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Prenatal Ontogeny as a Susceptibility Period for Cortical GABA Neuron Disturbances in Schizophrenia

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Abstract

Cognitive deficits in schizophrenia have been linked to disturbances in GABA neurons in the prefrontal cortex. Furthermore, cognitive deficits in schizophrenia appear well before the onset of psychosis and have been reported to be present during early childhood and even during the first year of life. Taken together, these data raise the following question: Does the disease process that produces abnormalities in prefrontal GABA neurons in schizophrenia begin prenatally and disrupt the ontogeny of cortical GABA neurons? Here, we address this question through a consideration of evidence that genetic and/or environmental insults that occur during gestation initiate a pathogenetic process that alters cortical GABA neuron ontogeny and produces the pattern of GABA neuron abnormalities, and consequently cognitive difficulties, seen in schizophrenia. First, we review available evidence from postmortem human brain tissue studies characterizing alterations in certain subpopulations of prefrontal GABA neuron that provide clues to a prenatal origin in schizophrenia. Second, we review recent discoveries of transcription factors, cytokine receptors, and other developmental regulators that govern the birth, migration, specification, maturation, and survival of different subpopulations of prefrontal GABA neurons. Third, we discuss recent studies demonstrating altered expression of these ontogenetic factors in the prefrontal cortex in schizophrenia. Fourth, we discuss the potential role of disturbances in the maternal-fetal environment such as maternal immune activation in the development of GABA neuron dysfunction. Finally, we propose critical questions that need to be answered in future research to further investigate the role of altered GABA neuron ontogeny in the pathogenesis of schizophrenia.

Keywords

parvalbumin; somatostatin; prefrontal cortex; interneuron; development

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1. Introduction

Schizophrenia is a devastating psychiatric disorder that afflicts ~1% of all humans and is a leading cause of morbidity and early mortality (Insel and Scolnick, 2006). The features of the disorder with the strongest association to poor long-term outcomes include cognitive deficits (Green, 2006), such as impairments in working memory and cognitive control (Lesh et al., 2011). Disturbances in cognitive functioning are commonly seen in the illness (Keefe and Fenton, 2007) and certain cognitive deficits have been linked to dysfunction of subsets of inhibitory (GABA) neurons in the prefrontal cortex (PFC) (reviewed in (Lewis et al., 2012) and discussed in greater detail below). Furthermore, cognitive dysfunction in schizophrenia is only minimally responsive to antipsychotic medications (Keefe et al., 2007a; Keefe et al., 2007b). This lack of effective treatments for the cognitive features of schizophrenia indicates the need for greater insight into the pathogenetic processes that lead to disturbances in PFC GABA neurons.

Interestingly, cognitive disturbances are present before the onset of psychosis and well before the diagnosis of schizophrenia is typically made in late adolescence/early adulthood (Woodberry et al., 2008). These data suggest that the disease process affecting PFC GABA neurons is already active during development. In previous reviews, we discussed the potential role of postnatal developmental changes in PFC GABA neurons during adolescence in creating a sensitive period for environment insults, such as a cannabis exposure, that may lead to the emergence of PFC GABA neuron disturbances in schizophrenia (Hoftman and Lewis, 2011; Beneyto and Lewis, 2011). However, the initial onset of the disease process may begin at an even earlier stage of life. For example, individuals with schizophrenia exhibit delays in achieving developmental milestones in early childhood (Jones et al., 1994), even during the first year of life (Ridler et al., 2006; Sorensen et al., 2010; Clarke et al., 2011). Furthermore, in utero environmental insults, such as exposure to maternal infection, during the first and second trimester, which is the time period when cortical GABA neurons are born (Jakovcevski et al., 2011), are associated with an increased risk of schizophrenia in offspring (Brown and Derkits, 2010). In addition, murine models of maternal immune activation have been reported to disrupt the development of PFC GABA neurons (Meyer et al., 2008; Richetto et al., 2013).

Taken together, these data raise the following question: could the disease process that produces the cortical GABA neuron disturbances present in adults with schizophrenia begin much earlier than adolescence, perhaps even prenatally? Here, we address this question through a consideration of the evidence supporting the idea that genetic and/or environmental insults during gestation could initiate a pathogenetic process that alters the development (e.g. migration, phenotypic specification, maturation, and survival) of cortical GABA neurons, resulting in the pattern of GABAergic alterations, and consequently cognitive difficulties, seen in the disorder. First, we review the wealth of data accumulated over the past decade characterizing alterations in subsets of PFC GABA neuron that are relevant for cognitive dysfunction and may provide clues to a prenatal pathogenetic origin in schizophrenia. Second, we review recent discoveries of developmental regulators that govern the birth, migration, specification, maturation, and survival of PFC GABA neurons. Third, we discuss recent studies demonstrating altered expression of these ontogenetic

factors in the PFC in schizophrenia. Fourth, we discuss the potential role of disturbances in maternal-fetal environment in the development of GABA neuron dysfunction in schizophrenia. Finally, we propose critical questions that need to be answered in future research on the role of altered GABA neuron ontogeny in the pathogenesis of schizophrenia.

