Effective Disconnection of Intrinsic Networks in the Prefrontal Cortex: Convergence across Primate and Mouse Models of Schizophrenia

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Clarification of the mode of connection between the innumerable endogenous and exogenous [elements], terminal and collateral branches arising from the thalamic, callosal, and association fibers at present constitutes an insuperable problem. In it many generations of future neurologists will put their sagacity and their patience to the test

- Santiago Ramón y Cajal, 1933

Abstract

Individuals who are afflicted with schizophrenia experience a disorienting array of symptoms that include sensations of nonexistent stimuli (hallucinations), fixed beliefs not grounded in reality (delusions), emotional disturbances, and a generalized disorganization of thought. Some of the most fundamental aspects of consciousness can be disrupted in schizophrenia, such as the capacity to maintain a continuous thought process, plan and predict future actions and consequences, discern threatening from beneficial stimuli, and consciously inhibit impulsive or harmful behavior. Descriptions of the subjective experience of schizophrenia often revolve around the idea that the executive "self" of an individual is disconnected or no longer whole. Executive functions are thought to be distributed throughout cortical and subcortical networks, but to the extent that they can be localized they tend to depend on proper functioning of regions within the prefrontal cortex. In particular, the dorsolateral prefrontal cortex (DLPFC) of primates is considered to be vital in the process of organizing thought, and likewise the disorganization of thought in schizophrenia is linked to dysfunction in this region. For example, the DLPFC contains a densely interconnected circuit of pyramidal neurons that can sustain neural activity in the absence of sensory input, which is thought to underlie our ability to maintain a concept "in mind" after it has disappeared. What happens when these fundamental processes are disrupted? The manifestations can range from subtle disturbances in the integration of sensory input to a failure to distinguish reality from imagination.

In this dissertation, I describe the contributions I have made to the understanding of schizophrenia during the course of my graduate school training. I was given the opportunity to begin my work on this project by analyzing preexisting neural data obtained

from the DLPFC in a pharmacological primate model of schizophrenia[1]. From there, I developed a surgical and recording protocol that allowed me to generate comparable *in vivo* data from the prefrontal cortex of awake *Dgcr8*$^{+/-}$ mice, an established genetic model of schizophrenia. Despite the disparities between these two animal models, I report convergent patterns indicating a disruption of neuronal correlations in the prefrontal regions of both monkeys given dissociative drugs and mice carrying a schizophrenia-associated mutation. In both studies, I found evidence that neurons in the disease state were not synchronizing their activity with each other as effectively as in the control state. Furthermore, the effective transfer of information between pairs of neighboring neurons was reduced. These results suggest that the intrinsic circuitry of the prefrontal cortex may be disconnected in schizophrenia, and that this disconnection relates to a reduction in coincident spiking activity of neighboring neurons. It is plausible that such a dissolution of local prefrontal connectivity could result in a failure to achieve the cognitively demanding task of thought organization. While much is yet to be learned about the nature of schizophrenia, my findings have the potential to motivate the development of novel approaches to the restoration of function in this devastating disease.

[1] Credit to Dr. Rachael Blackman, MD, PhD for performing the experiments that generated this dataset and making it available for further analysis.

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1. Introduction

Schizophrenia is a debilitating neuropsychiatric disorder that impairs a range of cognitive and emotional functions, including perception, executive reasoning, communication, affect, volition, and attention. The manifestations of these symptoms can vary widely across individuals in terms of character, severity, time course, and response to treatment, making schizophrenia a particularly challenging disorder to characterize mechanistically. Antipsychotic medications are currently the mainstay of treatment, but they are not effective in many patients or against all of the major classes of symptoms. It is thought that antipsychotic efficacy results from their relatively focused antidopaminergic actions. However, recent decades of research have uncovered patterns of dysfunction in schizophrenia and animal models that cannot be completely accounted for by the dopamine model. With the advent of new imaging technologies and advanced statistical methods for functional network analysis, more evidence has accrued that suggests that the symptoms of schizophrenia may result from an underlying dysfunction in the regulation of connectivity patterns in the brain. Evidence for this hypothesis comes primarily from the body of work in functional magnetic resonance imaging (fMRI) and other imaging techniques. As will be discussed below, there is reason to believe that functional connectivity at the systemic level both affects and is affected by the topology of the smaller-scale neuronal networks that make up these systems. Few studies, however, have investigated the dynamics of local populations of neurons in the context of schizophrenia, largely because of the difficulty of obtaining single-neuron data. The focus of the current work is to characterize how the functional relationships between neighboring cortical neurons are disrupted in two separate animal models of schizophrenia.

1.1. Schizophrenia as a disorder of neural connectivity

While some cases of schizophrenia-like symptomatology have been described since antiquity, the modern concept of schizophrenia is typically considered to begin around the start of the 20th century. The prior concept of *dementia praecox*, a term coined by Arnold Pick in 1891 to describe an early-onset type of dementia with manic symptoms, is thought to be a predecessor to the concept of schizophrenia. In 1899, Emil Kraepelin distinguished the disorder from "true" dementia, a concept that was emerging at the time with the description of Alzheimer's disease in 1908 by Kraepelin's colleague Alois Alzheimer. In 1911, the Swiss psychiatrist Eugen Bleuler (1857–1939) extended this distinction and coined the name 'schizophrenia' to describe the characteristic 'split' (schizo) of the 'mind' (phrenia) that was fundamental to the disorder. Bleuler wrote that his schizophrenic patients' symptoms manifested in a wide variety of ways but could all be understood in terms of a pervasive underlying deficit in the integration of mental processes. He named this disease process "Spaltung", meaning "a loosening of associations" and argued that it created a syndrome of disorganization of the mind (Bleuler 1911).

The treatment of patients with psychosis changed dramatically in the 1950s with the introduction of antipsychotic medications, which were later found to exert their actions through inhibition of dopamine receptors. The dopamine hypothesis of schizophrenia arose from this finding, and led to a wide array of research that implicated dysfunction in both cortical and subcortical dopaminergic systems in the disease. However, there are several aspects of schizophrenia that are not explained by a dopamine model, including most notably the observation that negative and cognitive symptoms usually predate positive symptoms in patients and are rarely influenced by dopaminergic antipsychotics. As such, it has been proposed that dopaminergic imbalances in schizophrenic patients may be a secondary feature of the disease, and research into characterizing dopaminergic dysfunction in schizophrenia has declined in recent decades in favor of efforts to identify other pathophysiological processes that could serve as targets for treatment (Lau *et al.*, 2013).

The development of imaging techniques such as MRI and PET in the late 20th century provided opportunities to investigate anatomy and function of brain regions *in vivo* in human patients. While some abnormalities in dopaminergic signaling have been confirmed, the body of work in this area has produced a wealth of evidence that schizophrenia results from pathophysiological processes that are distributed throughout neural systems (Bora *et al.*, 2011; Ellison-Wright and Bullmore 2009; Fornito *et al.*, 2012; Friston 2005; Glahn *et al.*, 2008; van den Heuvel and Kahn 2011). Functional imaging studies consistently report abnormalities in functional connectivity between brain regions, and, in conjunction with other lines of evidence from genetic and neurodevelopmental studies that implicated a disruption in the maintenance of synaptic connectivity in schizophrenia patients, these findings led to the formation of the dysconnection hypothesis of schizophrenia (Friston, 1998). In this framework, the signs and symptoms of schizophrenia can be understood in terms of an underlying deficit in disordered connectivity patterns between neurons and neuronal groups in the brain. Fittingly, this hails back to Bleuler's early insightful description of schizophrenia as a disease of "loose associations". The common thread linking early descriptions of schizophrenia with contemporary theories is a focus on the role of the brain's integrative processes—the substrate of which is connectivity—in the pathophysiology of schizophrenia.

1.2. Clinical Phenomenology of Schizophrenia

Schizophrenia has a worldwide incidence of approximately 1% of the population, a proportion that is relatively stable across geographical regions, cultures, and socioeconomic status (McGrath *et al.*, 2008). The presentation of schizophrenia in patients typically begins as a psychotic episode in adolescence or early adulthood (Paus *et al.*, 2008; Lewis and Lieberman, 2000), though it is common to retrospectively identify evidence of cognitive impairment during the years before the clinical diagnosis is made (Lesh *et al.*, 2011). The diagnosis of schizophrenia has been shown to be relatively stable across an individual's lifetime, though many symptoms exhibit phases of exacerbation and remission

over time. Psychotic episodes vary in severity and quality, but often involve bizarre behavior, delusions, hallucinations, disorganization of thought, and thought intrusion (American Psychiatric Association, 2013). While these episodes can be brought on by high levels of stress, in the majority of cases there is a history of bizarre behavior or cognitive deficiency that can be identified retrospectively (Schulz *et al.*, 2016; Laurens *et al.*, 2015). One of the strongest risk factors for developing schizophrenia is the presence of one or more family members with schizophrenia or another psychotic disorder, and both family studies and genetic linkage studies have generated a long list of genetic variants which can increase the risk for developing schizophrenia (Gejman *et al.*, 2011). However, the contribution from each of these factors is small and no single mutation has been shown to confer greater than a threefold increased risk for schizophrenia (Risch 1990). Furthermore, environmental stressors such as infections during gestation or early infancy, traumatic birth involving hypoxia, major life events, drug use, and others have also been implicated in modulating the risk of developing schizophrenia, especially in people who are already genetically predispositioned (van Os *et al.*, 2010). It appears that there are many possible combinations of genetic and environmental factors that can lead to the development of schizophrenia.

As might be expected with this variety of factors that influence whether schizophrenia will develop, there are as many ways that it can manifest in patients. The course of the illness is often composed of short periods of intense psychotic episodes with intervening periods of mild symptomatology, though there are many variations in severity and chronicity of these patterns (Fenton & McGlashan, 1994). Numerous attempts have been made over the years to parse schizophrenia into clinical subtypes (Linscott *et al.*, 2010), but for our purposes here we will consider the disorder as a whole. The most well-recognized symptoms of schizophrenia include delusions, hallucinations, and other types of disorganized and/or bizarre behavior. Antipsychotic medications are relatively effective at alleviating these symptoms, which are referred to as “positive” symptoms due to an excess or distortion of normal function. In contrast, “negative” symptoms of schizophrenia involve a loss or diminution in normal function; these include catatonia, flat affect, loss of

insight into one's mental state, poverty of speech and emotion, anhedonia, and amotivation. Patients' negative symptoms tend to be more resistant to pharmacological treatment than positive symptoms, contributing to their association with a larger social and economic burden than positive symptoms (Andreasen, 1982; Keefe & Fenton, 2007).

While not part of the DSM-V criteria for diagnosis in schizophrenia, deficits in cognitive function are also widely recognized as a core feature, and in fact the presence and degree of cognitive dysfunction in individuals with schizophrenia has been reported to be a better indicator of functionality (e.g., employment, social integration, and relapse) than positive or negative symptoms (Green, 2006; Ho *et al.*, 1998; Rosenheck *et al.*, 2006). Virtually all domains of cognitive performance are affected, including processing speed, attention, memory, social cognition, and executive function (Elvevag & Goldberg, 2000; Piskulic *et al.*, 2007). Several lines of evidence support the primacy of cognitive symptoms in schizophrenia; for example, these deficits tend to appear in early adolescence or childhood in patients who are later diagnosed with schizophrenia (Lesh *et al.*, 2011), earlier than the typical presentation of positive and negative symptoms (Lewis & Lieberman, 2000). Furthermore, mild cognitive deficits are often present in first-degree relatives of individuals with schizophrenia and other high risk individuals (Snitz *et al.*, 2005).

Longitudinal studies of schizophrenia patients illustrate the burden of the disorder on a patient's life. In a follow-up study of first-episode schizophrenic patients, only 29% of patients had gainful employment at 5 years post-diagnosis (Albus *et al.*, 2006). In another study, it was found that approximately three-fourths of people with schizophrenia experience ongoing disability with relapses (Smith *et al.*, 2009). Problems associated with long-term symptomatology include decreased life expectancy due to medication side effects, comorbid conditions, and a higher incidence of substance abuse and suicide (Laursen *et al.*, 2012), as well as a reduced ability to function in society. Active psychosis is ranked as the third-most disabling condition worldwide after quadriplegia and dementia, and ahead of paraplegia and blindness (Ustun *et al.*, 1999). With an estimated 29 million

people globally experiencing disability from the condition (WHO, 1997), the imperative to develop treatment strategies for schizophrenia that are safe and effective against all classes of symptoms is clear. This will require close study of the underlying physiological deficits in schizophrenia as well as the mechanisms of treatments that have already shown some promise.

1.3. Treatment of schizophrenia

By far the most common treatment for schizophrenia from the 1950s to present day is the class of medications referred to as antipsychotics. The first group of drugs that were developed for this purpose are referred to as first-generation antipsychotics (FGAs), and include chlorpromazine, haloperidol and fluphenazine. While these medications were groundbreaking for the treatment of psychotic symptoms, they were also associated with serious side effects, most significantly extrapyramidal symptoms (EPS). EPS refers to motor symptoms whose origin lies in dysfunction of motor regions other than the primary motor output (pyramidal) system, generally involving the basal ganglia. Antipsychotics act on dopamine D2 receptors to reduce their signaling, and while this appears to be the primary mechanism by which they alleviate psychotic symptoms, D2 receptors in the striatum are necessary for normal motor control, and their inhibition can lead to Parkinsonian-like symptoms such as akathisia, dystonia, tremor, and rigidity. While most of these EPSs tend to resolve with discontinuation of the medication, one class of symptoms that sometimes persists is referred to as tardive dyskinesia (TD). TD typically involves involuntary movement of the oral and facial muscles, including tongue protrusion, lip puckering, or grimacing; however, in severe cases TD can affect the trunk and limbs. Over time, individuals treated with FGAs have a 20-30% chance of developing TD, which can lead to significant impairments in physical functionality and quality of life (see for review: Schulz *et al.*, 2016).

Newer medications with good antipsychotic efficacy and a reduced risk for development of EPSs are now available, but they are not without their own side effects. Clozapine was the first antipsychotic to be introduced without the typical association with EPSs, but it was not approved in the United States until the 1990s, more than 20 years after it was first introduced in Europe, due to its association with a serious hematological condition known as agranulocytosis. More recent medications (referred to as second-generation antipsychotics or SGAs) have a reduced association with EPSs but can cause a range of metabolic side effects such as weight gain, diabetes, and dyslipidemia. While antipsychotic medications have served as a useful tool in the treatment of schizophrenia, they are not sufficient to optimize the clinical course of the disease (Schulz *et al.*, 2016). The inherently disabling nature of schizophrenia leaves many patients with the disorder unable to afford or access medications or psychiatric care. For those who do have access to medication, many are either nonresponsive or have intolerable side effects that necessitate discontinuation of the drug. Furthermore, as mentioned above, the cognitive and negative symptoms of schizophrenia are often the most disabling, but unfortunately these are the symptoms that are modulated the least by antipsychotic medications. Increased attention has been paid to non-pharmacological treatments for schizophrenia, and interventions such as cognitive behavioral therapy (CBT) and cognitive rehabilitation or remediation have shown some promise in improving functionality in people with schizophrenia (Sohlberg *et al.*, 2017; Peña *et al.*, 2018).

1.4. Pathophysiology of Schizophrenia

The task of reconciling theoretical frameworks of schizophrenia with physiological observations has puzzled researchers and clinicians since the earliest descriptions of the disease. Investigations into nearly all facets of this disorder have revealed a number of consistent patterns, even if no all-encompassing explanation for the development and proper treatment for schizophrenia has been found. This section will review some of the biological changes that are thought to contribute to the manifestation of schizophrenia, with

some discussion of the implications of these disruptions. The following section will dive deeper into the potential causative factors that could underlie the generation of this pathophysiology in schizophrenia.

1.4.1. *Neurodegeneration in Schizophrenia*

As referenced by the name *dementia praecox*, psychiatrists originally believed that schizophrenia arose from a pathological process that was similar in nature to that of dementia, though with a uniquely precocious onset. This was largely based on the presence of similar cognitive and behavioral deficits in these patients, as well as on the progressively worsening dysfunction observed in some schizophrenic patients over the course of their lifetimes. However, a century of research has changed our thinking about both schizophrenia and neurodegenerative disorders, and it is no longer believed that schizophrenia has a degenerative basis. While many patients with schizophrenia do experience worsening quality of life over time, systematic longitudinal studies of neurocognitive functioning in patients suggest that the disease process is relatively stable over an individual's lifetime (see for review: Rund, 1998; Kurtz, *et al.*, 2005), in contrast to the clinical courses of patients with neurodegenerative diseases.

In recent decades, imaging studies have revealed a number of structural changes to the brains of patients with schizophrenia. Early computed tomography (CT) studies demonstrated an increase in ventricular volume in schizophrenic patients as compared to controls (Johnstone *et al.*, 1978), and many more investigations into the structural differences between schizophrenic and non-schizophrenic brains have since followed, using newer techniques such as PET, MRI, and DWI (see for review: Konrad & Winterer, 2008). The most robust findings appear to be the following: *1)* a reduction in the volume of the temporal lobes; *2)* larger ventricles than healthy controls (suggesting reduced cortical tissue); and *3)* reduced volume of frontal lobes (Shenton *et al.*, 2001). Furthermore, in most of these studies, structural brain changes have been found already at the time of onset

of psychosis (Pantelis, *et al.*, 2003) or even prior to onset in high-risk individuals who later develop clinical symptoms (Gur *et al.*, 1998). The presence of these structural abnormalities in the brains of schizophrenic patients has been used to argue in support of a neurodegenerative process in schizophrenia (see Rund, 2009), but the lack of evidence for progressive structural changes argues against neurodegeneration as the primary underlying disease process in schizophrenia.

It is generally thought that reductions in grey matter volume are likely to underlie the smaller cortical and hippocampal volumes that are seen in schizophrenia (Glahn *et al.*, 2008). Early histological studies reported evidence of neuronal loss in some cortical areas of patients with schizophrenia (Benes *et al.*, 1991; Falkai & Bogerts, 1986), but more careful studies have generally failed to confirm this (Marenco & Weinberger, 2000), and the absence of reactive gliosis in schizophrenia has been used to argue against neurodegeneration (e.g. Casanova *et al.*, 1990; Roberts *et al.*, 1986, 1987; Stevens *et al.*, 1988). On the contrary, other histological studies reported a reduction of neuronal cell body size in conjunction with neuropil volume, resulting in an *increased* neuronal density in prefrontal cortical areas (Lewis & Anderson, 1995; Selemon *et al.*, 1998) and in the medial temporal lobe (see Falkai & Bogerts, 1986). This has been supported by additional studies showing a reduction in neuropil volume, dendritic spine density, and dendritic branching complexity in the DLPFC (Glantz & Lewis, 1997). Therefore, while a reduction in the volume of grey matter tissue could result from cell death as in a neurodegenerative disease, in schizophrenia this finding appears to result from the loss of axonal and dendritic components of grey matter.

In general, while it is believed that schizophrenia involves some progressive changes, the disorder is not well characterized by cell death as in neurodegenerative diseases. We will return to this concept below in the context of the neurodevelopmental and dysconnectionist theories of schizophrenia pathogenesis.

1.4.2. *Neurotransmitter Abnormalities in Schizophrenia*

Dopamine

As discussed above, the dopamine hypothesis of schizophrenia emerged from the serendipitous discovery of Chlorpromazine in 1952, which was followed soon after by other typical and, later, atypical antipsychotic medications. Originally developed as a sedative for surgical purposes, the mechanism of action of Chlorpromazine was not identified for another 20 years, when it was discovered that dopamine D2 receptor blockade was a common property of all known antipsychotic drugs (Carlsson *et al.*, 1973; Walinder & Skott, 1976), and their affinity for this receptor correlated with clinical potency (Seeman and Lee, 1975; Seeman *et al.*, 1976; Creese *et al.*, 1976). This discovery established the validity of the dopamine hypothesis, which became the leading explanatory model for schizophrenia at the time (Snyder, 1976) and had a greatly influential role on the direction of schizophrenia research for decades to come.

There are four major dopamine pathways in the central nervous system, two of which have been implicated in schizophrenia. The *mesolimbic* dopamine system originates in the midbrain, at the ventral tegmental area (VTA) in rodents and the dorsal aspect of the substantia nigra in humans. These neurons project to the medial brain areas of the limbic system, including the hippocampus, nucleus accumbens/ventral striatum, bed nuclei of stria terminalis, amygdala, lateral septal nuclei, and the entorhinal cortex (Ikemoto, 2010). The *mesocortical* dopamine system also originates in the VTA, but projects to the prefrontal cortex, providing a substrate for the modulation of executive functions like motivation, attention, and social behavior.

An abnormal increase in mesolimbic pathway activity (via D2, D3, and D4 receptor activation) is thought to be primarily responsible for the generation of the positive symptoms of schizophrenia (see for review: Davis & Kahn, 1991). Positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) studies

have demonstrated alterations in neurotransmitter release, synthesis, and availability of postsynaptic receptors in schizophrenic patients that generally point to an increase in the activity of the dopaminergic system (see for meta-analyses: Laruelle, 1998; Zakzanis & Hansen, 1998). These findings are substantiated by post-mortem histological studies, which consistently report elevated densities of D2 receptors in the striatum of patients with schizophrenia (Owen *et al.*, 1978; Mackay *et al.*, 1980a; Seeman *et al.*, 1984). It is important to note that many of these results are potentially confounded by the effects of chronic antipsychotic treatment, and the patterns of dopamine receptor expression in the natural history of schizophrenia are unknown. However, efforts to examine dopamine signaling in untreated patients and in animal models of schizophrenia have largely substantiated these findings (see Lau *et al.*, 2013 for review).

While it has been clear for some time that the positive symptoms of schizophrenia are associated with alterations in mesolimbic dopamine system signaling, more recent research has drawn more attention to alterations in the mesocortical dopamine system (for review see Knable and Weinberger 1997). In contrast to the hypothesized increase in activity through the mesolimbic pathway in schizophrenia, mesocortical dysfunction in schizophrenia appears to result from a reduction in signaling between the midbrain and the prefrontal cortex. Projections within this system that activate D1 receptors in the dorsolateral prefrontal cortex (DLPFC) are thought to be the substrate for cognitive dysfunction in schizophrenia (Weinberger 1987; Davis *et al.*, 1991; Goldman-Rakic *et al.*, 2000). For example, as will be discussed below, functional imaging studies consistently report blunted prefrontal cortical activation in schizophrenic patients during working memory performance, and this disruption can be normalized following the administration of a dopamine agonist (Manoach, 2003). Furthermore, the mesocortical system also includes projections to medial and cingulate cortex that are likely involved in generating the negative symptoms of schizophrenia, including loss of motivation and flattened affect. Rather than a global increase in dopamine signaling in schizophrenia, it has been suggested that there are likely regionally selective disruptions, with low cortical dopamine accounting for the negative and cognitive symptoms (Laruelle, 2014).

Imaging and histological studies have confirmed a reduction in the dopamine synthesizing enzyme tyrosine hydroxylase and dopamine receptor expression in the prefrontal cortex of patients with schizophrenia (see for review: Howes *et al.*, 2015; Abi-Dargham & Moore, 2003). An influential reconceptualization of the dopamine hypothesis in the 1990s proposed hyperactivity in the subcortical dopamine system was secondary to mesocortical hypoactivity, in particular in frontal regions (Davis *et al.*, 1991). According to this model, the mesocortical pathway acts as a brake by inhibiting the mesolimbic pathway; in schizophrenia, this balance is disrupted, resulting in disinhibition of the mesolimbic dopamine system. This is consistent with similar hypotheses that negative and cognitive deficits are primary in schizophrenia (Andreasen, 1999) and that positive symptoms arise as a result of secondary hyperfunction in the striatum (Abi-Dargham & Moore, 2003).

The dopamine hypothesis of schizophrenia is additionally supported by the findings of genetic studies, which have identified numerous polymorphisms related to the dopamine system that contribute to a vulnerability to schizophrenia, including genes for dopamine receptors (Itokawa *et al.*, 2010), Catechol-O-methyltransferase (COMT), a catabolic enzyme involved in degradation of dopamine and related molecules (Ermis *et al.*, 2015), and others (see for review: Williams *et al.*, 2007). However, there are limitations to the explanatory power of this model. As discussed above, the treatments for schizophrenia that center on modulating the dopamine system are generally only effective in treating the positive symptoms of schizophrenia, but still nearly one-third of patients fail to respond to first generation drug treatments (Mortimer *et al.*, 2010) despite high levels of D2 receptor occupancy (Kapur *et al.*, 2000). This raises the possibility of a subtype of schizophrenia that is "nondopaminergic", or at least that there is a significant number of patients whose principal symptoms are wholly or partially independent of dopaminergic excesses (Howes & Kapur, 2014).

Another limitation of the dopamine hypothesis of schizophrenia is that dopamine dysfunction is clearly linked to the positive symptoms of schizophrenia, but the dopamine system's involvement in the negative and cognitive symptoms is much less evident (Javitt and Zukin, 1991; Tamminga *et al.*, 1995). The negative and cognitive symptoms associated with schizophrenia are only marginally improved by antipsychotic medications, and even attempts to administer partial dopaminergic agonists in clinical practice have produced marginal improvements (Murphy *et al.*, 2006) or even potentially worsened cognitive function (Kim *et al.*, 2013b). These findings suggest that antipsychotic medications may compensate for deficiencies related to schizophrenia without treating the cause for the altered mechanism itself, which is likely to involve additional pathways. In particular, much attention has been drawn to glutamatergic signaling pathways that are known to be important for cognitive function.

