THE SYSTEMIC EFFECTS OF GLUTAMATERGIC DYSFUNCTION IN SCHIZOPHRENIA: FROM RECEPTORS TO NETWORKS

by

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(Under the Direction of James D. Lauderdale)

ABSTRACT

Schizophrenia is a devastating psychiatric illness characterized by a diverse array of structural, functional, and molecular brain abnormalities and a concomitant range of psychotic, affective, and cognitive symptoms. Despite over a century of research on this debilitating illness, the biological mechanisms of schizophrenia remain unclear. Dysfunction of the glutamatergic neurotransmitter system is, to date, one of the most influential hypotheses of schizophrenia, and many of the structural and functional abnormalities observed in schizophrenia can be linked to N-methyl-D-aspartate receptor hypofunction. Understanding the role of glutamatergic neurotransmitter system dysfunction promises to aid in elucidating the etiology of schizophrenia. Motivated by a need to synthesize findings across a wide range of fields within the neurosciences, this review will summarize extant literature of glutamatergic neurotransmission in terms of cellular mechanisms, anatomical and oscillatory networks, and genetics related to schizophrenia, and how these factors play a role in other illnesses spanning the psychosis spectrum.

INDEX WORDS: Glutamate, Gamma Oscillations, Schizophrenia, Psychosis

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DEDICATION

I dedicate this work to my parents Jacob and Donna, who have nurtured my curiosity from birth, and to my husband David, whose tireless love and support continue to hold me together.

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CHAPTER 1

INTRODUCTION

Schizophrenia is a devastating psychiatric illness that affects 1% of the world population (Jablensky, 2000). It is characterized by an array of clinical observations, typically divided into positive symptoms, such as hallucinations and delusions, and negative symptoms, such as reductions in affect, speech, and movement. Cognitive impairments (e.g., deficits in IQ, verbal memory, sustained attention, response inhibition; Heinrichs & Zakzanis, 1998; Aleman, Jijman, DeHaan, & Kahn, 1999; Dickinson, Ramsey, & Gold, 2007) are also a core feature of schizophrenia, and are associated with poor functional outcomes (Gold, 2004; Green, 1996). Consequently, individuals with schizophrenia often have difficulty reaching social and occupational fulfillment, and more hospital beds are filled by patients with schizophrenia than any other illness, psychiatric or otherwise (Buchanan & Carpenter, 2000). Despite over a century of research on schizophrenia, the burden of schizophrenia (e.g., prevalence and course) remains unchanged (Hegarty, Baldessarini, Tohen, & Waternaux, 1993; Siu, Agid, & Remington, 2013) and the etiology is currently unknown. With the biological substrates still in question, the diagnosis of schizophrenia relies heavily on reported symptoms rather than biological mechanisms, and treatment options remain imprecise (Insel, 2014). Accordingly, gaining insight into the etiology of schizophrenia promises to improve the course and outcome in patients dealing with the effects of this debilitating illness.

Despite being highly heritable (80-85%; Sullivan, Kendler, & Neale, 2003), the genetic origins have yet to be determined. Concordance rates of only 60% in monozygotic twins indicate

that complex environmental and epigenetic interactions are responsible for the expression of this illness (Cardno & Gottesman, 2000; Tsuang, 2000). Genetic and epidemiological studies have revealed high levels of heterogeneity within the diagnosis of schizophrenia and great degrees of overlap between schizophrenia and other illnesses that share psychotic symptoms, such as bipolar disorder and schizoaffective disorder, and course of treatment is similar across diagnostic groups (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002; Lichtenstein et al., 2010; Moskvina et al., 2009; Tamminga et al., 2013; and reviewed in Bramon & Sham, 2001; Craddock & Owen, 2010; Murray et al., 2004).

Since the mid 1960's, a majority of schizophrenia research and treatment has focused on the dopamine hypothesis of schizophrenia, which suggests dysregulation of dopaminergic neurotransmission as the key feature underlying the illness. This idea was initially supported by evidence that drugs acting as D2 dopamine receptor antagonists reduced psychotic symptoms (Carlsson, Lindqvist, & Magnusson, 1957; Arnold & Freeman, 1956; Walinder and Skott, 1976), and was further supported by studies demonstrating that the administration of amphetamines, which increase extracellular concentrations of dopamine, resulted in psychotic symptoms (see Lieberman, Kane, & Alvir, 1987 for review). Weinberger and colleagues suggest that disruptions in the prefrontal cortex or hippocampus may lead to an imbalance within the dopamine system, as the prefrontal cortex (PFC) function has been linked to attenuation of subcortical dopamine systems as well as hippocampal output systems (Belujon & Grace, 2008; Grace, 1991; Weinberger et al., 1988, 1992, 1993). These findings led to semi-effective treatment, with both typical and atypical antipsychotic drugs targeting the dopamine system, either by direct dopamine D2 receptor antagonism or D2 partial agonism (Kapur & Seeman, 2001; Meltzer, Matsubara, & Lee, 1989). However, limitations of the dopamine hypothesis

surfaced as it became apparent that antipsychotic drugs acting as D2 dopamine receptor antagonists had limited efficacy, only ameliorating positive symptoms in schizophrenia and leaving negative symptoms and cognitive impairments unimproved (Jones et al., 2006; Meltzer, 1997), suggesting limited involvement of D2 dopamine receptors in negative and cognitive symptoms of schizophrenia.

As concerns with the dopamine hypothesis of schizophrenia surfaced, other neurotransmitter systems became research targets. Glutamatergic neurotransmission garnered attention as a potential mechanism of schizophrenia after the observation that administration of dissociative anesthetics such as phencyclidine (PCP) and ketamine, which act as non-competitive antagonists of the N-methyl-D-aspartate glutamate receptor (NMDAR), in healthy individuals resulted in a syndrome that was strikingly similar to schizophrenia (Collins, Gorospe, & Rovenstine, 1960; Corssen & Domino, 1965; Luby et al., 1962). Further studies that administered NMDAR antagonists revealed a wide range of symptoms associated with schizophrenia, including positive symptoms (delusions and illusions), negative symptoms (withdrawal, blunted affect, psychomotor retardation), and cognitive deficits in performance on tasks which call upon frontal cortex and hippocampus, such as verbal declarative memory, delayed word call, and verbal fluency (Goff & Coyle, 2001; Javitt & Zukin, 1991; Krystal et al., 1994; Tamminga, 1999). Additionally, imaging studies of individuals exposed to NMDAR antagonists demonstrated similarities to many of the physiological abnormalities noted in schizophrenia, such as aberrant event-related potentials (ERPs), disrupted eye movements, and reduced frontal lobe blood flow similar to hypofrontality (Hertzman, Reba, & Kotlyarov, 1990; Malhotra et al., 1997; Newcomer et al., 1999). Administration of ketamine or PCP in patients with chronic schizophrenia exacerbated pre-existing symptoms but did not induce new ones

(e.g., dissociative anesthetics did not illicit delusions in patients who did not previously experience them; Lahti, Koffel, LaPorte, & Tamminga, 1995), indicating that the drug stimulates existing mechanisms, rather than acting on parallel psychoto-mimetic pathways (Tamminga, Lahti, Medoff, Gao, & Holcomb, 2003). Administration of NMDAR agonists also improved negative symptoms in schizophrenia (Goff, Tsai, Manoach, & Coyle, 1995). Intriguingly, dysfunction of glutamatergic neurotransmitter systems relates to alterations in dopaminergic function in schizophrenia, as reciprocal synapses between forebrain dopamine projections and glutamate systems are well documented (Carlsson & Carlsson, 1990). Collectively, these findings support an NMDAR hypofunction model of schizophrenia.

Given the close connection of NMDAR antagonists with the schizophrenia syndrome, dysfunction of the glutamatergic neurotransmitter system is, to date, one of the most influential hypotheses of schizophrenia. Many abnormalities observed in schizophrenia can be linked to NMDAR hypofunction. For instance, schizophrenia is believed to have a neurodevelopmental component, and NMDARs play a critical role in guiding axons to their targets during development (Rakic, Bourgeois, & Goldman-Rakic, 1994) and in synaptic pruning during adolescence (Feinberg, 1990). Grey matter reduction, which is seen in schizophrenia, may be due to excitotoxicity related to NMDAR dysfunction (Zipursky et al., 1992). Further, many cognitive functions that show deficits in schizophrenia are related to NMDAR-mediated plasticity (Daw, Stein, & Fox, 1993), and recent *in vivo* imaging studies have provided interesting clues to the involvement of glutamatergic neurotransmission dysfunction in the positive, negative, and cognitive symptoms, as well as the widespread cortical dysfunction observed in schizophrenia (for review, see Bressan & Pilowsky, 2000; Poels et al., 2014). Thus, understanding the role of dysfunction of the glutamatergic neurotransmitter system may be of

paramount importance in elucidating the etiology of schizophrenia and related psychotic illnesses. As this hypothesis encompasses such a vast range of pathology, it has become particularly important as recent shifts in research endeavor to redefine complex mental illness based on a dimensional approach spanning a full range of research domains (Clementz, Sweeney, Keshavan, Pearlson, & Tamminga, 2015; Cuthbert & Insel, 2013; Insel, 2014). Motivated by a need to synthesize these findings, this review will summarize extant literature of glutamatergic neurotransmission in terms of the cellular mechanisms, anatomical and oscillatory networks, and genetics related to schizophrenia, and how these factors play a role in other illnesses spanning the psychosis spectrum.