2. Alterations in subpopulations of PFC GABA neurons contribute to cognitive dysfunction and provide clues to a prenatal pathogenetic origin in schizophrenia

The most consistently reported disease-related findings in the PFC in schizophrenia involve GABA neurons. For example, deficits in mRNA levels for the GABA synthesizing enzyme GAD67 have been replicated across multiple subject cohorts and do not appear to be attributable to antipsychotic medications (Akbarian et al., 1995; Guidotti et al., 2000; Volk et al., 2000; Vawter et al., 2002; Straub et al., 2007; Duncan et al., 2010; Curley et al., 2011). Interestingly, the majority of PFC GABA neurons appear to express normal levels of GAD67 mRNA in schizophrenia (Volk et al., 2000). Furthermore, approximately 50% of GABA neurons in primate PFC express the calcium-binding protein calretinin (Conde et al., 1994; Gabbott and Bacon, 1996). Calretinin mRNA levels have been reported to be unchanged in the PFC in schizophrenia (Hashimoto et al., 2003; Volk et al., 2012), suggesting that calretinin neurons are largely unaffected in the disorder.

However, two other subsets of GABA neurons have been consistently reported to be altered in the PFC of subjects with schizophrenia. For example, a subpopulation of GABA neurons identified as abnormal in schizophrenia includes those that express the calcium-binding protein parvalbumin (PV), which includes ~25% of PFC GABA neurons in primate PFC (Conde et al., 1994; Gabbott and Bacon, 1996). Lower PV mRNA levels in schizophrenia have also been consistently reported in PFC gray matter by different research groups (Hashimoto et al., 2003; Mellios et al., 2009; Fung et al., 2010; Volk et al., 2012). Diminished PV neuron regulation of pyramidal neuron activity may have negative consequences for cognitive functioning in schizophrenia (Lewis et al., 2012). Fast-spiking PV neurons provide powerful perisomatic inhibitory regulation of pyramidal neuron output and enable synchronization of cortical neuron activity at gamma frequencies (30–80 Hz) (Sohal et al., 2009; Sohal, 2012). Gamma frequency oscillations are important for perceptual and PFC-related cognitive processes such as working memory (Howard et al., 2003), and individuals with schizophrenia show altered PFC gamma activity while performing tasks that require cognitive control (Cho et al., 2006; Minzenberg et al., 2010). Disrupting PV neuron function results in reduced gamma oscillatory power (Whittington et al., 1998; Gulyas et al., 2010). Thus, pathological processes affecting PV neurons may adversely affect the synchronization of cortical neural activity and contribute to cognitive dysfunction in schizophrenia.

Interestingly, in situ hybridization grain counting studies have found that PFC GABA neurons underexpress PV mRNA, but that the number of neurons expressing detectable PV mRNA levels in the PFC gray matter appears unchanged (Hashimoto et al., 2003). Similarly, immunohistochemistry studies have also found a normal complement of PV neurons in the

PFC in schizophrenia (Woo et al., 1997). Some studies have reported a lower density of PFC PV-immunoreactive neurons in the disorder (Beasley and Reynolds, 1997; Beasley et al., 2002), but these findings could reflect subthreshold levels of PV protein due to insufficient transcript levels which rendered the neurons undetectable under conditions suboptimal for immunohistochemistry (Stan and Lewis, 2012). Furthermore, 50% of PFC PV neurons lack detectable GAD67 mRNA in schizophrenia (Hashimoto et al., 2003). Thus, PV neurons may complete the process of tangential migration but fail to develop the normal GABAergic phenotype reflected in lower levels of PV and GAD67 mRNAs (Figure 1).

The neuropeptide somatostatin (SST), which is expressed by ~20% of GABA neurons, has also been shown to have lower mRNA levels in the PFC across several large cohorts of schizophrenia subjects (Morris et al., 2008; Mellios et al., 2009; Fung et al., 2010; Volk et al., 2012). In situ hybridization grain counting analysis found a lower density of gray matter neurons that express detectable levels of SST mRNA in the PFC, which could reflect fewer gray matter SST neurons and/or SST neurons that do not express adequate levels of SST mRNA to reach the threshold of detection (Morris et al., 2008). Interestingly, some (Yang et al., 2011), though not all (Morris et al., 2008), studies have found a higher density of SST neurons in cortical white matter in the disorder. One potential parsimonious explanation for this pattern of findings across studies involves a pathogenetic process in some subjects that arrests the migration of SST neurons in white matter early in development leading to fewer SST neurons reaching their final destination in gray matter (Figure 1) (Yang et al., 2011). Indeed, other studies have also reported a higher density of neurons in the interstitial white matter in schizophrenia (Anderson et al., 1996; Kirkpatrick et al., 2003; Eastwood and Harrison, 2005), including nitric oxide synthase-containing neurons in deeper white matter (Akbarian et al., 1993). Understanding the potential divergence of prenatal pathogenetic origins for PV (i.e. incomplete phenotypic specification) and SST (i.e. failure to complete tangential migration) neuron disturbances in schizophrenia requires knowledge of the developmental factors that regulate cortical GABA neuron ontogeny.