Glutamate

Glutamate is the primary excitatory neurotransmitter in the central nervous system, and the receptors that bind glutamate fall into three broad categories: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, N-methyl-D-aspartate (NMDA) receptors, and metabotropic glutamate receptors. Both AMPA and NMDA receptors are ionotropic sodium channels, but the activation time of the AMPA receptor is several orders of magnitude faster than the NMDA receptor, and NMDA receptors also admit calcium ions into the cell. While AMPA receptors (AMPARs) are among the most abundant neurotransmitter receptors in the nervous system, NMDA receptors (NMDARs) have more selective anatomical distributions, and the population of NMDARs in the prefrontal cortex is of particular relevance to schizophrenia. Unlike AMPARs, activation of NMDARs requires both the binding of glutamate (and a co-agonist glycine or D-serine) and a preexisting depolarization of the intracellular fluid. This two-step activation mechanism provides a basis for logical coincidence detection in the nervous system, a critical component for synaptic plasticity. Furthermore, NMDARs are permeable to both Ca^{2+} and

Na^+ ions, and it is believed that NMDAR-mediated Ca^{2+} influx is a necessary component for activating the cellular mechanisms involved in synaptic plasticity (Kandel *et al.*, 2000).

The first indication that glutamatergic signaling might be disrupted in schizophrenia was the observation of reduced glutamate in the cerebrospinal fluid (CSF) of patients with schizophrenia (Kim *et al.*, 1980). The reproducibility of this finding was contested (Perry, 1982; Korpi *et al.*, 1987; though see the following studies for updates: Bendikov *et al*, 2007; Hashimoto *et al*, 2005; Javitt, 2012), but it prompted further exploration into the potential role of this neurotransmitter in schizophrenia pathophysiology. Later studies reported that the NMDAR antagonists ketamine and phencyclidine (PCP) could lead to relapse of psychosis in previously stabilized patients with schizophrenia (Luby *et al.*, 1959; Rosenbaum *et al.*, 1959; Davies & Beech 1960), in addition to producing symptoms of psychosis in healthy patients at subanesthetic levels (Javitt and Zukin, 1991; Krystal *et al.*, 1994; Lahti *et al.*, 1995a,b; Breier *et al.*, 1997). Remarkably, these compounds have the potential to induce dose-dependent effects that encompass all three dimensions of schizophrenia symptoms, potentially providing a long-sought mechanistic basis for the cognitive and negative symptoms of the disease.

Further studies using NMDAR antagonists in rodents led to a modification of the glutamate hypothesis with a primary focus on the NMDA subtype of glutamate receptors (Stone *et al.*, 2007). This framework was put forward as a supplementary model to the dopamine hypothesis that could account for previously unexplained features such as the negative and cognitive symptoms of schizophrenia, the lack of response to treatment in some patients, the adolescent onset of the disorder, and the ongoing neurodegenerative changes and cognitive deterioration seen in some patients (Olney & Farber, 1995; Olney *et al.*, 1999). These authors found the predominant anatomical sites of action of NMDAR antagonists to be in the thalamus and basal forebrain, where they observed increases in measures of neurotoxicity that appeared to preferentially affect GABAergic interneurons (Homayoun & Moghaddam, 2007), which could lead to an increase in pyramidal cell firing due to

disinhibition, followed by excitotoxicity (Olney and Farber, 1995). Furthermore, these neurotoxic effects could be blocked by AMPAR antagonists, suggesting that glutamate release might underlie the neurotoxicity that results from NMDAR antagonism. This hypothesis was subsequently confirmed in microdialysis studies of patients with schizophrenia (Moghaddam *et al.*, 1997) and more recently with proton magnetic resonance spectroscopy studies following systemic ketamine administration in animals (Kim *et al.*, 2011). However, there is also evidence that NMDAR antagonism may result in cellular damage through changes in reactive oxygen species (Behrens *et al.*, 2007; Levkovitz *et al.*, 2007; Sorce *et al.*, 2010; Monte *et al.*, 2013), and the precise mechanism through which NMDAR antagonists exert their effects is unknown[2].

Later findings revealed that PCP's ability to elicit the breadth of symptoms seen in schizophrenia might arise from the fact that it does not just bind to NMDARs, but is also partially active at other receptors known to be involved in schizophrenia. PCP inhibits nicotinic acetylcholine receptors (Aguayo *et al.*, 1982), which have been shown to interact with NMDARs to influence the postsynaptic maturation of glutamatergic synapses (Lin *et al.*, 2010). Interestingly, PCP can also inhibit dopamine reuptake (Rothman *et al.*, 1989) and act as a partial D2 agonist (Seeman *et al.*, 2005). This may explain the presence of positive symptoms in PCP intoxication, and why acute intoxication can be mediated by the D2 antagonist haloperidol (Giannini *et al.*, 1984). These studies and others have led some to propose that dopaminergic dysregulation in schizophrenia may be secondary to a deficit in glutamatergic NMDAR function (Olney & Farber, 1995; Miller & Abercrombie, 1996; Kegeles *et al.*, 2000).

[2] The absence of gliosis in post-mortem tissue has served as a major argument against a neurodegenerative process in schizophrenia (Harrison, 1999). However, neurodegeneration in rats following NMDA receptor blockade leads to a transient gliosis, lasting only a few days (Olney et al., 1999). Furthermore glutamate-mediated excitotoxicity has been found to induce apoptotic loss of dendrites and synapses without cell-body death or gliosis (Jarskog et al., 2005; Glantz et al., 2006). Thus the absence of gliosis does not necessarily exclude NMDA-mediated excitotoxicity in schizophrenia.

Several post-mortem studies have supported the NMDAR hypofunction hypothesis, such as reduced NMDAR1 subunit density in the frontal cortex (Sokolov, 1998; Woo *et al.*, 2004) and the superior temporal cortex (Humphries *et al.*, 1996). However, many of these results have been inconsistent (McCullumsmith *et al.*, 2012), and it has been proposed that the primary abnormality in schizophrenia may primarily be abnormal localization of glutamate receptor as opposed to a generalized deficit in receptor function (Hammond *et al.*, 2014). The potential role of glutamate in the pathophysiology of schizophrenia is also supported by genetic studies (Ripke *et al.*, 2014; Bishop *et al.*, 2015; Chen *et al.*, 2005; Egan *et al.*, 2004; Joo, 2008), as well as some imaging studies (Modinos *et al.*, 2015; Stone *et al.*, 2009), though glutamatergic abnormalities have not been explored as thoroughly *in vivo* as the dopaminergic system in schizophrenia.

The contemporary interpretation of these findings is that a combination of both NMDAR hypofunction and dopaminergic dysfunction are likely to be fundamental to the pathophysiology of schizophrenia. However, as the data in patients are limited at this time (Stone *et al.*, 2010), the relation between these systems requires further investigation. While dopamine is strongly linked to positive symptomatology in psychosis, glutamate models involving NMDA receptor blockade appear to be better able account for the range and nature of the cognitive and negative aspects schizophrenia (Javitt, 2010). Furthermore, it is important to note that the glutamate and dopamine systems show extensive and reciprocal interactions, and thus it may be difficult to determine which is primary, with different authorities on the subject suggesting that both glutamate and dopamine drive abnormalities in the other system (Olney and Farber, 1995; Harrison and Weinberger, 2005; Coyle, 2006; Stone *et al.*, 2007). The possibility that mesolimbic dopaminergic hyperactivity is secondary to diminished inhibitory control had also been suggested before the glutamatergic system was explicitly identified as a candidate (Weinberger, 1987). Dopamine neurons are regulated by glutamatergic projections to the midbrain dopamine nuclei, which makes them potentially sensitive to changes in glutamatergic function (Miller and Abercrombie, 1996). This suggests that the dopamine function seen in schizophrenia could be secondary to altered glutamatergic function (McGuire *et al.*, 2008). Supporting

this, preclinical studies show that NMDA blockers such as ketamine and PCP change dopamine neuron firing patterns and increase dopamine release (Miller and Abercrombie, 1996; Tsukada, 2000; Balla *et al.*, 2003; Jackson *et al.*, 2004; Breier *et al.*, 1998; Smith *et al.*, 1998; Vollenweider *et al.*, 2000), and baseline D2/D3 receptor availability is associated with increased sensitivity to the psychotogenic effects of ketamine in humans (Vernaleken *et al.*, 2013), further supporting the close interaction between these two systems.

1.4.3. *Neuronal Connectivity in Schizophrenia*

A growing understanding of the distributed nature of schizophrenia paralleled and arose from advances in imaging technology in the late 20th century. As discussed above, imaging studies have revealed a number of structural abnormalities in the brains of human patients with schizophrenia, including a loss of volume in prefrontal and medial temporal lobes. Despite known reductions in grey matter tissue, it is generally accepted that cell death is not a major component of schizophrenia. In fact, these losses are thought to primarily result from a reduction in neuropil, the component of grey matter that is made up of local axonal connections and dendritic trees. Some of these findings include reduced myelination and organization of white matter tracts on voxel-based morphometry analysis (Ellison-Wright and Bullmore 2009; Kubicki *et al.*, 2007; Skudlarski *et al.*, 2013), and DWI analysis that suggest reduced white matter projections linking frontal, temporal and parietal regions (Skudlarski *et al.*, 2010; van den Heuvel 2010; Zalesky 2011b). Corresponding histopathological studies have supported these findings with evidence of an increased count of pathological myelinated fibers in the prefrontal cortical regions of schizophrenia patients (Uranova *et al.*, 2013). However, it is still unclear whether white matter abnormalities constitute a primary feature of schizophrenia pathology or arise secondarily to some other disease process, such as a fundamental disruption in synaptic integrity and plasticity that then leads to the degradation of neuropil (see Marenco & Weinberger, 2000; Konrad & Winterer, 2007). Because axonal projections are the means through which various areas of the brain communicate with each other, it is plausible that an alteration in the structure of inter-area projections could lead to the symptoms of

executive function and disorganization seen in schizophrenia; however, the dynamic nature of cognitive processes limits the conclusions that can be drawn by structural data alone.

With the advent of functional MRI (fMRI) technology came a wave of investigations into functional disruptions in the brains of schizophrenia patients (See for review: Fornito *et al.*, 2012). Based on variations of blood oxygen levels across the brain as different areas increase or decrease metabolism during particular tasks or resting states, fMRI allows researchers to identify regions with abnormal activity levels even in the absence of gross structural differences. One of the most consistent findings in fMRI of schizophrenic patients is a reduction in blood flow to prefrontal and parietal cortical regions, areas known to be important for executive function (Schulz *et al.*, 2016; Berman, 2002), a finding that has also been demonstrated in PET analysis of metabolic activity (Farkas *et al.*, 1984). This has been demonstrated in resting state studies (van den Heuvel & Pol, 2010) as well as during the performance of executive function tests that expose cognitive dysfunction in schizophrenia patients (Barch *et al.*, 2001).

In addition to allowing comparison of activity levels in particular brain regions between patient groups, fMRI allows quantitative measurement of the correlation between temporal changes in activity levels. The term *functional connectivity* is used to describe statistical dependencies between spatially distinct neurophysiological signals. This construct is based on the assumption that synchronized activity[3] between two or more brain regions reflects some degree of communication occurring between them. While neural communication is not possible without structural connectivity, i.e. axonal connections, functional connectivity refers to the degree to which anatomical connections are utilized during state-

[3] Typically inferred from simple Pearson or partial correlation analysis, but coherence and mutual information have also been used (Bassett et al., 2011; Micheloyannis et al., 2006; Salvador et al., 2008; Stam et al., 2006; Stam and Reijneveld 2007). Functional connectivity and associated metrics are discussed extensively in Chapters 2 and 3 of this dissertation.

dependent execution of brain functions. Furthermore, functional connectivity analyses can identify regions whose activity is strongly correlated in the absence of a direct anatomical link, suggesting indirect communication (e.g. Honey *et al.*, 2007; Skudlarski *et al.*, 2008; Vincent *et al.*, 2007).

In 1988, a critical PET study demonstrated an altered covariance in inter-regional cerebral metabolism and blood flow measures in patients with schizophrenia (Volkow *et al.*, 1988), and this report ultimately led to a new framework for thinking about schizophrenia pathophysiology. The authors suggested that their findings were reflective of disordered connectivity of widely distributed brain macro-circuits in schizophrenia, and that the resulting disruptions in functional communication form the basis for the expression of schizophrenia. This finding, along with the results of several related studies (e.g., Friston & Frith 1995), led to a formalized disconnection hypothesis of schizophrenia proposed by Karl Friston (Friston, 1998). This framework was expanded by Stephan *et al.*, 2006, who used the term "dysconnectivity" to denote disordered rather than simply reduced connectivity in schizophrenia.

Since the introduction of the disconnection hypothesis, numerous studies have reported findings in that support this model, using modalities such as PET, fMRI, and electroencephalography (see for review: Konrad & Winterer, 2008). As emerging investigations from cognitive neuroscience revealed that even relatively simple information is processed by distributed cortical networks (Mesulam *et al.*, 1990; McIntosh, 1999), it has been increasingly accepted that impaired neuropsychological performance and related pathophysiological findings in patients with schizophrenia are manifestations of altered functional connectivity of macro-circuits that are distributed throughout the brain (see Stephan *et al.*, 2006; Konrad & Winterer, 2008 for further discussion and review).

Functional imaging studies have identified a number of disruptions in functional connectivity in the brains of patients with schizophrenia, many of which involve prefrontal cortical brain regions (e.g. Cole *et al.*, 2011; Fornito 2012b; Liang 2006; Zalesky 2011a,b; Repovs *et al.*, 2011). Together, these findings are consistent with those of structural connectivity studies in the implication of pathology in (mostly frontal) hub regions as a core feature of schizophrenia. However, while structural studies overwhelmingly report reductions in anatomical connectivity in schizophrenia (Pettersson-Yeo *et al.*, 2011), functional connectivity reports include evidence of both abnormally increased and abnormally decreased functional connectivity between various brain regions in schizophrenia patients (Liu *et al.*, 2008; Skudlarski *et al.*, 2010), though reductions are still more common (Fornito *et al.*, 2012; Pettersson-Yeo *et al.*, 2011; van den Heuvel *et al.*, 2013). These discrepancies are consistent with the idea that functional connectivity can increase or decrease to compensate for a lesion, and it is likely that increases in functional connectivity in patients with schizophrenia are a result of to the rerouting of other damaged pathways (van den Heuvel *et al.*, 2010).

In further support of the dysconnectivity hypothesis, the magnitude of functional connectivity metrics has also been shown to correlate with the degree and type of cognitive dysfunction in patients. In healthy patients, both connectivity and topological measures of network integration have been related to individual differences in cognitive processing (Bassett *et al.*, 2009; Li *et al.*, 2009; van den Heuvel *et al.*, 2009; Zalesky *et al.*, 2011a,b; Reijmer *et al.*, 2013) and functional network cost-efficiency has been shown to be highly heritable (Fornito *et al.*, 2011a; van den Heuvel 2012b), suggesting a possible genetic basis for these changes. In patients, the severity of positive symptoms is linked to the degree of structural and functional connectivity changes (Skudlarski *et al.*, 2010; Wang *et al.*, 2012), and poor cognitive performance is associated with reduced functional connectivity in some areas (Cole *et al.*, 2011; Repovs *et al.*, 2011). Additionally, a positive relationship between structural network efficiency and intelligence that is normally observed in control subjects has been found to be absent in schizophrenia patients (Zalesky *et al.*, 2011). In another

study which used a different temporally dynamic technology known as magnetoencephalography (MEG), schizophrenia patients had reduced network cost-efficiency (a metric that balances competing constraints of network integration with connectivity costs), and this reduction was correlated with poorer working memory performance (Bassett *et al.*, 2009).

A limitation of this area of research is that the methods that can be used to non-invasively investigate the structure and function of living patients tend to have relatively low spatial resolution. Thus for the most part these investigations can only reveal information about connectivity between brain regions and only to a small if any degree within discrete areas. Brain function at the level of individual neurons, or local populations of neurons, might be expected to be altered in some meaningful ways in humans with schizophrenia, particularly in regions such as the prefrontal cortex that are repeatedly implicated in imaging studies. This hypothesis is supported by histopathological findings that indicate a reduction in neuropil in the prefrontal cortex (see section 1.4.1). However, we do not yet have suitable technological options to safely and effectively measure cellular-level activity *in vivo* in human patients.

In summary, a wide range of neurophysiological abnormalities have been identified in human patients with schizophrenia. We know that cell death is not a primary feature of the disease, but there is some degradation of the axons and dendrites neurons need to communicate with each other; that multiple neurotransmitter systems are dysregulated, primarily dopamine and glutamate; and that functional communication between brain regions (and possibly within brain regions) is disrupted in the brains of patients with schizophrenia. What type of originating disease process could produce this range of findings? In the next section I will discuss the current understanding of the processes by which the signs and symptoms of schizophrenia emerge from causal and exacerbating factors.

1.5. Pathogenesis of Schizophrenia

While imaging studies and investigations into the effects of pharmacological compounds revealed much about the physiological basis of dysfunction in schizophrenia, the underlying causes of the disease remain unknown. The maturation of the NMDAR hypofunction hypothesis of schizophrenia paralleled advances in developmental neuroscience that lent insight into the possible ways in which neurotransmitter dysfunction in adults with schizophrenia could emerge, and it is currently believed that abnormal developmental processes play a large role in schizophrenia.

In normal development, adolescent maturation of the prefrontal cortex is marked by the elimination of synaptic connections, a process referred to as "synaptic pruning" (Rakic *et al.*, 1986; Zecevic *et al.*, 1997; Huttenlocher *et al.*, 1997; Petanjek *et al.*, 2011). Eliminated synapses appear to be exclusively excitatory contacts (Rakic *et al.*, 1986; Zecevik *et al.*, 1997), and therefore this process is thought to be critical in establishing excitatory/inhibitory balance in the cortex. Just as the dorsolateral prefrontal cortex is the last region of the cortex to begin generation of the cortical plate, it is also the last cortical region to finish the maturational process and achieve the adult state (Huttenlocher *et al.*, 1997; Giedd, 1999; Sowell *et al.*, 1999a,b), and the process of synaptic pruning in human prefrontal cortex may even extend through the third decade of life (Petanjek *et al.*, 2011). The timing of these morphologic changes in synaptic number corresponds strongly to the emergence of adult executive functioning of the prefrontal cortex, such as rational thinking, attention, internally guided behavior, cognitive control, and impulse inhibition (Reiss *et al.*, 1996; Sowell *et al.*, 2001a).

The concept of schizophrenia as a neurodevelopmental disorder dates back to original descriptions by Kraepelin and Bleuler, who studied children that later developed schizophrenia and identified premorbid signs of psychosis as well as deficits in social interaction. As far back as 1915, neuropathologic signs were reported in the brains of 25

patients with dementia praecox, which further pointed to a neurodevelopmental etiology of the disorder (Southard, 1915). In 1982, Feinberg proposed that schizophrenia could be caused by a fault in programmed synaptic elimination during adolescence (Feinberg, 1982), and this was soon followed by a comprehensive neurodevelopmental hypothesis for the etiology of schizophrenia that was put forward in 1987 (Weinberger, 1987). This hypothesis gained widespread acceptance when epidemiologic studies found that prenatal and perinatal factors such as antenatal maternal virus infection and obstetric complications that involve hypoxia contribute to the risk of developing schizophrenia (see Brown, 2012; Schmitt *et al.*, 2014). In general, it is believed that these insults affect the proliferation and differentiation of neural progenitors in the cortex, resulting in reduced grey matter (Stolp *et al.*, 2011; Stolp *et al.*, 2013). This constitutes an alternative explanation for reduced gray matter that has more supporting evidence than the neurodegeneration hypothesis (Selemon, 2015).

Recent conceptualizations of the neurodevelopmental factors in schizophrenia suggest that genetic and environmental factors combine to trigger the activation of pathologic neural circuitry during adolescence, leading to manifestations of overt disease (Fatemi & Folsom, 2009). This framework is supported by the results of genetic studies that point to numerous genetic mutations implicated in schizophrenia risk that are also known to be necessary for healthy neural development (e.g., Kamiya *et al.*, 2005; Walsh *et al.*, 2008; Fromer *et al.*, 2014; Hall *et al.*, 2015). For many years, twin and family pedigree studies of patients with schizophrenia indicated a strong heritability of the disease, but the tools needed to probe the genetic architecture of the syndrome did not exist. As molecular genetic tools have been developed and applied to increasingly large samples of patients and control subjects in order to identify genetic variations that occur more frequently in people with schizophrenia, the picture that emerges is one of extreme complexity. The early search for a single "schizophrenia gene" that could predict the development of schizophrenia in line with the non-Mendelian inheritance patterns of schizophrenia produced several promising gene candidates (e.g. DISC1), but none that displayed a strong statistical association in larger samples (Kamiya *et al.*, 2005; see for review: Giusti-Rodriguez & Sullivan, 2013).

The advent of genome sequencing allowed investigators to search more broadly for genetic variants that could confer increased risk for schizophrenia. Genome-wide association studies (GWAS) are designed to look for differences in allele frequencies as a function of a phenotype of interest, i.e. patient vs. nonpatient, and generally involve very large sample sizes. The most recent GWAS study in schizophrenic patients included close to 150,000 subjects and identified 108 genomic regions of interest—including an estimated 8,400 independent single nucleotide polymorphisms—that contribute to the risk of schizophrenia (Ripke *et al.*, 2014). Gene-coding regions at these loci were found to include several previously-implicated genes such as those for *DISC1* and *DRD2*, in addition to a wide array of genes known to be involved in other cellular functions hypothesized to be involved in the pathophysiology of schizophrenia. In particular, there appears to be a large degree of functional convergence on genetic pathways that are involved in the regulation of synaptic communication and plasticity.

While promising, these findings essentially eliminated any remaining possibility that a single or small group of genes would be found to explain an appreciable portion of schizophrenia risk, and thus have pushed researchers to develop new frameworks for understanding the genetics of schizophrenia. It appears to be the case that overall genetic risk is distributed across many variants that work in combination (additively or multiplicatively) to predispose an individual to developing schizophrenia. A model referred to as the "common variant, common disease" or CV/CD model predicts how debilitating diseases such as schizophrenia could remain prevalent in the population over evolutionary time if the selective disadvantage of individual mutations is small (Reich & Lander, 2001). This model predicts a relatively small number of rare mutations with strong risk-modulating effects, in combination with a large number of common variants that individually only weakly modulate risk for schizophrenia. Under this model, each individual's combination of genetic mutations (in addition to the complement of environmental risk factors) would contribute to whether or not schizophrenia might

develop. Importantly, subsets of mutations that work synergistically on the same cellular functions would mediate the particular manifestation of schizophrenia in that individual, potentially accounting for some of the disease's heterogeneity.

Within this framework, one can see some of the cellular functions that appear to be consistently affected in schizophrenia. Perhaps most revealing in this context are the genetic insults that impact synaptic plasticity in the brain. Synaptic plasticity itself follows a stereotyped developmental time course and processes involved in short-term plasticity (STP) are refined and matured in a circuit-specific manner during adolescence (Feldmeyer & Radnikow, 2009). For example, STP maturation in neocortical synapses follows a clear developmental trajectory from strongly depressing to weakly depressing or even facilitating over the course of early development (Oswald & Reyes, 2008; Frick *et al.*, 2007). In particular, the earlier suggestion by Feinberg that implicated altered synaptic pruning during adolescence in schizophrenia has led to a broader theory that incorporates two separate critical periods (Selemon & Zecevic, 2015): one during early prenatal development and a second during adolescence. It is therefore likely that genetic variants or early developmental lead to cellular dysfunction that can predispose an individual to schizophrenia; depending on the type of insult and the circumstances of the person's environment, these disruptions can be unmasked or exacerbated during adolescence and lead to development of the schizophrenia syndrome.

As discussed in Section 1.4, there is extensive evidence that functional connectivity between brain regions, particularly the prefrontal cortex, is disrupted in schizophrenia. The mechanisms by which this pattern arises, however, are less clear. Functional connectivity between brain regions could be abnormal because their anatomical connections are altered, for example through misdirection of the formation of synaptic connections. Alternatively, functional coupling could be disturbed due to impairments in synaptic transmission and plasticity. These mechanisms are not necessarily exclusive but could coexist and influence each other. For example, several genes linked to schizophrenia are involved in both

establishing long-range connections during development and in regulating synaptic plasticity (e.g., NRG1 or dysbindin; Harrison & Weinberger 2005). Conversely, any impairment in synaptic plasticity would affect the way long-range and short-range connections are established in the developing brain, as the strength of functional coupling between two neurons has been shown to determine whether their connection survives developmental pruning (Hua & Smith 2004). Furthermore, functional coupling is a function of experience-dependent synaptic plasticity (Zhang & Poo, 2001), and a disruption in this mechanism is consistent with the observation that schizophrenia cannot be explained by genetics alone but only by interactions between genes and environment (Sullivan *et al.*, 2003).

The implication of this framework is that a small difference in the developmental rules guiding network formation may create a vulnerability for non-optimal brain network topology, forming a pathogenic mechanism for development of schizophrenia (see Collin 2013; van den Heuvel & Kahn, 2011). This has been supported by computational modeling studies that attempt to simulate the ways in which the complex manifestations of schizophrenia can emerge from relatively simple disruptions in network function. For example, Vertes *et al.*, (2012) grew simulated neural networks whose topology emerged primarily from two constraints: bias towards clustered connectivity and a penalty on the formation of long-distance links. Using these networks, the authors were able to both reproduce a diverse range of topological properties observed experimentally in functionally healthy brains and demonstrate how adjusting model parameters to relax the clustering bias and reduce the penalty on long-distance connections accurately modeled topological alterations observed in childhood-onset schizophrenia.