CHAPTER 2

CELLULAR MECHANISMS

Dysfunction of the glutamatergic neurotransmitter system is, to date, one of the most influential hypotheses of schizophrenia. Glutamate is the most abundant excitatory neurotransmitter in the human brain (Meldrum, 2000). Glutamatergic neurons form the major excitatory pathway between the cortex, limbic system, and thalamus (Goff & Coyle, 2001), and have been implicated in several brain functions such as cognition, learning, and memory (for review, see Headley & Grillner, 1990). Glutamate receptors are found on most neurons (Bergles, Roberts, Somogyi, & Jahr, 2000; Conti, Barbaresi, Melone, & Ducati, 1999; Hosli & Hosli, 1993; Steinhäuser & Gallo, 1996; Vernadakis, 1996), and can be located on the dendrites, axon terminals, and/or cell bodies of neurons (Danbolt, 2001), thus having a wide-reaching effect on neuronal function.

Reduced concentrations of glutamate were initially reported in the cerebrospinal fluid (CSF) of patients with schizophrenia (Kim, Kornhuber, Schmid-Burgk, & Holzmüller, 1980), however, follow-up studies reported conflicting results (Bjerkenstedt, Edman, Hagenfeldt, Sedvall, & Wiesel, 1985; Macciardi et al., 1990; Gattaz, Gattaz, & Beckman, 1982; Perry 1982; Tsai, Yang, Chung, Lange, & Coyle, 1998). In postmortem brains, lower concentrations of glutamate were found in the prefrontal cortex and hippocampus of schizophrenia patients (Tsai et al., 1995), and glutamate receptor abnormalities have been found in both receptor density and subunit composition in prefrontal cortex, thalamus, and temporal lobe (Gao et al., 2000; Ibrahim et al., 2000; Meador-Woodruff & Healy, 2000; M. D. Rubio, Drummond, & Meador-Woodruff,

2012). Interestingly, these same areas show impaired activation in schizophrenia during cognitive tasks (Heckers et al., 1999; Heckers et al., 2000).

Glutamatergic neurotransmission dysfunction in schizophrenia could occur due to several mechanisms; at the synaptic level, abnormalities in glutamatergic receptors may stem from deficits in receptor availability, function, or subunit stoichiometry. In order to determine whether receptor abnormalities occur due to availability, histological studies have focused on quantifying the expression of glutamate receptors and receptor subunits. There are two families of glutamate receptors; metabotropic receptors, which are coupled to G-proteins that affect metabolic processes within the cell, and ionotropic receptors, which are gated cation channels (Nakanishi, Axel, & Shneider, 1992). The structure and function of metabotropic and ionotropic glutamate receptors are discussed briefly below, in order to provide a background for understanding glutamate receptor irregularities in schizophrenia.

Metabotropic Receptors

Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that allow for the modulation of excitatory signaling via a second messenger. The binding of glutamate to the extracellular N-terminal domain of mGluRs results in a conformational change that activates a G protein, resulting in the modulation of the function of effector molecules such as enzymes, ion channels, and transcription factors. This in turn allows for the modulation of cellular excitability and synaptic transmission. mGluRs are broadly distributed across the brain and are divided into groups that may be distinguished by some general characteristics. Group I mGluRs (mGluR1 and 5) activate phospholipase C which produces diacylglycerol and inositol triphosphate as second messengers; this group of receptors are usually localized postsynaptically, and activation typically results in depolarization and increased excitability (Meldrum, 2000;

Niswender & Conn, 2010). Groups II (mGluR2 and 3) and III (mGluR4, 6, 7, and 8) are negatively coupled to adenylyl cyclase and are usually found on presynaptic terminals or preterminal axons and typically inhibit neurotransmitter release when activated (Meldrum, 2000; Niswender & Conn, 2010).

Metabotropic receptors have historically been given relatively little attention in schizophrenia research; however, recent studies targeting metabotropic receptors as adjuvant treatments in schizophrenia suggest that metabotropic receptors may be a fruitful therapeutic target in schizophrenia. Metabotropic receptors are distributed diversely in the brain, with subtypes localized specifically on certain neurons or within certain brain regions. This allows for a more selective pharmacological activation of mGluRs, as direct stimulation of pharmacological agents targeted to specific metabotropic receptor subtypes will not produce deleterious, widespread disruptions in brain function, thus avoiding profound side effects (Moghaddam, 2004). Further, two classes of mGluR subtypes, mGluR5 and mGluR2/3, have been shown to potentiate NMDA receptor function (Attucci, Albani-Torregrossa, Moroni, & Pellegrini-Giampietro, 2001; Awad, Hubert, Smith, Levey, & Conn, 2000; Battaglia, Monn, & Schoepp, 1997; Cartmell & Schoepp, 2000; Doherty, Palmer, Henley, Collingridge, & Jane, 1997; Mannaioni, Marino, Valenti, Traynelis, & Conn, 2001; Pisani, Calabresi, Centonze, & Bernardi, 1997). Preclinical trials targeting the mGluR2 have shown promise. LY-404039, a glutamate analog which only acts on mGluR2 (Fell, Svensson, Johnson, & Schoepp, 2008) has been shown to improve positive and negative symptoms (Rorick-Kehn et al., 2007; Takamori, Hirota, Chaki, & Tanaka, 2003). Another potentiator of mGluR2, LY-487379, has been investigated in rodent models with promising results (Galici, Echemendia, Rodriguez, & Conn, 2005). Future study of

mGluRs as treatment targets in schizophrenia may provide meaningful information on the mechanisms of aberrant glutamate receptor function in schizophrenia.

Ionotropic Receptors

Whereas metabotropic glutamate receptors are G protein-coupled receptors, the ionotropic receptors are simple ion channel pores that, when activated, allow for the flow of sodium into the cell and potassium out of the cell. Ionotropic receptors are named for the glutamate analogues that selectively activate them: the α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor (AMPAR), the kainate receptor (KAR), and the N-methyl-D-aspartate receptor (NMDAR). Abnormalities have been noted in the expression of AMPA, KA, and NMDA receptors in schizophrenia, and deviations in the function of these receptors may collectively contribute to the schizophrenia syndrome.

AMPARs have a relatively low affinity for glutamate compared to other glutamate receptors; however, they display fast kinetics and play a primary role in generating fast excitatory postsynaptic potentials (EPSPs) (Goff & Coyle, 2001; Meldrum, 2000). Similar to AMPA receptors, KA receptors mediate synaptic currents and EPSPs; however, they differ from AMPARs in their kinetics. Despite KARs having a higher affinity for glutamate, their EPSCs are much slower and smaller in amplitude than those of AMPARs (Frerking & Ohliger-Frerking, 2012). Slow EPSPs provide a synaptic mechanism for encoding temporal information (Frerking & Ohliger-Frerking, 2012; Lerma & Marques, 2013; Straub et al., 2011). KARs also modulate the synaptic release of GABA and glutamate and aid in the maturation of neural circuits during development (Lerma & Marques, 2013). They are less evenly distributed in the brain than AMPA and NMDA receptors, with a higher rate of expression in hippocampus, cerebral cortex,

striatum, and cerebellar granule cell layer than other brain regions, though the reason for this specific pattern of expression is currently unknown (Foster et al., 1981; Straub et al., 2011).

While AMPARs and KARs mediate synaptic transmission, NMDARs are involved in inducing synaptic plasticity (Straub et al., 2011). NMDARs generate slow, long lasting EPSPs that are important in generating spike bursts (Grienberger, Chen, & Konnerth, 2014; Tong, Overton, & Clark, 1996) and in long-term potentiation and depression (Collingridge, Peineau, Howland, & Wang, 2010). NMDARs are often conceptualized as "coincidence detectors" of postsynaptic depolarization and glutamate release because a number of conditions must be met before NMDARs are able to open their ion channel pore (Dingledine, Borges, Bowie, & Traynelis, 1999; Goff & Coyle, 2001; Traynelis et al., 2010). Two molecules of glutamate are required to bind to the GluN2 subunits, while two molecules of glycine must also bind to the co-agonist site on the GluN1 subunits. Finally, in order to open the ion channel pore, the cell must be depolarized via AMPA and/or KA receptors; this depolarization removes a magnesium (Mg2+) block that is present in the ion channel pore at resting membrane potential. Collectively, these unique conditions allow NMDARs to act as "coincidence detectors"—the presence of presynaptic glutamate and depolarization of the cell by other glutamate receptors are *both* necessary for NMDAR activation.

Abnormalities have been noted in the expression of AMPA, KA, and NMDA receptors in schizophrenia; however, findings are inconsistent, with results varying by receptor subtype and brain region, and even within studies of particular subtypes and regions (for review, see Howes, Mccutcheon, & Stone, 2015). Inconsistencies may stem from differences in experimental technique or subject characteristics that can have an effect on post-mortem studies, such as differences in medication, length of illness, and age at death (Beneyto & Meador-Woodruff,

2008). Alternatively, differences may indicate complex abnormalities that are both region- and receptor subtype-specific (McCullumsmith, Clinton, & Meador-Woodruff, 2004; McCullumsmith, Hammond, Funk, & Meador-Woodruff, 2012), or may hint at an elaborate interplay of genetic and environmental risk factors, as well as heterogeneity of the clinical diagnosis in schizophrenia.