3. Ontogenetic transcription factors regulate different stages of prenatal development of cortical GABA neuron subpopulations

In the past decade, great advances have been made in understanding the prenatal ontogeny of cortical GABA neurons. In humans, calretinin neurons appear to derive from the subventricular zone of the dorsal pallium (Letinic et al., 2002; Zecevic et al., 2005; Fertuzinhos et al., 2009; Zecevic et al., 2011; Jakovcevski et al., 2011). In contrast, evidence from studies of holoprosencephaly suggests that PV and SST neurons in humans, as in mice, originate from the ganglionic eminence of the subpallium (Fertuzinhos et al., 2009). In mice and humans, the medial region of the ganglionic eminence is the primary site of origin for these neurons (Xu et al., 2004; Butt et al., 2005; Cobos et al., 2006; Zecevic et al., 2011). Thus, a developmental pathogenetic process focused in the medial ganglionic eminence may contribute to the selective disturbance in PV and SST neurons, while sparing calretinin neurons, in schizophrenia.

The migration, phenotypic specification, maturation, and survival of cortical PV and SST neurons depend upon adequate expression of cell-type specific ontogenetic transcription

factors (Figure 2). For example, the transcription factor Lhx6 is expressed by cortical PV and SST progenitor cells (Liodis et al., 2007; Zhao et al., 2008; Neves et al., 2012) in the medial ganglionic eminence as early as 7 weeks gestation in humans (Jakovcevski et al., 2011). A complete loss of Lhx6 at this critical developmental stage leads to deficits in neurodevelopmental signaling molecules, delayed migration, and impeded differentiation into PV and SST neurons (Liodis et al., 2007; Zhao et al., 2008; Neves et al., 2012). Similarly, other transcription factors such as Nkx2.1, Sox6, MafB, Zeb2/Sip1/Zfhx1b, and Dlx5/6 are also expressed early in gestation in the medial ganglionic eminence and regulate the migration, specification, and maturation of PV and/or SST, but not calretinin, neurons (Figure 2) (Sussel et al., 1999; Cobos et al., 2006; Du et al., 2008; Xu et al., 2008; Azim et al., 2009; Batista-Brito et al., 2009; Wang et al., 2010; van, V et al., 2013; McKinsey et al., 2013).

Cytokine receptors and a diverse array of other molecules also play a crucial role in the ontogeny of cortical PV neurons (Figure 2). For example, the cytokine receptors CXCR4 and CXCR7 are heavily expressed in the medial ganglionic eminence and are required for successful tangential migration of PV neurons (Wang et al., 2011; Sanchez-Alcaniz et al., 2011; Meechan et al., 2012). Furthermore, ErbB4 is a receptor tyrosine kinase for the trophic factor neuregulin 1 that is involved in the migration of, and development of excitatory inputs to, PV neurons (Flames et al., 2004; Fazzari et al., 2010; Ting et al., 2011). In addition, homozygous deletion of urokinase plasminogen activator receptor (Powell et al., 2003), a key factor in hepatocyte growth factor activation, or fibroblast growth factor receptor 1 (Muller et al., 2008), results in disturbances in cortical PV (and SST neurons for fibroblast growth factor receptor 1) but not calretinin neurons.

Furthermore, other transcription factors and developmental regulators are involved in the maturation and survival of different classes of cortical GABA neurons (Figure 2). For example, Dlx1 was one of the earliest reported factors that regulates cortical GABA neuron development (Anderson et al., 1997). More recent evidence suggests that Dlx1 is not required for tangential migration, but is required for maintenance of GAD67 expression postnatally (Cobos et al., 2005). Furthermore, Dlx1 is expressed by SST neurons but not PV neurons postnatally, and accordingly homozygous deletion of Dlx1 results in a failure of SST but not PV neurons to survive the preadolescent period in mice (Cobos et al., 2005). In addition, nuclear matrix and genome organizer Special AT-rich DNA Binding Protein 1 (SATB1) begins to be expressed by most cortical PV and SST, but not by calretinin neurons (Denaxa et al., 2012), after tangential migration has completed. Homozygous knockout of SATB1 produces large reductions in mRNA and protein levels of SST (but not PV) without a reduction in cell density indicating a role in terminal differentiation and maturation of SST neurons (Denaxa et al., 2012). In contrast, the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is initially expressed by PV neurons postnatally after migration is complete and is required for the development of the PV phenotype (Lucas et al., 2010).

In summary, normal expression of a broad range of molecules is required for successful early development of cortical GABA neurons (Figure 2). These findings raise the following question which we address next: Could altered prenatal expression of these ontogenetic

regulators initiate a disease process that disrupts the normal developmental trajectory of cortical GABA neurons and produces the phenotype of GABA abnormalities seen in schizophrenia?

