83)	CC (N=22)	
Age (SD)	30.6 (9.7)	33.2 (10.0)	33.0 (10.6)	0.248
Sex (%F)	60.5	53.0	40.9	0.244
WM performance (%correct) (SD)	91.4 (12.3)	90.9 (13.9)	91.9 (7.6)	0.927

Due to a trending towards significant correlation between age and beta band desynchronization in the DLPFC ($r(179) = -.12$, $p = .10$), age was regressed out by modeling beta desynchronization at the mean age (32.1 yrs.). A main effect of genotype on WM-related beta band desynchronization in the right DLPFC was revealed by ANOVA ($F(2,178) = 3.49$, $p = .03$). Post-hoc t-tests revealed the CC genotype to have significantly reduced desynchronization compared to both CT ($t(103) = 2.54$, $p = .013$) and TT genotypes ($t(96) = 2.49$, $p = 0.014$). There was no difference in desynchronization between CT and TT genotypes (Figure 4.5).

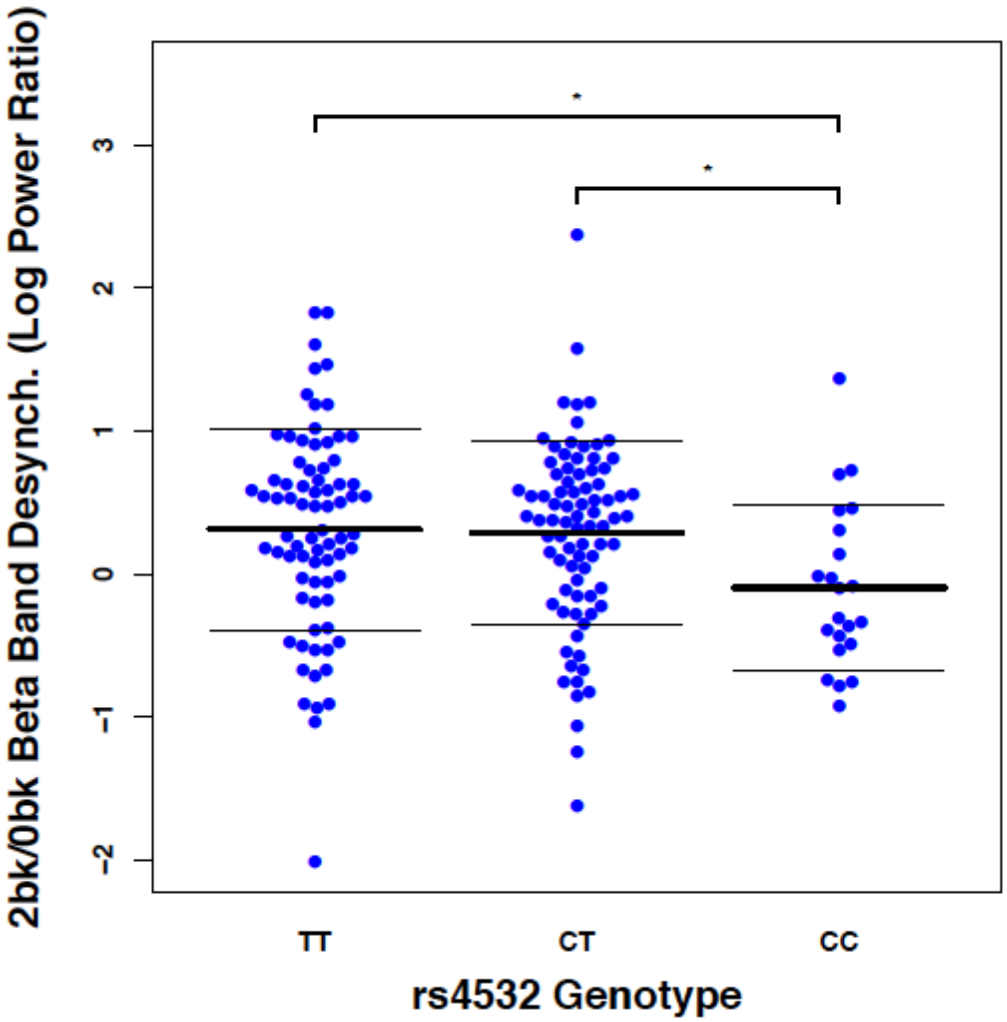

Figure 4.5. Scatterplots showing beta band desynchronization of right DLPFC by rs4532 genotype. Horizontal lines indicate sample means and standard deviations. * = $p < .05$.