Despite a considerable amount of variation in the schizophrenia literature, there are a few consistent region-specific trends. Ligand binding studies in postmortem brains have consistently found increased KA receptors in the prefrontal cortex (Deakin, Slater, Simpson et al, 1989;Nishikawa, Takashima, & Toru, 1983) and decreased AMPA and KA receptors in the hippocampus in individuals with schizophrenia, (Kerwin, Patel, Meldrum et al., 1988; Kerwin, Patel, & Meldrum, 1990) but results for NMDA receptors have been less consistent. Studies using ligands that bind to the PCP binding site of NMDARs have not found consistent alterations in receptor availability, but increased binding has been demonstrated for the glycine site of NMDARs in primary sensory cortex (Ishimaru, Kurumaji, & Toru, 1992, 1994).

Receptor subunit cloning is another method used to measure receptor expression. Different receptor subunit compositions result in varying degrees of synaptic efficacy and plasticity, with certain subunits allowing for a varied degree of calcium conductance (Barry & Ziff, 2002; Bredt & Nicholl, 2003; Dingledine et al., 1999; Gardner, Trussell, & Oertel, 2001; Rubio & Wenthold, 1997). Abnormal proportions of receptor subunits may therefore affect receptor kinetics and neuronal function. Low levels of AMPA and KA receptor mRNA expression has been detected in hippocampus and parahippocampus in postmortem tissue samples of schizophrenia patients (Meador-Woodruff & Healy, 2000), while increased levels of unedited AMPA GluR2 subunit mRNA were found in PFC compared to healthy comparisons; a

higher proportion of GluR2 subunits would lead to increased Ca2+ permeability, increasing risk of neurotoxicity (Akbarian et al., 1996). Lower levels of AMPA, KA, and NMDA receptor mRNA expression has been found in the thalamus, along with lower binding to the polyamine and glycine sites of thalamic NMDARs (Ibrahim et al., 2000). Lastly, reduced expression of NMDAR subunit GluN1 expression has been noted in the hippocampus of schizophrenia samples. GluN1 subunits are necessary for NMDARs to function; reduced availability of GluN1 subunits in the hippocampus would result in diminished responsiveness of NMDARs in schizophrenia.

Despite a lack of consistent NMDA receptor expression abnormalities in schizophrenia, three general trends have emerged. First, protein expression shows fewer changes in schizophrenia than transcript expression, perhaps indicating that increased transcription may occur as a compensatory mechanism in the face of abnormal receptor expression or function (Kristiansen, Beneyto, Haroutunian, & Meador-Woodruff, 2006). Second, differences between schizophrenia and healthy groups tend to be most prominent in regions with reciprocal projections to limbic regions (Goff & Coyle, 2001). Third, recent evidence suggest that deficits are related more to the localization of the receptors rather than their density or function (Hammond, Shan, & Mccullumsmith, 2014). This finding has created interest in identifying receptor trafficking mechanisms and possible trafficking abnormalities in schizophrenia.

Receptor Trafficking Abnormalities in Schizophrenia

Glutamate receptors are targeted to the post-synaptic density (PSD), a protein-rich area on the post-synaptic membrane near the neurotransmitter active zone (Beneyto & Meador-Woodruff, 2008). Receptors are localized and inserted into the synaptic membrane by interacting with specific proteins in the PSD. These proteins also help regulate the receptor's

functionality and response to glutamate by modulating the receptor's signaling cascades through the linkage of intracellular effector molecules and signaling elements (Craven & Bredt, 1998; Garner, Nash, & Huganir, 2000; Hsueh and Sheng, 1998; Kennedy, 1997). Three PSD proteins in particular have garnered attention in schizophrenia research for their interaction with NMDA receptors; the synapse-associated protein SAP102, the postsynaptic density protein PSD95, and neurofilament-light (NF-L).

Synapse-associated protein SAP102 is a component of the cortical cytoskeleton that binds to the GluN2 subunit of NMDARs. This protein is involved in the transport of the receptor from the endoplasmic reticulum to the postsynaptic membrane (Sans et al., 2003). Though no changes have been measured in SAP102 protein in the brain overall in schizophrenia (Clinton, Haroutunian, Davis, & Meador-Woodruff, 2003; Toyooka et al., 2002), decreased levels of SAP102 protein have been noted specifically in the hippocampus (Toyooka et al., 2002). Like SAP102, PSD95 also binds to the GluN2 subunit. PSD95 couples NMDARs to intracellular proteins and signaling enzymes such as nitric oxide (Aarts et al., 2002). Increased PSD-95 has been observed in the thalamus in schizophrenia (Clinton, Haroutunian, Davis, & Meador-Woodruff, 2003; Toyooka et al., 2002), though results are less consistent in the cortex (Beneyto & Meador-Woodruff, 2008; Funk, Rumbaugh, Harotunian, McCullumsmith, & Meador-Woodruff, 2009; L V Kristiansen et al., 2006; Lars V. Kristiansen, Patel, Haroutunian, & Meador-Woodruff, 2010; Ohnuma, Augood, Arai, McKenna, & Emson, 1998). Neurofilament-light (NF-L) binds to GluN1, anchoring NMDARs to the cytoskeleton of the dendritic spine (Beneyto & Meador-Woodruff, 2008). There are reports of decreased NF-L transcript (Beneyto & Meador-Woodruff, 2008) and decreased NF-L protein expression (Kristiansen et al., 2006) in DLPFC. Decreased levels of NF-L could affect the stability of NMDARs in the postsynaptic

membrane through abnormal recycling and turnover of NMDARs in the dendritic spine, or their clustering at the synapse (Beneyto & Meador-Woodruff, 2008). Further study of receptor trafficking and localization in schizophrenia could prove to be fruitful in identifying whether glutamatergic hypofunction is a primary vulnerability factor of psychosis or a secondary response to other deficits, such as generalized cytoarchitectural or trafficking abnormalities.

CHAPTER 3

ANATOMICAL AND OSCILLATORY NETWORKS

Anatomical Differences in Schizophrenia

Aberrant neuronal migration and reduced synaptic connections are observed in schizophrenia. Although speculative, there is evidence to suggest that these differences in schizophrenia may be related to glutamatergic dysfunction, as the function of glutamate receptors plays a role in migration, neurite outgrowth, synaptogenesis, and pruning (Kerwin, 1993; McDonald & Johnston, 1990; McGlashan & Hoffman, 2000). Glutamate acts as a trophic factor, or a substance that allows neurons to develop and maintain connections with neighboring neurons. Both NMDA and non-NMDA receptors have been shown to be trophic factors during development, with NMDARs promoting granule-cell survival and stimulating neurite outgrowth (Balazs, Jorgensen, & Hack, 1988; Pearce, Cambray-Deakin, & Burgoyne, 1987) and KARs promoting synaptogenesis (Mattson, Dou, & Kater, 1988). Neuronal growth and maintenance also depend on microtubule assembly (Nunez 1986), and microtubule organization and stabilization, in turn, depends on glutamatergic stimulation (Bigot et al., 1991). With glutamatergic receptors playing such an active and wide-reaching role in the development and maintenance of neuro-architectural integrity, they remain a topic of interest in determining the mechanisms of structural differences in schizophrenia.

Increased ventricular volume, widespread decreases in grey matter volume (notably in dorsolateral prefrontal cortex (DLPFC), hippocampus, and thalamus, which are all regions connected by excitatory glutamatergic pathways; Goff & Coyle, 2001), and widespread

decreases in white matter volume are the most noted anatomical differences in schizophrenia. Suddath et al. (1990) examined MR images from 15 monozygotic twin pairs and found anatomical changes in the brains of nearly every schizophrenia twin, including enlargement in lateral and third ventricles and reductions in temporal lobe volume (including anterior hippocampus, and total gray matter volume in left temporal lobe) but not in unaffected twins. Increased ventricular volume in schizophrenia, particularly in lateral & third ventricles (Blackwood et al., 1991; Lieberman et al., 1992; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990) was one of the initial anatomical findings in schizophrenia research. Increased ventricular volume was often, though somewhat inconsistently, observed in schizophrenia using pneumoencephalography; larger ventricles in schizophrenia were later confirmed by Johnstone and colleagues using computerized tomography (CT) scans (1976, 1989). Ventricular enlargement in schizophrenia is present before clinical onset and in ultra-high risk individuals (Lawrie et al., 1999; Vita et al., 1994) as well as in first-episode patients (Cahn et al., 2005; Lim et al., 1996; Zipursky, Lambe, Kapur, & Mikulis, 1998), and a recent meta-analysis conducted by Fusar-Poli and coauthors (2013) indicates that increases in lateral ventricle volume are progressive throughout the illness. There is evidence to suggest that ventricular enlargement in schizophrenia is related to volume loss in the thalamus, particularly the medial nuclei and the adjacent striatum and insular cortex (Gaser, Nenadic, Buchsbaum, Hazlett, & Buchsbaum, 2004).