4. Lhx6 and other candidate neurodevelopmental regulators may be involved in PFC PV and SST neuron dysfunction in schizophrenia

While it is not feasible to directly study developmental processes in the prenatal brains of individuals who will eventually develop schizophrenia, many ontogenetic factors continue to be robustly expressed in a cell-type specific manner in PV and SST neurons in adult cortex (Cobos et al., 2006; Georgiev et al., 2012). Thus, knowledge of whether certain key candidate developmental regulators are abnormally expressed in adult schizophrenia brain may provide clues to earlier pathogenetic processes that lead to alterations selective for PV and/or SST neurons. For example, we recently found deficits in Lhx6 mRNA levels in the PFC in schizophrenia (Volk et al., 2012). Most Lhx6-containing neurons had lower Lhx6 mRNA levels, and Lhx6 mRNA deficits were found in the same cortical layers that contain most PV neurons (layers 3–4) (Hashimoto et al., 2003) and SST neurons (layers 2, 5, 6) (Morris et al., 2008), suggesting that PV and SST neurons expressed lower Lhx6 mRNA levels. However, Lhx6 mRNA levels did not differ in layer 1 where calretinin neurons are more common than PV or SST neurons. Lhx6 mRNA levels were also not related to substance abuse, psychotropic medications, or smoking in schizophrenia, suggesting that Lhx6 mRNA deficits reflect the disease process of schizophrenia and not factors that commonly accompany the illness.

Given the role of Lhx6 in the tangential migration, cell type specification, and maturation of cortical PV and SST neurons, the disease-related consequences of Lhx6 deficits may depend upon the developmental stage at which Lhx6 deficits first appear. For example, deficits in Lhx6 that occur at the earliest gestational periods in the medial ganglionic eminence may impair the migration of cortical GABA neurons. The findings of lower densities of Lhx6- and SST-containing neurons in the gray matter (Morris et al., 2008), and a higher density of SST-containing neurons in the white matter (Yang et al., 2011), in the PFC in schizophrenia are consistent with arrested migration of some SST neurons. Alternatively, lower levels of Lhx6 present after migration is complete might interfere with continued maturation of the GABAergic phenotype. In this case, the lower density of PFC Lhx6-containing neurons could also mean that some of these neurons successfully migrated but have undetectable levels of Lhx6 mRNA and an altered phenotype. Consistent with this interpretation, the density of PFC PV mRNA-containing neurons is not altered in schizophrenia, but many of these neurons have lower levels of PV and GAD67 mRNAs (Hashimoto et al., 2003).

However, since the timing of the emergence of Lhx6 deficits in the disorder cannot be directly assessed, we cannot rule out that deficits in Lhx6 first appear in late adolescence or early adulthood after cellular maturation has been completed. Consequently, other upstream etiological factors must also be considered. Interestingly, another ontogenetic transcription factor Nkx2.1 regulates Lhx6 levels prenatally and a loss of Nkx2.1 profoundly disrupts the development of PV and SST neurons but not calretinin neurons (Sussel et al., 1999; Du et al., 2008; Xu et al., 2008), suggesting that a loss of Nkx2.1 could be upstream to Lhx6

deficits in schizophrenia. However, while Nkx2.1 is strongly expressed prenatally in the medial ganglionic eminence, Nkx2.1 becomes undetectable in adult human brain (unpublished data) and thus cannot be directly studied in postmortem tissue from individuals with schizophrenia.

In addition, mRNA levels for Dlx1 have recently been reported to be reduced in orbital frontal cortex gray matter in schizophrenia (Joshi et al., 2012). Since Dlx1 plays a critical role in the postnatal maturation and survival of SST neurons (Cobos et al., 2005), reduced levels of Dlx1 may potentially contribute to deficits in SST mRNA levels and in the number of neurons that express detectable levels of SST mRNA in cortical gray matter in schizophrenia (Morris et al., 2008).

5. Cortical GABA neuron development is disrupted by disturbances in the maternal-fetal environment such as maternal immune activation

In utero environmental exposures may also play a role in the etiopathogenesis of cortical GABA neuron dysfunction in schizophrenia. For example, maternal exposure to parasitic (Brown et al., 2005) or viral (Brown et al., 2004a) infections during the first and second trimesters, the time period when cortical PV and SST neurons are born (Jakovcevski et al., 2011), and the induced immune response of elevated serum cytokine levels (Brown et al., 2004b) are associated with an increased risk of schizophrenia in offspring. Furthermore, the population attributable risk for schizophrenia due to maternal infection has been recently estimated to be ~30% (Brown and Derkits, 2010).