4.4 Discussion

In this study I found that DLPFC-specific function of the dopamine D_1 receptor predicted the degree of WM-related beta band desynchronization also in the DLPFC. While this correlation was significant only in the right DLPFC at the predicted time window, it was also tentatively present in the left DLPFC at its time of greatest activation – the time of the button press response. The relationship between D_1 receptor and prefrontal beta activity was further found to exist at the genetic level, such that C allele homozygotes of the *DRD1* SNP rs4532 exhibited significantly less WM-related beta band activation in the DLPFC.

Few studies have examined the effect of D_1 receptor function on WM performance in healthy adults (see section 1.6.2.2). One study utilizing pharmacological agents showed improvements of WM function in response to D_1 agonist treatment (Müller et al., 1998). However, this may or may not be due to the agent's actions at prefrontal cortical dopamine receptors. Abi-Dargham et al. (2002) used NNC to examine the relationship between WM performance D_1 receptor availability in the DLPFC, and found no relationship in healthy controls, but rather found that in patients higher D_1 receptor availability correlated with poorer WM performance.

More studies have examined the relationship between D_1 receptors and prefrontal function in schizophrenia. In contrast to Abi-Dargham (2002), Okubo et al. (1997) used PET to demonstrate decreased D_1 receptor availability in patients, which also correlated with worse negative symptoms and poor cognitive

performance. This discrepancy may be partially explained by the different D_1 receptor ligand used, or the clinical severity of the patient samples (Abi-Dargham et al., 2002). While the direction of findings are mixed, they tend to suggest significant modulation of prefrontal activity by D_1 receptor function (although see Girgis et al., 2014). While I did not observe a correlation between D_1 receptor availability and WM accuracy, the correlation with prefrontal activity provides a potential mechanism by which such an effect on performance could take place. Undoubtedly, prefrontal beta band desynchronization only partially contributes to the complex phenotype of WM performance.

Still, this study's finding of increased beta band desynchronization associated with increased D_1 receptor availability is the first to demonstrate a relationship between DLPFC-specific dopamine receptor function and DLPFC-specific electrophysiological activity in humans. The electrophysiological component of this study is important as it allows for more straightforward association with primate studies and computational models, as well as providing a more direct measure of neural activity compared to fMRI or PET. A limitation of this finding is that NNC has been shown to bind to serotonin (5-HT) receptors as well, based on the observation of that 5-HT_2 receptor antagonist ketanserin reduces NNC signal in cortical regions by ~30% (Catafau et al., 2010). It is thus possible that the correlation of NNC with beta band desynchronization also reflects an underlying serotoninergic association with beta band. Testing the association of beta desynchronization with *DRD1* variance served to partly address this uncertainty.

While this study is the first to report an association of the *DRD1* SNP rs4532 with WM-related prefrontal activity in healthy individuals, several previous studies have examined this relationship in individuals with schizophrenia (see section 1.6.2.1). The findings of these studies are mixed, but where they do find significant associations, they agree on the C allele conferring schizophrenia risk (Allen et al., 2008), correlating with negative symptoms related to schizophrenia (Gurvich et al., 2016), and indirectly associating with reduced *DRD1* expression (Huang et al., 2008). This is all consistent with my finding that C allele homozygotes exhibited reduced prefrontal beta band desynchronization, similar to that observed in patients (see Chapter 3).