Widespread reductions have been noted in grey and white matter volume in CT and MRI studies of schizophrenia, with reductions most robust in frontal and temporal cortices as well as subcortical regions such as striatum and thalamus (Harrison, 1999; Okazaki, 1998; Suddath et al., 1990). Decreased grey matter volume is observed in both cerebral hemispheres (Pakkenberg,

1990). While bilateral changes are usually seen, the abnormalities are often more extensive in left hemisphere, particularly in the temporal lobe. Grey matter loss in schizophrenia is present early in the disease, with the most dramatic reduction in volume occurring within the first few years of symptom onset (Andreasen et al., 2011; Borgwardt et al., 2007; Cahn et al., 2002). A study by Borgwardt and colleagues (2007) also found reduced grey matter volume in individuals with very high risk of developing a psychotic disorder, particularly in left insula, superior temporal gyrus, cingulate gyrus, and precuneus. Longitudinal and cross-sectional studies suggest that grey matter volume loss is not progressive (for review, see Isobe et al., 2015), with rates of change similar to healthy groups across age. Post-mortem studies suggest that grey matter volume loss in schizophrenia is not due to neuronal loss itself, but rather cytoarchitectural changes in neuronal size, dendritic spine density, dendritic length, and synaptic proteins (Harrison, 1999). These changes in cytoarchitecture may be due to NMDAR dysfunction early in development, as NMDARs play a critical role in guiding axons to their targets during development (Rakic, Bourgeois, & Goldman-Rakic, 1994) and in synaptic pruning during adolescence (Feinberg, 1990).

Alternatively, several studies suggest that low levels of excitotoxicity may be the underlying cause of grey matter volume reduction in schizophrenia (Hertzman et al., 1990; Keshavan, 1999; Newcomer et al., 1999; Okugawa, Tamagaki, & Agartz, 2007; Olney & Farber, 1995). Excitotoxicity occurs when NMDA and AMPA receptors are overstimulated by excess glutamate. Ca^{2+} rushes into the neuron and activates enzymes that damage the cell membrane, cytoskeleton, and DNA; this damage leads to eventual cell death (Ankarcrona et al., 1995). Other studies have demonstrated that high doses of NMDAR antagonists induce excitotoxicity in pyramidal neurons and interneurons (Ikonomidou et al., 1999); administration of the non-

competitive NMDAR antagonist MK-801 in mice early in development results in apoptotic cell death, affecting nearly 50% of parvalbumin-expressing (PV+) interneurons and 42% of pyramidal neurons (Coleman, Jarskog, Moy, & Crews, 2009). Any excitotoxic effects in schizophrenia, however, are not accompanied by gliosis (Benes, Davidson, & Bird, 1986; Bogerts, Hantsch, & Herzer, 1983; Pakkenberg 1990; Roberts et al., 1986; Roberts, Colter, Lofthouse, Johnstone, & Crow, 1987). Gliosis is an increase in the number or size of glial cells, sometimes resulting in the formation of a glial scar, and is considered a necessary hallmark of neurodegenerative diseases (Oppenheimer, 1984). For this reason there remains a fair amount of controversy regarding whether there is a neurodegenerative component to schizophrenia. Some evidence suggests a progressive nature to the certain aspects of this disorder (Lieberman, 1999), but further study is needed to definitively determine whether schizophrenia is truly a neurodegenerative disease.

The observed differences in grey matter volume could also be affected by indirect or nonspecific aspects of illness, such as exposure to neuroleptics, nutritional status, or stress level (Suddath et al., 1990). However, many studies show no correlation between drug exposure or illness duration and the degree of anatomical change in patients (Golden et al., 1981; Kelsoe, Cadet, Pickar, & Weinberger, 1988; Nasrallah, Jacoby, McCalley-Whitters, & Kuperman, 1982; Shelton & Weinberger, 1986; Weinberger, Torrey, Neophytides, & Wyatt, 1979; Williams, Reveley, & Kolakowska, 1985; but see DeLisi, Sakuma, Maurizio, Relja, & Hoff, 2004). Additionally, evidence of enlarged ventricles and reduced hippocampal volume is seen in first-episode patients (Weipke Cahn et al., 2005; Lim et al., 1996; Seidman et al., 1999; Zipursky, Lamb, Kapur, & Mikulis, 1998), further indicating that these anatomical differences are not due

to exposure to neuroleptics or duration of the illness, but instead reflect disease pathology related to aberrant glutamatergic input during neuronal development.

Mounting evidence suggests that differences in grey matter volume in schizophrenia are accompanied by changes in white matter. Using MRI, Wible and colleagues (1995) reported correlations between white matter volume and temporal lobe grey matter volume reduction (particularly in superior temporal gyrus, the amygdala–hippocampal complex, and parahippocampal gyrus). Similar correlations were also reported between prefrontal white matter and reductions in amygdala-hippocampal complex volume (Breier et al., 1992), indicating a possible link between white and gray matter difference in schizophrenia. As was the case with grey matter volume, glutamatergic dysfunction may also underlie the observed changes in white matter in schizophrenia. Glutamate receptors have a significant effect in regulating oligodendrocyte progenitor cell proliferation and differentiation. Yuan and colleagues (1998) found that administration of AMPA and KA antagonists reduced the proliferation of certain oligodendrocyte progenitor cell groups, and Wang and coauthors (1996) demonstrated that NMDARs were important in regulating the migration of oligodendrocyte progenitor cells. Abnormalities in overall white matter volume have been reported in schizophrenia using magnetic resonance imaging (MRI).

There are reports of total white matter volume reductions in schizophrenia (Christensen, Holcomb, & Garver, 2004), though the current literature suggests that white matter deficits are predominantly located in temporal and frontal lobes (Burns et al., 2003; Kubicki et al., 2002; Paillère-Martinot et al., 2001; Sigmundsson et al., 2001; Spalletta et al., 2003). Interestingly, fronto-temporal connections have been implicated in the pathogenesis of schizophrenia in

models that frame schizophrenia as a disorder of connectivity (Friston & Frith, 1995; McGuire & Frith, 1996; Weinberger et al., 1992).

Structural Network Differences in Schizophrenia

Abnormal white matter connections in schizophrenia support hypotheses of dysconnectivity in psychosis, which suggest that the cognitive deficits observed in schizophrenia stem from compromised integration of cortical circuits. Compromised integration of cortical circuits could arise from insufficient connection of cortical nodes by axonal projections or from abnormal function of the cortical nodes themselves (Bullmore, Frangou, & Murray, 1997). There is a growing body of evidence of altered structural projections between distant cortical nodes in schizophrenia; these alterations in white matter tract integrity are investigated using diffusion tensor imaging (DTI).

DTI is a magnetic resonance method that can reveal the coherence, organization, and density of fiber tracts within white matter fiber bundles (Kubicki, McCarley, & Shenton, 2012). Fractional anisotropy (FA) is commonly used as an index of white matter coherence by quantifying the direction and magnitude of water diffusion in the brain detected by DTI sequences. FA values range from 0 to 1, with higher values indicating a greater degree of myelination or axonal coherence (Beaulieu, 2009; Song et al., 2002) and lower FA values reflecting axon death, myelin damage, axonal membrane damage, and/or reduced "fiber coherence" (Kubicki et al., 2007). Low FA is a common finding in schizophrenia (Gasparotti et al., 2009; Ohtani et al., 2014; Zhang, Stein, & Hong, 2010), and it is believed that low FA in schizophrenia are related to abnormal axon membranes and myelin sheath integrity (Davis, Stewart, Friedman, & Buchsbaum, 2003; Uranova et al., 2007). Altered myelination in schizophrenia is also supported by histological studies of postmortem brain tissue. Uranova and

coauthors (2004) found reduced number and size of oligodendrocytes in prefrontal and thalamic areas in schizophrenia. In line with these findings, Flynn et al. (2003) found reduced immunoreactivity in the oligodendrocyte-associated proteins cyclic nucleotide phosphodiesterase (CNPase) and myelin-associated glycoprotein (MAG), providing further evidence of abnormal myelination in schizophrenia.

Low FA values have been observed in schizophrenia in major fiber tracts such as the uncinate fasciculus, arcuate fasciculus, inferior longitudinal fasciculus, and corpus callosum (Ardekani, Nierenberg, Hoptman, Javitt, & Lim, 2003; Burns et al., 2003; Hubl, 2011). Collectively, these tracts connect regions in the temporal lobe to other frontal and occipital regions. The uncinate fasciculus connects limbic areas of the temporal lobe, such as the hippocampus and amygdala, with frontal regions; the arcurate fasciculus connects temporal cortex and inferior parietal cortex to areas of the frontal lobe, and the inferior longitudinal fasciculus connects the temporal lobe and occipital lobe (Catani & de Schotten, 2008). Disturbances in the connectivity of major fiber tracts may underlie abnormal functional integration of cognitive processes (Stephan, Friston, & Frith, 2009), such as auditory sensory, language, and memory processing, all of which are well established in schizophrenia (Bilder et al., 2000; DeLisi, 2001; Rabinowicz, Silipo, Goldman, & Javitt, 2000; Saykin et al., 1994). In addition to evidence suggesting dysconnectivity in structural networks such as axonal projections, there is also evidence of aberrant oscillatory network synchrony in schizophrenia. Glutamatergic function plays a role in the connectivity of oscillatory networks. The mechanisms by which glutamate affects network synchrony are discussed below.

