



Neural stem cell regulation, fibroblast growth factors, and the developmental origins of neuropsychiatric disorders

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There is increasing appreciation for the neurodevelopmental underpinnings of many psychiatric disorders. Disorders that begin in childhood such as autism, language disorders or mental retardation as well as adult-onset mental disorders may have origins early in neurodevelopment. Neural stem cells (NSCs) can be defined as self-renewing, multipotent cells that are present in both the embryonic and adult brain. Several recent research findings demonstrate that psychiatric illness may begin with abnormal specification, growth, expansion and differentiation of embryonic NSCs. For example, candidate susceptibility genes for schizophrenia, autism and major depression include the signaling molecule Disrupted In Schizophrenia-1 (DISC-1), the homeodomain gene engrailed-2 (EN-2), and several receptor tyrosine kinases, including brain-derived growth factor and fibroblast growth factors, all of which have been shown to play important roles in NSCs or neuronal precursors. We will discuss here stem cell biology, signaling factors that affect these cells, and the potential contribution of these processes to the etiology of neuropsychiatric disorders. Hypotheses about how some of these factors relate to psychiatric disorders will be reviewed.

Keywords: Neural stem cell, cerebral cortex, fibroblast growth factor, autism, schizophrenia, depression, bipolar disorder

INTRODUCTION

There is a growing appreciation for the neurodevelopmental underpinnings of many psychiatric disorders. While the importance of the growth and structuring of the brain has long been recognized for disorders that begin in childhood such as autism, language disorders or mental retardation, there is consensus building that adult-onset mental disorders also have origins early in neurodevelopment. In order to expand our understanding of these origins, the National Institute of Mental Health (NIMH) is investing in studies of developmental neurobiology, choosing one of its strategies to be the support of “research to improve our basic understanding of the development, structure, and function of neural circuits, with a focus on those most relevant to mental disorders” (NAMHC, 2008). Forwarding this agenda requires a better understanding of the neurobiology of neural stem cells (NSCs) and the factors that regulate them in the developing brain.

Neural stem cells can be defined as self-renewing, multipotent cells that are present in both the embryonic and adult brain. Several recent research findings demonstrate that psychiatric illness may begin with abnormal specification, growth, expansion and differentiation of embryonic NSCs. For example, candidate susceptibility genes for schizophrenia, autism and major depression include those specifying the signaling molecule Disrupted In Schizophrenia-1 (DISC-1), the homeodomain gene engrailed-2 (EN-2), and several receptor tyrosine kinases (RTKs), including brain-derived neurotrophic factor (BDNF) and fibroblast growth factors (FGF), all of which have been shown to play important roles in NSCs or neuronal precursors. Hypotheses about how some of these factors relate to psychiatric disorders are now the focus of much neurodevelopmental work (see several reviews: Arnold et al., 2005; Buckley et al., 2007; Eisch et al., 2008; Thomas and Peterson, 2008; Jaaro-Peled et al., 2009; Vaccarino et al., 2009).

This review will lay out some aspects of the new frontier represented by stem cells for understanding the origins of mental illness. In section I, we will review embryonic central nervous system (CNS) development, focusing on forebrain NSCs and the role of the RTKs, such as FGF receptors (FGFRs), in the earliest developmental processes. RTKs are transmembrane proteins that, upon binding a ligand presented or secreted by nearby cells, phosphorylate intracellular signaling molecules and transduce cell-to-cell signaling in the brain. FGF receptors (FGFRs) are among the earliest RTKs expressed in the developing brain, but also continue to be expressed in the mature brain.

Following this review of NSCs and FGFs in embryonic development, in section II we will describe neurobiological findings in clinical populations that support disrupted embryonic stem cell activity. In section III, adult NSC functioning and connections with mental illness will be reviewed. In section IV, we will discuss how new research with inducible pluripotent stem cells derived from patients with neuropsychiatric disorders may further our understanding of developmental aspect of psychopathology and reveal potential targets for psychiatric treatment.