However, one may also interpret reduced beta band desynchronization as neural efficiency rather than a deficit (Altamura et al., 2016), in which case the C allele is a beneficial mutation in healthy individuals, with respect to WM-related prefrontal function. While beta band desynchronization has been associated with fMRI BOLD signal, it is not a direct measure of energy usage, so the inefficiency argument may not be as applicable to this measure of neural activity. Nevertheless, a differential relationship of the SNP with prefrontal activation in people with schizophrenia versus healthy individuals would be consistent with the hypothesis that these groups of individuals lie on opposite sides of the inverted-U curve of dopaminergic modulation of prefrontal activity (Vijayraghavan et al., 2007). In support of this alternative, Zhu et al. (2011) report that the C allele is protective, although this result was not significant.

The observation that increased D_1 receptor availability correlates with increased beta band desynchronization may also be re-interpreted in the same light. While some have found that D_1 receptor availability is reduced in patients (Okubo et al., 1997), others have more recently found the opposite (Abi-Dargham et al., 2012), in particular in drug-naïve patients. This may suggest that increased D_1 receptor availability is a risk phenotype, which would be consistent with the notion that beta band desynchronization is a marker of neural inefficiency rather than healthy prefrontal function. More within-individual investigations, with perhaps more difficult WM conditions, are needed to better resolve this question of inefficiency.

To conclude, I provide evidence for the association of prefrontal electrophysiological activity with D_1 receptor function via two separate markers – both at the expression level using PET, and at the genetic level using the SNP rs4532. While more work is needed to determine the precise physiological ramifications of these PET and genetic markers, they tentatively suggest that the influence of D_1 receptors on WM activity in the prefrontal cortex is mediated/indexed by prefrontal beta oscillations.

CHAPTER 5 CONCLUSIONS

While prefrontal dysfunction and aberrant dopamine signaling are heavily implicated in the etiology of schizophrenia, the relationship between these two dimensions has not been adequately examined in humans. In this thesis, I therefore aimed to enhance our understanding of the neural underpinnings of dysfunctional activation of prefrontal cortex in schizophrenia, and how dopamine receptor function is associated with a specific index of neural activity in healthy individuals. To achieve these aims, I first used MEG to define in a large group of healthy volunteers, and in a more precise neurophysiological manner, the spatiotemporal signature of prefrontal activity during a prefrontal-dependent task – the visuospatial n-back (Chapter 2). I found that WM-related prefrontal activation was most characterized by beta band ERD in the pre-response, executive period of the task, during which WM updating and manipulation demands were hypothesized to be greatest. I then tested for abnormalities in pre-response beta ERD in a group of patients with schizophrenia, while both on and off antipsychotic medication, to examine its effects on this physiological response (Chapter 3). I found that prefrontal beta desynchronization was deficient in patients while off medication, suggesting that beta ERD may contribute to the prefrontal dysfunction observed in other modalities. I also observed that antipsychotic medications, D_2 receptor antagonists, partially but significantly "normalized" this deficiency. In Chapter 4, I

discuss my subsequent examinations, in healthy individuals, of associations between various aspects of dopamine function and beta band ERD in the DLPFC, using PET and genetic methods. I report that D_1, but not D_2 receptor function as assessed by PET, and polymorphic variance in the D_1 receptor gene, were significantly associated with WM-related beta ERD. Taken together, these results point towards a significant association between prefrontal dopamine D_1 receptor function and prefrontal beta band desynchronization during working memory.

This represents some of the first work to examine such an association of DLPFC-specific WM-related electrophysiology with dopaminergic parameters in humans. As discussed earlier, human electrophysiological findings may help link the extensive research in non-human primate models of schizophrenia with the similarly extensive, but more macroscopic fMRI and PET findings in humans. For example, when combined with recent models of beta band oscillations (Sherman et al., 2016), my results suggest specific abnormalities in the task-modulated synchronization of different types of thalamocortical inputs to DLPFC. More generalized models that incorporate various neurochemical parameters may be able to generate predictions about the effects of specific dopaminergic alterations (such as those hypothesized in schizophrenia) and dopaminergic interventions on cortical network activity.