Oscillatory Networks: GABA and the Gamma Band

Gamma oscillatory disturbances are reported in schizophrenia. Synchronization of neuronal activity within the gamma frequency band (~30-100 Hz) is believed to be the neural substrate of cognition (Gonzalez-Burgos & Lewis, 2012) as it provides the temporal structure for information processing (Bartos, Vida, & Jonas, 2007). Gamma band synchronization may play an important role in the flow of neural activity within and between cortical regions (Fries, 2009) and may represent sensory binding (Gray & Singer, 1989) as well as the storage and recall of information (Buzsaki & Chrobak, 1995; Lisman & Idiart, 1995). Dysfunction in the gamma band is thought to underlie cognitive deficits (Lesh, Niendam, Minzenberg, & Carter, 2011; Lewis & Sweet, 2009), and disruptions in gamma band synchrony and cognitive deficits are both displayed in schizophrenia. Moreover, abnormalities in the balance of excitation and inhibition in corticolimbic circuits have been implicated in mood disorders as well as in schizophrenia (Brambilla, Perez, Barale, Schettini, & Soares, 2003; Sanacora & Saricicek, 2007).

Network oscillations in the gamma band depend on excitatory drive from glutamatergic pyramidal cells and inhibitory input from GABAergic interneurons (Whittington, Traub, & Jeffreys, 1995). Specifically, glutamatergic pyramidal cells provide phasic excitatory drive on GABAergic interneurons; in turn, the activated interneurons synchronize the pyramidal cells via feedback inhibition (see Figure 1), eliciting rhythmic inhibitory postsynaptic potentials (IPSPs) in pyramidal cells (Uhlhaas & Singer, 2010). GABA is the primary inhibitory neurotransmitter in the human cortex (Ribak & Yan, 2000). A single GABA neuron may synchronize hundreds of pyramidal cells (Cobb, Buhl, Halasy, Paulsen, & Somogyi, 1995), and the duration of the pyramidal cell IPSPs determines the frequency of oscillations within that network (Wang & Buzsáki, 1996).

Synchronization in the gamma band relies heavily on the activation of a specific type of fast-spiking GABA neuron which contains the protein marker parvalbumin (Cardin et al., 2009; Sohal, Zhang, Yizhar, & Deisseroth, 2009). There are two main types of parvalbumin positive (PV+) GABA neurons, PV+ basket cells (PVBCs), which innervate soma and proximal dendrites of pyramidal cells, and PV+ chandelier cells, which innervate the axon initial segment of pyramidal cells (Gonzalez-Burgos & Lewis, 2012). However, many lines of evidence suggest that only PVBCs contribute to the synchronization of gamma rhythms. The fast spiking patterns of PVBCs is phase locked to the gamma rhythm (Jonas, Bischofberger, Fricker, & Miles, 2004), and as PVBCs mature in rats, synchronization increases in the gamma range (Goldberg et al., 2011). Additionally, selective optogenetic activation of PVBCs amplifies gamma power (Cardin et al., 2009, Sohal et al., 2009). Conversely, GABAergic inputs from PV+ chandelier cells onto pyramidal cells appear to be excitatory (Szabadics et al., 2006), thus having little contribution to the rhythmic IPSPs that give rise to network synchronization. Thus, PVBCs appear to be the GABA interneuron subtype that contributes the most to the generation of gamma band synchrony.

AMPA vs NMDA Contribution to Gamma Synchrony

It has been proposed that abnormalities in gamma band and the concomitant deficits in cognitive abilities in schizophrenia may be due to hypofunction of glutamatergic signaling, as inhibitory GABAergic interneurons rely on excitation via AMPA and NMDA glutamate receptors. AMPAR-mediated excitation of PV+ cells has been shown to be crucial in the production of gamma oscillations (Fuchs et al., 2007). Excitatory postsynaptic currents (EPSCs) from AMPARs are short, providing the fast timescale necessary to generate high-frequency oscillations such as those in the gamma band. Additionally, EPSCs from AMPARs have been

shown to be sufficient to support gamma oscillations (Rotaru, Yoshino, Lewis, Ermentrout, & Gonzalex-Burgos, 2011) and elicit a large amplitude response in PVBCs (Gonzalez-Burgos & Lewis, 2012). Fuchs et al. (2007) demonstrated reduced excitation of fast-spiking interneurons in AMPAR knockout mice, which resulted in reduced gamma oscillations in hippocampal slices.

In contrast to the action of AMPARs on PV+ interneuron excitation, NMDAR currents are slow and long lasting. The slow kinetics of NMDARs is contrary to the extremely fast-spiking behavior of PV+ interneurons (Hu, Martina, & Jonas, 2010), and produces delayed firing of postsynaptic interneurons which is not locked to the pyramidal cell inputs (Maccaferri & Dingledine, 2002; Rotaru et al., 2011). NMDAR-mediated excitatory postsynaptic currents (EPSCs) in PV interneurons are also much weaker compared to those elicited by AMPARs (Gonzalez-Burgos & Lewis, 2012). Although this evidence suggests that NMDARS do not seem to play a primary role in the initiation of PVBC excitation, NMDARs do seem to be important in the modulation of PVBC-induced gamma band synchronization. Administration of NMDAR antagonists has been shown to either disrupt (Cunningham et al., 2006) or potentiate (Kehrer et al., 2007) gamma rhythms, as well as eliciting cognitive deficits similar to those in schizophrenia (Coyle, Tsai, & Goff, 2003; Javitt & Zukin, 1991). Moreover, optogenetic disruption of NMDARs in fast-spiking interneurons led to disrupted gamma band oscillations and associated deficits in working memory and associative learning in mice (Carlén et al., 2012), and computational models suggest that the sustained excitatory drive on fast-spiking interneurons from NMDARs is necessary for proper gamma band oscillatory behavior (Kirli, Ermentrout, & Cho, 2014). Compte and colleagues (2000) reconcile the differing effects of AMPA and NMDA time courses on PV+ interneurons by suggesting that AMPARs provide the timescale for the gamma rhythm, while NMDARs have a more modulatory effect on the gamma rhythm.

An additional hypothesis of the role of NMDARs in the generation of gamma rhythms is that NMDAR dysfunction in early development affects the function of PV+ interneurons differently than it does in the adult brain. Deletion of NMDARs in mice early in development led to behavioral alterations similar to those in schizophrenia in adulthood (Belforte et al., 2010; Wang, 2010). This corroborates studies that show that NMDAR current have strong inputs onto PV+ interneurons early in development, which weaken over time and may even become absent in adult PV+ interneurons (Wang & Gao, 2009, 2010). The reduced contribution of NMDARs on gamma oscillations during development appears to optimize gamma oscillation production as cortical circuits are refined (Wang & Gao 2009; Wang & Gao 2010). Thus, NMDAR hypofunction appears to have a more robust effect on the functioning of GABA neurons early on in development, when PV+ interneurons are still strongly influenced by NMDARs. This dysfunction occurs years before other psychotic symptoms become present, and corroborates the consistent evidence that cognitive deficits are present years before the first episode of psychosis occurs (Cannon et al., 2000; Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Erlenmeyer-Kimling et al., 2000; Jones, Murray, Rodgers, & Marmot, 1994; Niendam et al., 2006).

In sum, gamma band synchrony depends on excitatory drive from glutamatergic neurons. Disruptions gamma band synchrony in schizophrenia most likely stem from NMDAR hypofunction early in development and may be exacerbated by suboptimal AMPAR-mediated signaling. These disruptions account for the cognitive deficits in schizophrenia and are present early in development, well before psychotic (positive and negative) symptoms are manifested. Overall, evidence supports glutamatergic dysfunction as an important factor underlying the cellular, structural, and functional abnormalities that characterize schizophrenia. However, the

factors that contribute to glutamatergic dysfunction itself are still unknown. Genetic studies are well positioned to explain the mechanisms leading to glutamatergic dysfunction, and may be an invaluable technique in understanding the etiology of complex mental illnesses such as schizophrenia.

CHAPTER 4

GENETIC EVIDENCE OF GLUTAMATERGIC DYSFUNCTION IN SCHIZOPHRENIA

Genetic studies of neuropsychiatric illnesses have had relatively little success compared to other illnesses, both neurological and otherwise. The difficulty in identifying risk genes for psychiatric syndromes may stem from the complex interactions between development, anatomical structure, circuit dynamics, and environmental influences on phenotype expression. Additionally, a problem arises when flaws in the diagnoses themselves prevent accurate gene identification; this occurs when studies aim to match genes to current diagnostic categories that are highly heterogeneous and largely invalid, based on collections of subjective symptom expression rather than objective physiological testing. Despite these limitations, however, moderate progress has been made toward identifying genes associated with risk for developing schizophrenia.