As described earlier, the cytokine receptors CXCR4 and CXCR7 are expressed prenatally by cortical PV neurons in the medial ganglionic eminence, and disrupted expression of these receptors or their ligand (CXCL12) adversely affects the development of cortical PV neurons (Wang et al., 2011; Sanchez-Alcaniz et al., 2011; Meechan et al., 2012). These data suggest that altered cytokine levels in fetal brain in response to maternal immune activation may disrupt the development of CXCR4/7-expressing PV neurons. Consistent with this hypothesis, animal models using the viral mimic poly I:C, a synthetic double stranded RNA that binds to and activates toll-like receptor 3, have shown that maternal immune activation alters levels of multiple cytokines and CXCR4/7 in fetal brain (Meyer et al., 2006; Oskvig et al., 2012). Furthermore, maternal immune activation induces long-lasting epigenetic changes in the promoter regions of genes which could also contribute to perturbations of gene expression postnatally (Tang et al., 2013). In addition, postmortem brain tissue studies have reported higher mRNA levels for markers of immune activation in schizophrenia (Arion et al., 2007; Saetre et al., 2007; Fillman et al., 2012) which may in part reflect an early immune challenge that may have acted earlier during brain development (Arion et al., 2007) though additional proof-of-principle testing is needed. Interestingly, the effects of poly I:C-induced maternal immune activation on offspring include lower PV immunoreactivity and deficits in GAD67 mRNA and protein levels in the PFC (Meyer et al., 2008; Richetto et al., 2013) and impaired spatial working memory (Meyer et al., 2008). Taken together, these data suggest that in some schizophrenia subjects, maternal immune activation disrupts cortical PV neuron ontogeny and leads to disturbances in PFC PV neurons (Hashimoto et al., 2003; Curley et al., 2011; Volk et al., 2012). Furthermore, the shared site of origin and developmental

regulation of PV and SST neurons suggests that maternal immune activation may also have similar deleterious effects on SST neuron development.

6. Unanswered Questions and Topics for Future Research

In summary, evidence from postmortem brain tissue studies from schizophrenia subjects suggests that abnormalities in PFC GABA neurons are consistent with a prenatal pathogenetic origin linked to the medial ganglionic eminence. The critical role that ontogenetic transcription factors and other developmental regulators play in the birth, migration, specification, maturation, and survival of cortical PV and SST neurons suggests that altered expression of these factors in schizophrenia could contribute to GABA-related disturbances in the PFC. Consistent with this hypothesis, recent postmortem studies have found deficits in the cortical expression of some ontogenetic transcription factors such as Lhx6 and Dlx1 in schizophrenia. Finally, evidence from animal models suggests that perturbations of maternal-fetal environment such as maternal immune activation alter levels of cytokines, cytokine receptors, and developmental regulators in fetal brain that also disrupt the development of cortical PV and SST neurons. These findings suggest the following important areas for future study.

6.1 Postmortem studies of GABA-related markers

As described above, some in situ hybridization studies of postmortem brain tissue have reported evidence consistent with arrested tangential migration of SST neurons (Yang et al., 2011) and incomplete phenotypic specification of PV neurons (Hashimoto et al., 2003) in schizophrenia. However, cellular levels of analysis have also yielded some inconsistent results in regards to neuron density across subject cohorts such as higher (Yang et al., 2011) and lower (Morris et al., 2008) densities of SST neurons in the superficial white matter and no change (Woo et al., 1997; Hashimoto et al., 2003) or lower (Beasley and Reynolds, 1997; Beasley et al., 2002) densities of PV neurons in the gray matter in schizophrenia. One possible explanation for the discrepancy among these findings is that the pathogenetic mechanisms underlying disturbances in SST and PV neurons differ among individuals with schizophrenia. That is, distinct disease processes, such as those involving abnormal expression of certain developmental regulators (section 6.3), may interfere with different stages of GABA neuron ontogeny (i.e. birth, migration, specification, maturation, and/or survival) in different schizophrenia subjects. However, these distinct and individualized pathogenetic processes (i.e. impaired neuronal migration, incomplete phenotypic specification, failure to complete maturation, excessive apoptosis) may all produce the commonly observed molecular phenotype of deficits in SST and PV mRNA levels in gray matter homogenates that has been replicated across large schizophrenia cohorts (Mellios et al., 2009; Fung et al., 2010; Volk et al., 2012). Future studies involving detailed cellular level analysis of PV and SST neurons in large cohorts of schizophrenia subjects and also measures of key candidate developmental regulators may permit the identification of subgroups of subjects with distinctive disease processes that yield the commonly reported finding of deficits in gray matter SST and PV mRNA levels (section 6.3).

6.2 Animal models that disrupt cortical GABA neuron ontogeny

While knowledge of the role of ontogenetic transcription factors, cytokine receptors, and other developmental regulators in the birth, migration, specification, maturation and survival of cortical GABA neurons has increased exponentially over the past decade, applying this knowledge to hypotheses of the disease process of schizophrenia requires addressing additional questions. First, are the effects of a loss of gene function on cortical GABA neuron development dose-dependent? For example, most studies of factors that regulate GABA neuron development utilize animal models with a complete loss of gene function. However, schizophrenia is not a genetic disorder of homozygous null mutations. Indeed, evidence from postmortem human brain tissue studies have reported partial reductions in the levels of ontogenetic transcription factors such as Lhx6 (Volk et al., 2012) and Dlx1 (Joshi et al., 2012). Consequently, animal models that employ a partial loss of gene function such as heterozygous null mutation mice are needed to determine whether smaller losses of ontogenetic transcription factors are sufficient to produce disturbances in cortical PV and SST neurons similar to those seen in schizophrenia.