Results presented here linking D_1 receptor-related features of the dopamine system with WM-related beta ERD are limited by their correlative nature. While here-presented results cannot alone demonstrate a causative role of D_1 receptor

function on beta oscillations, they are consistent with many primate WM studies with more direct interventions. Those primate studies have shown that increasing D_1 receptor stimulation to a certain point enhances WM activity in DLPFC neurons (Vijayraghavan et al., 2007). One intriguing caveat is that the beta band ERD observed here may be more related to executive rather than mnemonic function, and response-related DLPFC activity has been shown to be more dependent on D_2 rather than D_1 receptors (Wang et al., 2004). However, due to the continuous nature of the n-back task, maintenance demands exist to some extent throughout the task. A more temporally-refined analysis of which task epochs are most correlated with D_1 versus D_2 receptor availability in DLPFC may thus be fruitful. One may predict that correlations with D_2 may be greater during more executive-related task epochs compared to other epochs, and correlations with D_1 may be greater during more maintenance-related periods compared to other time windows.

While in healthy controls I could only demonstrate a correlation between beta ERD and dopamine function, in patients with schizophrenia I was able to show a causative role of dopaminergic intervention, namely that D_2 receptor antagonists partially "normalized" prefrontal beta ERD. One important question that remains is what underlies this effect? One set of possibilities is via medication binding to prefrontal D_2 receptors either directly in DLPFC or in the striatum, where they are most abundant (Meador-Woodruff et al., 1996). One could test these possibilities by examining D_2 receptor availabilities in unmedicated patients in both DLPFC and striatum, assuming that receptor availabilities would be markers of the action

potential of medications. While my sample size was small, I found preliminary evidence that antipsychotics modulated prefrontal function via indirect striatal connections, since striatal D_2 receptor availability (measured by fallypride) strongly predicted left prefrontal beta band "normalization" following medication ($r_s(10)$ = .78, p = .0047; Figure 5.1). This statistical association was not found between beta band "normalization" and D_2 receptor availability in DLPFC ($r_s(10)$ = .37, p = .24). However, there was only a trend-level significant difference between these two correlations ($t(9)$ = 1.94, p = .08).