Heredity

The rate of heritability in schizophrenia is consistently reported between 80-85%, however, twin studies of schizophrenia show concordances around 41–65% in monozygotic (MZ) pairs and 0–28% in dizygotic (DZ) pairs (Cardno & Gottesman, 2000). Concordance rates of less than 100% in monozygotic twins indicate an interaction between both genetic and non-inherited risk factors, further exacerbating the difficulty in identifying mechanisms of schizophrenia risk. The recent availability of genome-wide sequencing, however, have aided in the understanding of the genetic factors associated with risk for developing schizophrenia. Genome-wide association studies (GWAS) were previously limited due to the prohibitively high

monetary and time costs of genetic sequencing, which forced researchers to limit their search by a priori identification of genes that were believed to play a role in the illness based on symptomatology. GWA studies have become cheaper, faster, and more readily available due to a range of developments, such as biobanking (Greely, 2007), high-capacity genotyping arrays that allow for the investigation of genes in parallel (Schena, Sahlon, Davis, & Brown, 1995), and initiatives such as the HapMap project that identify the most common DNA sequence variants and their relative frequencies in samples around the world (Gibbs et al., 2003). Now that GWAS techniques are more feasible, researchers have the freedom to explore genetic associations with far less limitation.

GWA Studies of Schizophrenia

GWAS allow for the identification of single nucleotide polymorphisms (SNPs). A SNP is a difference in nucleotide (e.g. a guanine instead of an adenine) in the DNA string. Though SNPs occur somewhat frequently in people, they can act as a biological marker of a gene that may be associated with a disease, as SNPs located within a regulatory region of a gene may affect the gene's function. In the 1970's, SNPs were found on the region of a gene complex now known as Disrupted-In-Schizophrenia-1 (DISC1). The DISC1 gene complex has since been implicated in cell migration, neurite outgrowth, and synaptogenesis (Kamiya et al., 2006; Millar et al., 2000; Ozeki et al., 2003). Though DISC1 was originally linked to, and named after, schizophrenia, further study revealed that mutations within this complex are not exclusive to schizophrenia, but is instead related to risk for several psychiatric disorders including bipolar disorder, major unipolar depression, and autism spectrum disorders (Blackwood et al., 2001; Kilpinen et al., 2008; Millar et al., 2000).

GWAS studies investigating SNPs have implicated several candidate genes involved in glutamate neurotransmitter systems, with genome-wide significant findings for loci encompassing genes that encode for glutamate receptor subunits (*GRIA1*, *GRM3*, *GRIN2A*), genes that act to modify NMDAR activity (SRR and DAOA, also known as G72), as well as the dopamine D2 receptor (DRD2) (Ripke et al., 2014). *GRIA1* codes for the AMPA receptor subunit GluA1 (Collingridge et al., 2010) and *GRM3* codes for metabotropic glutamate receptors, (Bishop et al., 2014), while *GRIN2A* codes for the NMDA receptor subunit GluN2A (Takano et al., 1993). SRR encodes serine racemase, which is an enzyme that generates D-serine; D-serine activates NMDA receptors in the brain (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). DAOA encodes for D-amino acid oxidase activator, which increases D-amino acid oxidase (DAAO) activity; DAAO encodes a D-serine degrading enzyme which plays an active role in regulating the availability of D-serine. Four SNPs in particular on the DAAO gene have been linked to schizophrenia (Chumakov et al., 2002). *DRD2* encodes the D2 subtype of the dopamine receptor; the SNPs associated with schizophrenia are thought to increase D2 availability (Duan et al., 2003; Hirvonen et al., 2004). Although the effects of the SNPs on the function of these candidate genes are for the most part not well understood, they suggest a model where dysregulation of cortico-limbic GABAergic interneurons and/or enhanced cortico-limbic dopamine signaling could result in disinhibition of glutamatergic pyramidal cells, which would disrupt cortical processing.

In addition to mutations in genes regulating glutamate receptor function, studies have also found mutations that affect GABA. Mutations in the gene neuregulin 1 have been linked to risk for schizophrenia; this gene regulates NMDAR function and also modulates PV+ interneuron signaling through the receptor tyrosine kinase ErbB4 (Gu, Jiang, Fu, Ip, & Yan,

2005; Huang et al., 2000; Okada & Corfas, 2004; Ozaki, Sasner, Yano, Lu, & Buonanno, 1997; Rieff et al., 1999). A SNP in Gad1 is associated with decreased expression of Gad1 mRNA in prefrontal cortex in schizophrenia (R. E. Straub et al., 2007). The gene Gad1 encodes GAD67, one of two homologues of glutamic-acid-decarboxylase (GAD), which is the rate limiting enzyme in the production of cortical GABA.

Whole-genome array-based association methods, when applied to collaborative studies with large sample sizes, also allow for the detection of de novo ("new") copy number variant (CNV) mutations and indels (insertions or deletions in the DNA base). By comparing a patient to their unaffected biological parents, rare de novo CNVs can be identified by investigating mutations that are only present in the patient, revealing unique and potentially pathogenic variations related to the illness. Recent evidence investigating de novo CNVs that contribute to risk for schizophrenia is converging on proteins that play a role in regulating synaptic plasticity (Kenny et al., 2014; Pinto et al., 2010). Kirov et al. (2012) identified de novo CNVs at four loci that have been previously implicated in schizophrenia, 3q29, 15q11.2, 15q13.3, and 15p11.2. Several of these CNVs spanned genes that encode the discs large (DLG) family of membrane-associated guanylate kinases (MAGUKS) that are components of the postsynaptic density (PSD). Additionally, two CNVs spanned tEu-MTase1 (EHMT1), which is a histone methyl transferase that directly regulates the DLG family.

Because these CNV mutations have an effect on the function of several genes, it becomes difficult to link the mutation to specific mechanisms related to the pathology of a disorder. To overcome this issue, Kirov and colleagues (2012) used a systems-based approach to reveal biological pathways that were enriched for genes affected within the loci of the previously identified CNVs. They found that de novo CNVs were enriched for the postsynaptic density

proteome, particularly affecting members of the NMDAR and neuronal activity-regulated cytoskeleton-associated protein (ARC) gene families. These results support the hypotheses implicating aberrant NMDA receptor function in schizophrenia pathology and corroborate earlier reports of PSD abnormalities in schizophrenia.

Interestingly, recent genetic studies indicate that there is much greater overlap in etiological factors of disorders (such as schizophrenia, autism spectrum disorders, and intellectual disability) than is currently accounted for in traditional diagnostic schemes (Owen, 2012). Current literature suggests stronger findings for general risk across psychopathology (and across a spectrum of psychotic disorders), rather than specific findings for particular disorders. A study by the Psychiatric Genomics Consortium (2013), which pooled GWAS data from over 19 countries, examined genetic risk shared between schizophrenia, bipolar disorder, depression, and autism. They found that general risk for psychiatric illness seems to point to genes coding for calcium channels (CACNA1C, CACNB2, CACNA1I) or immunological issues (CD19, CD20). Shared risk across the 5 disorders was also linked to gene 10q24 on chromosome 10. Rather than being discouraging, null results and overlapping findings indicate an important link between disorders. These issues open up new lines of research aimed at revealing the biological etiologies--as well as refining the definition and diagnosis--of psychiatric illnesses.

CHAPTER 5

FINDINGS ACROSS THE PSYCHOSIS SPECTRUM

Heterogeneity within the diagnostic groups in the psychosis spectrum has been a major hindrance in determining the etiology of schizophrenia, bipolar disorder, and schizoaffective disorder. Several converging lines of evidence suggest considerable overlap across these disorders, and mounting research suggests that the traditional dichotomy between schizophrenia and affective disorders may not be biologically valid (Craddock & Owen, 2010). Current categorization schemas lead to heterogeneity within each diagnosis; for example, a typical sample of bipolar disorder will include both psychotic and nonpsychotic individuals; furthermore, bipolar groups often include both mood-congruent and mood-incongruent psychotic symptoms. Likewise, a typical sample of individuals with schizophrenia may include those who are purely psychotic as well as those who also display affective symptoms. In addition to heterogeneity within diagnosis, the tradition of not allowing for comorbidity in study groups leads to a poor reflection of reality, as comorbidity between schizophrenia and BP is estimated at 63% (Lichtenstein et al., 2009), with significantly elevated risk of bipolar disorder in siblings of probands with schizophrenia. Using a *non*-hierarchical lifetime-ever approach to defining disease groups, however, allows a patient to be comorbid for both schizophrenia and bipolar disorder. A study by Cardno and colleagues (2002) re-analyzed their data using a non-hierarchical lifetime-ever approach and found a significant genetic correlation of 0.68 between schizophrenia and bipolar disorder in monozygotic twin pairs, despite previously finding no genetic correlation between the groups using a hierarchical diagnostic scheme. A similar study

(Lichtenstein et al., 2009) found elevated risk for both disorders in the siblings of probands even when probands with comorbidity were excluded; thus, the familial coaggregation is not driven by comorbidity.

Family, Twin, and adoption studies show notably similar patterns of heritability for illnesses in the psychosis spectrum, with 70-80% heritability reported for both bipolar disorder and schizoaffective disorder (Cardno et al., 1999; Lichtenstein et al., 2009; McGuffin et al., 2003; for review, see Cardno & Owen, 2014). However, twin studies of schizoaffective and bipolar disorder show concordances around 40-45% in monozygotic twins and 0-10% in dizygotic twins (Allan et al., 2009; Cardno & Gottesman, 2000; Kieseppä, Partonen, Haukka, Kaprio, & Lönnqvist, 2004; McGuffin et al., 2003); similar to schizophrenia, these concordance rates of less than 100% in monozygotic twins indicate a complex interaction between both genetic and non-inherited risk factors. With such extensive overlap in heritability across disorders in the psychosis spectrum, recent studies have focused on determining whether abnormalities in glutamatergic neurotransmission underlie bipolar and schizoaffective disorder as well as schizophrenia.