While a developmental perspective of schizophrenia provides insight into how genetic and environmental factors combine to produce the disease, it also underlines one of the features that makes schizophrenia so difficult to characterize. Specifically, it provides an axis, in the form of time, along which all of the other causal or exacerbating factors, physiological

features, and symptoms of the disease must fall. It is not sufficient to study only genes, or only the behavioral outcomes; rather, if we are to understand how to intervene in the development of schizophrenia, it will be necessary to characterize the timeline along which schizophrenia emerges. A second important axis in this work is that of physical scale: the evidence suggests that there is no level of brain function, from genetic to cellular to systemic to action generation, that is not affected in schizophrenia. Interactions occur in both directions along this axis in both normal and abnormal brains: for example, genetic insults can lead to abnormal system-level function, and the activity patterns of neuronal networks can shape their own anatomical structure through plasticity and adaptation. However, a broad look at the range of findings in schizophrenia research reveals a pattern in which most of our understanding of the disease lies at opposite ends of the physical scale spectrum: geneticists have identified numerous small-scale factors, and psychologists have characterized the wide array of behavioral manifestations, but the links between these factors are less well-characterized. Attempts to fill in this gap have largely focused on two major approaches: measuring physiological abnormalities in the brains of living patients with schizophrenia, and using animal models of schizophrenia to test hypotheses that cannot be investigated in humans. The experiments I describe in the following chapters utilize single unit electrophysiological recordings in two animal models of schizophrenia to evaluate the function of local neuronal circuits, a technique which cannot be safely implemented in humans at this time. Animal studies can also contribute to a better understanding of the temporal axis along which schizophrenia develops. For example, any perturbations that are thought to be causal in the formation of schizophrenia can only be studied in a retrospective manner in humans. In contrast, the influence of a particular genetic mutation or environmental stressor can be tested in a causal manner in animal models. For this reason it is informative to extrapolate from both the ways in which animal models of schizophrenia can be generated and the pathophysiological manifestations that emerge in these models.

1.6. Rationale for Current Work

An important component of the work described in this dissertation is the comparison of pathophysiology across two distinct animal models of schizophrenia[4]. While the ideal subjects for investigating the nature of any disease are often the individuals that have been afflicted themselves, the use of animal models with overlapping phenotypic characteristics has the potential to provide key insights into some of the mechanistic questions that remain unanswered in schizophrenia. The limitation of animal models is, of course, that their biology is not identical to human biology. In particular, executive functions such as those affected in schizophrenia only exist in an extremely small proportion of the animal kingdom, and so the translational relevance of any animal model is likely to scale with the similarity between the nervous systems of the model species and humans. Furthermore, since schizophrenia does not occur naturally in other species, those seeking to study animal models of the disease must find ways to model the features of schizophrenia by implementing perturbations that are able to causally reproduce the features under investigation.

One approach for creating models of schizophrenia is with the aim of reproducing the signs and symptoms of the disease first, then studying the types of physiological disruptions that underlie that dysfunction. For example, as described above, healthy humans that are administered NMDAR antagonists like ketamine and PCP exhibit many signs and symptoms that overlap those seen in schizophrenia. This phenomenon has two major implications: *1)* the relevance of NMDARs in the pathophysiology of schizophrenia is validated, and *2)* a method for actively inducing a schizophrenia-like state is identified. Administration of pharmacological NMDAR antagonists to research subjects can therefore be used as a model of schizophrenia with high *face validity*, as these compounds produce the outward manifestations of the disease. However, because the disease under

[4] This section is largely speculative, and thus I have limited the use of citations in the interest of readability. Much of the relevant literature is referenced in previous sections, so only new topics are cited here.

investigation arises naturally in the human population without NMDAR antagonists, this type of model does not provide insight into the underlying causes of the schizophrenia.

In contrast, a model with high *construct validity* is one that focuses on a known causal factor, with the intent to provide insight into the pathogenesis of schizophrenia. In practice, this involves exposing animals to some of the genetic or environmental factors that increase risk for developing schizophrenia. Neurodevelopmental models of schizophrenia have high construct validity; this typically involves subjecting animals to an insult during a particular period of perinatal development, which has been shown to reproduce many features of schizophrenia (Modinos *et al.*, 2015). Another type of model with high construct validity involves using genetic engineering tools to induce mutations in genes that have been known to increase risk for schizophrenia. A disease that is caused by a single known highly-penetrant gene mutation would be ideal for this type of study, but unfortunately no such mutation exists for schizophrenia. An alternative strategy is to target genes that are rare and only account for a fraction of schizophrenia cases, but have a large impact on the risk for developing the disease. For example, deletion of a region of the 22nd chromosome in humans, referred to as 22q11.2 microdeletion syndrome or DiGeorge syndrome, is relatively rare, but leads to a 30-fold increase in the risk for developing schizophrenia. (Karayiorgou *et al.*, 1995). Reproduction of this mutation in an animal whose genes can be edited could be said to represent a model of schizophrenia (or, more specifically, DiGeorge syndrome) with high construct validity.

Most animal models of schizophrenia have some degree of both face and construct validity, as these concepts are not mutually exclusive. Another important characteristic of any disease model is *predictive validity.* Models with high predictive validity will respond to interventions in a way that predicts the response that could be expected in humans with the disorder. For example, evidence that antipsychotic medications can alleviate the effects of NMDAR antagonists on executive cognitive function in humans (Krystal *et al.*, 1999c) in

addition to other assays in animal models (Freed *et al.*, 1980, 1984; Tiedke *et al.*, 1990; Corbett *et al.*, 1995), lends predictive validity to of this model.

Which animal model an investigator chooses to use to illuminate the nature of schizophrenia thus is largely dependent on which features of the disease are the intended focus: pathogenesis, pathophysiology, or therapeutics? As discussed above, there are large gaps in our knowledge of schizophrenia with respect to each of these components. In the work I describe here, my primary focus is that of providing a better understanding of the pathophysiology of schizophrenia. Most of our understanding of neurophysiological abnormalities in schizophrenia lies at extreme ends of the physical scale spectrum, from cellular and synaptic function to long-distance projections between cortical areas. However, the processes that lie at intermediate scales are not easily accessible for study in humans, and as a result we have a poor understanding of how the complex manifestations of schizophrenia emerge through intermediate levels from cellular dysfunction.

A consistent pattern that emerges from the body of work in schizophrenia is that of disrupted connectivity. It is tempting to speculate that synaptic disconnection at the microscopic level (inferred to occur in schizophrenia based on histological findings) is causally linked to the findings of disconnection at the macroscopic level. However, relatively little research has been performed to investigate the nature of these links at the intermediate (mesoscopic) levels. In previous sections I described evidence suggesting that connectivity strength and distribution are disrupted in schizophrenia, whether the nodes of the system are defined as individual neurons or entire brain regions. Network science gives us vocabulary and methodology to understand the implications of these parallels across physical scale. For example, the nervous system can be characterized as a *scale-free* system, i.e. one with a fractal-like reproduction of both functional and structural patterns as one scales up from neurons to groups of neurons to whole systems (Sporns, 2010). Furthermore, there are several known mechanisms by which neural systems can interact across these scales (e.g. cross frequency coupling, spike-field coupling, and in a

broader sense, Hebbian plasticity), and the behavior of macroscale systems as a whole is thought to emerge from the behavior of meso- and microscale systems (Buzsaki, 2006). This leads us to a central question: is schizophrenia a disorder of disrupted connectivity across all physical scales of the nervous system? If so, is it possible that macroscale dysconnectivity *arises from* disordered connectivity at smaller scales? One potential mechanism for this would be a primary deficit in neuronal communication within a brain region that results in a failure to produce a coherent signal for inter-regional communication, manifesting as a deficit in functional connectivity between brain regions. However, at this time very little is known about functional connectivity in schizophrenia at the micro- or mesoscale, and so the first step is to ask whether disruptions in functional connectivity exist at all on these scales.

The primary goal of my thesis work is to investigate functional connectivity within local populations of neurons in the prefrontal cortex in the context of schizophrenia. We chose to use animal models of schizophrenia so that we could focus on electrophysiological activity from single units in local populations. In order to maximize the translational potential of our findings, we sought out to compare analogous sets of data obtained from two separate animal models of schizophrenia. In Chapter 2, I will describe the analysis I performed[5] to characterize network dynamics in the prefrontal cortex of nonhuman primates after administration of the NMDAR antagonist phencyclidine (PCP). This is a schizophrenia model with high face validity, due to both the similarity in cortical architecture between human and nonhuman primates and the established ability of NMDAR antagonists to reproduce signs and symptoms of schizophrenia. In Chapter 3, I report an extension of this work as applied to the *Dgcr8*$^{+/-}$ mouse model of schizophrenia. By adapting the same recording system that had been used for the primate dataset described in Chapter 2, I was able to record single unit activity from the prefrontal cortex of awake

[5] Using a collection of electrophysiological data that was obtained by Dr. Rachael Blackman prior to the start of my work on this project: see Blackman et al., 2013. Chapter 2 includes a description of the division of work between myself and Dr. Blackman.

mice and accumulate a dataset that was similar in format and character to the primate data. The two animal models used here, pharmacological NMDAR antagonism in nonhuman primates and gene deletion in mice, differ greatly both in terms of the nature of the perturbation used and the phylogenic distance between humans and each animal. However, these disparities are actually what lends such strength to our approach: by comparing findings across one model with high face validity and a second model with high construct validity, we maximize the translational relevance of our findings to human schizophrenia. As will be seen below, the two datasets compared in this dissertation reflect similar patterns of dysfunctional neuronal communication, in addition to some insightful differences, that appear to represent a fundamental deficit in synaptic transmission in schizophrenia. These findings have the potential to provide both a functional correlate to histopathological findings in schizophrenia as well as a microcircuit correlate of system-wide disruptions in functional connectivity in schizophrenia.

For the studies described here, we used 16-electrode recording arrays designed to be inserted into a localized brain region, with a planar coverage totaling approximately 1 mm^2. As discussed above, neurophysiological abnormalities in schizophrenia are not limited to any single brain region or system. Still, some consistent patterns emerge in the association between dysfunction in particular subsystems of the brain and subsets of symptoms in schizophrenia. For example, dysregulation of the dopaminergic system is strongly associated with the positive symptoms of psychosis. However, research into the dopaminergic system has been less fruitful than originally anticipated in terms of directing the development of comprehensive treatments for schizophrenia. Several lines of evidence suggest that dysfunction in the prefrontal cortex (or in its connections) precedes dysfunction in other systems in schizophrenia. Furthermore, prefrontal hypofunction is behaviorally linked to cognitive dysfunction in schizophrenia, the class of symptoms that is both most debilitating and least modifiable at this time, and the dorsolateral prefrontal cortex (DLPFC) in primates is thought to be an underlying substrate for thought disorder in schizophrenia (Goldman-Rakic, 1991). For these reasons, we chose to target prefrontal regions in the rhesus macaque (Chapter 2; primate DLPFC) and the mouse (Chapter 3;

infralimbic and prelimbic regions) that were as homologous as possible to the human DLPFC.

In the following chapters, I will describe my efforts to test the following hypotheses regarding local network dynamics in animal models of schizophrenia:

Hypothesis 1: Pharmacological NMDAR antagonism is associated with a reduction in the temporal correlations in activity within local circuits in the prefrontal cortex.

Hypothesis 2: Deletion of a single copy of the Dgcr8 gene in mice is associated with a reduction in the temporal correlations in activity within local circuits in the prefrontal cortex.

We expect this dysfunction to manifest in the following ways:

Reduced synchrony: if the DLPFC is unable to form a functional unit that can send a coherent signal to other regions, this could be reflected in an inability to synchronize at the pairwise level. This could represent a local correlate of the long-distance correlational disruptions previously described in schizophrenia.

Reduced functional and/or effective connectivity: histological studies repeatedly suggest that the basal dendrites of layer 3 neurons are diminished in number and complexity in schizophrenia. These dendrites primarily form short-range reciprocal connections between neighboring neurons. If structural connections between neighboring neurons are reduced in number in schizophrenia, this should be reflected in the form of reduced functional and effective correlations between neighboring neurons during awake activity.

Validation of these hypotheses would support a broader theory of schizophrenia as a disease that emerges from early disruptions in developmental processes that regulate synaptic development in the cortex, leading to a fundamental deficit in effective network communication that ultimately causes the phenotype of schizophrenia.

2. Blocking NMDAR degrades spike correlation in primate prefrontal networks

Portions of the content of this chapter have been published in the journal *Neuron* (Zick *et al.*, 2018). Some minor changes have been made for this publication in order to emphasize my own contributions.

2.1. Introduction

Schizophrenia is a devastating illness with no clearly identified cause. Multiple genetic, environmental, and developmental predisposing factors have been identified, all of which incrementally increase risk, but none of which is sufficient to cause the disease or explain its pathogenesis (see Chapter 1). This suggests that schizophrenia can result from a variety of potential insults or 'hits', and that the multiple factors identified as increasing risk converge on a common pathophysiological process. Although numerous functional imaging studies have documented that altered prefrontal network activation in patients associated with deficits in cognitive functions that rely on prefrontal cortex, these data are not able to address how risk factors in schizophrenia change the function of prefrontal networks at the cellular level. Genetic mutations, environmental factors and developmental events all must exert their effects on brain function by changing the functional properties of neurons and how they interact in networks. Since we do not have a clear picture of how neuronal function is impacted in schizophrenia, we have a limited basis for identifying

better treatments, the efficacy of which will depend on their ability to normalize prefrontal neuron and network function.

2.1.1. *NMDAR antagonist-based animal models of schizophrenia*

As discussed in Chapter 1, NMDAR antagonists such as phencyclidine (PCP), ketamine, and MK-801 have been used to elicit schizophrenia-like symptoms in humans and other mammals. This model is based on a variety of supporting evidence such as the observation that NMDAR antagonists exacerbate symptoms in schizophrenic patients (Mahlhotra et al., 1997), and even in asymptomatic people these drugs cause an acute psychosis that can reproduce nearly all of the symptoms of psychosis in patients with schizophrenia and associated disorders, including hallucinations and delusions, catatonia and poverty of affect, and cognitive control errors (Javitt and Zukin, 1991; Krystal et al., 1994; Lahti et al., 1995a,b; Breier et al., 1997). It is notable that these symptoms include negative and cognitive deficits, as attempts to model schizophrenia through dopaminergic dysfunction generally only reproduce positive symptoms.

The fact that drugs that block NMDAR replicate so many of the symptoms of schizophrenia may not be coincidental. Genome-wide association studies (GWAS) have identified a large number of genetic mutations that increase risk for schizophrenia, and a cluster of the affected genes code for proteins involved in signal transmission at synapses that utilize NMDAR (Ripke et al., 2014). Consequently, defects in NMDAR synaptic transmission may be causal factors in the human disease that can be mimicked by drugs blocking NMDAR in animal models.

Various investigations have been performed to study the underlying neural mechanisms leading to schizophrenia through administration of NMDAR antagonists to animals, with the majority of these studies using rats (e.g. Jackson et al., 2004; Homayoun & Mohgaddam, 2007; Hakami et al., 2009; Molina et al., 2014). Prior studies in nonhuman

primates have addressed the question of how NMDAR antagonism changes task-related signals in prefrontal neurons of monkeys performing cognitive tasks. This work has revealed that blocking NMDAR weakens delay period activity associated with working memory (Wang et al., 2013), reduces the strength and task selectivity of neural signals reflecting executive control in rule-based tasks (Ma et al., 2015; Skoblenick and Everling, 2012), and modifies prefrontal oscillations reflecting trial outcome (Skoblenick et al., 2015, 2018). However, none of these studies addressed how reduced NMDAR synaptic function modifies the dynamics of prefrontal neuron spike timing and correlation on a cellular scale, which is the focus of Chapter 2.

2.1.2. *Source of neural data in Chapter 2: Prior work in an NMDAR antagonist model of context processing failure in nonhuman primates in the Chafee lab*

Dr. Rachael Blackman, a previous student in the Chafee lab, performed the first behavioral studies of the effects of ketamine and PCP in nonhuman primates on context processing, and the neural recordings from these experiments provide the data for the analysis in this chapter. Context processing (also referred to as cognitive control) is a set of cognitive abilities that enable the brain to use rules or contextual information, typically stored in working memory, to modify behavioral responses to subsequent stimuli. This ability enables the context-dependence and flexibility that characterizes human behavior, and it is a form of cognitive processing that is selectively impaired in schizophrenia (MacDonald, 2008; Uhlhaas & Singer, 2010). After training two rhesus macaques to perform a cognitive control task that had previously been shown to isolate specific deficits in schizophrenic patients (Barch *et al.*, 2003; Jones *et al.*, 2010; MacDonald *et al.*, 2005; MacDonald *et al.*, 2003), Dr. Blackman measured the monkeys' performance with and without systemic subanesthetic doses of ketamine (a shorter acting analog of PCP) (Blackman *et al.*, 2013), providing evidence that reducing NMDAR synaptic function caused monkeys to commit a trial-type specific pattern of errors in the task that very closely resembled the error pattern of patients with schizophrenia performing the same task. To elucidate the underlying change in prefrontal neuron and network function, a computer controlled motor drive

allowing independent advance of 16 microelectrodes (70 µm diameter each) into dorsolateral prefrontal cortex was used to isolate single-unit activity and relate it to task performance under three experimental conditions: (1) *drug-naïve* (before first injection of PCP), (2) *saline* (immediately after a control injection of saline), and (3) *drug* (after an injection of phencyclidine). Phencyclidine was used during neural recording because it produces more persistent cognitive deficits (lasting 2-3 hours) in comparison to ketamine (lasting 15-30 minutes), making it possible to record neural activity under NMDAR blockade for a longer period. This increases the power of statistical techniques we employed to characterize spike timing and correlation in prefrontal networks under control conditions and following NMDAR blockade. This chapter constitutes a description of the analysis I have performed on this neural dataset over the course of my graduate research, as well as the conclusions that can be drawn about disruptions in cellular communication under NMDAR antagonism. The goal is that this work will provide insights into core phenotypes that may be common between the nonhuman primates used in the current study and humans with schizophrenia.

2.1.3. *The DPX task: a translational cognitive control paradigm*

My work focuses on the analysis of how NMDAR blockade influences relative spike timing and correlation between neurons in prefrontal networks – the focus is on temporal dynamics of prefrontal neuron activity and not its behavioral correlates (e.g. relation to cognitive control success or failure). Additional information regarding the relation of prefrontal network dynamics to cognitive control performance is provided in our *Neuron* publication (Zick *et al.*, 2018), and will be the focus of additional studies in the Chafee lab. I provide a brief description of the cognitive control task used to collect the neural data in Chapter 2 here. The task employed was the dot-pattern expectancy (DPX) task, which is a variant of the AX continuous performance task (AX-CPT) that has been widely used to characterize cognitive control failure in patients with schizophrenia (MacDonald, 2008). In the DPX task, monkeys view a cue followed by a probe stimulus (**Figure 2.1A, B**), and then move a joystick either to the left or right depending on the cue and probe presented.

Cue (**Figure 2.1C**) and probe (**Figure 2.1D**) stimuli were dot patterns presented on a video monitor during fixation of a central gaze target. One cue dot pattern was designated the A-cue, and 5 alternative dot patterns were collectively designated B-cues (**Figure 2.1C**). Similarly, one probe dot pattern was designated the X-probe, whereas 5 alternative dot patterns were collectively designated Y-probes (**Figure 2.1D**). On 69% of trials, the A-cue was followed by the X-probe (AX trials). This was the target sequence requiring a target response (leftward movement of the joystick). All other combinations of cues and probes were nontarget sequences that required a nontarget response (rightward movement of the joystick; BX, AY, BY). The preponderance of AX trials established a prepotent motor habit to move the joystick to the left (target response) whenever the X-probe appears. On BX trials, when the X-probe appears, cognitive control must utilize information about the B-cue (stored in working memory) to override the prepotent left (target) response and move the joystick to the right (nontarget response) instead. Both patients with schizophrenia (Barch *et al.,* 2003; Jones *et al.,* 2010; MacDonald *et al.,* 2005; MacDonald *et al.,* 2003), and monkeys following administration of NMDAR antagonists (Blackman *et al.,* 2013) **(Figure 2.1G**), make a larger number of errors on 'BX' trials, releasing the habitual target response to the X-probe and failing to override this response based on the prohibitive B-cue stored in working memory. This deficit could either reflect a basic defect in working memory function (in which case failing successful maintenance of the contextual cue, monkeys release the habitual target response as a default), or a more specific deficit in the neural mechanism by which information stored in working memory is utilized to intervene in the case that habitual responses to stimuli are incorrect (cognitive control). Prefrontal neuronal responses in the DPX task are highly biased toward stimuli (for example B-cues) and actions (for example nontarget responses) that are rare and reflect the countermanding of the habitual response in the task (Blackman *et al.,* 2016). That bias suggests that the working memory functions of PFC in the DPX task are optimized to provide cognitive control when environmental cues indicate habitual responses will be unsuccessful. The errors that patients with schizophrenia and monkeys given NMDAR antagonists exhibit therefore appear to reflect loss of a basic neural mechanism for cognitive control.

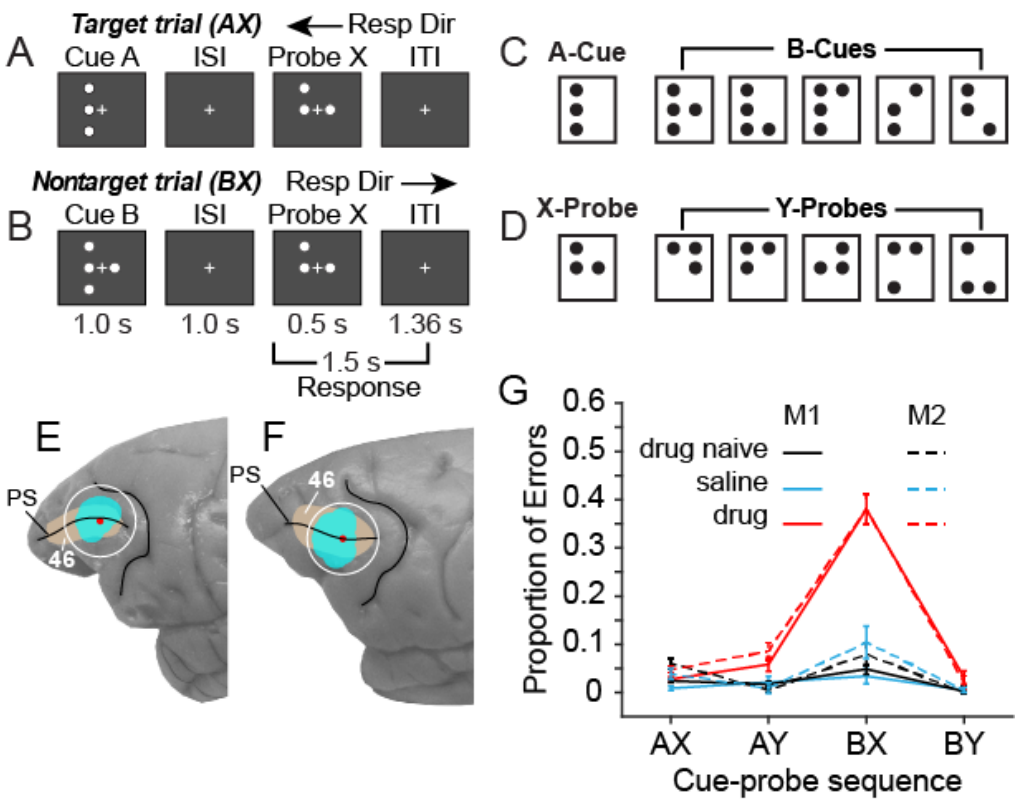

Figure 2.1: ***DPX task, recording locations, and task performance.***

A, B. Event sequence in the DPX task. A cue and a probe stimulus are displayed each trial. A. On AX trials, the A-cue is followed by the X-probe. This is the target sequence, and the monkey is rewarded for moving the joystick to the left (target response). B. On BX trials, the B-cue stored in working memory must override the habitual target response to the X-probe to produce the correct nontarget response to the X-probe in this context. C. Cue stimuli. One dot pattern was designated the A-cue, and five dot patterns were collectively designated B-cues. D. Probe stimuli. One dot pattern was designated the X-probe, and five dot patterns were collectively designated Y-probes. E, F. Locations of ensemble neural recording (cyan) in Brodmann's area 46 (tan) surrounding the principal sulcus (PS) in monkeys 1 (E) and 2 (F). Red dots indicate the centers of the recording chambers. G. Behavioral performance on the DPX task while the neural data described in this chapter was recorded. The y-axis indicates the proportion of errors (± 2 SE above and below the mean) committed during DPX task performance separated by cue-probe sequence (trial type) and experimental condition in Monkey 1 (solid) and 2 (dashed).

Combinations of cues and probes defined four different trial types (AX, AY, BX and BY). We presented these four trial types in the following proportion. Most trials (69%) were AX (target trials), to increase the prepotency of the target response and establish a habit to

produce the target response when the X-probe appears. The remaining 31% of trials were nontarget trials and were either AY (12.5%), BX (12.5%), or BY (6%). This is the same proportion of trial types used to characterize cognitive deficits in patients with schizophrenia (Jones *et al.*, 2010). Most of trial sets included between 200 and 400 correctly performed trials. We restrict the analysis of neural dynamics in the present report to correctly performed DPX trials.

2.1.4. *Inferring functional and effective connectivity between neurons based on statistical dependencies in their spiking patterns*

Functional connectivity, as introduced in the previous chapter, refers to a consistent statistical relationship in the activity time series of two nodes in a network. In network science terminology, *nodes* are the bodies that are communicating (e.g., individual cells or brain regions) and *edges* are the connections between these bodies. Edges can be weighted (strong or weak) and directed or undirected, and are classified as physical, functional, or effective. In neuroscience, physical (structural) connections are the synapses or gap junctions between neurons. Functional connections are inferred by temporal correlations in the activity of neurons or groups of neurons, and are thought to be reflective of shared communication that can be direct or indirect. Because functional correlation can be detected in nodes that are not connected but share a common synchronizing input, the presence of functional connectivity between two nodes does not necessarily inform whether direct communication is occurring between them or in what direction. *Effective* connections are inferred between two nodes of a network when information about the activity of one node can be used to predict the activity of the other node after a lag, suggesting a causal influence. Physical connections delimit the ways in which activity *could* flow within a circuit, whereas effective connections identify the ways in which activity *typically* flows.