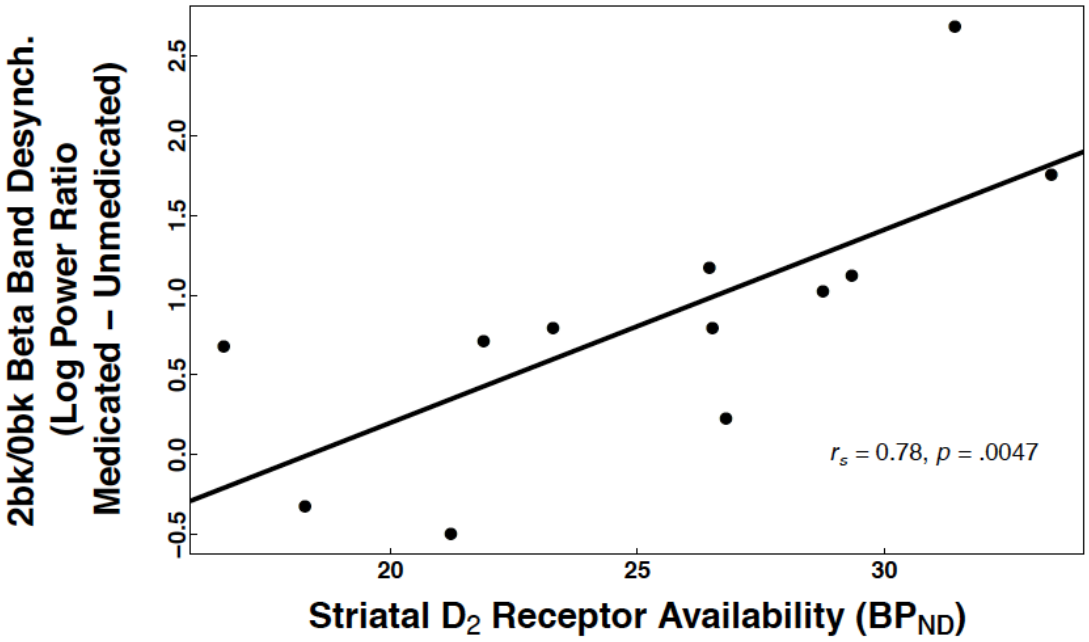

Figure 5.1. Correlation between striatal D_2 receptor availability and "normalization" (medicated – unmedicated) of left DLPFC beta band desynchronization.

This result strongly suggests that prefrontal function in individuals with schizophrenia is associated with striatal D_2 receptor activation. This is consistent with previous findings linking WM-related prefrontal activity with striatal

dopaminergic synthesis capacity (Meyer-Lindenberg et al., 2002), as well as with the mechanism of action of antipsychotics being based on binding to striatal D_2 receptors (Howes et al., 2009). However, it does not exclude the possibility that D_1 receptors also partly underlie medication effects, especially since some antipsychotic medications bind to D_1 receptors as well (Richtand et al., 2007). This possibility was thus tested using NNC to measure D_1 receptor availability. No statistically significant correlation was found between beta band "normalization" and D_1 receptor availability in either DLPFC ($r_s(10) = -0.31$, $p = 0.33$) or striatum ($r_s(10) = -.04$, $p = .90$). Furthermore, the correlation between beta band "normalization" and striatal D_2 receptor availability was significantly greater than with striatal D_1 receptor availability ($t(9) = 2.92$, $p = .017$). However, larger sample sizes are needed to more definitively examine the relationship between D_1 and D_2 receptor availabilities and prefrontal function in patients alone. Larger sample sizes and additional experiments may yield insight into the potential contributions of serotonin, histamine, muscarinic, and other receptors to which atypical antipsychotics also bind, with sometimes greater affinity than to dopamine receptors themselves (Goldstein, 2000; Richtand et al., 2007).

The correlation between striatal D_2 receptor availability and WM-related beta band "normalization" in patients also raises an interesting possible discrepancy between patients and controls, highlighting the differential and complex relationship between D_1 and D_2 receptor-based modulation of WM-related prefrontal activity (see section 1.6.3). Specifically, in healthy individuals there is a

strong association of beta band desynchronization with D_1 receptor function, while in patients this neural response is associated more with D_2 receptor function. One possibility for this divergence is that the prefrontal cortical network in patients may be shifted into a regime in which it is modulated more by D_2 receptors than D_1 receptors. This differential relationship may reflect a D_2-dominated state that indeed partly defines the disorder (Rolls et al., 2008). Thus, while many relatively healthy individuals and some patients may benefit from D_1 receptor agonists, other patients may not (Girgis et al., 2014), depending perhaps on which regime – D_1 or D_2 – dominates their dysfunctional prefrontal cortex activity. If the differential relationship between patients and controls does reflect a shift to a D_2-dominated state, one might predict that antipsychotic medication may shift patients back into a D_1-dominated state, in which the same correlation between beta band desynchronization and prefrontal D_1 receptor availability observed in controls, is also present in these patients. However, I do not observe any evidence for this in this study, since there was no significant correlation between WM-related beta ERD and D_1 receptor availability in the DLPFC, in patients while on medication ($r_s(10) = .23$, $p = .47$). A larger sample size may be necessary to observe such a "normalization" of dopaminergic association, or alternatively, one may need to examine only patients who responded sufficiently to medication (perhaps using "normalization" of beta band desynchronization as a measure of medication response).