Second, what is the combined effect of smaller deficits in multiple ontogenetic transcription factors on cortical GABA neuron development? For example, a reduction in expression of both Dlx1 and Lhx6 in the same individuals may be predicted to have an additive effect that could impact multiple stages of migration, phenotypic specification, maturation and even survival of PFC PV and SST neurons in schizophrenia. However, at present time, mRNA levels of Dlx1 and Lhx6 have not been studied by quantitative PCR or in situ hybridization in the same cohort of schizophrenia subjects, and studies of the ontogeny of cortical GABA neurons have not included partial manipulations of more than one transcription factor. Still, reductions in Dlx1 and Lhx6, while not affecting each other directly (Cobos et al., 2005; Zhao et al., 2008), have multiple downstream effects on other transcription factors (Zhao et al., 2008; McKinsey et al., 2013), which could create a deleterious cascade of transcriptional regulator deficiencies with diverse disrupting effects on cortical GABA neuron development. Animal models that employ smaller deficits in multiple transcription factors found to be deficient in schizophrenia would represent an important advance in modeling potential pathogenetic processes in the disorder.

Third, are the relevant developmental processes conserved across species? The vast majority of studies of cortical GABA neuron ontogeny employ mouse models. However, significant differences exist in the composition and phenotypic properties of cortical GABA neuron subpopulations between rodent and primate brain (Conde et al., 1994; Gabbott and Bacon, 1996; Povysheva et al., 2008). Furthermore, while the vast majority of cortical GABA neurons are derived from the ganglionic eminence in mouse, a substantial number of cortical GABA neurons, likely calretinin, have been reported to derive from the subventricular zone of the pallium in humans (Letinic et al., 2002; Zecevic et al., 2005; Fertuzinhos et al., 2009; Zecevic et al., 2011; Jakovcevski et al., 2011). Thus, additional studies in embryonic human brain are needed to determine the applicability of mouse-related findings to human brain.

6.3 Altered expression of ontogenetic transcription factors in schizophrenia

While Lhx6 and Dlx1 have recently been studied in schizophrenia (Volk et al., 2012; Joshi et al., 2012), further investigation into the expression levels of key candidate developmental regulators in schizophrenia may provide additional insight into potential mechanisms that could disrupt cortical GABA neuron development at different stages of the disorder. In particular, knowledge of the status of developmental regulators in the same schizophrenia subjects for whom we have knowledge of the nature of disturbances in PFC PV and SST neurons (section 6.1) may provide insight into individualized pathogenetic processes. For example, Sip1 is expressed early in the medial ganglionic eminence and is necessary for tangential migration of cortical PV and SST neurons (van, V et al., 2013; McKinsey et al., 2013). Thus, schizophrenia subjects with deficits in Sip1 would be predicted to have fewer PFC PV and SST neurons. In addition, PGC1α is critical for mature levels of PV mRNA expression, but not migration of PV neurons (Lucas et al., 2010). PGC1α also continues to be expressed in adult brain. Thus, inadequate levels of PGC1α during development in schizophrenia would be predicted to not affect the migration of PV neurons but instead to interfere with the development of the GABAergic phenotype of PV neurons, as has been reported in schizophrenia (Hashimoto et al., 2003). In contrast, SATB1 plays a critical role in the terminal differentiation and maturation, but not migration, of cortical SST neurons (Denaxa et al., 2012). Thus, schizophrenia subjects with deficits in SATB1 would be predicted to have normal numbers of SST-containing neurons but less SST per neuron. Finally, since calretinin mRNA levels appear to be largely unaffected, or even slightly higher (Volk et al., 2012), in schizophrenia, one may predict that developmental regulators that are not specific to PV and SST neurons and that are also involved in the development of calretinin neurons (Figure 2) (e.g., Arx (Colombo et al., 2007; Colasante et al., 2008), COUP-TF II (Kanatani et al., 2008; Reinchisi et al., 2012), Gsx2 (Fogarty et al., 2007), Nkx6.2 (Fogarty et al., 2007)) will not be altered in schizophrenia. Thus, while basic neuroscience studies continue to elucidate the role of important neurodevelopment regulators in the ontogeny of GABA neurons, additional postmortem schizophrenia brain tissue studies are needed to characterize and correlate any deficits (or potential compensatory upregulation) of these markers to alterations in SST and PV neurons in the same schizophrenia subjects.