In the networks considered here, communication cannot be measured deterministically, but only in a statistical sense. If NMDAR blockade disrupts functional and/or effective

connectivity between prefrontal neurons, this would be reflected in a weaker statistical association between the time series data obtained from such neurons. In the analysis described here, we take advantage of the binary nature of action potentials ("spikes") to quantify neurons' behavior in terms of the probability that a given cell will spike (1) or not spike (0) at any particular point in time. Cross-correlations between each pair of simultaneously-recorded cells are evaluated by computing the *relative* probability that a given cell will spike around the same time in which a spike occurs in a neighboring cell. If two trains of spikes are strongly correlated at a consistent time lag, the neuron pair can be said to be functionally correlated. A functional correlation between two neurons suggests the presence of either a) input from a common source or b) a direct causal influence from one neuron to the other.

Unfortunately, cross-correlation-based methods provide limited information to help determine whether an interaction is direct or indirect, and thus are insufficient for quantifying effective connectivity. The search for a measure of effective connectivity that is as model-free as possible naturally leads to information theoretic techniques. In his formal definition of causality, Norbert Wiener (1956) proposed that a causal interaction can be inferred if one's ability to predict the time series *X* is improved by incorporation of information about a second time series *Y*. By integrating this principle with traditional covariance methodology, Schreiber (2000) defined a metric called transfer entropy that could nonparametrically distinguish the driving and responding elements of an asymmetric (causal) interaction. This metric has been used to detect functional interactions between neurons, and has been shown to reflect true connectivity in both slice preparations (Nigam *et al.*, 2016) and computational network models (Ito *et al.*, 2011).

In Chapter 1, I provide evidence from an array of studies that have led researchers to think of schizophrenia as the ultimate consequence of disrupted neural connectivity. We see evidence of this pattern across both physical and developmental time scales, yet numerous gaps remain in our understanding of the nature of these deficits. The neural data available

from the primate experiments performed in the Chafee lab provide a unique opportunity to investigate cellular dynamics in awake primates during the expression of schizophrenia-like cognitive dysfunction. By characterizing temporal relationships in the activity patterns of simultaneously recorded neurons, we measure the degree to which neurons are able to functionally and effectively communicate after pharmacological NMDAR blockade. In the present chapter, we describe the results of performing cross-correlation and transfer entropy analysis in order to characterize the temporal relationships between neighboring neurons in the prefrontal cortex. We provide evidence that NMDAR antagonism leads to a reduction in both synchrony and effective connectivity between neuron pairs in the prefrontal cortex, and discuss the implications of these findings in the context of schizophrenia.

2.2. *Methods*

2.2.1. *Monkeys*

Two adult male rhesus macaques (8-10 kg) were used for neural recording in prefrontal cortex during DPX task performance in this study. Both animals had participated in a prior study in which they received subanesthetic doses of ketamine to evaluate the impact of NMDAR blockade on DPX task performance (Blackman *et al.*, 2013). Some features of task-related signals in prefrontal cortex were described in a prior report, where additional experimental details can be found (Blackman *et al.*, 2016). All animal care and experimental procedures conformed to National Institutes of Health guidelines and complied with protocols approved by the Animal Care and Use Committee at the University of Minnesota and Minneapolis Veterans Administration Medical Center.

2.2.2. *Surgery*

Monkeys were prepared for acute neural recording in an aseptic surgery performed under general gas (isoflurane, 1-2%) anesthesia. Craniotomies were made overlying the dorsolateral prefrontal and posterior parietal cortex. Spiking dynamics based on analysis of neural activity in prefrontal cortex are reported here. Plastic recording chambers were cemented over the craniotomies using surgical bone cement anchoring the chambers to screws placed in the surrounding surface of skull to enable neural recording. Titanium posts were attached to the skull to make it possible to stabilize head position for neural recording. Surgical bone cement was applied to anchor the recording chambers to the posts. Monkeys received injectable analgesics for several days postoperatively (Buprenex; 0.05 mg/kg twice a day, i.m.).

2.2.3. *Drug Administration*

We recorded neural activity in prefrontal cortex following systemic intramuscular injections of an NMDAR antagonist (Phencyclidine, Sigma Pharmaceuticals, diluted in sterile saline at 5 mg / ml, administered in a dose of 0.25-0.30 mg/kg I.M.), or an equivalent volume of sterile saline (0.05 – 0.06 ml/kg, or a total volume of approximately 0.5 ml) in the quadriceps muscle. We opted to conduct all neural recording within a single optimal dose range of phencyclidine. Holding the dose constant across days when drug was injected allowed us to accumulate the largest number of simultaneously recorded neural ensembles possible at that dose, thereby maximizing statistical power, and the chances to detect functional interactions between neurons based on correlation analysis applied to spike trains. We recorded neuronal activity in prefrontal cortex under three experimental conditions (). In the drug-Naïve condition, neural data was recorded before animals had received their first injection of phencyclidine[6]. After neural data had been recorded in the

[6] In some of the earliest days of drug-Naïve data collection, animals received no injection, while on later days they received an injection of sterile saline. For the purposes of this dissertation, these two conditions are combined into drug-Naïve.

drug-Naïve condition, interleaved daily intramuscular injections of PCP (Drug condition) or saline (Saline condition) began. Phencyclidine is an anesthetic, and at the subanesthetic doses we employed, monkeys were drowsy for a period and then began to work consistently on the DPX task (exhibiting the behavioral deficit illustrated in **Figure 2.1**G).

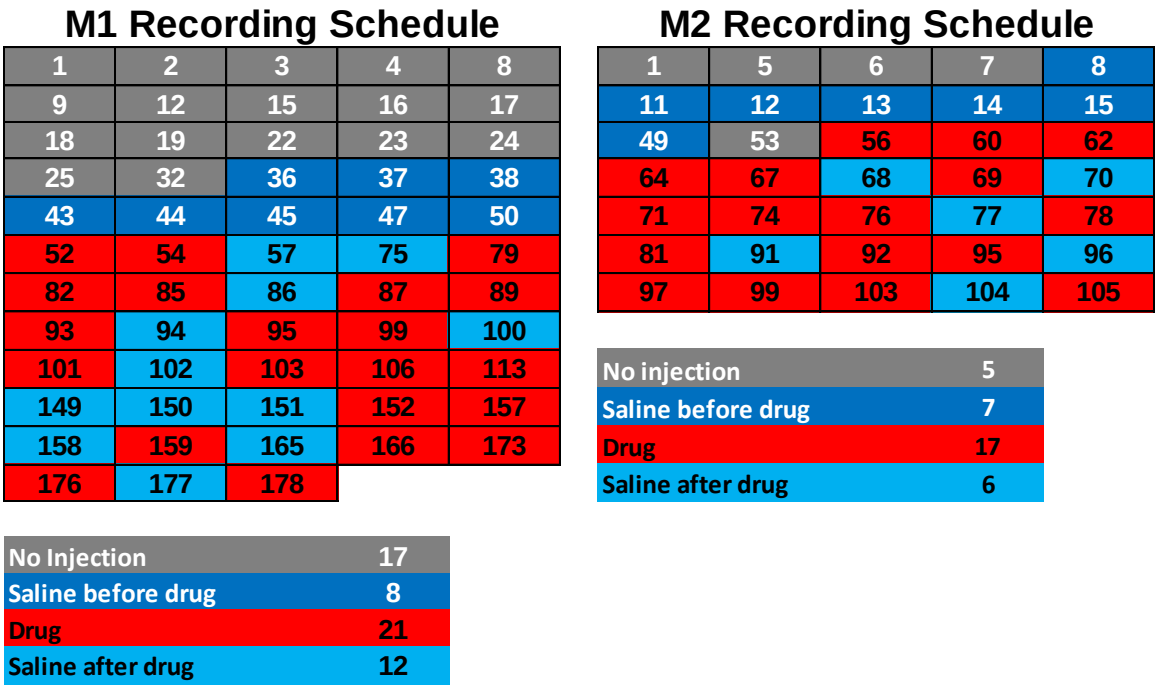

Figure 2.2: ***Schedule of recording and experimental conditions by monkey.***

Experimental condition and recording schedule for monkeys M1 (left) and M2 (right). Days are numbered consecutively from the first day of neural recording (missing numbers indicate days when no recording was conducted and no injection administered). Color indicates experimental condition. 'No injection' (gray) corresponds to days in which neural recording was conducted before monkeys were exposed to drug (phencyclidine) and no injection of saline was given. 'Saline before drug' (dark blue) corresponds to days in which recording was conducted before monkeys were exposed to drug (phencyclidine) and an injection of saline was administered before recording. 'Drug' (red) corresponds to days in which recording was conducted and monkeys received an injection of drug prior to recording. 'Saline after drug' (light blue) corresponds to days in which recording was conducted and an injection of saline was administered prior to recording, after monkeys had been previously exposed to phencyclidine on a prior recording day.

2.2.4. *Neural recording*

We recorded the spiking activity of single units in the prefrontal cortex using an Eckhorn microelectrode drive (Thomas recording, GmbH) equipped with 16 glass-coated platinum iridium microelectrodes (70 µm o.d.). The depths of the electrodes were adjusted independently to maximize the numbers of action potential waveforms from spiking neurons that were detectible above the background signal. We isolated the waveforms of individual neurons online using spike sorting software (Alpha Omega Engineering; Nazareth, Israel). Spike times were stored with 40 µs resolution (DAP 5200a Data Acquisition Processor; Microstar Laboratories, Belleview, WA). We recorded the activity of 89 neural ensembles containing on average 19 individually isolated units for a total of 1708 prefrontal neurons. The neural data were divided between the three experimental conditions as follows: drug-Naïve (38 ensembles, 753 neurons), Saline (16 ensembles, 288 neurons), and Drug (35 ensembles, 667 neurons).

2.2.5. *Artifact removal*

We detected a small overrepresentation of action potentials at fixed times relative to the motor response that were most likely caused by electrical artifact associated with the reward passing through spike waveform isolation windows. These excess spikes were manually removed through visual inspection of the data based on their consistent relationship to the time of the motor response, and both the CCH and TE correlation analyses were applied to the filtered data after these spurious spikes were removed. We confirmed that the presence of the zero-lag peak in the CCH and its reduction in the Drug relative to drug-Naïve and Saline conditions persisted in a separate CCH analysis using spike trains restricted to a window beginning at probe onset and extending to 25 msec before the motor response that excluded spurious spikes (data not shown).

2.2.6. *Cross-correlation analyses*

CCHs were constructed from the spike trains of simultaneously recorded pairs of neurons (Perkel *et al.*, 1967a,b). Data from cue onset to the end of the trial were included in this

analysis, and only CCHs containing >100 spike pairs were analyzed. Neuron pairs in which the two neurons were recorded on the same electrode were not included in this analysis to eliminate correlations that could be the result of indiscriminate spike sorting.

Correlations in spike times in two neurons can be expected to occur by chance at a level that scales with the firing rates of the two neurons (Baker & Lemon, 2000). To account for this, we applied the following rate normalization procedure. For each neuron pair, we generated 100 bootstrap CCHs by shifting each spike by a random interval between -30 and +30 ms and then computing a CCH using the jittered spike times. (The same set of neuronal pairs was found to be significantly zero-lag coupled by the CCH analysis after jittering spike times within the window from -10 and +10 ms, and consequently the size of the jitter window did not alter the pattern of coupling results.) We used this method of jittering spike times rather than shift predictors or trial shuffling because it applied randomness to the precise timing of action potentials but preserved local modulations in firing rate as well as the relationship between spike trains and behavioral variables such as the stimuli presented and response at the trial level.

We considered the mean count of joint spikes in each bin across the 100 bootstrap CCHs constructed for that neuron pair to be the expected baseline count of joint spikes under the null hypothesis that the spike trains of the two neurons were independent, and joint spiking was driven by modulations in firing rate alone. For each neuron pair, we computed the sum of joint spike counts in the -1, 0 and +1 lag bins (defining this as the zero-lag peak height) in the original CCH and in each of the 100 spike-time jittered CCHs. We identified neuron pairs as significantly coupled at zero-lag if the zero-lag CCH peak height in the original data exceeded the 99^{th} percentile of the bootstrap distribution of zero-lag peak heights computed using spike-time jittered data. To construct the population-average CCHs (Fig. 2.3C), for each neuron pair we first normalized the CCH by dividing joint spike counts in each bin by the mean count in the same bin calculated over the bootstrap distribution. We then averaged the normalized CCHs over all neuron pairs. To compute the median

population zero-lag CCH peak heights (Fig. 2.3D), we first normalized the zero-lag peak for each neuron pair by dividing the zero-lag peak height in the original data by the mean height of zero-lag peaks calculated over the bootstrap distribution of spike-time jittered CCHs. We then calculated the median of the resulting normalized zero-lag peak heights over the population of neuron pairs in each experimental condition (along with the 95% bootstrap confidence interval of the median; 1000 iterations) (Fig. 2.3D).

We characterized the variability of spike counts by calculating the Fano Factor in each neuron. All spike trains were divided into time bins of 50 ms, and the Fano Factor was computed as the ratio of the variance to the mean of the spike counts across all bins for each neuron.

2.2.7. *Transfer Entropy*

Transfer entropy was calculated between neuron pairs using the algorithm of Ito *et al.* (2011). We employed their open source MATLAB transfer entropy toolbox – the details of their algorithm, along with a software package and sample data set for MATLAB, are included on the lab's project website (http://code.google.com/p/transfer-entropy-toolbox/, Text S1). In neuroscience terms, transfer entropy (TE) between spike trains of neurons *I* and *J* is nonzero if including information about the spiking activity of neuron *J* improves the prediction of the activity of neuron *I* beyond the prediction based on the past of neuron *I* alone. The original definition of TE (Schreiber, 2000) was given as follows:

$$TE_{J\to I} = \sum p\left(i_{t+1}, i_t^k, j_t^l\right) \log_2 \frac{p\left(i_{t+1} \middle| i_t^k, j_t^l\right)}{p\left(i_{t+1} \middle| i_t^k\right)}$$

Here, i_t and j_t denote the status of neurons I and J, respectively, at time t; the values at each time bin are either 1 (spike) or 0 (no spike); i_{t+1} denotes the status of neuron i at time

$t + 1$; and p denotes the probability of the statement in parentheses. The sum is taken over all possible combinations of i_{t+1} , i_t^k, and j_t^l, and a logarithm with base 2 is used so that the TE output measure is in units of bits. The order parameters k and l represent the number of time bins in the past describing the spiking patterns of neurons i and j, respectively, when predicting the activity state of neuron i; we used $k = l = 1$ so that only single time bins were considered. The code provided by Ito *et al.* (2011) applies a modified equation including a delay term d which can be used to compute TE between two pairs as a function of time lag between signals, allowing for some variation in synaptic delay across cell pairs. Transfer entropy is conceptually similar to mutual information, but differs in that it incorporates time lags and takes into account the auto-prediction provided by the past of neuron I in the prediction of spike probability, and thus is designed to isolate the influence from neuron J onto the activity of neuron I.

Pairwise relationships were evaluated using TE analysis of spike trains starting at cue onset and extending to the probe onset. In general, naïve estimation of information-theoretic quantities from limited experimental samples results in positive bias (Panzeri *et al.*, 2007). Therefore, all TE estimates were bias-corrected using bootstrap distributions in which potential causal interactions were destroyed. Specifically, for each neuron pair, we constructed 100 bootstrap samples and estimated TE functions after shifting each spike by a random interval between 1 and 50 msec. The statistical significance of TE values in the original data was evaluated by comparison to the distribution of TE values obtained in each pair's corresponding bootstrap data. The jitter amount was set to be high enough to allow for computation of TE over an extended synaptic time scale for visualization purposes, and it was confirmed empirically that variations in this value did not appreciably affect the results described here either qualitatively or quantitatively (data not shown).

The TE measures used by Ito *et al.* (2011) were tested and validated in a computational model of spiking Izhikevich neurons (Izhikevich, 2003). Using peak TE values and a Coincidence Index metric (described below), they verified that "true" synaptic connections

between model neurons could be identified from spiking data. In 2016, the same group published an extension of this analysis (Nigam *et al.*, 2016) in which they applied these analyses to neural spiking data obtained from both *in vitro* and *in vivo* multielectrode recordings of rodent cortex. The approaches described here are largely based on the methods described in these two reports, with some minor modifications.

2.3. Results

2.3.1. *Blocking NMDAR reduces synchronous spiking in prefrontal ensembles*

We first evaluated the effect of reducing NMDAR synaptic function on the temporal dynamics of spiking between neurons in prefrontal ensembles by computing cross-correlation histograms (CCHs) to quantify the distribution of intervals between spikes in simultaneously recorded neurons (Perkel *et al.*, 1967). CCHs for many individual neuron pairs exhibited a prominent peak at zero-lag (±1 ms; **Figure 2.3A**), and in the population average CCH zero-lag spiking was the dominant pattern (**Figure 2.3C**). To determine whether the zero-lag peak was significant in each neuron pair, we generated a bootstrap distribution of 100 CCHs after randomly jittering the time of each spike within a ± 30 msec window. This removed precise spike timing relationships but maintained slower overall fluctuations in mean firing rate. We considered zero-lag peaks significant if they exceeded the 99th percentile of the bootstrap distribution of zero-lag peaks computed from the spike-jittered data.

When we compared the prevalence and strength of synchronous spiking in prefrontal cortex across experimental conditions, we found that blocking NMDAR reduced zero-lag spike synchrony in neuron pairs. Administration of NMDAR antagonist significantly reduced both the proportion of neuron pairs exhibiting a significant zero-lag peak (**Figure 2.3B**; red), and the height of the zero-lag peak ("0-lag"; **Figure 2.3C, D**, red) relative to the Saline condition (**Figure 2.3B, C, D**; blue).

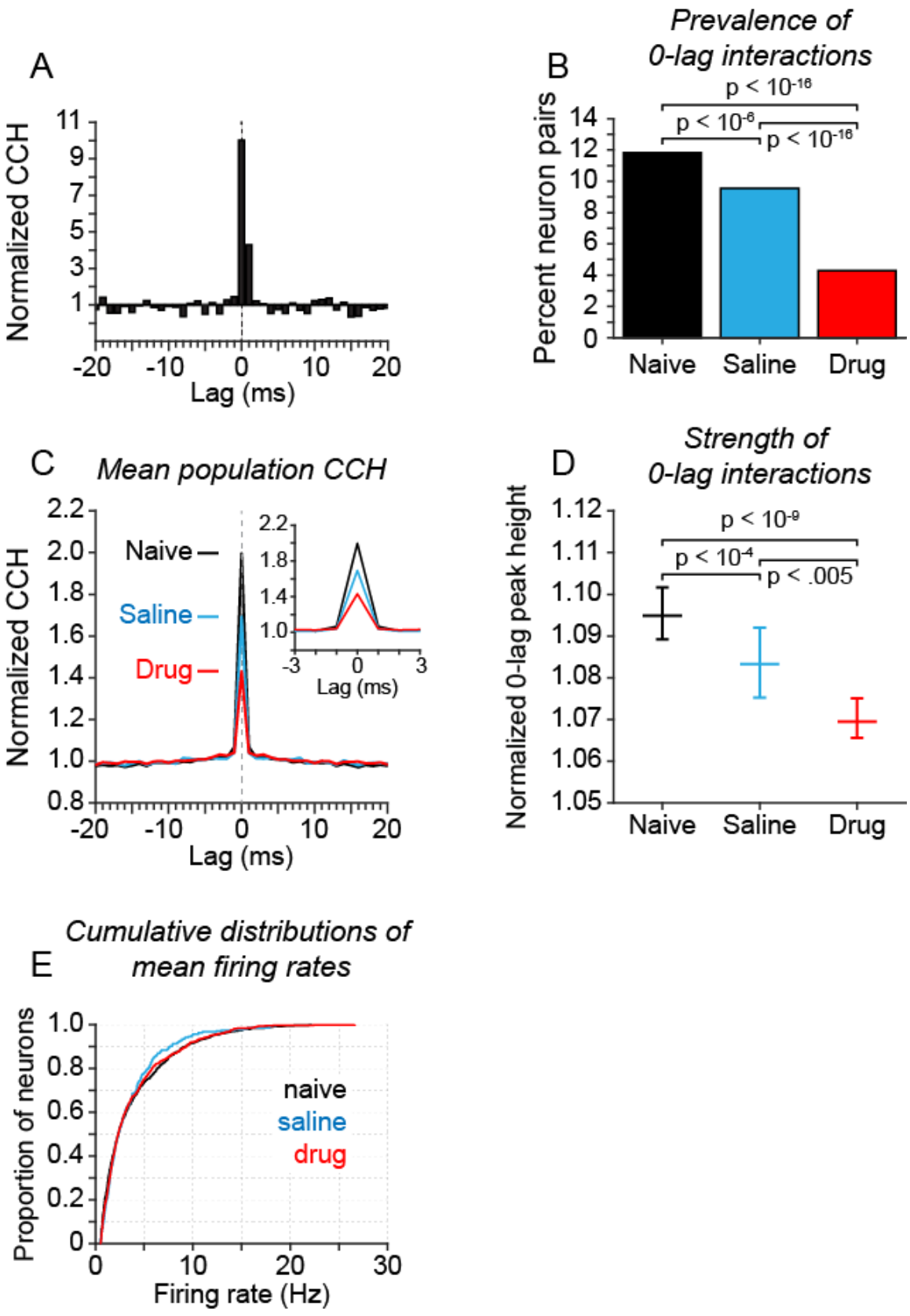
A
Normalized CCH
11
9
7
5
3
1
-20
-10
0
10
20
Lag (ms)
B
Prevalence of
0-lag interactions
p < 10-16
p < 10-6
p < 10-16
Percent neuron pairs
14
12
10
8
6
4
2
0
Naive
Saline
Drug
C
Mean population CCH
Normalized CCH
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
Naive
Saline
Drug
2.2
1.8
1.4
1.0
-3
0
3
Lag (ms)
-20
-10
0
10
20
Lag (ms)
D
Strength of
0-lag interactions
Normalized 0-lag peak height
1.12
1.11
1.10
1.09
1.08
1.07
1.06
1.05
p < 10-9
p < 10-4
p < .005
Naive
Saline
Drug
E
Cumulative distributions of
mean firing rates
Proportion of neurons
1.0
0.8
0.6
0.4
0.2
0
naive
saline
drug
0
10
20
30
Firing rate (Hz)

Figure 2.3: Influence of phencyclidine (PCP) on pairwise spike synchrony in prefrontal cortical neurons.

(Opposite page) Results of cross-correlation analysis applied to the spike trains of pairs of simultaneously recorded prefrontal neurons. Experimental condition is indicated by color (panels B-E): drug-Naïve (black), Saline (blue), and Drug (red). ***A.*** *Example CCH of a neuron pair recorded in the drug-Naïve condition with a significant CCH peak at zero-lag. The CCH is normalized by dividing counts in each bin in the original data by the mean count of the bootstrap distribution of spike-jittered CCHs at that bin.* ***B.*** *Proportion of all neuron pairs recorded that exhibited a significant peak at zero-lag (± 1 ms). A neuron pair was considered to exhibit a significant zero-lag CCH peak if the sum of the counts of joint spikes at lags -1, 0, and +1 exceeded the 99th percentile of the distribution of corresponding sums computed from the spike-jittered CCHs. P-values reflect significance of differences in proportion of significantly coupled neuron pairs across experimental conditions (Fisher's exact test; N = 1736/14674, 469/4908, and 518/12112 significant pairs out of total for Naïve, Saline, and Drug, respectively).* ***C.*** *Mean population CCHs separated by experimental condition (insert shows the zero-lag peak of the same data on an expanded ± 3 msec lag time scale). All recorded neuron pairs were included. CCH normalization as in (A).* ***D****. Median zero-lag CCH peak height as a function of experimental condition. For each neuron pair, zero-lag peak height was computed as the sum of joint spike counts in the -1, 0 and +1 lag bins of the original data, and was normalized by dividing by the mean of the sum of counts in the same bins of the spike-jittered CCHs. Data plotted in D reflect the median of the distribution of normalized zero-lag peak heights across all recorded neuron pairs (error bars reflect 95% confidence intervals of the median; p-values calculated by Kruskal-Wallis test followed by Tukey's HSD test). E. Cumulative distributions of mean firing rate separated by experimental condition. No significant differences in mean firing rate were found (Kruskal-Wallis test; Saline vs. Drug, p = 0.99; Naïve vs Drug, p = 0.90, Saline vs. Drug = 0.97).*

In addition, we found that both the prevalence and strength of zero-lag spiking was significantly reduced in the Saline condition (**Figure 2.3B, D**; blue) relative to the drug-Naïve condition (black). Because saline and PCP injections were interleaved, reduction in synchronous spiking on Saline days following Drug days suggests that exposure to PCP produced persistent changes in the spiking dynamics of prefrontal networks. We examine these persistent effects in greater detail below.

The above changes in synchronous spiking were not attributable to changes in mean firing rate—we found no significant differences in mean rate across experimental condition (**Figure 2.3E**, see legend for statistics), and there was no clear relationship between firing rate and the height of the zero-lag peak across experimental conditions on a per neuron pair basis (**Figure 2.4A**). Considering all recorded neuron pairs, synchronous zero-lag spikes occurred at a low rate (**Figure 2.4B**), indicating that synchronous spikes were infrequent events embedded within the irregular spike trains of pairs of simultaneously recorded neurons.