EMBRYONIC CNS DEVELOPMENT

AN INTRODUCTION TO NEUROGENIC STEM CELLS (NSCs)

Perturbations in early development of the CNS may increase an individual's susceptibility to neuropsychiatric disorders. These perturbations may occur at the earliest stages of development, when the primordium of the brain is a sheet of neuroepithelial stem cells. The functioning of NSCs is tightly regulated by both intrinsic and extrinsic factors (Johnson et al., 2009a). Intrinsic factors that shape the development of NSCs include transcription factors, non-coding RNAs and covalent modifications of chromatin in the

nucleus (epigenetic modifications). All of these factors, a description of which is outside the scope of this review, can influence stem cells and their proliferation, or the migration and terminal differentiation of their progeny into defined neural cell types with specific connectivity (**Figure 1**).

The specific “mix” of intrinsic factors that characterizes distinct neural stem cell function and identity acts in conjunction with a local “mix” of extracellular signaling molecules bathing NSCs. There are four major classes of secreted extracellular signaling molecules that are expressed in the developing brain during embryogenesis and that participate in the patterning of the nervous system – FGFs, WNTs, Sonic Hedgehog (SHH) and Bone Morphogenetic Proteins (BMP). FGFs diffuse from the anterior neural ridge, a region corresponding later in development to the commissural plate, which is the foremost rostral boundary of the telencephalon; WNTs and BMPs emanate from the cortical hem, comprising the medial margin of each hemisphere; BMPs are secreted from the roof plate, the dorsal region in between the cerebral hemispheres; and SHH diffuses from the ventral portion of the neural tube or floor plate (**Figure 2**). In addition to these long-range signals, the balance between Notch ligands and Notch receptors, which are membrane bound, strongly influences neural stem cell fate (Johnson et al., 2009a). Extracellular signals shape CNS morphogenesis and regulate

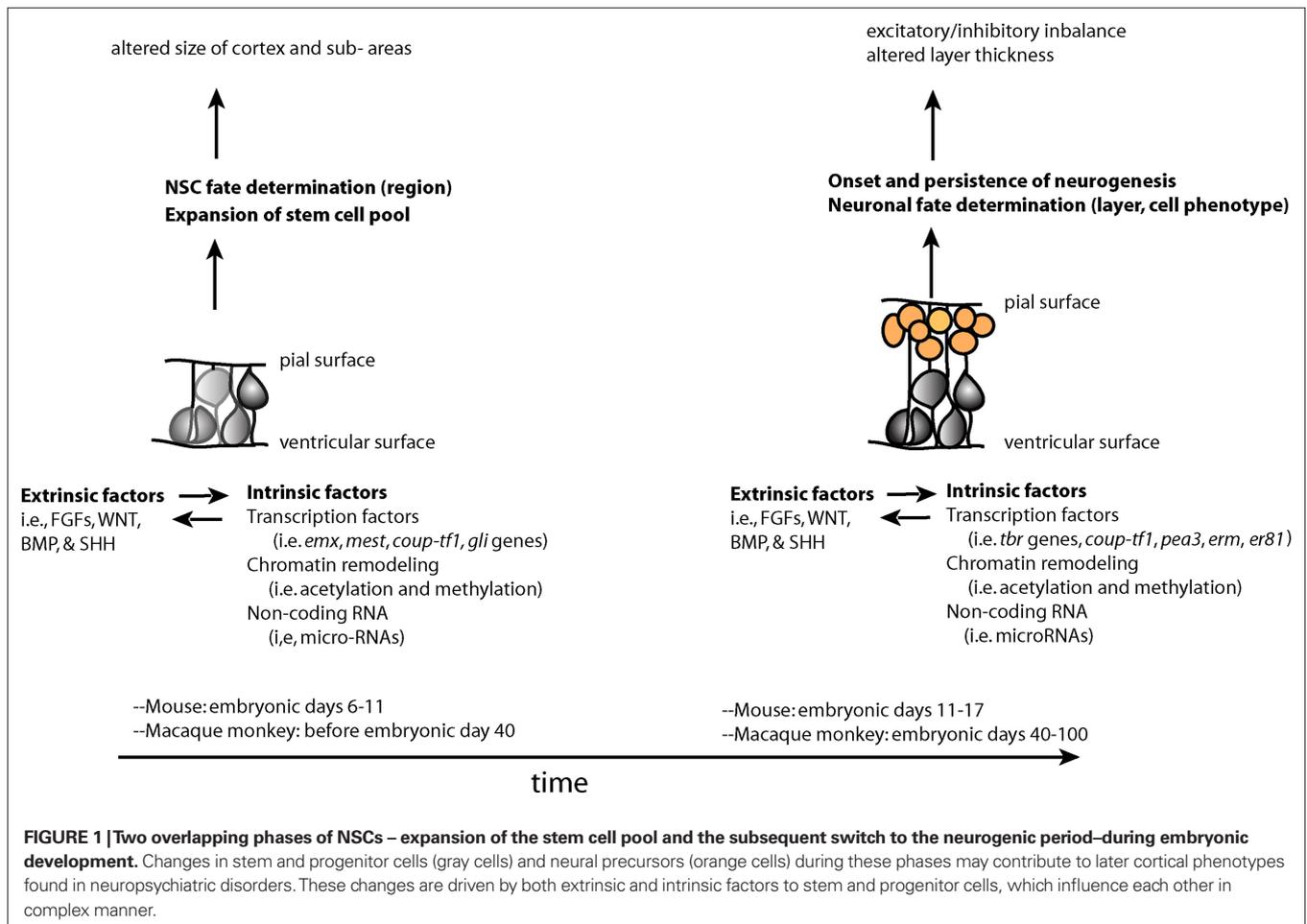
cell fate by influencing the specific “mix” of intrinsic factors present at specific locations and times in the developing CNS (**Figure 1**).