Another outstanding question, which may also shed some light on the D_1/D_2 interplay, is the lack of prefrontal gamma band abnormalities in patients, given the

robust prefrontal gamma activation in controls. The absence of any observed abnormalities may be partly explained by the weakness of the gamma signal in general, combined with the strict statistical threshold used, of FDR $q < .05$. Another possibility is that gamma activity is more related to stimulus encoding rather than WM execution, in which case using stimuli as the anchoring events rather than responses may reveal greater abnormalities in patients. Preliminary results suggest that this was the case. While both patients and controls exhibited increased post-stimulus gamma synchronization in the right prefrontal cortex, in unmedicated patients this activation measure was enhanced compared to controls ($Z = 3.23$, $p = .0012$, uncorrected; Figure 5.2).

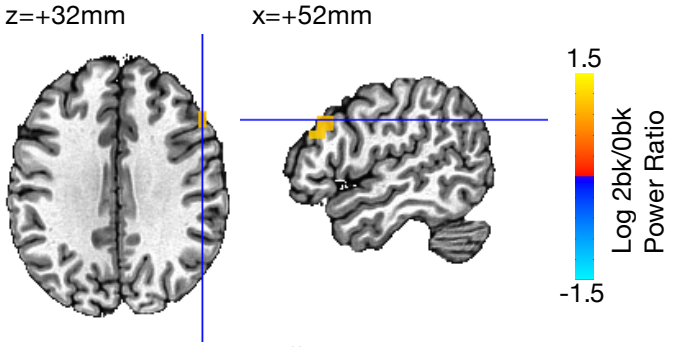

Figure 5.2. Activation differences in gamma band between controls and unmedicated patients, 200ms after stimulus presentation. Orange indicates greater activation in patients (threshold at $p < .005$).

This hyperfrontality complements the hypofrontality observed in beta band, and presents a second aspect of the prefrontal inefficiency often reported in schizophrenia (Potkin et al., 2009). Interestingly, medication significantly "normalized" this gamma band manifestation of inefficiency as well ($t(24) = -2.93$, $p = .0073$). Clearly this result merits more investigation, particularly into whether beta

and gamma band prefrontal abnormalities in schizophrenia may reflect common dysfunctions, or instead independent aspects of prefrontal dysfunction that combine to produce prefrontal inefficiency. These results are consistent with previous findings by Barr et al. (2010) who also found both reduced beta and increased gamma activity in patients during a WM task. They noted that GABA-related dysfunction may underlie this abnormal shift between beta and gamma band, since a $GABA_B$ antagonist was shown to shift EEG-measured spectral power from beta to gamma, albeit in a mouse model of epilepsy (Marrosu et al., 2004).

Other future directions include testing the effect of *DRD1* genetic polymorphisms on D_1 receptor availability. This may help to associate SNPs such as rs4532 with specific physiological function. Based on the results presented here, one would expect the C allele homozygotes of the rs4532 SNP to have decreased D_1 receptor availability. Future work will also examine the differential effects of these PET-measured and genetic differences in dopaminergic function in people with schizophrenia, to help determine what kind of D_1-related treatment would be expected to best alleviate their cognitive deficits. Based on the early evidence showing association of rs4532 to negative symptoms (Gurvich et al., 2016) and treatment resistance (Potkin et al., 2003), one may predict that different groups of patients may benefit from different types of dopaminergic treatment. Results here suggest that prefrontal beta band oscillations may be a useful marker of such differential treatment response. However, more work relating beta band desynchronization to other neural systems associated with dopamine's effect on

prefrontal activity, such as GABAergic signaling, may be necessary to fully develop beta band as a useful marker.

To conclude, while this work raises many questions about the dopaminergic modulatory mechanisms of prefrontal neurophysiology, it also significantly advances the current state of understanding of this rich research area by linking findings from other studies to in vivo human neurophysiology. And by anchoring beta band oscillations to different aspects of prefrontal and dopaminergic function, my findings place this electrophysiological signature of cortical activity firmly in the mix of crucial measures to investigate more closely with respect to schizophrenia. More spatiotemporally-resolved investigations of prefrontal neurophysiology and its association to different neurochemical and genetic dimensions may help to gradually solve the puzzle of cognitive deficits in schizophrenia.

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