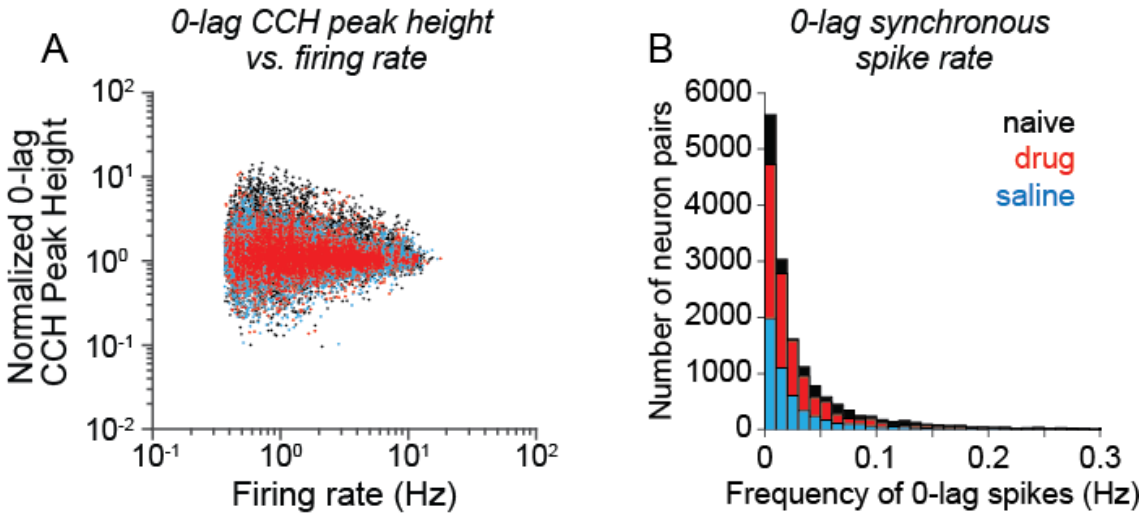

Figure 2.4: Relation between firing rate and zero-lag peak height and frequency of zero-lag spiking.

A. The zero-lag CCH peak height (y-axis) for each neuron in a pair is plotted against mean firing rate (x-axis). Each dot is one neuron pair. Color indicates experimental condition**. B.** Distributions of mean zero-lag (+/- 1 ms) spike rates (averaged over the trial) for neuron pairs by experimental condition.

Considering the two monkeys individually, both exhibited the same order of median zero-lag CCH peak amplitude across experimental conditions (data not shown): Naïve > Saline > Drug (**Figure 2.5A, B**). Overall, zero-lag spike correlation was weaker in Monkey 2 than Monkey 1. Considered individually, the differences in median zero-lag peak height were significant across experimental conditions in Monkey 1, and trended in the same direction in Monkey 2. Combining the 89 ensembles across both monkeys improved the sensitivity of the analysis. For example, the reduction in the median zero-lag peak amplitude between the Saline and Naïve conditions was a trend in both monkeys considered individually (**Figure 2.5A, B**) but became significant when the data were combined (**Figure 2.3D**). These data provide evidence that blocking NMDARs reduces zero-lag spike synchrony in prefrontal networks, suggesting that the synaptic actions of NMDARs contribute to zero-lag spike synchrony in these networks under normal conditions.

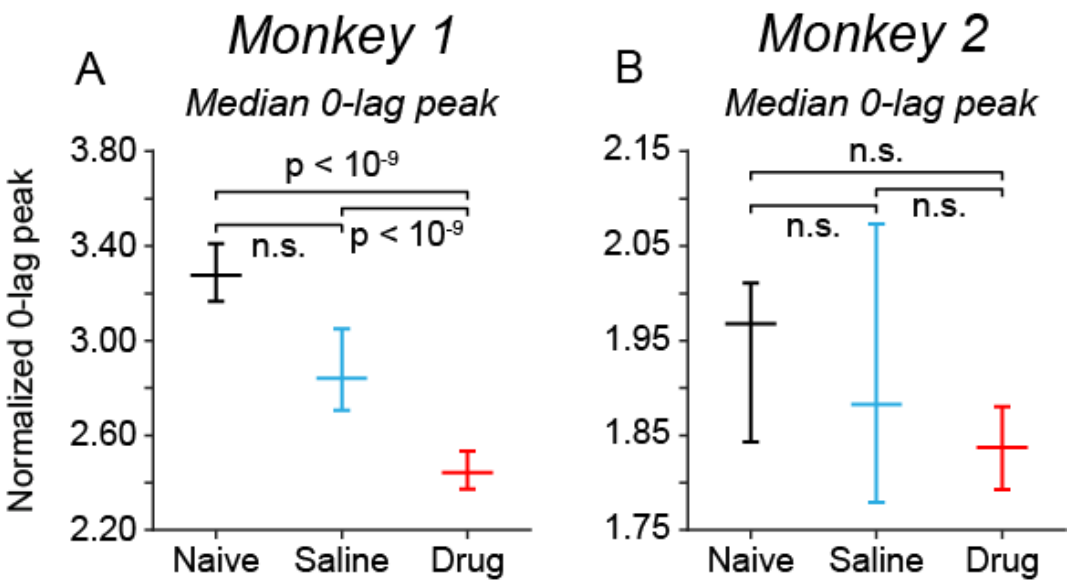

Figure 2.5: ***Zero-lag spike correlation separated by monkey*****.**

A, B. *Median zero-lag peak height in Monkey 1 (A) and Monkey 2 (B) considered individually. For each neuronal pair, the lag-0 CCH value was normalized by dividing by the average lag-zero value of the bootstrapped data; error bars represent 95% confidence intervals of the bootstrap-corrected median for each group; p-values calculated by Kruskal-Wallis test followed by Tukey's HSD test. The data in are restricted to neuronal pairs exhibiting a significant zero-lag peak.*

2.3.2. *Blocking NMDAR reduces spike rate variability over time.*

To examine the influence of NMDARs on the variability in spike counts over time, we computed the Fano factor (variance divided by the mean) using the bin-wise spike counts of all recorded neurons. Blocking NMDAR significantly reduced the median Fano factor in the Drug condition (**Figure 2.6A-C**; red), relative either to the Saline condition **(Figure 2.6A, C**, blue) or the drug-Naïve condition (**Figure 2.6B, C**, open bars and black), indicating reduced variance in spike counts over bins relative to the mean. The Fano factor did not differ significantly between the drug-Naïve condition and the Saline condition (**Figure 2.6B, C**). The reduction in variance relative to the mean observed to result from NMDAR blockade suggests that prefrontal circuits were less strongly modulated by inputs (resulting in reduced variance in spike rate over time).

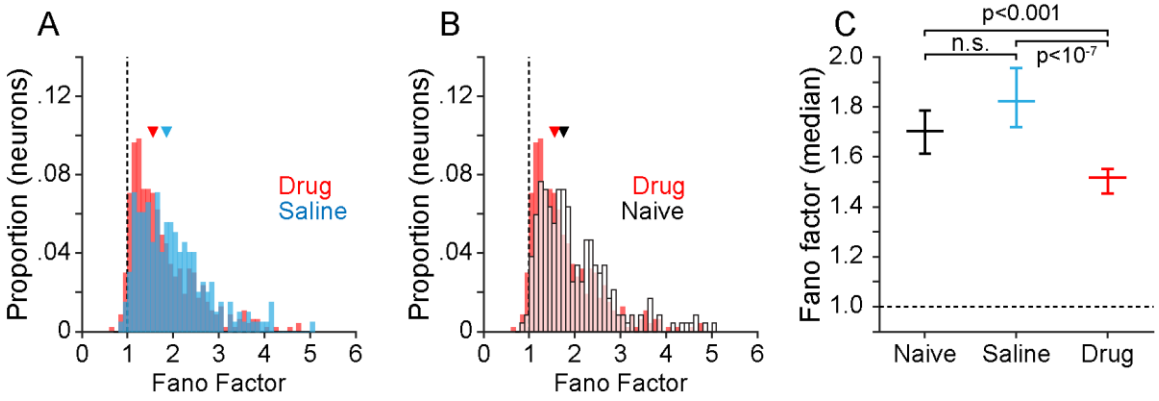

Figure 2.6: Influence of NMDAR antagonists on spike timing variability in prefrontal cortex.

To quantify variability in spike timing we computed the Fano factor as the variance in spike counts over a sequence of 50 msec bins divided by the mean firing rate on a per-neuron basis. ***A, B****. Frequency distribution of individual neuron Fano factor values for Drug and Saline (A), and Drug and drug-Naïve (B) conditions. Vertical dashed lines in A and B indicate a Fano factor of 1, triangles represent the median of each distribution.* ***C****. Median Fano factor (and 95% confidence intervals) as a function of experimental condition; p-values calculated by Kruskall-Wallis test followed by Tukey's HSD test.*

2.3.3. *NMDAR blockade is associated with persistent reduction of effective connectivity within prefrontal local circuits*

Zero-lag synchrony could be generated physiologically either by common input or by reciprocal excitatory connections between neighboring prefrontal neurons (Amit and Brunel, 1997; Korndörfer *et al.*, 2017; Pipa and Munk, 2011). However, in addition to these synchronous dynamics, monosynaptic and polysynaptic communication between neurons in local circuits would result in time-lagged spike correlation. To examine such delayed interactions in prefrontal circuits in more detail, we performed transfer entropy (TE) analyses (Garofalo *et al.*, 2009; Ito *et al.*, 2011; Schreiber, 2000; Wibral *et al.*, 2013) (**Figure 2.7**).

Transfer entropy is an information-theoretic measure (Schreiber, 2000) used to evaluate the causal relationship between two processes X and Y using their observed time series (Garofalo *et al.*, 2009; Vicente *et al.*, 2011 Ito *et al.*, 2011; Wibral *et al.*, 2013). In our application, TE is a measure of information flow from neuron X to neuron Y obtained from

the timing of their respective spike trains. It quantifies in units of bits of information about the future of spiking activity of neuron *Y* that the past activity of neuron *X* can provide in addition to the information provided by the past activity of neuron *Y* alone. We computed TE using an open source toolbox (Ito *et al.*, 2011) over a range of lags from 1 to 30 msec. Naïve estimation of information-theoretic quantities from limited experimental samples results in positive bias (Panzeri *et al.*, 2007). We bias-corrected the original TE values at each lag by subtracting the mean of a bootstrap distribution of TE values at the same lag computed using spike trains in which we randomly jittered the time of each spike by ± 30 msec. For each neuron pair, we identified the peak TE value across lags. The distribution of the lags at which TE peaks occurred was skewed toward lags under 10 ms (**Figure 2.7C**), broadly consistent with functional interactions between neurons at mono- or di-synaptic timescales. We considered neuron pairs to be significantly coupled if the amplitude of the peak TE value exceeded the 99.9^{th} percentile of the bootstrap distribution of all TE peaks across all lags computed using spike jittered data.

Previous histological and electrophysiological studies suggest that the distribution of connectivity strength in the cortex is heavy tailed, with few strong links and many weak links (e.g., Nigam *et al.*, 2016; Schneidman *et al.*, 2014; Constantinidis *et al.*, 2001). Because multielectrode recordings necessarily sample from a small number of cells in a localized region of the full network, this technique would only rarely be expected to lead to the detection of statistically robust causal relationships between neurons. This presents one of the challenges of comparing effective connectivity measures between experimental conditions in our dataset: the number of neuron pairs in *any* sample that are monosynaptically connected will be only a small proportion of the potential number of connections ($N_{cells} \times (N_{cells} - 1)$). In order to characterize the effects of PCP on the effective weight of both strong and weak connections, we computed *1)* the proportion of possible neuron pairs that exhibit extreme values of TE, suggestive of putative monosynaptic connections (**Figure 2.7C**), and *2)* the central tendency of all TE values

within each experimental condition, representing a scalar metric of the total information transferred in local DLPFC circuits (**Figure 2.7B**).

We found evidence that periodic pharmacological blockade of NMDAR persistently reduced effective connectivity in prefrontal networks. The prevalence of significant TE coupling between neurons (**Figure 2.7B**), as well as the strength of that coupling measured by the amplitude of the TE peak (**Figure 2.7D**) were significantly reduced in both the Drug and the Saline conditions relative to the drug-Naïve condition.

We found no significant difference in TE metrics between Saline and Drug conditions (**Figure 2.7B, D**). These data suggest that blocking NMDAR mediated synaptic transmission on Drug days had a lasting effect on prefrontal circuits by reducing both the strength and prevalence of effective connectivity between neurons that persisted on Saline days.

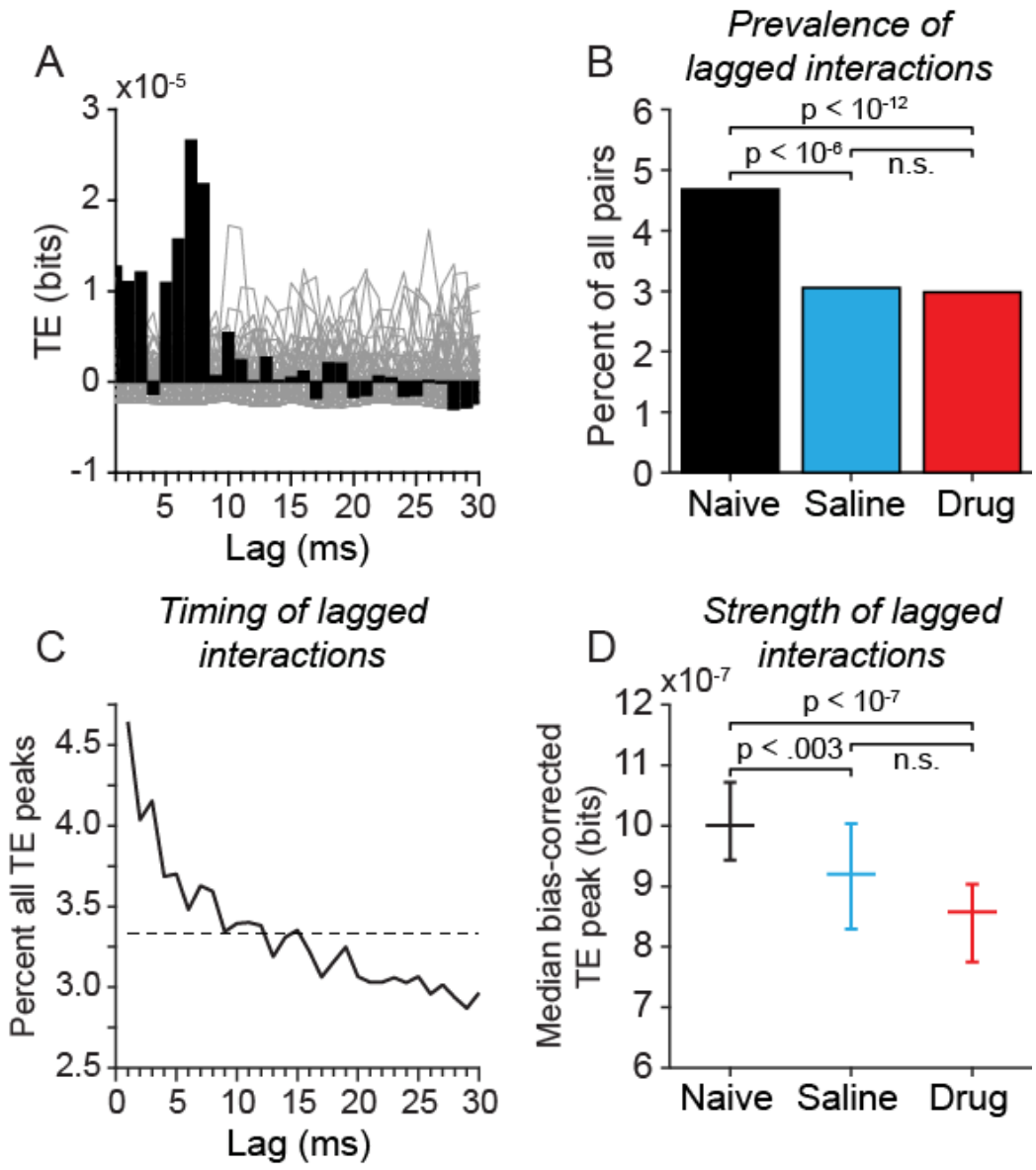

Figure 2.7: Transfer entropy (TE) in pairs of simultaneously recorded prefrontal neurons.

(Continues on opposite page) ***A.*** *Example bias-corrected TE function for a pair of prefrontal neurons recorded in the drug-Naïve condition. For each neuron pair, TE values (black bars) in each lag bin were bias corrected by subtracting the mean at the corresponding lag bin of a bootstrap distribution of TE values obtained from the same neurons after randomly jittering all spike times within a 1-50 ms window to destroy the temporal relationship between the spike trains (gray lines plot TE functions computed from spike jittered data).* ***B.*** *The proportion of all neuronal pairs recorded that were identified as significantly coupled by TE analysis separated by experimental condition. Neuron pairs were considered significantly coupled if the peak of the TE time course exceeded the 99.9th percentile of peaks in any lag bin in 1000 spike-jittered bootstrap iterations of the analysis. Neuron pairs (coupled / all): drug-Naïve: 677 / 14,468 pairs; Saline: 150*

/ 4,914 pairs; Drug: 365 / 12,230 pairs. P-values reflecting the significance of differences between experimental conditions were calculated using Fisher's exact test. ***C.*** *Distribution of time bins (lags) in which peak TE values occurred, across all neuron pairs. Dashed line indicates the expected values if peak locations were uniformly distributed across lags.* ***D.*** *Median bias-corrected peak TE values across all neuron pairs; p-values reflecting the significance of differences between experimental conditions were calculated using the Kruskall-Wallis test followed by Tukey's HSD test.*

2.4. Discussion

In this chapter we characterize the effects of PCP administration on local network dynamics in the prefrontal cortex of nonhuman primates. Prior studies in monkeys have described local field potentials in prefrontal cortex during AX-CPT performance (Dias *et al.*, 2006), and investigated how blocking NMDARs influences prefrontal oscillatory rhythms (Skoblenick *et al.*, 2016) as well as encoding of behavioral information by individual prefrontal neurons related to working memory (Wang and Arnsten, 2015; Wang *et al.*, 2013), and executive control (Ma *et al.*, 2015; Skoblenick and Everling, 2012, 2014) in saccade tasks. However, these studies have not specifically evaluated how reduced NMDAR function affects the interactions between cortical neurons. This may be a crucial level of analysis because the sustained activity that is necessary for maintaining a stimulus in working memory is likely to rely on recurrent synaptic connections between pyramidal neurons in the prefrontal cortex (Levitt *et al.*, 1993; Kritzer & Goldman-Rakic, 1995; Murray *et al.*, 2017). Furthermore, changes in relative spike timing could influence synaptic connectivity of prefrontal circuits via spike-timing dependent synaptic plasticity mechanisms (Feldman, 2012), resulting in further disconnection.

The primary findings we report here are significant reductions in pairwise synchrony and effective connectivity between neurons as a result of pharmacological NMDAR blockade. As measured with CCHs, precise synchrony between neighboring neurons in these data was significantly reduced after administration of PCP (**Figure 2.3**). Furthermore, cell pairs

in the PCP condition exhibited a reduction in the predictive information between neuron pairs, suggesting a loss in synaptic connectivity (Error! Reference source not found.).

2.4.1. *Synchronous Activity in Neocortex*

Zero-lag synchronization is a consistently detected pattern of activity in cortical ensembles that is thought to play a role in the transmission of certain types of information. For example, pyramidal neurons in the primary motor cortex display an increase in zero-lag synchronization around the time of movement initiation, and this synchrony contributes additional information about movement direction that cannot be decoded from rate changes alone (Hatsopoulos *et al.*, 1998). Similar findings have been reported in the primary visual cortex (Schwarz & Bolz, 1991; Nowak *et al.*, 1995), primary auditory cortex (Eggermont, 1992), middle temporal visual area (MT; Kreiter & Singer, 1996a,b; de Oliveira *et al.*, 1997), and prefrontal cortex (Constantinidis *et al.*, 2001). Prior studies in the prefrontal cortex have shown that the frequency of joint spike events is modulated during behavior independently of firing rate (Pipa and Munk, 2011; Riehle *et al.*, 1997) and that the strength of zero-lag interactions scales with the similarity in spatial tuning properties of prefrontal neurons (Constantinidis *et al.*, 2001). The functional relevance of zero-lag synchronization in prefrontal cortical information processing is unknown, but it is thought to improve signal-to-noise ratios (Abeles, 1991) and support the formation of cell assemblies that are necessary for flexible information processing (Aertsen *et al.*, 1989).

The simplest mechanism that can lead to the synchronization of two neurons is a common source of input. However, such an input would be unlikely to produce the remarkably precise synchronization that we report here. One of the defining features of pyramidal neurons in the PFC is the high density of reciprocal connectivity (Pucak *et al.*, 1996; Melchitzky *et al.*, 1998), and artificial neural network models have been used to demonstrate that zero-lag synchrony tends to emerge from networks with a preponderance of reciprocal connections (Juergens & Eckhorn, 1997), even in spite of long conduction

delays (Vicente *et al.*, 2008). In addition, zero-lag spiking between prefrontal neurons is present in medial prefrontal cortex of rats and it has been shown that blocking NMDARs reduces the strength of this zero-lag synchrony and reduces the distribution of Fano factor values to reflect increased randomness in spiking (Molina *et al.*, 2014). This result in conjunction with our findings here suggest that the relationship between NMDAR and spike synchrony in prefrontal circuits is conserved between rodents and primates.

2.4.2. *Blocking NMDARs reduced coincident spiking activity and pairwise synaptic efficacy measures in prefrontal cortex*

Our findings suggest a close association between zero-lag synchrony and NMDAR function: during acute NMDAR antagonism (Drug), coincident spiking activity was reduced in multiple metrics, and this effect was partially reversed upon drug washout (Saline) (**Figure 2.3**). This association could be at least partially attributed to the slow kinetics of the NMDA receptor (Forsythe & Westbrook, 1988), which is known to facilitate sustained recurrent activity that is necessary for the organization of synchrony in cortical networks (Wang, 1999). However, the mechanisms by which NMDAR blockade disrupts zero-lag synchrony are likely to be multifactorial. Because zero-lag synchrony in theoretical models is strongly dependent on the presence of recurrent connections (Juergens & Eckhorn, 1997), disrupted synaptic efficacy within a recurrent network could prevent zero-lag synchrony from emerging. Our findings do indeed suggest that PCP administration results in both a population-level reduction in information transfer between DLPFC neurons and a reduction in the number of effective connections between pairs (**Figure 2.3, Figure 2.7**). Furthermore, post-mortem studies of the cortical architecture of humans with schizophrenia have reported a reduced density of basilar dendritic spines on layer 3 pyramidal neurons (Garey *et al.* 1994; Glantz & Lewis, 1994), the same connections that are thought to form the structural basis for recurrent connectivity in the PFC.

Whether there is a causal relationship between disruptions in zero-lag synchrony and effective connectivity in the PFC, and which causes which, is yet to be determined. It is plausible, however, that both of these signatures can worsen or exacerbate each other. For example, loss of accurate spike timing in networks, operating through spike-timing dependent synaptic plasticity mechanisms (Feldman, 2012), could lead to synaptic disconnection of prefrontal networks through an activity-dependent process. If zero-lag synchrony is dependent on the presence of reciprocal connections, then a loss of those connections would further serve to desynchronize the population, creating a positive feedback cycle that results in further disconnection.

2.4.3. *Chronicity of effects*

Interestingly, we also found evidence of a possible chronic effect of PCP on synaptic efficacy reflected in a significant reduction in the proportion of significantly coupled pairs in the Saline condition as compared to drug-Naïve (**Figure 2.7B, D**). However, this result was less robust to variations in analysis methodology using different normalization and cutoff procedures than the difference observed between drug-Naïve and Drug data (data not shown). The Saline condition also had fewer number of ensembles and cell pairs (see Section 2.2.4), reducing the statistical power. Additionally, the time course of drug administration (see **Figure 2.2**) was not designed for comparative analysis of the acute and chronic effects of PCP. A robust and dose-dependent effect of PCP on cellular effective connectivity is plausible, given that previous studies have demonstrated the presence of abnormal neural activity in rodents after a series of injections of NMDAR antagonists (Dawson *et al.*, 2014). The characterization of the development of schizophrenia-like pathophysiology over time through repeated doses of PCP would be an informative extension of the work described here. Particularly, the use of chronic electrodes that could detect the activity of the same neurons over time would be ideal for this type of analysis.

In summary, we observed an association between a reduction in spike timing synchrony in prefrontal circuits and the effective disconnection of prefrontal circuits after pharmacological blockade of NMDAR-mediated synaptic transmission. Multiple lines of evidence link NMDAR dysfunction to schizophrenia, suggesting that the cellular-level asynchrony and disconnection seen here may also be present in patients. If we can develop a more complete understanding of the interactions between the network architecture of the prefrontal cortex, spike synchrony within local populations, and the ways in which these characteristics are involved in executive function, then we may be able to develop better treatments for the cognitive symptoms of schizophrenia.

3. Altered spike correlation in medial prefrontal cortex of a mouse genetic model of schizophrenia

3.1. Introduction

The findings reported in Chapter 2 reflect evidence for functional disruptions in cortical spiking activity in nonhuman primates after exposure to NMDAR antagonists. This animal model has high face validity in that it reproduces key signs and symptoms of schizophrenia; however, because it does not account for the genetic and developmental factors that are known to contribute to schizophrenia pathogenesis, the relevance of these findings to human disease is unknown. If reductions in synaptic functional and effective connectivity represent a fundamental phenotype of schizophrenic pathophysiology, then we would expect to see evidence of similar patterns of disruption in humans as well as in animal models with higher construct validity than the primate pharmacological model described in Chapter 2. To test this prediction, we performed a series of experiments to collect neural spiking data from prefrontal cortical regions in the *Dgcr8*$^{+/-}$ mouse model of schizophrenia. Through the use of similar recording methodology and analytical techniques, we present a close replication of the findings described in Chapter 2 in an entirely separate animal model of schizophrenia. We also describe the novel finding of abnormally high rates of population bursts in the *Dgcr8*$^{+/-}$ mouse that may be indicative of a disruption in resting-state hippocampal-prefrontal circuitry.