One mechanism by which changes in embryonic NSCs could lead to behavioral symptoms include an imbalance between production of specific types of excitatory and inhibitory neurons, resulting in abnormal levels of activation in cortical circuits (Rubenstein and Merzenich, 2003). A second mechanism may involve impairments in the relative size of cortical areas receiving specific thalamic inputs or sending projections to subcortical stations that play an important role in emotional/behavioral regulation (**Figure 1**).

WNT, SHH, and BMP decrease in expression with age, indicating that their primary function is in establishing early identities of NSCs. Continued expression of WNT and SHH in the adult NSC niches regulates stem cell proliferation (Lai et al., 2003; Lie et al., 2005; Palma et al., 2005). In contrast, FGFs continue to be widely expressed and play a role not only in adult NSC niches (Zheng et al., 2004) but also in the maturation of the postnatal cerebral cortex.

FGF LIGANDS, STEM CELL AMPLIFICATION AND CORTICAL NEUROGENESIS

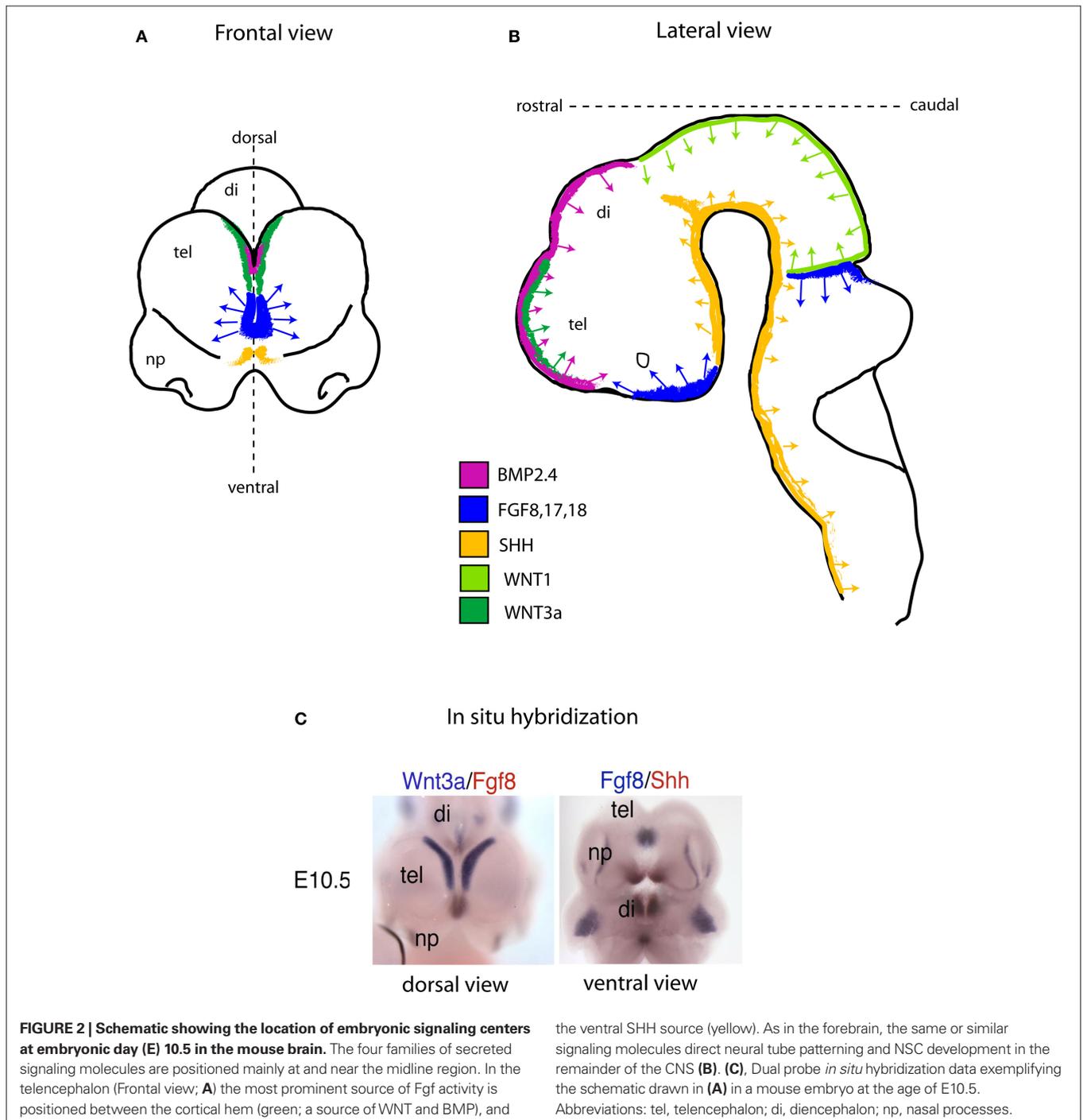
Fibroblast growth factor ligands are peptides that act both intracellularly and through secretion into the extracellular space. There are 22 known FGFs which act upon the four membrane bound



FGFRs. Amongst the FGF ligands, 13 are known to be expressed in the CNS during embryonic development (Fgf1,2, 3,7,8, 9,10,13,15,16,17,18,22) in specific regions of the neuroepithelium (Figure 2). Three of the receptors, FGFR1, FGFR2 and FGFR3 are present in the embryonic brain. Indeed, FGFRs are among the earliest RTKs expressed in brain development.

Two FGF ligand molecules must bind a receptor dimer in order to cause receptor activation. FGF receptors, akin to other members of the RTK family of proteins, cross-phosphorylate their part-