6.4 Applying models of maternal immune activation to schizophrenia

What stage of cortical GABA neuron development is most susceptible to maternal immune activation? One study recently reported that maternal immune activation at a late gestational stage in mice (gestation day 17) leads to deficits in PFC GAD67 mRNA levels (Richetto et al., 2013) similar to that seen in schizophrenia (Curley et al., 2011). However, are certain stages of cortical GABA neuron development such as birth or migration more susceptible to maternal immune activation? Identifying the most susceptible gestational period for maternal immune activation may inform preventative strategies involving maternal prenatal care to reduce infection rates and potentially reduce risks for developing schizophrenia in at-risk offspring. Furthermore, additional studies are needed to determine the extent to which maternal immune activation can reproduce the pattern of abnormalities in PFC PV and SST neurons reported in schizophrenia (section 2). Finally, the extent to which maternal immune activation alone is sufficient to replicate disease-related pathology in PFC GABA neurons in

schizophrenia is unclear; some evidence suggests that maternal immune activation interacts with other insults, such as peripubertal stress (Giovanoli et al., 2013) or preexisting genetic abnormalities, to produce more severe disease pathology. For example, the combination of Lhx6 deficits and maternal immune activation may interact to severely disrupt PV and SST neuron development. In fetal brain, loss of Lhx6 induces deficits in CXCR4/7 (Zhao et al., 2008), and maternal immune activation lowers Lhx6 levels (Oskvig et al., 2012). Consequently, disturbances in PFC PV and SST neurons in schizophrenia may reflect the long-lasting consequences of an interaction in prenatal insults that are fetal (i.e. deficits in developmental regulators such as Lhx6) and/or maternal (i.e. immune activation) in origin.

6.5 Summary

In summary, a cross-species translational approach is required to investigate the potential interaction between genetic and gestational environmental insults that could initiate a disease process that disrupts cortical GABA neuron ontogeny and produces the pattern of GABA neuron abnormalities, and consequently cognitive difficulties, seen in schizophrenia. Such studies may provide a biological basis for preventative strategies that target the prenatal period, such as maternal prenatal care to reduce infection rates, and potentially reduce risks for developing schizophrenia in at-risk offspring.

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Highlights

- Cortical GABA neuron abnormalities in schizophrenia may have a prenatal origin.
- Transcription regulators and other developmental factors govern GABA neuron ontogeny.
- Deficits in ontogenetic transcription factors have been reported in schizophrenia.
- Maternal immune activation may be involved in GABA neuron deficits in schizophrenia.

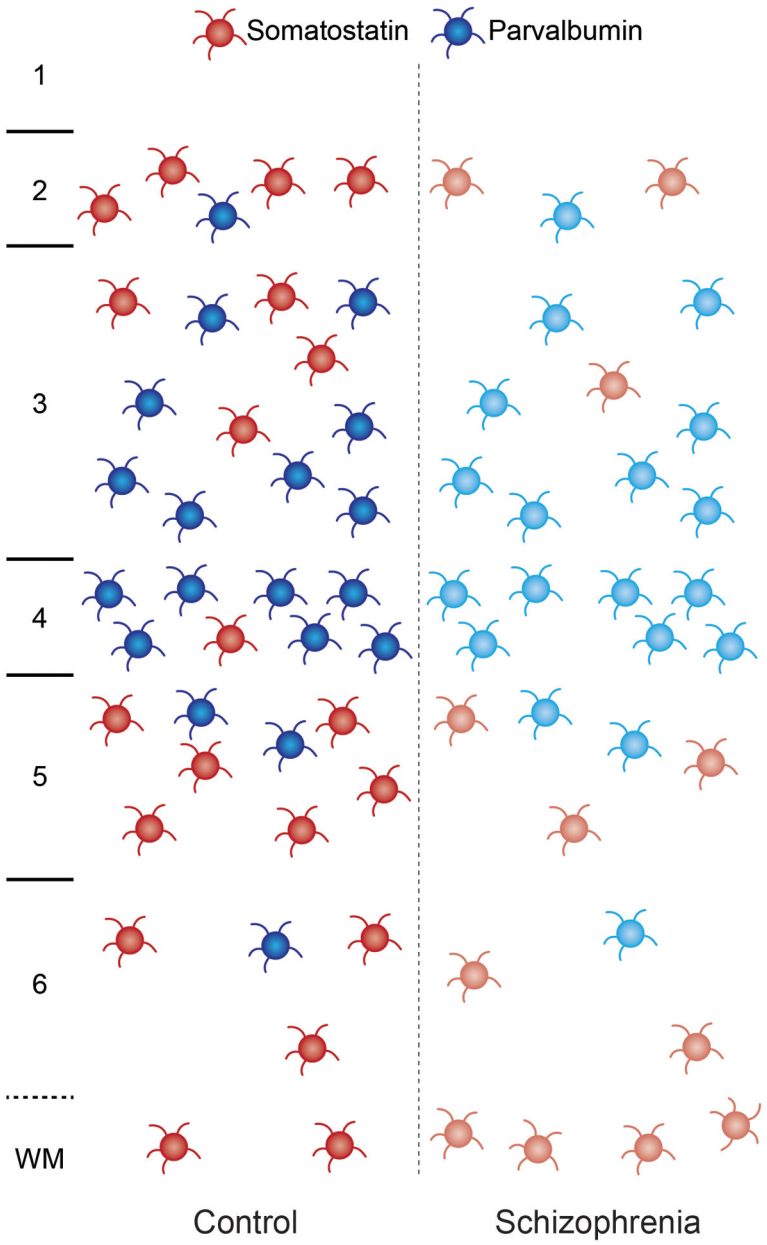

Figure 1. Schematic illustrating reported disturbances in PV and SST neurons in the PFC in schizophrenia