3.1.1. *The Dgcr8$^{+/-}$ mouse model of schizophrenia*

As discussed in Chapter 1, schizophrenia is a highly polygenic disorder in which many cellular functions appear to be disrupted, including neurotransmitter signaling, regulation of synaptic plasticity, metabolic activity and others (Ripke *et al.*, 2014). This presents a problem for studying the pathophysiology of schizophrenia in animal models, whose complement of genetic variations could not be expected to capture the variability of genetic influences in human patients with schizophrenia. One approach to this issue is to focus on rare but highly penetrant genetic variations that may characterize core phenotypes of the disorder, such as the 22q11.2 microdeletion syndrome. Also known as DiGeorge syndrome, the phenotype of this disorder is variable but typically includes cardiovascular and craniofacial developmental abnormalities in addition to a range of psychiatric and neurological disturbances. Importantly, approximately 30% of patients with DiGeorge syndrome meet diagnostic criteria for schizophrenia, a 30-fold increase in relative risk from the general population (Murphy *et al.*, 1999; Chow *et al.*, 2006; Bassett & Chow, 2008; Monks *et al.*, 2014). While only approximately 1% of sporadic cases of schizophrenia result from a deletion of the 22q11.2 region (Karayiorgou *et al.*, 1996; Xu *et al.*, 2008), studies show that patients with the deletion do not vary significantly in their disease presentation from those that do not carry the deletion, indicating that this is only one of many genetic mutations that can predispose individuals to the common phenotype of schizophrenia.

Several mouse models of the 22q11.2 deletion currently exist for use in research. The first model that was generated included a deletion of a segment of chromosome 16 of the mouse genome that corresponds to the 22q11.2 region in humans, and is referred to as the *Df(16)A*$^{+/-}$ mouse, though several variants exist (Stark *et al.*, 2008). Mice carrying this mutation exhibit behavioral characteristics similar to other rodent models of schizophrenia, including sensorimotor deficits, impaired performance on spatial working memory and fear conditioning tasks (Stark *et al.*, 2008), and impaired nesting behavior (Ouchi *et al.*, 2013). Sequencing of the genes included in this deletion reveals several candidate genes with key

functions that have been implicated in schizophrenia, including genes necessary for dendritic spine regulation, growth factor production, vesicle transport, and neurotransmitter receptor expression (Ouichi *et al.*, 2013; Stark *et al.*, 2008). One gene within this region, referred to as *Dgcr8* (DiGeorge syndrome critical region 8), was found to have the most influence on the behavioral and neural phenotype associated with mice carrying the full deletion (Stark *et al.*, 2008; Chun *et al.*, 2014). *Dgcr8* encodes a protein (DGCR8 or Pasha in *Drosophila melanogaster*) that is required for RNA interference in the brain, a cellular process in which small RNA segments are used to regulate gene expression by binding to messenger RNA transcripts and reversibly inhibiting their translation into proteins. DGCR8 binds to primary microRNA transcripts in the nucleus and is necessary for their cleavage and export into the cytoplasm where they can exert their effects on mRNA transcripts. As such, deletion of this gene would be expected to result in dysfunction across a wide range of cellular functions, particularly those that require dynamic regulation of gene expression. Indeed, it has been shown that deletion of a single copy of this gene (the *Dgcr8*$^{+/-}$ mouse) results in altered expression of proteins that form neurotransmitter receptors, ion channels, growth factors, extracellular matrix proteins, and others (Ouchi *et al.*, 2013). Cognitive and behavioral deficits in these mice do not differ significantly from those of *Df(16)A*$^{+/-}$ mice (Stark *et al.*, 2008). Histologically, there are no gross differences in neural tissue in *Dgcr8*$^{+/-}$ mice (Stark *et al.*, 2008; Fenelon *et al.*, 2011; Schofield *et al.*, 2011; Ouchi *et al.*, 2013), but reductions in dendritic spine density and complexity have been reported in the hippocampus (Stark *et al.*, 2008) and cortex (Hsu *et al.*, 2012), in addition to reduced hippocampal neurogenesis (Ouchi *et al.*, 2013). It is notable that deletion of both copies of either the *Df(16)A* region or the *Dgcr8* gene in mice is nonviable due to a generalized cell proliferation defect (Stark *et al.*, 2008; Ouchi *et al.*, 2013). The effects of a heterozygous deletion (denoted by the superscript " $^{+/-}$ ") are likely more reflective of schizophrenia pathophysiology, as the 22q11.2 microdeletion in humans is also nonviable if the deletion occurs on both chromosomes (Chen *et al.*, 2012).

Physiological characterization of the *Dgcr8*$^{+/-}$ mouse in slice preparations has revealed disruptions in hippocampal short-term potentiation and temporal summation (Fenelon *et*

al., 2011), in addition to more subtle disruptions in long-term potentiation (Arguello & Gogos, 2011), findings which have also been described in the *Df(16)A*$^{+/-}$ mouse (Fenelon *et al.*, 2013; Drew *et al.*, 2011). Single-cell patch recordings of layer 5 (L5) medial prefrontal cortex (mPFC) neurons from *Dgcr8*$^{+/-}$ mice reflected several differences, including reduced input resistance, the change in voltage across the membrane in response to a small hyperpolarizing current step. Morphometric analyses found this to be associated with a reduction in the branching and complexity of the basal dendrites of pyramidal neurons (Schofield *et al.*, 2011), as has been shown in human studies of schizophrenia (Glantz & Lewis, 1997). Other passive membrane properties of *Dgcr8*$^{+/-}$ L5 neurons, such as excitability in response to injected depolarizing currents, did not differ from those of control mice, suggesting that intrinsic spike firing capabilities are intact in this mouse model. In contrast, measures of synaptic input revealed a reduction in the frequency of spontaneous excitatory post-synaptic potentials (EPSCs). This finding was dependent on the developmental stage of the mouse preparation, as both EPSC frequency and measures of DGCR8 gene expression levels were indistinguishable from controls prior to postnatal day 25 (P25). The latter finding is interesting in that it suggests that monoallelic loss of *Dgcr8* is compensated for during early developmental processes, such as neuronal differentiation, and could explain the relatively mild and late onset of the *Dgcr8*$^{+/-}$ behavioral phenotype. Because the frequency of inhibitory post-synaptic potentials (IPSCs) was not changed, the authors speculate that an imbalance between excitatory and inhibitory synaptic function during a crucial developmental time point may be a key component of the developmental pathogenesis of schizophrenia (Schofield *et al.*, 2011). In a separate study using slice preparations of *Df(16)A*$^{+/-}$ and *Dgcr8*$^{+/-}$ mice, pyramidal neurons in the auditory cortex displayed a reduced frequency of excitatory post-synaptic potentials (EPSCs) in response to stimulation of thalamocortical projections (Chun *et al.*, 2014).

The effects of DiGeorge syndrome-related deletions on neuronal function in awake animals have been less well-characterized, though there is evidence that long-range functional connectivity may be disrupted. Simultaneous *in vivo* recordings of the mPFC and CA1

region of the hippocampus in *Df(16)A*$^{+/-}$ mice during the performance of a working memory task revealed a reduction in synchrony between the two regions, as measured by the phase locking of prefrontal neurons to hippocampal theta oscillations. Importantly, the extent of this deficit in *Df(16)A*$^{+/-}$ mice correlated with deficits in spatial working memory during the behavioral task, as well as a longer time to learn to perform the task. Because prefrontal neurons in the *Df(16)A*$^{+/-}$ mouse did not display a reduction in phase locking to the local prefrontal theta rhythm, the authors suggested that local synchrony within the prefrontal cortex is relatively intact in this model (Sigurdsson *et al.*, 2010). However, further investigation is necessary to fully characterize prefrontal circuit dynamics in mouse models of the 22q11.2 microdeletion.

The characterization of local synchrony and effective connectivity within the prefrontal cortex in the context of schizophrenia is of particular interest to our work for the following reasons: **1)** pyramidal neurons in layers 3 (and, to a lesser extent, layers 2 and 5) of the PFC form a dense network of recurrent horizontally-oriented excitatory synapses that synapse within the basal dendritic tree of neighboring neurons (Levitt *et al.*, 1993; Kritzer & Goldman-Rakic, 1995; González-Burgos *et al.*, 2000). It is thought that reverberation through these connections is necessary for producing the persistent activity necessary for working memory (Goldman-Rakic, 1995; Wang *et al.*, 2006; Wang *et al.*, 2001; Durstewitz *et al.*, 2000). **2)** Patients with schizophrenia have been reported to exhibit a decreased density of dendritic spines on layer 3 pyramidal neurons (Garey *et al.* 1994; Glantz & Lewis, 1994), lower measures of synaptic markers (Glantz & Lewis, 1994) and loss of synaptic building blocks (Pettegrew *et al.*, 1991), in addition to deficits in working memory. 3**)** *Dgcr8*$^{+/-}$ mouse brains also reflect a reduction in the density of basilar dendritic branching of layer 3 prefrontal pyramidal neurons (Schofield *et al.*, 2011). Characterization of effective connectivity and synchronous activity within local prefrontal ensembles of the *Dgcr8*$^{+/-}$ mouse could provide valuable insights into the underlying deficits that ultimately lead to cognitive dysfunction in patients with schizophrenia. To the author's knowledge, the present chapter is the first description of findings obtained from *in vivo* recordings of the prefrontal cortex in *Dgcr8*$^{+/-}$ mice.

3.2. Methods

3.2.1. *Mice*

Male *Dgcr8*$^{+/-}$ and wild-type littermate mice 3 to 5 months old were used for all experiments. *Dgcr8*$^{+/-}$ mice were generated by crossing Nestin-Cre mice (strain: B6.Cg (SJL)-TgN(NesCre)1Kln; stock #003771) and Dgcr8^{flox} mice (strain: B6.Cg-Dgcr8$^{tm1.1Blel}$/Mmjax; stock #0032051) obtained from Jackson Laboratories. The Nestin-Cre female breeders were crossed with male Dgcr8^{flox} mice, such that 25% of the F1 generation were functionally heterozygous for *Dgcr8* in all neuronal lineages. Wildtype littermates served as controls for our experiments. The genotype of each animal was confirmed by performing a tail biopsy at 10-21 days of age according to the NIH guidelines for genotyping of mice and rats.

3.2.2. *Surgical implantation of recording chamber*

Animals were anesthetized by isoflurane, and a small (3 mm diameter) craniotomy was made overlying one side of the frontal cortex for placing microelectrodes during the experiments to record cortical neurons (the dura mater was left intact). A 3-D printed cylindrical chamber was placed over the craniotomy and secured via dental cement to three screws anchored into the skull in the regions surrounding the craniotomy. A removable cap was placed on the chamber and secured in place with silicone elastomer glue. Once the surgery was complete, lidocaine (0.5%, 0.03mL) was injected subcutaneously surrounding the surgical site, and slow-release buprenorphine (1mg/kg) was injected subcutaneously. The mice were allowed to recover for a minimum of 4-5 days after surgery before neural recordings took place.

3.2.3. *Neural recording*

In the experimental session, the mice were awake with their head restrained. A metal plate with a hole designed to fit around the craniotomy chamber was secured with a screw to a nut embedded in the 3-D printed chamber piece. The mouse was secured via this metal plate to a frame that positioned the mouse over a rotary wheel, allowing the animal to run during the recording session, which we have found reduces distress. Black curtains were also installed around the recording setup to reduce animal stress from laboratory lighting. The mice were habituated to tolerate this setup for a minimum of four 1-hour sessions of wheel-running while in the head fixation apparatus prior to the first neural recording session. In order to maximize the opportunity for direct comparison between primate and mouse data, we used the same recording matrix that was employed in the primate recordings described in Chapter 2.

The microelectrode recording matrix (Thomas Recording, GmbH), which can independently drive sixteen (70 μm o.d.) glass coated platinum iridium microelectrodes, was positioned above the surgically implanted craniotomy chamber. Electrodes were driven under computer control through the dura mater into the underlying cortex to isolate the spiking of activity of multiple neurons simultaneously. The center of the electrode matrix (within the recording chamber) was localized to the following coordinates (infralimbic/prelimbic regions of mouse prefrontal cortex): 1.7 mm anterior to Bregma, 0.4 mm lateral to the midline and 1.5 mm below the brain surface (Paxinos & Franklin, 2004). We adjusted the depths of the electrodes individually to maximize the numbers of action potential waveforms that were detectable above the background signal using online data acquisition software (OpenSorter, Tucker Davis Technologies). After refining each electrode depth and trigger threshold, we waited at least 20 minutes before beginning the recording in order to allow the brain tissue to structurally adjust to electrode penetration, then initiated the recording and refrained from adjusting any parameters during the recording session. Typically, two ensembles of neurons were recorded in a single day from each mouse for approximately 40 minutes. Following the second recording, the mouse was

anesthetized, perfused, and the brain was saved for histological verification of electrode targeting. For consistency across ensembles and to reduce the effects of drift in the signal over time, all analyses presented in this chapter were performed over the first 30 minutes of each recording session.

Action potentials were sorted using the MClust spike sorting toolbox (version 4.3; Redish, 2008). In addition to recording the spiking activity of isolated neurons, we also recorded local field potentials (LFP) on up to four of the 16 electrodes lowered into prefrontal cortex. LFP signals were sampled at 2000 Hz and bandpass filtered 1-100 Hz. Analysis of LFP data is a potential avenue of future work.

For the analysis described here, we recorded 12 neural ensembles from control animals and 11 ensembles from the mPFC of *Dgcr8*$^{+/-}$ mutant mice. In both groups, the average number of units per ensemble was approximately 18, and a total of 426 single units met minimum criteria for inclusion in analysis, i.e. a waveform that could be reasonably separated from noise data and a baseline firing rate of at least 0.5 Hz. A total of 4,732 pairs from control mice and 5,574 pairs from *Dgcr8*$^{+/-}$ mice were included in pairwise analysis of simultaneously recorded cells with cell pairs recorded on the same electrode excluded from analysis. An additional 137 cells were recorded from electrodes that were later found to be mislocalized, primarily to the primary motor cortex; these cells were excluded from analysis.

3.2.4. *Histology*

Brains were sliced into 40 um-thick coronal slices using a microtome and mounted on slides for visualization. Tracks of tissue damage caused by the electrodes could be identified in most cases, and the location of these tracks were compared to the online Allen Mouse Brain Atlas (2015; Available from: brain-map.org/api/index.html). Each electrode from each mouse was coded as a “hit” or “miss” based on whether it appeared to have

entered the medial prefrontal cortical areas of the mouse brain (infralimbic, prelimbic, or orbital cortex; see Figure 3.1). Only data obtained from "hit" electrodes were analyzed in this study.

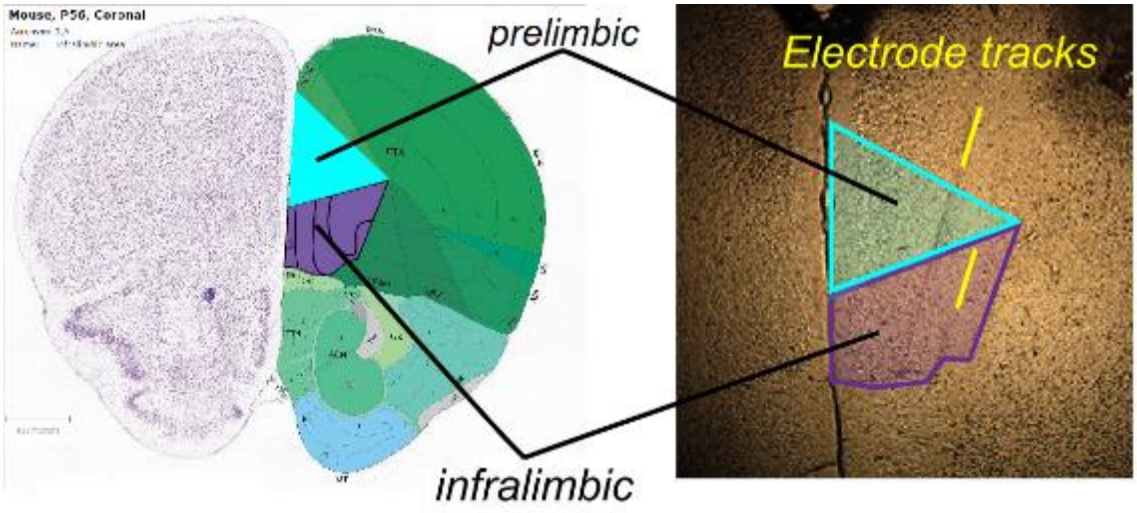

Figure 3.1: Histological localization of recording sites in mouse prefrontal cortex.

Prelimbic (cyan) and infralimbic (magenta) prefrontal areas are superimposed on an atlas (left) and histological section (right) of Dgcr8$^{-/+}$ mouse prefrontal cortex for visualization of the electrode tracks (yellow). Atlas image modified from the online Allen Reference Atlas (2015). Image credit: Allen Institute

3.2.5. *Burst identification*

During many of the recording sessions, we detected a preponderance of synchronous bursting activity across nearly all channels. Subjectively, these bursts tended to last 1-3 seconds and occurred at irregular intervals throughout the recording session (see Figure 3.3). Observation of the animals' behavior during bursting activity revealed that bursts occurred exclusively when the mice were awake and stationary in the head fixation apparatus, and became undetectable during periods in which the animal walked on the rotary wheel. Bursts were identified manually by two unbiased and blinded (to genotype) observers who examined raster plots of the spike data and identified start and end times for each burst. We then generated a second copy of all of the neural spiking data in which all

spikes from all cells within each bursting window were removed. The results described below are generated from the full dataset unless otherwise stated.

3.2.6. *Cross-correlation analyses*

To quantify the frequency distribution of spike pairs in simultaneously recorded neurons as a function of the lag (1 ms resolution) between the two spikes, we computed cross-correlation histograms (CCHs) (Perkel *et al.*, 1967) using the same methods as described in the previous chapter (see **Section 2.2.6** for further details). For each neuron pair, we generated 100 bootstrap CCHs by shifting each spike by a random interval between -30 and +30 msec and then computed a CCH using the jittered spike times. Normalized CCHs (**Figure 3.5A**), were calculated by dividing each pair's CCH count by the baseline (bootstrap) coincidence count. Cell pairs with significant rates of coincident spiking were identified using a z-test of proportions on the fraction of total spikes emitted by both cells that occurred in the ± 1 ms bins of the CCHs. The Benjamini-Hochberg procedure for correcting multiple comparisons was used to limit the false discovery rate to 0.05.

3.2.7. *Transfer entropy*

Transfer entropy was calculated between neuron pairs using the algorithm developed by Ito *et al.* (2011). We employed their open source MATLAB transfer entropy toolbox, which can be found at their laboratory's web page: http://code.google.com/p/transfer-entropy-toolbox. Transfer entropy (TE) between spike trains of neurons *I* and *J* is nonzero if the spiking pattern of neuron J can be used to improve the prediction of the spike probability of neuron I, beyond the prediction based on the past of neuron I alone. The original definition of TE (Schreiber, 2000) was given as follows:

$$TE_{J\to I} = \sum p\left(i_{t+1}, i_t^k, j_t^l\right) \log_2 \frac{p\left(i_{t+1} \middle| i_t^k, j_t^l\right)}{p\left(i_{t+1} \middle| i_t^k\right)}$$

Here, i_t and j_t denote the status of neurons I and J, respectively, at time t; the values at each time bin are either 1 (spike) or 0 (no spike); i_{t+1} denotes the status of neuron i at time $t+1$; and p denotes the probability of the statement in parentheses. The sum is taken over all possible combinations of i_{t+1} , i_t^k, and j_t^l, and a logarithm with base 2 is used so that the TE output measure is in units of bits. The order parameters k and l represent the number of time bins in the past describing the spiking patterns of neurons I and J, respectively, when predicting the activity state of neuron I; we used $k = l = 1$ so that only single time bins were considered. The code provided by Ito *et al.* (2011) uses a modified equation that includes a delay term d which can be used to compute TE between two pairs as a function of time lag between signals, allowing for some variation in synaptic delay across cell pairs. Transfer entropy is conceptually similar to mutual information, but differs in that it incorporates time lags and takes into account the auto-prediction provided by the past of neuron I in the prediction of spike probability, and thus is designed to isolate the influence from neuron J onto the activity of neuron I.

Pairwise relationships between simultaneously recorded neurons in *Dgcr8*$^{+/-}$ and control mice were evaluated using TE analysis of spike trains for the first 30 minutes of each ensemble recording. In general, naïve estimation of information-theoretic quantities from limited experimental samples results in positive bias (Panzeri *et al.*, 2007). Therefore, all TE estimates were bias-corrected using bootstrap distributions of TE; specifically, for each neuron pair we constructed 100 bootstrap samples and estimated TE functions after shifting each spike by a random interval between 1 and 50 msec. The jitter amount was set to be high enough to allow for computation of TE over an extended synaptic time scale for visualization purposes, and it was confirmed empirically that variations in this value did not appreciably affect the results described here either qualitatively or quantitatively (data not shown).

The TE measures used by Ito *et al.* (2011) were tested and validated in a computational model of spiking Izhikevich neurons (Izhikevich, 2003). Using peak TE values and a

Coincidence Index (CI) metric (described below), they verified that "true" synaptic connections between model neurons could be recovered from spiking data. In 2016, the same group published an extension of this methodology (Nigam *et al.*, 2016) in which they applied TE analysis to neural spiking data obtained from both *in vitro* and *in vivo* multielectrode recordings of rodent cortex. These authors were able to reliably differentiate real spiking data from surrogate data by characterizing both the magnitude of each pairwise TE function and the sharpness of the peak. In Chapter 2, I described the results of transfer entropy analysis as based primarily on using the magnitude of TE values within a lag window that was consistent with monosynaptic delays (see **2.2.7**). In the present chapter I have incorporated an additional component to this analysis, the coincidence index (CI), in order to account for the effects of common network drive, which has the potential to artificially elevate TE functions between pairs of cells that receive simultaneous bursts of input. This component of the TE feature space was particularly relevant to the analysis of *Dgcr8*$^{+/-}$ mouse neural activity, which, as will be seen below, exhibited elevated bursting activity in the mPFC.

The purpose of using TE in this dataset was to test the hypothesis that local effective connectivity between mPFC neurons is reduced or altered in *Dgcr8*$^{+/-}$ mice as compared to controls. Two major components of the pairwise TE functions, termed here as AUC and CI, were used for summary analysis. **Figure 3.2** displays a visualization of these metrics as applied to two example TE functions for two pairs obtained from control mPFC neurons, one with high CI and intermediate AUC (**Figure 3.2**, 'Example pair 1', top two panels) and one with a high AUC but low CI (**Figure 3.2**, 'Example pair 2', bottom two panels). AUC can be conceptually understood as a scalar metric of total information exchanged from neuron *J* to neuron *I*. Mathematically, this value was calculated for each pair by taking the positive difference between the TE delay function and the mean TE values of the spike-jittered bootstraps, then summating this difference across the lag space. The spike-jittered bootstraps can be thought of as representing the baseline level of shared information between the two neurons that likely reflects common inputs or other types of

correlated noise, and thus the AUC metric describes information transmission between two neurons that exceeds this baseline.

While the AUC can identify the presence of information exchange between two neurons, it cannot be used to distinguish the sharp, narrow peaks at short lags that are thought to reflect monosynaptic connections from broad, delayed peaks that result from network bursts (Beggs & Plenz, 2003; Nigam *et al.*, 2016). For this purpose, Ito *et al.* (2011) developed a metric referred to as the Coincidence Index (CI)[7], defined as the ratio between the area under the TE curve in the bins centered around the peak value, and the area under the curve of the entire function. This results in a fraction that describes the relative precision of the apparent timing relationship between one neuron onto another. If no relationship exists, the TE function will be approximately flat and the CI will not be discernible from chance, while the sharpest peaks represent a precise and consistent relationship. In order to enhance detection of monosynaptic connections, we modified the numerator of the CI metric to be a constant window between 2-8 ms rather than a window centered around the lag at which TE peaked for a given pair.

Cell pairs were considered to be coupled if both their AUC and CI values fell in the upper quartile of the distributions of these values across all cell pairs (see ***Figure 3.6***). This cutoff was chosen to most closely mimic the significance cutoffs used by Nigam *et al.* (2016), who found that the region of the output data space characterized by extreme values of both of these metrics reflected the most separation between real and jittered spike data (see figure 1 in Nigam *et al.*, 2016). That is, TE values generated from randomly jittered spike data could, by chance, result in functions with either high CI or high AUC values, but only very rarely with high values in both metrics. Variation of this two-part cutoff from the

[7] The CI has been used to identify connections in the context of cross-correlation studies (Juergens & Eckhorn, 1997; Jimbo *et al.*, 1999; Tateno & Jimbo, 1999; Chiappalone *et al.*, 2006).

50th, 60th, and 75th percentiles of each distribution changed the absolute number of pairs that reached significance but not the relative difference between genotypes described in the Results section of this chapter (data not shown). The 75th percentile was chosen because it classified approximately 6% of neuron pairs in the control data as significant connections, a fraction that is consistent with other studies of cortical connectivity (Nigam *et al.*, 2016; Constantinidis *et al.*, 2001; Song *et al.*, 2005).