Abnormalities in glutamate transmission have been suggested in major depression and bipolar disorder (Belsham, 2001; Du et al., 2004; McCullumsmith & Meador-Woodruff, 2002; J H Meador-Woodruff, Hogg Jr., & Smith, 2001; Molnar, Potkin, Bunney, & Jones, 2003; Mueller & Meador-Woodruff, 2004; Woo, Walsh, & Benes, 2004). Compared to healthy participants, reduced GluN1 subunit mRNA expression was found in the hippocampus in BP (Law & Deakin, 2001), along with lower binding at the MK-801 site of the NMDAR (Scarr, Pavey, Sundram, MacKinnon, & Dean, 2003). Beneyto and Meador-Woodruff (2008) found altered GluN1 subunit transcripts in DLPFC in BP, as well as decreased transcripts encoding

SAP102. SAP102, the PSD protein that binds to the GluN2 subunit, plays a role in transporting NMDARs from the endoplasmic reticulum to the postsynaptic membrane (Sans et al., 2003). Reduced SAP102 in BP has also been observed by McCullumsmith et al. (2007) in the hippocampus and by Clinton and Meador-Woodruff in the thalamus (2004), indicating abnormal intracellular signaling and trafficking of glutamatergic receptors in BP.

Similar to schizophrenia, several anatomical abnormalities are found in BP. Ventricular enlargements are reported for general affective psychosis, though with a smaller effect size than in schizophrenia (Elkis et al., 1995), and some evidence points to ventricular enlargement in BP (Bearden, Hoffman, & Cannon, 2001) in those who have more severe illness expression or more frequent episodes (Paolo Brambilla et al., 2001; Hauser et al., 2000; Stephen M. Strakowski et al., 2002). CT and MRI studies of affective disorders have found abnormalities in cortical sulci, lateral ventricle, striatum, pituitary, and adrenal glands (Okazaki, 1998). Increased volume in temporal lobe has been noted in BP (Harvey, Persaud, Ron, Baker, & Murray, 1994), though other studies report no volume differences in hippocampus between BP and healthy comparisons (Altshuler et al., 2000; Hauser et al., 2000; Hirayasu et al., 1998; Pearlson et al., 1997; Strakowski et al., 1999). More severe reductions in temporal lobe volume in schizophrenia has been attributed to grey matter reduction, an effect that seems to be specific to schizophrenia, as general reductions in grey matter have not been observed in BP (McDonald et al., 2004).

Though grey matter seems to be unaffected in BP, there is evidence of a loss of white matter network connectivity in BP, particularly in prefrontal and frontal regions (Heng, Song, & Sim, 2010). Less consistent evidence also points to deficits in subcortical and non-frontal lobes (Adler et al., 2004; Beyer et al., 2005; Mahon et al., 2009; McIntosh et al., 2008). Abnormal myelination and white matter changes in BP, though less extensive than in schizophrenia,

suggest that hypotheses of dysconnectivity is not exclusive to schizophrenia, but instead extends to other pathologies within the psychosis spectrum.

In addition to evidence suggesting reduced white matter network connectivity, there is also evidence of abnormal oscillatory network activity in BP. Enhanced gamma oscillations were observed prior to stimulus presentation in both schizophrenia and BP (Hamm et al., 2012), and late gamma band enhancements in response to target stimuli differentiated BP from schizophrenia and H in a study by Ethridge and colleagues (2012). Reduced gamma band activity in BP, however, was observed by Ozerdem and colleagues (2011). Gamma rhythms are involved in lower-order primary sensory representation (Singer & Gray, 1995) as well as higher-order cognitive functions such as selective attention and working memory (Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998; Tiitinen et al., 1993); thus, the aberrations observed in gamma band activity in BP align with observed cognitive impairments in deficits in working memory, cognitive control, and processing of emotional stimuli (Kerr, Scott, & Phillips, 2005; Lyon, Startup, & Benall, 1999; Murphy et al., 1999; Rajkowska, Halaris, & Selemon, 2001; Stephen M. Strakowski et al., 2005). Overall, differences in gamma band signaling suggest that aberrant glutamate-GABA interactions may extend to BP as well as schizophrenia. Further study would be fruitful in determining whether the deficits in gamma band in schizophrenia and BP stem from divergent or convergent mechanisms. Genetic studies of affective disorders may offer important starting points in narrowing down mechanisms of interest.

A recent meta-analysis of bipolar disorder investigated 4 GWAS studies (total 8760 probands and 11763 healthy comparisons) and found gene mutation enrichment in pathways involving glutamate receptor signaling, hormone regulation, calcium channel, and second messenger systems (Nurnberger et al., 2014). Other collaborative GWAS studies have identified

single-nucleotide polymorphisms (SNPs) in voltage-gated calcium channel CACNA1C and ankyrin 3 (ANK3), both of which have been implicated in schizophrenia. However, studies investigating copy number variants (CNVs) in BP have found no evidence of increased burden of rare, large CNVs, even suggesting that they are less common in BP than in healthy comparisons (Grozeva et al., 2010, 2013; McQuillin et al., 2011). This evidence diverges from findings implicating pathogenic CNVs contributing to risk for developing schizophrenia and suggests that in addition to shared risk factors, there are also unique genetic risk factors that contribute to the risk for schizophrenia or BP. As genetic technology continues to become more feasible and affordable, and as more optogenetic techniques become available to manipulate identified genes and mechanisms, the findings will help progress us toward a more thorough understanding of the etiology of illnesses within the psychosis spectrum.

CHAPTER 6

DISCUSSION AND CONCLUSIONS

Because it encompasses so many aspects of the clinical and physiological presentation of psychosis, glutamatergic dysfunction, and NMDAR hypofunction in particular, remains a popular hypothesis of schizophrenia, and is emerging as a potential mechanism of psychotic illnesses at large. Thus, understanding the role of dysfunction of the glutamatergic neurotransmitter system is of paramount importance in elucidating the etiology of psychotic illness, especially as redefining complex mental illness based on a dimensional approach spanning a full range of research domains becomes a predominant focus in psychiatric research. Future research of the effects of glutamatergic neurotransmission abnormalities promises to uncover the etiology of psychotic illnesses, with the ultimate goal of creating more accurate and effective diagnosis and treatment of these devastating disorders. In order to successfully hone in on a biological mechanism undergirding schizophrenia, however, it may first be necessary to redefine how schizophrenia is diagnosed, moving away from symptom-based diagnostic schemes and instead focusing on evidence for biological differentiation across the psychosis spectrum.

The current diagnostic scheme for schizophrenia is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) as it is the current gold (albeit often poor) standard for diagnosing mental illness. In the DSM-V, disease constructs are based on clinical phenomenology and illness course; for example, schizophrenia and bipolar disorder are characterized by psychotic and mood symptoms respectively, and are thus diagnosed as distinct and separate entities. While this approach to diagnostics has improved reliability in identifying

mental illnesses, there is mounting evidence that these existing disease constructs may lack biological validity (see Keshavan, Clementz, Pearlson et al., 2013 for review). For example, neither schizophrenia nor bipolar disorder "breed true" (Lichtenstein et al., 2009a; Cardno, Rijsdijk, West, et al., 2012; Gershon, Badner, Goldin, et al., 1998), and there is little evidence for a natural boundary, or "zone of rarity," between psychotic illnesses as currently diagnosed (Kendell & Gourlay, 1970; Kendell & Jablensky 2003). Issues related to questionable biological validity in current DSM-based diagnostic constructs, such as overlap across and heterogeneity within groups, have contributed to the difficulty in determining the etiology of psychotic disorders and hindered advances in disease treatment and prevention. For this reason, a reconceptualization of psychotic illnesses as a continuum informed by biological differentiation rather than clinical phenomenology alone, may reduce heterogeneity within, and better differentiate, disease groups; thus providing a potential aid in understanding the etiology of psychotic illnesses (Keshavan et al., 2011; Henry & Etain, 2010; Skudlarski et al., 2013).

Neurophysiological markers of schizophrenia have gained attention in recent studies that aim to inform disease classification and etiology based on biological differentiation of psychosis groups (Clementz, Sweeney, Hamm, et al., 2015). A promising avenue for identifying neurophysiological markers of schizophrenia lies in studies that probe the auditory system, as deviations in auditory processing are core features of the disorder. As opposed to tasks that require input from people with schizophrenia (which is often confounded by the presence or absence of symptoms) auditory tasks can be elicited by passively listening to simple stimuli, and are easily and reliably measured using non-invasive neuroimaging techniques such as electro- and magneto-enchephalography (EEG and MEG, respectively). Auditory studies can be used to examine glutamatergic hypofunction in schizophrenia by probing the synchrony of gamma band

oscillations (30-90 Hz). The gamma band has been implicated in the formation and maintenance of cell assemblies during sensory processing (Veirling-Claassen, Siekmeier, Stufflebeam, & Kopell, 2008; Farmer 1998), with gamma activity ostensibly important in forming coherent percepts during sensory processing in local circuitry (Jokeit & Makeig, 1994; Engel & Singer, 2001). Further, certain gamma band abnormalities in schizophrenia have been found to be heritable (Hall et al., 2011), highlighting their potential as a phenotypic marker that may inform biological differentiation of psychosis groups. Thus, dysfunction within this frequency band could underlie disruptions in sensory processing, contributing to disorganized symptoms in schizophrenia (Haig et al., 2000; Phillips & Silverstein, 2003).