In the PFC of healthy human subjects (left panel), PV neurons (blue) are predominantly found in layers deep 3 and 4, while SST neurons (red) are predominantly localized to cortical layers 2, superficial 3, 5, and 6 and are also found in the superficial white matter (Hashimoto et al., 2003; Morris et al., 2008). In schizophrenia subjects (right panel), reduced mRNA levels of GAD67 and PV have been reported in PV neurons without a change in the number of PV neurons per tissue area (Hashimoto et al., 2003), suggesting incomplete phenotypic specification and/or maturation of PV neurons (lighter shade of blue) in the disorder. In contrast, a lower density of gray matter neurons that express detectable levels of SST mRNA has been reported in schizophrenia (Morris et al., 2008), which could reflect

fewer gray matter SST neurons and/or neurons that do not express detectable levels of SST mRNA (lighter shade of red). Interestingly, some (Yang et al., 2011), though not all (Morris et al., 2008), studies have found a higher density of SST neurons in cortical white matter in the disorder, suggesting that the migration of some SST neurons may be arrested, leading to fewer SST neurons reaching their final destination in gray matter.

<table>
<tr><th>Stage of Development</th><th colspan="2">Parvalbumin Neurons</th><th colspan="2">Somatostatin Neurons</th><th>Calretinin Neurons</th></tr>
<tr><td>Migration to cortex</td><td>CXCR4
CXCR7
Dlx5/6
ErbB4</td><td colspan="2">Lhx6
Nkx2.1
Sox6
Zeb2/Sip1/Zfhx1b</td><td>Nkx6.2</td><td>Arx
COUP-TFII
Gsx2
Nkx6.2</td></tr>
<tr><td>Phenotypic specification and maturation</td><td>Dlx5/6
ErbB4</td><td colspan="2">Lhx6
Nkx2.1
Sox6
Zeb2/Sip1/Zfhx1b</td><td>Dlx1
Nkx6.2
SATB1</td><td>COUP-TFII
Dlx1
Gsx2
Nkx6.2</td></tr>
<tr><td>Postnatal survival</td><td colspan="2"></td><td colspan="2">Dlx1</td><td>Dlx1</td></tr>
</table>

Figure 2. Figure illustrating some of the major roles of developmental regulators including ontogenetic transcriptional regulators, cytokine receptors, and other factors in various stages of development of cortical PV, SST, and calretinin neurons

This figure is based on published reports that largely utilized single, complete loss of gene function murine models. This list of factors is not exhaustive, and many of the factors may play additional roles beyond those listed here. Since many gene mutations are lethal postnatally, knowledge of the potential role of many factors in postnatal maturation and survival is not known. Full gene name and associated references: **Arx**: aristaless related homeobox (Colombo et al., 2007); **COUP-TFII**: chicken ovalbumin upstream promoter-transcription factor II (Kanatani et al., 2008; Reinchisi et al., 2012); **CXCR4** and **CXCR7**: chemokine (C-X-C motif) receptors 4 and 7 (Wang et al., 2011; Sanchez-Alcaniz et al., 2011; Meechan et al., 2012); **Dlx1**: Distal-less homeobox 1 (Cobos et al., 2005); **Dlx5/6**: Distal-less homeobox 5/6 (Wang et al., 2010); **ErbB4**: receptor tyrosine-protein kinase erbB-4 (Flames et al., 2004; Fazzari et al., 2010; Ting et al., 2011); **Gsx2**: genomic screened homeobox 2 (Fogarty et al., 2007); **Lhx6**: LIM homeodomain factor 6 (Liodis et al., 2007; Zhao et al., 2008; Neves et al., 2012); **Nkx2.1**: NK2 homebox 1 (Sussel et al., 1999; Xu et al., 2004; Butt et al., 2008; Nobrega-Pereira et al., 2008); **Nkx6.2**: NK6 homeobox 2 (Fogarty et al., 2007); **SATB1**: Special AT-rich DNA Binding Protein 1 (Denaxa et al., 2012); **Sox6**: SRY (sex determining region Y)-box 6 (Azim et al., 2009; Batista-Brito et al., 2009); **Zeb2/Sip1/Zfhx1b**: zinc finger E-box binding homeobox 2 (van, V et al., 2013; McKinsey et al., 2013).