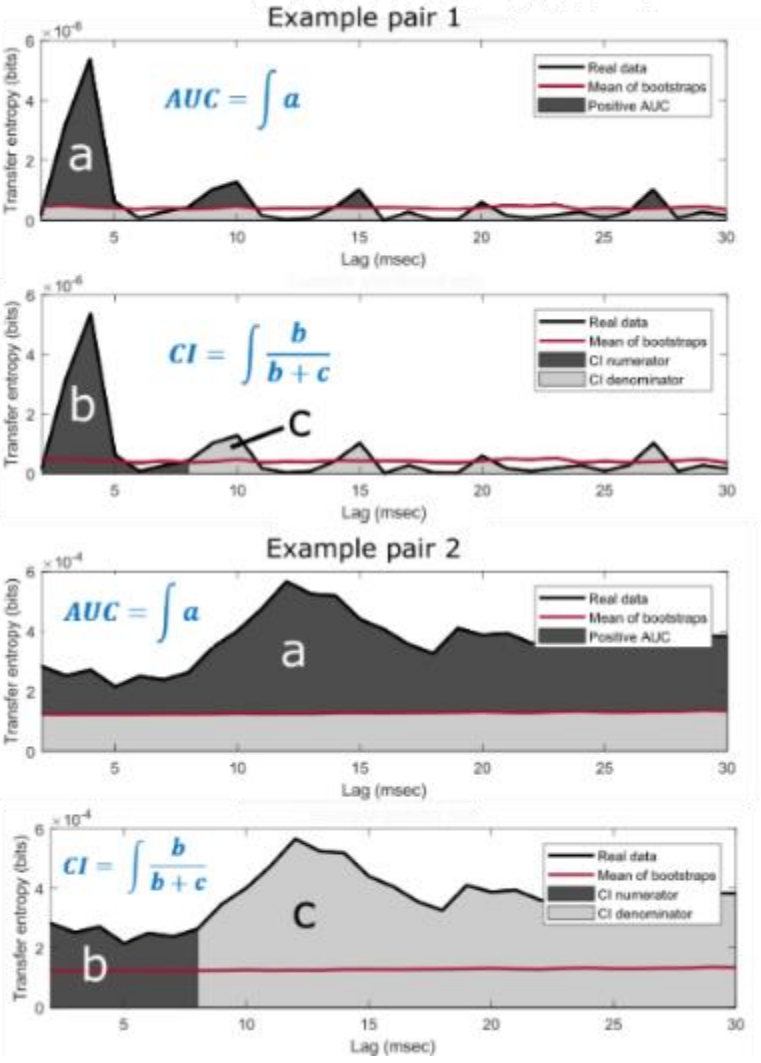

Figure 3.2: Features of pairwise transfer entropy functions used for identification of putative monosynaptic connections.

TE functions from two unique pairs are shown (Example pair 1, upper two panels; Example pair 2, lower two panels). The area under the curve (AUC) is computed by finding the area ("a") of each TE function (black lines) that exceeds the mean of its corresponding bootstrap distribution (red lines). The Coincidence Index (CI) is computed by finding the area ("b") of each TE function within a lag that would be consistent with a monosynaptic connection (2 to 8 msec used here) and dividing this value by the area under the entire TE function ("b + c"), without respect to bootstrap data. Example pair 1 (top two panels) reflects a relationship in which the postsynaptic cell's activity is reliably predictable from the presynaptic cell's activity at a relative lag of approximately 4 msec, though the transfer of information between these cells in this direction is weak at longer lag times. This pattern is consistent with monosynaptic connectivity due to a moderately high TE value and a very high CI value. In contrast, Example pair 2 (bottom two panels) reflects a large and very broad peak that is highest at lags above 10 msec, and thus is likely to reflect a common network drive rather than a monosynaptic interaction. This pair would have a very high AUC if the entire lag space was considered, potentially leading to its miscategorization as a monosynaptic interaction. Because the CI value of this pair is very low, however, it is relatively easy to distinguish these two pairs.

3.3. Results

3.3.1. *Bursting*

The most apparent distinction between wild-type and *Dgcr8*$^{+/-}$ neural data was the presence of large bursts of activity that were audibly and visually identifiable during live recordings and subjectively seemed to be more frequent in *Dgcr8*$^{+/-}$ mice. To quantify the frequency of these bursts in an unbiased way, we asked two neuroscience students to independently estimate the start and end times of bursts by visually inspecting raster plots of spike times, some examples of which can be seen in **Figure 3.3**.

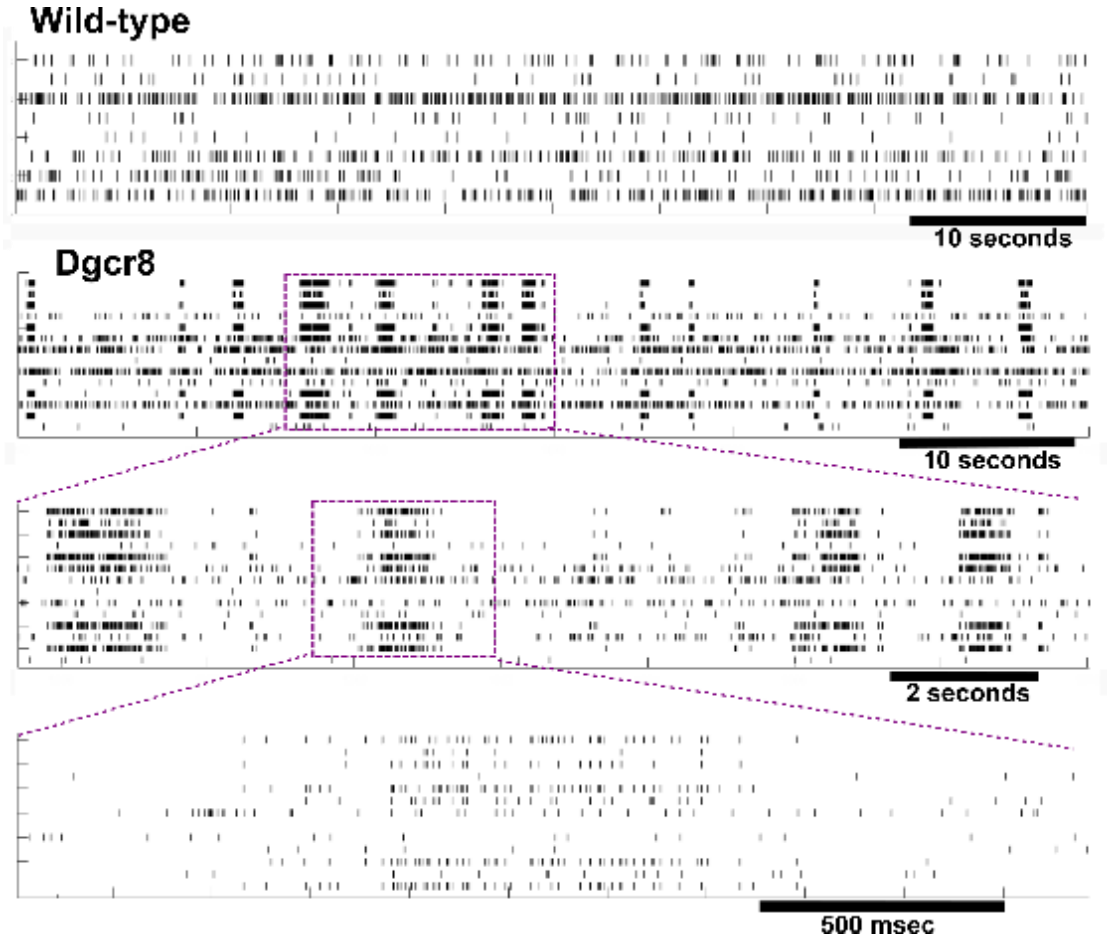

Figure 3.3: Spiking activity obtained from neural ensemble recordings in the prefrontal cortex of awake Dgcr8$^{+/-}$ mice.

Raster plots of spike times from a wild-type mouse (top panel) and a Dgcr8$^{+/-}$ mouse (bottom three panels). Each row of tick marks represents the spike times of a single unit (neuron). Magenta boxes indicate sections of rasters illustrated below at an expanded time scale to visualize bursting at higher temporal resolution (see scale bars).

The frequency distribution of inter-burst intervals for all ensembles is shown in **Figure 3.4** in *Dgcr8*$^{+/-}$ mice, the number of bursts was significantly higher than in wild-type mice (inset, p = 0.007). The statistical properties of these bursts, in combination with the observation that they only occurred when the mice were inactive, led us to infer that they are likely to represent input from hippocampal sharp wave oscillations (see *Discussion*).

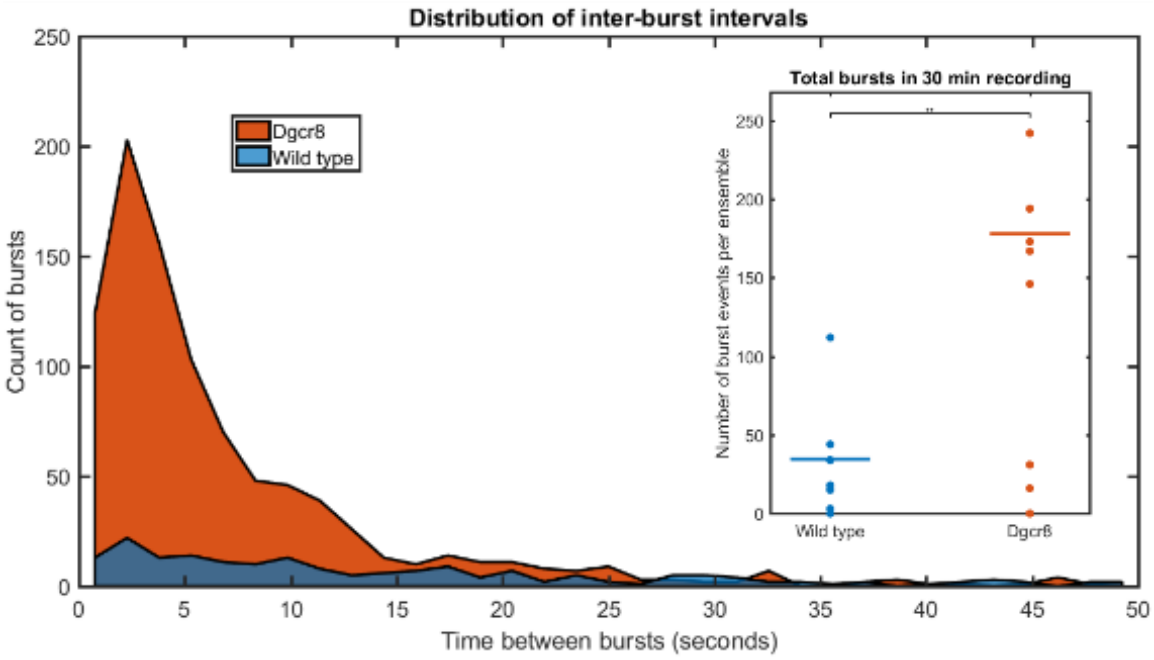

Figure 3.4: Characteristics of population bursts in mPFC of Dgcr8$^{+/-}$ mice.

Frequency of bursting events illustrated with inter-burst interval distributions for Dgcr8$^{+/-}$ mice (orange) and wild-type mice (blue). ***Inset****, bursting activity separated by genotype and ensemble. Symbols indicate number of bursts per ensemble detected in 30-minute recording sessions from wild-type and Dgcr8$^{+/-}$ mice. Two-tailed t-test by genotype, p = 0.007.*

3.3.2. *Zero-lag synchronization in the Dgcr8$^{+/-}$ mouse*

The highly synchronous bursts of activity observed in *Dgcr8*$^{+/-}$ cortical neurons suggests that there may be a change in synchrony in the opposite direction to that described in the primate data in Chapter 2. Several key differences exist between the two sets of data, including the species used, the manipulation employed to mimic aspects of schizophrenia (NMDAR antagonists in one case, a genetic mutation increasing risk in the other), as well as the behavioral state of the animal (at rest and alert or engaged in a cognitive task). Any

of these differences could have contributed to more prominent bursting in the mutant mouse model relative to the primate model. However, it is possible that the genetic mutation in the mouse model produces multiple pathophysiological phenotypes, that could potentially include a disruption in zero-lag spike correlation similar to that observed in the primate model during periods of regular spiking in between spike bursts. We therefore computed two cross-correlation histograms (CCHs) for each pair of cells: one generated from spike times in the entire dataset, and a second from data that only included spikes that occurred in the inter-burst intervals (see Methods). Considering the spiking data with bursts removed, I observed that the population average zero-lag peak in *Dgcr8*$^{+/-}$ mutant mice was lower relative to corresponding peak in the wild type mice (**Figure 3.5A**). Both the median zero-lag peak amplitude (**Figure 3.5B**), and the percentage of simultaneously recorded neuron pairs that exhibited a significant zero-lag peak (**Figure 3.5C**) were significantly reduced in *Dgcr8*$^{+/-}$ mice relative to wild type mice (see legend for statistics). There was no significant difference in the percentage of significantly coupled neuron pairs between genotypes when the CCH analysis was based on the full dataset (data not shown, z-test of proportions, $p > 0.05$). These findings mimic in several respects the reduction in zero-lag spike synchrony observed to result from NMDAR blockade in the nonhuman primate model (**Figure 2.3)**, which is noteworthy given that the two animal models involve different species and mechanistically distinct manipulations—a NMDAR antagonist in monkeys in one case and a genetic mutation in mice in the other.

The distribution of zero-lag peak values in each genotype both before ("all data") and after ("no bursts") removal of spike bursts can be seen in **Figure 3.5B**. There is a visibly bimodal distribution in the *Dgcr8*$^{+/-}$ neurons in the full dataset that is not present in the inter-burst interval data, suggesting that zero-lag synchrony is dramatically increased in a subset of cell pairs. Exclusion of burst time periods visibly eliminated the bimodality of the peak values in *Dgcr8*$^{+/-}$ mice, and also shifted the remaining sample towards smaller values of zero-lag synchrony (**Figure 3.5B**, compare orange solid line with orange dotted line). In contrast, removal of bursting activity from wild-type mice had a modest effect (**Figure 3.5B**, compare blue solid line with blue dotted line).

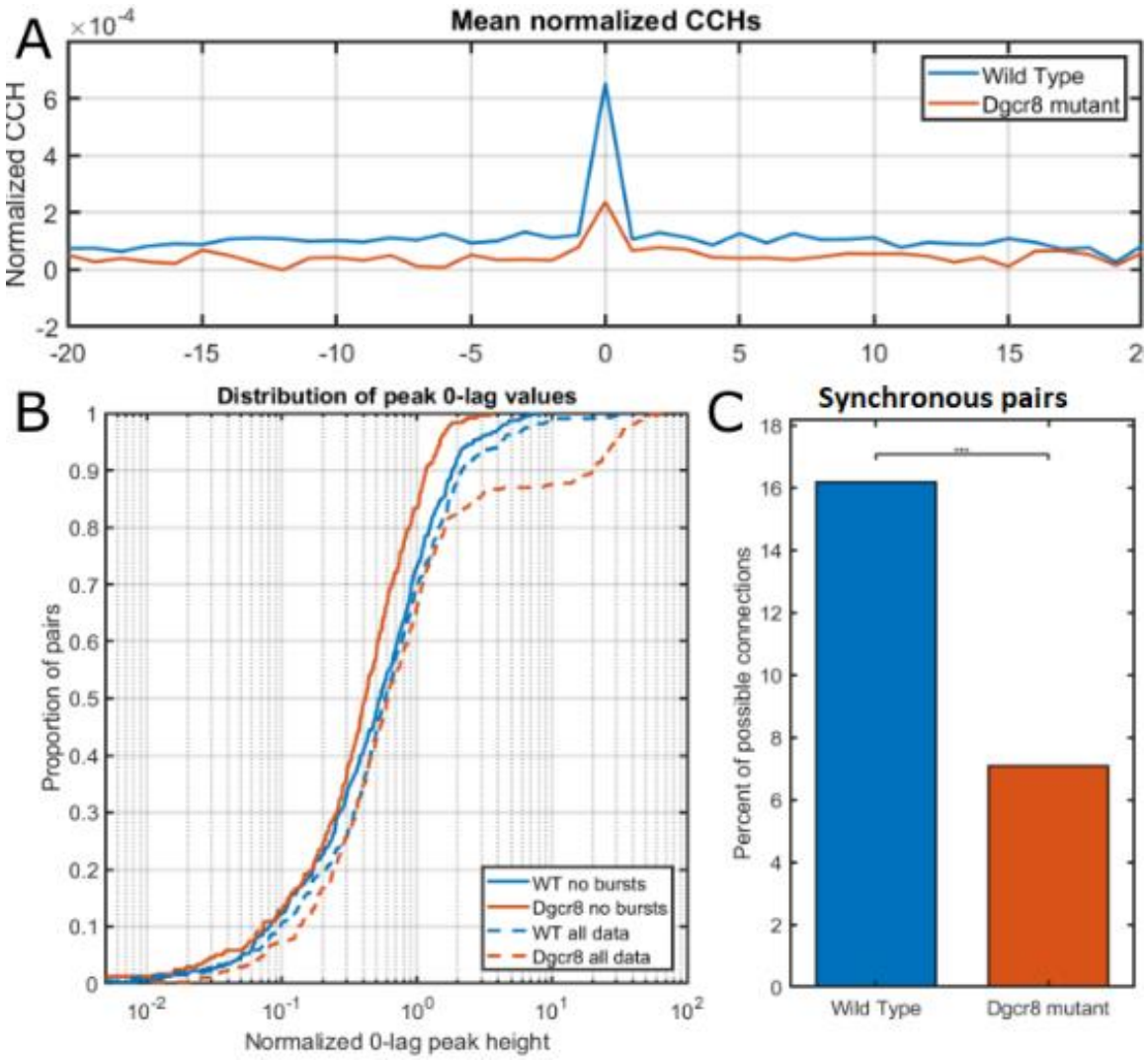

Figure 3.5: ***Reduced zero-lag synchrony in Dgcr8$^{+/-}$ mouse PFC***

A. *Mean CCHs across all cells after bursting events have been removed from the input data (see Methods), separated by genotype.* ***B.*** *Distribution of normalized zero-lag peak heights across populations of cells separated by genotype. X-axis represents normalized peak height, defined as the number of spikes in the 3-msec window surrounding zero-lag that exceed the mean number of spikes in this window of the corresponding bootstrap distribution, divided by the total number of spikes emitted by the neurons in the pair. Distributions are shown for the entire dataset (dashed lines) for comparison with the bursts-removed data (solid lines). Entire dataset, two-tailed Kolmogorov-Smirnov test between genotypes, p = 0.008, K-S statistic 0.1159; inter-burst interval ("no bursts") data, p = 0.003, K-S statistic 0.14614.* ***C.*** *Percentage of all possible pairs (limited to simultaneously-recorded pairs on separate electrodes) that exhibited significantly more spikes at zero-lag than spike-shuffled bootstraps (see Methods). Two-tailed z test of proportions, p = 2.117×10^{-4}.*

3.3.3. *Transfer Entropy*

Our next aim was to investigate whether deficits in effective connectivity were evident in *Dgcr8*$^{+/-}$ mice. To reduce the influence of population bursts on the calculation of effective connectivity in the *Dgcr8*$^{+/-}$ mouse, we used a combination of two features of the TE functions that described each pair's timing relationship. "AUC" represents the area under the curve surrounding the peak TE value for each pair of cells, and the "CI" is a measure of the sharpness of this peak (see section 3.2.7). The distribution of AUC and CI values for all pairs of cells is shown in ***Figure 3.6*A**. It is noteworthy that the overall distribution of AUC and CI values in wild-type mice is comparable to previous reports of cell pairs in wild-type *in vitro* and *in vivo* mouse cortical neurons (Nigam *et al.*, 2016). In contrast, neurons recorded from the *Dgcr8*$^{+/-}$ mice exhibited, at least on visual inspection, a strongly bimodal distribution of AUC values and a disproportionate number of pairs with CI values less than the value predicted by chance (dotted line).

The most conspicuous difference between the two genotypes in this figure is the cluster of neurons in the bottom right region of **Figure 3.6A**, which exhibit a low CI (broad peak) and high AUC that could be indicative of an external network drive. An example TE function from a pair in this cluster is shown in **Figure 3.7C.** The median AUC in *Dgcr8*$^{+/-}$ neuron pairs was significantly reduced compared to wild-type neuron pairs (**Figure 3.6B**; two-tailed Kolmogorov-Smirnov test, $p = 7.76 \times 10^{-28}$, K-S statistic 0.1944), suggesting that overall synaptic efficacy is reduced in the *Dgcr8*$^{+/-}$ mouse. This finding was significant despite the contribution from the cluster of *Dgcr8*$^{+/-}$ neurons with extremely high AUC values.

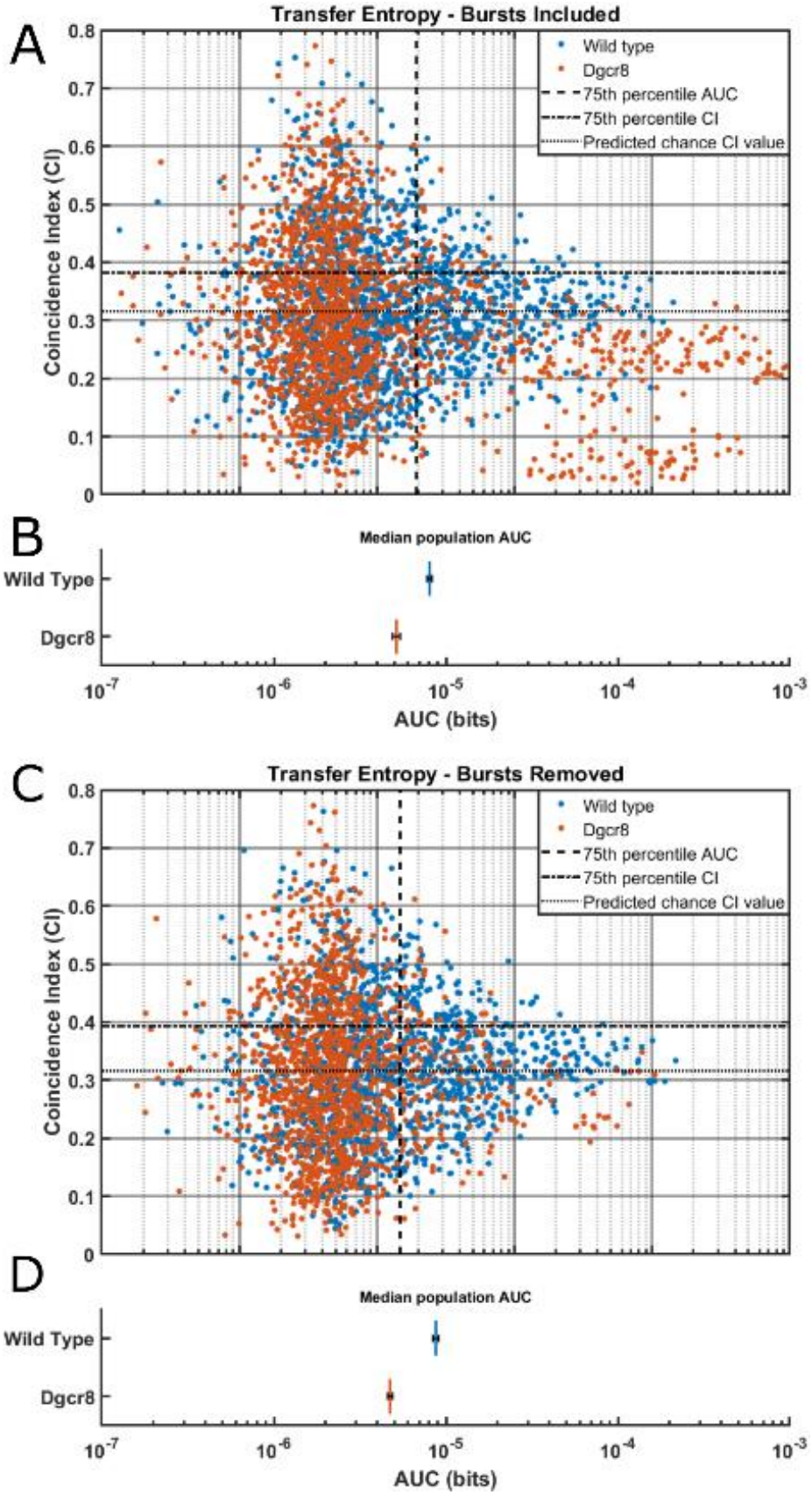
A
Transfer Entropy - Bursts Included
Wild type
Dgcr8
75th percentile AUC
75th percentile CI
Predicted chance CI value
Coincidence Index (CI)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
B
Median population AUC
Wild Type
Dgcr8
10^{-7}
10^{-6}
10^{-5}
10^{-4}
10^{-3}
AUC (bits)
C
Transfer Entropy - Bursts Removed
Wild type
Dgcr8
75th percentile AUC
75th percentile CI
Predicted chance CI value
Coincidence Index (CI)
D
Median population AUC
Wild Type
Dgcr8
AUC (bits)

Figure 3.6: Features of Pairwise Transfer Entropy between Simultaneously-Recorded mPFC Neurons in the Dgcr8$^{+/-}$ Mouse.

Opposite page: ***A.*** *Scatter plot of CI values (y-axis) against AUC (x-axis) for each pair of simultaneously-recorded neurons. Blue, wild type; Orange, Dgcr8$^{+/-}$ mouse. Dashed and dotted lines represent the 75th percentile of AUC and CI distributions, respectively, across all pairs (AUC cutoff = 1.93 × 10^{-5} bits; CI cutoff = 1.2).* ***B.*** *Median values (+/- SEM) of AUC across all pairs within each group. Two-tailed Kolmogorov-Smirnov test, p = 7.76 × 10^{-28}, K-S statistic 0.1944).* ***C, D.*** *As in A and B, but excluding all spikes that occurred within manually-identified periods of bursting activity.* ***D.,*** *Median values (+/- SEM)of AUC across all pairs within each group. Two-tailed Kolmogorov-Smirnov test, p = 1.13 × 10^{-56}, K-S statistic 0.3114). Note: see comparable figure in Nigam et al., 2016, Figure 1.*

As with the CCHs, we calculated TE for each pair of neurons first with all spike times as the input (**Figure 3.6A**), and a second time after excluding all spikes emitted during burst windows (**Figure 3.6C**). As can be seen in **Figure 3.6C**, omission of bursts disproportionately affected the cluster of *Dgcr8$^{+/-}$* neurons in the bottom right quadrant of the panel, most of which failed to meet the baseline firing rate cut off after bursting spikes were removed. In contrast, the majority of pairs in the rest of the dataset are apparently relatively unaffected by the removal of bursting activity, as the median AUC across all pairs within each genotype did not change dramatically (**Figure 3.6D**; compare with **Figure 3.6B**).