ner upon ligand binding, triggering the activation of three main intracellular pathways, the Ras/MAP Kinase, PI3 kinase, and PLC γ /Protein Kinase C (Schlessinger, 2000). The cascades eventually impinge upon the transcriptional machinery in the cell nucleus. Although RAS/MAPK and PI3K pathways are known to be important mediators of FGF signaling in the developing CNS, the relative role of each of these signaling pathways and of the other putative nuclear functions of FGF signaling for transcriptional regulation in stem/progenitor cells and biological functions are still unclear.



Concurrently with patterning in the developing dorsal telencephalon, NSCs expand in number. Through a developmental switch not yet fully understood, after the majority of this expansion has occurred, stem cells then begin to generate neuronal precursors in a neurogenic phase that lasts for approximately 6 days in rodents and 10–12 weeks in primates (Caviness et al., 1995; Rakic, 1995) (**Figure 1**). Cortical excitatory neurons are derived from NSC that line the dorsal telencephalic ventricle. The primary stem cells in this ventricular zone (VZ) are called radial glia because of their expression of glial markers such as GFAP and GLAST, and their cellular morphology. Radial glial cells have an apical end foot attachment at the ventricle, a cell body that is near the ventricle, and a long radial process that is attached at the pial surface (Levitt et al., 1981). Radial glia can undergo self-renewing cell divisions, or asymmetric cell divisions that directly give rise to neurons (Noctor et al., 2001). Another product of radial glial division are committed neurogenic progenitors that migrate to the subventricular zone (SVZ), above the VZ, where they in turn proliferate to give rise to neurons. The committed neuronal progenitors of the SVZ, referred to as intermediate progenitor cells (IPCs) express the transcription factor TBR2 and lack the self-renewal properties of true stem cells (Pontious et al., 2008). However, their proliferation is important for the expansion of cortical layers, as demonstrated by the decrease in cortical surface area and thickness in mice lacking *tbr2* (Arnold et al., 2008; Sessa et al., 2008).