Augmented gamma band activity in schizophrenia is consistent with the N-methyl-D-aspirate (NMDA) receptor hypofunction model of schizophrenia (Javitt, 2007; Rujescu et al., 2006). Cortical network synchrony, supported by oscillations in the gamma band, relies on inhibitory neurotransmission from GABAergic interneurons, which act as pacemaker cells by eliciting rhythmic inhibitory postsynaptic potentials (IPSPs) in pyramidal cells (Uhlhaas & Singer, 2010). GABA is the primary inhibitory neurotransmitter in the human cortex (Ribak & Yan, 2000). A single GABA neuron may synchronize hundreds of pyramidal cells (Cobb, Buhl, Halasy, Paulsen, & Somogyi, 1995), and the duration of the pyramidal cell IPSPs determines the frequency of oscillations within that network (Wang & Buzsáki, 1996). Synchronization of activity in the gamma frequency band (~30-100 Hz) is believed to provide temporal structure for information processing (Bartos, Vida, & Jonas, 2007) and is believed to be the neural substrate of cognition (Gonzalez-Burgos & Lewis, 2012). Gamma band synchronization may play an important role in the flow of neural activity within and between cortical regions (Fries, 2009) and may represent sensory binding (Gray & Singer, 1989) and the storage and recall of information

(Buzsaki & Chrobak, 1995; Lisman & Idiart, 1995). Gamma band synchronization has also been identified as a potential amplifier of salient neural signals (Donoghue et al., 1998; Fries, Roelfsema, Engel, König, & Singer, 1997; Gruber, Müller, Keil, & Elbert, 1999; Maldonado, Friedman-Hill, & Gray, 2000; Müller, Keil, Kissler, & Gruber, 2001). Specifically, gamma oscillations, controlled by fast-spiking parvalbumin-containing interneurons, promote the transmission of signals within local cortical microcircuits in a bottom-up manner, with increased gamma band synchrony corresponding to amplification of attended signals (Fries, Reynolds, Rorie, & Desimone, 2001; Sohal, Zhang, Yizhar, & Deisseroth, 2009).

Dysfunction in the gamma band is thought to underlie the cognitive deficits observed in schizophrenia (Lesh, Niendam, Minzenberg, & Carter, 2011; Lewis & Sweet, 2009). Cognitive deficits are considered a core feature of schizophrenia, are critically related to functional outcomes, and have been shown to be present more consistently in patients over time than positive or negative symptoms (Simpson, Kellendonk, & Kanel, 2010; Gold, 2004; Lesh, Niendam, Minzenberg, & Carter, 2011; Bestelmeyer et al., 2009). Moreover, abnormalities in the balance of excitation and inhibition in corticolimbic circuits related to cognitive deficits have been implicated in mood disorders as well as in schizophrenia (Brambilla, Perez, Barale, Schettini, & Soares, 2003; Sanacora & Saricicek, 2007), underscoring the importance of understanding glutamatergic neurotransmitter system dysfunction across psychotic disorders.

Conclusion

Although schizophrenia is a psychiatric illness that typically leaves affected individuals unable to attain social and occupational fulfillment and fills more hospital beds than any other illness, psychiatric or otherwise (Buchanan & Carpenter, 2000), we currently lack a definitive understanding of the mechanisms underlying this disorder. Thomas Insel (2010), former director

of the National Institute of Mental Health, has stated, "A century ago we had large public institutions for serious mental illness, tuberculosis and leprosy. Of these three, today only mental illness, especially schizophrenia, remains unchanged in prevalence and disability" (p.187). The dearth of information on the etiology of schizophrenia, which has perpetuated suboptimal diagnostic and treatment options, necessitates further research into the systems that give rise to schizophrenia and other psychotic disorders.

Based on the evidence reviewed here, understanding the role of glutamatergic neurotransmitter dysfunction in schizophrenia may lead to breakthroughs in elucidating the etiology of schizophrenia (and differentiation from other psychotic illnesses, such as bipolar disorder). Studies aimed at such topics are especially timely, as redefining complex mental illness based on a dimensional approach spanning a full range of research domains has become a predominant focus in psychiatric research (Insel, 2014). Future studies aimed at determining whether glutamatergic hypofunction is a primary vulnerability factor of psychosis or a secondary response to other deficits, such as generalized cytoarchitectural or trafficking abnormalities, will be necessary in understanding the etiology of schizophrenia. As our understanding of the biological correlates of schizophrenia improves, so too will our ability to diagnose psychotic disorders based on neurophysiological differentiation, which promises to benefit genetic studies. Future research on the effects of glutamatergic neurotransmission abnormalities promises to allow a more thorough understanding of the etiology of psychotic illnesses, with the ultimate goal of creating more accurate and effective treatments of these devastating disorders.

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FIGURE

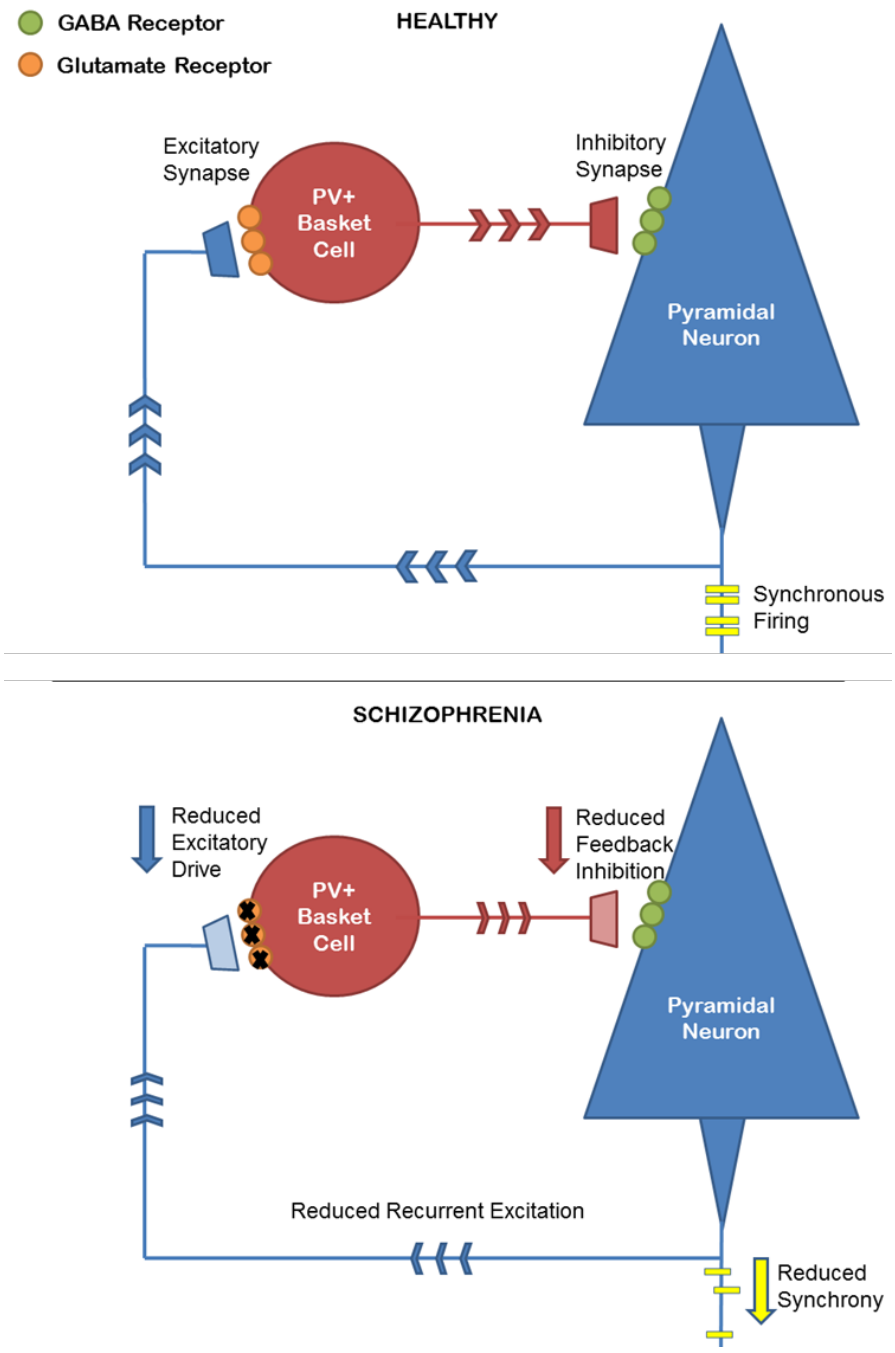

Figure 1. Network oscillations in the gamma band depend on the interplay between PV+ Basket Cells (PVBCs) and excitatory pyramidal cells. Glutamatergic pyramidal cells provide phasic excitatory drive on PVBCs; in turn, the activated PVBCs synchronize the pyramidal cells via feedback inhibition. When excitatory drive is reduced (via NMDAR hypofunction) in schizophrenia, gamma band synchrony is also reduced.