We defined causal interactions between neurons as being consistent with monosynaptic connectivity if TE functions exceeded the 75th percentile of the distribution of AUC values *and* the 75th percentile of the distribution of CI values were identified as putative monosynaptic connections. These pairs had comparatively strong interactions with sharp TE peaks in the lag range of 2-8 ms. The proportion of cell pairs that met this criteria for monosynaptic connectivity was significantly reduced in the *Dgcr8$^{+/-}$* mouse as compared to wild-type (**Figure 3.7A**; two-tailed z-test of proportions, p = 1.19 × 10^{-10}). Together, these findings constitute the first reported evidence of impaired effective connectivity within local cortical circuits in the *Dgcr8$^{+/-}$* mouse model of schizophrenia.

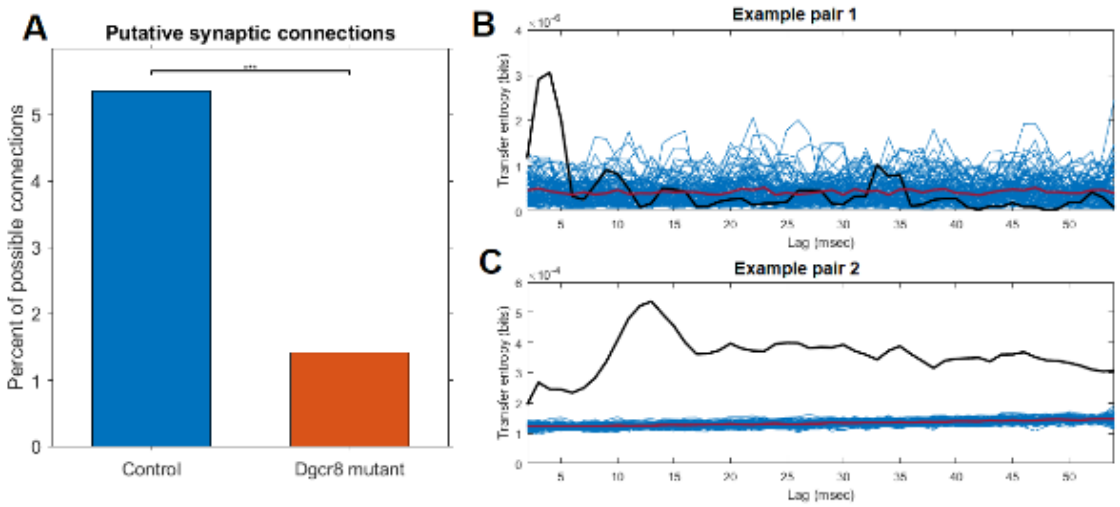

Figure 3.7: Reduction in number of pairs exhibiting significant effective connectivity in the Dgcr8$^{+/-}$ mouse.

A. *Percentage of all possible connections (limited to simultaneously-recorded pairs on separate electrodes) that met joint AUC and CI criteria to be considered as reflecting causal interactions consistent with monosynaptic connections. Bursting events were included. Two-tailed z-test of proportions between genotypes; $p = 1.19 \times 10^{-10}$.* ***B.*** *Example TE function from a wild-type pair with a high CI and moderate AUC. Black, TE function; blue, bootstrap TE functions generated by jittering spike times (n = 100); red, mean of bootstraps.* ***C.*** *Example cell pair from the cluster of Dgcr8$^{+/-}$ neuron pairs in the bottom right of Figure 3.6A. These cell pairs exhibited high AUC but very low CI, and formed a distinct cluster upon ward-based clustering analysis (data not shown). The TE functions of these pairs were remarkably consistent; as with the example in B, many remained higher than bootstrap data by several orders of magnitude throughout the computed lag space, with relatively low values in the time lags associated with synaptic connectivity and large and broad peaks around 10-15 msec.*

3.4. Discussion

In this chapter we characterize the effects of hemizygous deletion of the *Dgcr8* gene in mice on local network dynamics in the prefrontal cortex. Prior studies that investigated the effects of this deletion (as well as related models of the 22q11.2 microdeletion) established a number of findings that predicted a reduction in synchrony and synaptic efficacy in this mouse. First, histological studies of the *Dgcr8*$^{+/-}$ and *Df(16)A*$^{+/-}$ mice suggested that basilar dendritic branching complexity is reduced, most prominently in layer 3 pyramidal neurons of the PFC, whose local recurrent connections are thought to be necessary for sustained activity (Kritzer & Goldman-Rakic, 1995). Functionally, mPFC cells in the *Dgcr8*$^{+/-}$ mouse were previously found to exhibit a high input resistance (indicating reduced cell membrane surface area) and reduced spontaneous excitatory input frequency in slice preparations (Schofield *et al.*, 2011). However, the effects of the *Dgcr8*$^{+/-}$ mutation on inter-neuronal communication *in vivo* have not been previously studied. Here we present the first description of alterations in synchrony and functional connectivity between mPFC neurons in the awake *Dgcr8*$^{+/-}$ mouse.

As with the primate data described in Chapter 2, we measured synaptic efficacy using pairwise transfer entropy analysis, a statistical tool designed to identify causal interactions in spiking data. The results of this analysis provided evidence that *Dgcr8*$^{+/-}$ mice exhibit both a population-level reduction in information transfer (communication) between neighboring mPFC neurons (**Figure 3.6**) and a reduction in the number of effective connections between mPFC neurons (**Figure 3.7**). This reduction in information transfer was significant despite the inclusion of large synchronous bursts of activity that occurred in a subset of *Dgcr8*$^{+/-}$ neurons, whose transfer entropy values formed a clearly defined cluster that was distinguishable from the rest of the population of neuron pairs. *Dgcr8*$^{+/-}$ neuron pairs also exhibited a reduction in the frequency of synchronous spiking events and in the proportion of pairs with significant zero-lag synchrony (**Figure 3.5**), though this was only significant during inter-burst time periods.

Another finding described here is an increase in the frequency of bursts of spiking activity in mPFC neurons. During the recordings it was noted that the bursts did not seem to be a result of either motor artifacts or sleep states, as they occurred only when the mice were alert and immobile. One possible source of the spike bursts is that they represent the spiking response of PFC neurons to sharp wave signals originating in the hippocampus. If this is the case, then my data suggest that the frequency of sharp waves is significantly increased in the *Dgcr8*$^{+/-}$ mouse.

The hippocampus is an evolutionary ancient brain structure in the medial temporal lobe that is critical for episodic memory (Gaffan, 1994; Tulving & Donaldson, 1972; Scoville and Milner, 1957; Steele & Morris, 1999) and spatial learning (Morris *et al.*, 1982; O'Keefe and Nadel, 1978). Population activity in the hippocampus, measured through electroencephalography (EEG) or depth electrodes, reflects distinct patterns of activity depending on the behavioral state of the animal (Buzsaki, 1989), suggesting that the region transitions between different modes of information processing. For example, during active exploration or task engagement, hippocampal activity is dominated by a 4-10 Hz theta rhythm (Vanderwolf, 1969; Skaggs *et al.*, 1996). In contrast, periods of wakeful rest or disengagement are marked by irregularly occurring sharp waves (Buzsaki & Vanderwolf, 1983), which appear as large negative polarity deflections on EEG. Historically, non-theta states have been also referred to as large amplitude irregular activity (LIA, Vanderwolf, 1969), mainly because, in addition to SPWs or LIA spikes, other events such as slow and spindle oscillations are mixed with SPWs (Vanderwolf, 1969; Hartse *et al.*, 1978). However, in the alert but still animal, SPWs represent the only large-amplitude events. Sharp waves can also be detected during slow-wave sleep, when they are typically followed by a short-lived fast oscillatory pattern known as a "ripple". Sharp-wave ripple complexes (SPW-Rs) can involve up to 18% of the pyramidal neurons in the CA3 and CA1 regions of the rat, making them among the most synchronous physiological events in the brain (Chrobak and Buzsaki, 1996; Csicsvari *et al.*, 1999a,b). While ripples are strongly localized to the CA1 region of the hippocampus (Chrobak and Buzsaki, 1996; Csicsvari *et al.*, 2003), sharp wave activity bursts spread to the entorhinal and medial prefrontal cortical

regions, two highly interconnected hub regions of the cortex. While the specific role that SWR activity plays in memory retrieval and decision-making processes remains unclear, one possibility is that it contributes to deliberation by transmitting sequences corresponding to either specific past experiences (Carr *et al.*, 2011) or possible future options to other brain areas such as the PFC (Jai & Frank, 2015).

Investigations into the spike content of hippocampal neurons during various brain states has provided insight into the computational processes that underlie memory processing. Pyramidal neurons from areas CA1 and CA3 of the hippocampus referred to as place cells exhibit stable, spatially constrained firing fields that are tuned to a particular location of the animal in its external environment (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971). When an animal is in motion, the activity of a population of such place cells provides an accurate representation of its location (Wilson & McNaughton, 1993; Frank *et al.*, 2000). Furthermore, the sequence of place cell spiking activity within each theta cycle recapitulates the order of the animal's movement through a sequence of place fields (Skaggs *et al.*, 1996; Tsodyks *et al.*, 1996; Dragoi & Buzsaki, 2006). These "theta sequences" are thought to represent the initial encoding of a spatial memory trace, as they are replayed during periods of sleep that follow the initial exploration (Wilson & McNaughton, 1993). During SWRs, these sequences are replayed at a more compressed timescale that is suitable for synaptic plasticity, both during the awake state (Foster & Wilson, 2006; Jackson *et al.*, 2006; O'Neill *et al.*, 2006; Csicsvari *et al.*, 2007; Diba & Buzsaki, 2007; Johnson *et al.*, 2008; Karlsson & Frank, 2009; Davidson *et al.*, 2009) and in the period of sleep that follows active behavior (Wilson & McNaughton, 1994; Skaggs & McNaughton, 1996; Kudrimoti *et al.*, 1999; Nadasdy *et al.*, 1999; Lee & Wilson, 2002; Sutherland & McNaughton, 2000).

Behavioral studies in rodents have led to the hypothesis that sharp waves may serve as a mechanism to transfer compressed spike sequences from the hippocampus to neocortical regions for long term storage when the brain is disengaged from environmental stimulis

(Battaglia *et al.* 2004; Hoffman and McNaughton 2002; Qin *et al.* 1997; Skaggs and McNaughton 1996), perhaps by providing "teaching" signals that induce synaptic changes within the neocortex (Buzsaki, 1989; Marr, 1971; McClelland *et al.* 1995; Murre, 1996). For example, simultaneous recordings in the hippocampus and prefrontal cortex reveal that awake sharp wave-related activity in the PFC supports computations related to the specific content of the corresponding sharp wave-related hippocampal activity (Jai & Frank, 2015; Jadhav *et al.*, 2016). Awake SWRs in particular have been shown to reactivate sets of place fields encoding forward and reverse paths associated with both current and past locations (Foster & Wilson, 2006; Diba & Buzsaki, 2007; Karlsson & Frank, 2009; Davidson *et al.*, 2009; Gupta *et al.*, 2010). Furthermore, behavioral studies reveal impaired performance on memory tasks as a result of disruption of sharp-wave transmission, either through toxic insults to the CA3 cells projecting to CA1 (Nakashiba *et al.*, 2009) or through electrical microstimulation (Ego-Stengel and Wilson, 2010; Girardeau *et al.*, 2009; Jadhav *et al.*, 2012).

Several lines of evidence exist that implicate disrupted sharp wave generation in relation to schizophrenia. Intriguingly, case reports from EEG studies of human patients with schizophrenia have described a temporal association between increased sharp wave frequency and psychotic hallucinations (Heath & Walker, 1985). Additionally, in a mouse model of schizophrenia involving a knockout of the gene Calcineurin, a 2.5-fold increase in the abundance of sharp-wave events in hippocampal LFP during awake resting periods was reported (Suh *et al.*, 2013). More broadly, hippocampal abnormalities have been identified through imaging of patients with schizophrenia (Suddath *et al.*, 1990; Bertolino *et al.*, 1998; Weinberger *et al.*, 1991), and disruptions in hippocampal activity correlate with selective impairments in learning and memory (Small *et al.*, 2011). This may be related to changes in activity and regulation of the default mode network (DMN), a network that has been highly studied in functional imaging studies. The DMN consists of several cortical regions such as the ventral medial and dorsolateral PFC, anterior and posterior cingulate cortices, and inferior parietal cortex, in addition to temporal lobe structures such as the hippocampal formation; this network is characterized by increased activity at rest

and reduced activity when attention-demanding goal-directed cognition is undertaken (Shulman *et al.*, 1997; Gusnard *et al.*, 2001; Raichle *et al.*, 2001; Greicius *et al.*, 2003; Gusnard, 2005; Fox *et al.*, 2005). It has been proposed that the symptoms of schizophrenia could arise from an overactive or inappropriately active DMN (Buckner *et al.*, 2008), and this has been substantiated by studies that demonstrate increased DMN activity during rest correlating with positive symptoms of schizophrenia (Garrity *et al.*, 2007), functional dysconnectivity between the PFC and other DMN regions (Zhou *et al.*, 2007), as well as other disruptions in DMN activity (Whitfield-Gabrieli *et al.*, 2009; Camchong *et al.*, 2009; Calhoun *et al.*, 2007; see Bluhm *et al.*, 2007 for review).

As discussed in Chapter 1, the results of numerous investigations converge on a characterization of schizophrenia as a disease of abnormal maintenance and regulation of cortical connectivity. However, the mechanisms by which failures in synaptic function can lead to large-scale network disturbances have not been well-studied, particularly in awake and functioning nervous systems. In this Chapter, we provide evidence of a reduction in pairwise synchrony as well as a reduction in effective connectivity between mPFC neurons of the *Dgcr8*$^{+/-}$ mouse. These findings suggest an overlap in pathophysiological processes between the primate PCP model of schizophrenia and the *Dgcr8*$^{+/-}$ mouse model that may be reflective of a core deficit in synaptic communication between prefrontal neurons in schizophrenia. In addition, we provide the first evidence of increased sharp-wave frequency in the *Dgcr8*$^{+/-}$ mouse, suggesting an overlap in neurophysiological abnormalities of hippocampal function between this model and humans with schizophrenia.

4. Conclusions

My dissertation provides the first characterization of synchrony and effective connectivity at the level of neighboring prefrontal cortical neurons in animal models of schizophrenia. Additionally, I provide the first direct comparison between electrophysiological data obtained from both a primate and mouse model of prefrontal dysfunction in schizophrenia. By adapting primate recording equipment to be used with mice, I was able to collect neural spiking data from large numbers of mPFC neurons in wild-type and *Dgcr8*$^{+/-}$ mice. During the process of obtaining these data, I developed and refined analytical tools to characterize spiking dynamics in an already existing dataset obtained from primates exposed to pharmacological NMDAR blockade (Blackman *et al.*, 2013), thereby optimizing the potential for side-by-side comparison across disease models. I provide convergent evidence of deficits in synaptic communication between prefrontal neurons across two distinct mammalian species and two distinct methods of modeling the schizophrenic phenotype. These findings support the hypothesis that reduced spike correlation in prefrontal cortex is a fundamental pathophysiological process in schizophrenia that can result from multiple pathogenic insults.

4.1. Summary of Findings

In Chapter 2, I describe the effects of reduced NMDAR function on synchrony and effective connectivity in prefrontal cortical neurons during the performance of a cognitive control task. Pairwise analysis of simultaneously-recorded pyramidal neurons revealed prominent spike-level synchrony reflective of high rates of coincident firing during

baseline task performance. Administration of PCP, a pharmacological compound that can be used to model aspects of schizophrenia, significantly reduced the degree of coincident firing in these cells. Furthermore, quantification of the influence that each neuron exerted on the activity of neighboring neurons revealed that repeated PCP administration may cause a reduction in synaptic efficacy within the prefrontal cortex. In Chapter 3, I provide a replication of these findings in the *Dgcr8*$^{+/-}$ mouse model of schizophrenia. Neurons recorded from the mouse medial prefrontal cortex, a homologous area to the dorsolateral prefrontal cortex in primates, displayed a similar rate of coincident firing during awake resting-state recordings. In mice carrying a single copy of the *Dgcr8* gene, which is thought to lead to a general impairment in the regulation of neuronal gene expression, the degree of coincident firing between neighboring neurons was significantly reduced. Similarly, measures of synaptic efficacy between neuron pairs reflected a possible reduction in local circuit connectivity in the PFC. These results may reflect a functional correlate of the reduced dendritic spine density that has been reported on histopathological observations of cortical tissue in schizophrenia (Lewis & Anderson, 1995). Furthermore, they provide insight into local network dynamics that could be causally related to system-wide functional connectivity deficits that have been described in imaging studies of patients with schizophrenia.

As discussed in Chapter 1, the two animal models compared in this dissertation occupy nearly opposite ends of the spectrum between face validity and construct validity. When considering the disparity in pathogenic insults that were used to model schizophrenia, the convergence of findings across animal models as described in Chapter 2 and 3 is remarkable. One effect of this convergence is to reinforce the conclusions that can be drawn from either study in isolation, as it is unlikely that measures of synaptic connectivity and pairwise synchrony would show parallel reductions in both studies through chance alone. A second effect of convergent results is that both models serve to cross-validate each other as informative models of schizophrenia. These two considerations are not independent, as the modeling of disease in general often involves repeated cycles of validation and replication. In this dissertation I contribute to the scientific knowledge of

schizophrenia through the identification of physiological abnormalities that span disparate animal models and are thereby more likely to constitute fundamental characteristics of the disease.

I also provide evidence in Chapter 3 of a novel finding in the *Dgcr8*$^{+/-}$ mouse that is not present in the primate data, i.e. that the abundance of hippocampal sharp wave signals appears to be significantly increased in the *Dgcr8*$^{+/-}$ mouse. Previous studies on a closely related genetic model, the *Df(16)A*$^{+/-}$ mouse, reported reduced phase-locking of prefrontal neurons to hippocampal theta oscillations during the execution of a spatial working memory task (Sigurdsson *et al.*, 2010), however no mention of irregular sharp-wave activity was made. This could be due to the fact that sharp waves are known to occur only during periods of inactivity, which may also explain the absence of these signals in the primate data described in Chapter 2. Additionally, increased sharp wave frequency has been reported in the Calcineurin knockout model of schizophrenia (Suh *et al.*, 2013), and circumstantial evidence has temporally linked psychotic symptoms with sharp wave generation in humans (Heath & Walker, 1985). Together, these findings help characterize disruptions in intracortical and hippocampal-prefrontal communication that appear to be a fundamental feature of schizophrenia (Harrison, 2004).

4.2. Limitations

There are several limitations of my work that should be kept in mind when interpreting results. While I attempted to reproduce the recording conditions of the primate experiments as much as possible in my mouse recordings, many differences remain that limit their comparability. The largest difference is the brain itself: primates and rodents have significant differences in the architecture and connectivity of the prefrontal cortex, and the extent of prefrontal homology across species is debated (see Preuss, 1995). In addition, the DLPFC in primates is physically much larger, and the prefrontal region that we targeted in the mouse was approximately the same width as the electrode matrix itself, and it is likely

that some neural recordings included in the analysis were obtained from neurons outside of the mPFC borders. However, it is unlikely that there was any appreciable difference in the success of localization between *Dgcr8*$^{+/-}$ and wild-type mice, so this would be unlikely to affect our results regarding differences in spiking dynamics between genotypes.

Another major difference between the primate experiments conducted by Dr. Blackman and the mouse experiments I performed is the behavioral state of the animals during the recording. In both cases the animals were awake, but the primates were actively engaged in a working memory task while the mice were in a head-fixed resting state. This limits the comparability of the two datasets, though the fact that we saw a replication of both our zero-lag and effective connectivity results suggests that the statistical dependencies between neurons' activity may be robust to changes in cognitive state.

An important difference between the findings reported in Chapter 2 (primate data) and Chapter 3 (mouse data) is the increase in frequency of sharp waves in the *Dgcr8*$^{+/-}$ mouse. While the presence of sharp waves was not explicitly looked for in the primate data, there were no obvious bursts of activity such as those seen in the *Dgcr8*$^{+/-}$ mouse. Additionally, an increase in sharp wave frequency would have manifested as an increase in zero-lag activity with PCP rather than the decrease that we reported. This claim is consistent with the finding that NMDAR blockade in rat hippocampal slices have been shown to increase the rate of spontaneous sharp wave generation (Colgin *et al.*, 2005). The body of research into sharp wave generation in primates is much more sparse than in rodents, and while a few studies involving hippocampal recordings have been performed, it is notable that the presence of synchonous bursts of activity in the prefrontal cortex correlating with hippocampal sharp waves has not been described to the author's knowledge. A seminal study that investigated sharp wave activity in the awake macaque, Skaggs *et al.*, (2007) reported many features of primate sharp waves that correlated with described findings in rodents. In particular, they list several important conclusions of their work: first, hippocampal pyramidal cells in monkeys are complex spike cells similar to those described

in rodents, with overall rates well under 1 Hz, and the current sinks and sources that underly sharp wave generation are primarily localized to the CA1, as in rats. Additionally, the behavioral state of the monkeys in their study had a profound effect on the occurrence of sharp waves; as with rodents, sharp waves were associated with drowsiness and inactivity in primates. However, there were some quantitative differences between sharp waves identified in monkeys and rats. For example, the ripple oscillations in monkeys had frequencies of ~100-120 Hz, compared with 130-200 Hz in rats (Csicsvari *et al.*, 1999), and the overall incidence of sharp waves during drowsy/sleeping behavior appeared to be lower in monkeys (Skaggs *et al.*, 2007). Given that high-frequency ripples have also been described during quiescent and sleep periods in the epileptic human hippocampus and temporal lobe (Bragin *et al.* 1999; Staba *et al.* 2002, 2004, 2007), it is likely that these observations carry over to humans as well. Another important difference between primate and rodent sharp waves may be related to behavioral state, as described by Leonard *et al.* (2015). In this study, primates were given a task that involved visual exploration across an image in search for a particular fixation point, which often took up to 45 seconds. These authors described the presence of SWRs during the periods of visual exploration in this task, and even increased in frequency when the target was fixated upon, suggesting that SWRs are involved in active exploration in addition to inactive periods as previously described. In order to detect a change in sharp wave frequency with the administration of PCP in primates, it may be necessary to adopt a task that includes such long time periods of visual exploration, or at least longer periods of quiescence than the 500 msec to 1 second pre-fixation periods included in the dataset described in Chapter 2. It would also be informative to perform simultaneous recordings in the primate hippocampus during these tasks in order to verify the association between bursts of PFC activity and hippocampal sharp waves. Thus the question of disrupted hippocampal-PFC communication in primate pharmacological models of schizophrenia, particularly with regard to the generation of sharp wave ripple complexes, remains to be elucidated and could be an important focus for future work.

4.3. Future Directions

My dissertation work sets the stage for further investigation into how local interactions between neurons in the prefrontal cortex are disrupted in schizophrenia. A natural extension of my work could involve additional mouse experiments with chronically implanted electrodes. Chronic recordings could provide more data from each pair of cells, which would (theoretically) improve the ability to identify pairwise correlations from spike statistics. The recording equipment that was used in both the primate and mouse experiments was designed for acute recording sessions, and so it was not possible to obtain data from the same set of cells on separate days. This methodology was an advantage in that repeated recordings allowed for the accumulation of data from a large number of simultaneously recorded neuronal ensembles, which increased our probability of finding effective connections, and held neuron sampling considerations between mice and monkeys relatively fixed. However, chronic recordings would be particularly informative with respect to the evolution of cellular interactions over time. For example, one could compare the differences in correlation strength between the same two cells before and after administration of an NMDAR antagonist, throughout different periods of development in a mouse genetic model.

Another important future direction for this research would be to investigate prefrontal activity in *Dgcr8*$^{+/-}$ mice during the performance of a behavioral task that demands some degree of executive function. Combined with chronic recordings, it would be interesting to see how temporal interactions between neighboring cells change with time and cognitive state. Additional experiments could also be attempted to reinforce the overlap between the two disease models discussed here, such as administering PCP to wild-type mice or measuring resting state prefrontal spiking dynamics in primates.

The bursting activity that I observed in *Dgcr8*$^{+/-}$ mice was a serendipitous discovery, and we were not positioned to fully investigate the nature of this abnormality in the time that

was available to perform experiments. A relatively simple follow-up experiment would involve insertion of an LFP electrode into the hippocampus during PFC recordings to determine if there is a temporal association between spike wave-ripple complexes and bursting events in the PFC.

Lastly, computational modeling techniques have the potential to be particularly informative with regard to the questions addressed in this dissertation. A simulated network of spiking processes with statistical similarities to prefrontal neurons could help untangle some of the complexities of cellular interactions in our data, as nearly all features of a model network can be changed systematically. Even more importantly, computational models can serve as an initial proof-of-concept test for potential treatments. In particular, the effects of neuromodulation (e.g. via implanted electrodes or noninvasive technologies such as transcranial magnetic stimulation) could be evaluated in a simulated network identify neuromodulatory techniques with promise for treating schizophrenia.

4.4. Concluding comments

The psychiatrist Adolf Meyer stated that "the history of dementia praecox is really that of psychiatry as a whole" (quoted in Sass, 1994). Similarly, the study of schizophrenia is in many ways the study of the brain as a whole. Schizophrenia affects some of the most complex and highly distributed processes that have evolved within nervous systems, and therefore some of the processes that are most unique to humans. Just as Feinberg's hypothesis about the role of synaptic pruning in schizophrenia only came about with a growing understanding that neural development continues long after birth and into adolescence, it is only with an understanding of the interconnected nature of the nervous system that we could begin to consider behavior as the output of distributed processes in networks. Advances in our ability to measure, characterize, and predict the outcomes of distributed processes will likely bring new insights into the ways in which network activity is disrupted in schizophrenia, as well as the ways in which it could be more effectively treated.

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