Fibroblast growth factor signaling is important for the regulation of neurogenesis in the developing cortex. Studies *in vitro* originally suggested that the ability of a cortical NSC to stop self-renewing and begin the differentiation process was somehow delayed by increased FGF signaling, resulting in an expanded stem cell pool (Kilpatrick and Bartlett, 1993). The first *in vivo* demonstration was provided by injection of an FGF ligand, FGF2, in rat embryonic brain ventricles, which resulted in an expanded cortex with increased excitatory neuron production (Vaccarino et al., 1999). Conversely, the deletion of the *fgf2* gene resulted in a cortex with reduced numbers of glutamatergic excitatory neurons, particularly in the anterior neocortex (Raballo et al., 2000; Korada et al., 2002). This was not due to a change in the cell cycle or by alterations in cell survival, suggesting that FGF signaling might affect the early amplification of stem cells or their immediate descendants (Raballo et al., 2000). This was confirmed by later work performed on FGF receptor knockout mice (see FGFs and the Developing Dorsal Telencephalon).

Similarly, mice with reduced *fgf8* gene expression have decreased proliferation and increased numbers of apoptotic cells in the developing telencephalon (Fukuchi-Shimogori and Grove, 2001; Garel et al., 2003; Storm et al., 2006). However, reducing the gene dosages of *fgf15* has opposite effects (Borello et al., 2008) with *fgf15* expression in the telencephalon promoting cell differentiation, inhibiting proliferation, and promoting the expression of the *coup-tf1* transcription factor, which plays a role in the development of layer four neurons and posterior cortex (Gimeno et al., 2003; Borello et al., 2008). Therefore, the combination of different FGFs and other cell extrinsic signaling proteins expressed in the neurogenic period may regulate the behavior of stem cells and the production of neuroblasts in a precise sequence, resulting in the establishment of a cortex with the correct number of neurons.

FGFs AND THE DEVELOPING DORSAL TELENCEPHALON

An essential feature of secreted morphogens during development is their ability to regulate the neurogenic process in a spatially restricted manner. Two distinct areas of the dorsal telencephalon are of relevance to the pathophysiology of neuropsychiatric disorders, the cerebral cortex and the hippocampus, the first developing primarily prenatally, and the second both prenatally and postnatally. In this section we will focus more on the prenatal role of FGF receptors on cortical development. Later sections will discuss the role of FGF on hippocampal development and relate these phenomena to neuropsychiatric disorders.

FGF8, FGF17 and FGF18 are expressed in the anterior telencephalon (**Figure 2**), and evidence suggests that this high rostral and low caudal gradient of FGF signaling contributes to prefrontal cortex (PFC) development (Fukuchi-Shimogori and Grove, 2001; Cholfin and Rubenstein, 2007). A given amount of FGFs in the developing cortical field can determine whether stem cells will form specific sub-regions such as somatosensory cortex or PFC (Fukuchi-Shimogori and Grove, 2001). Alterations in the level of FGFs have been shown to lead to abnormal behaviors in animals (Searce-Levie et al., 2008). FGF8 is negatively regulated by BMP (Crossley et al., 2001; Ohkubo et al., 2002) and in turn, FGF8 restricts WNT3a expression, confining it into the hem region (Shimogori et al., 2004). WNT3a expression in posterior hem regions is important for the formation of the hippocampus (Lee et al., 2000).

If we consider the secreted signaling molecules expressed by NSCs in the cortical primordium, only disruptions in the FGF pathways have thus far resulted in major defects in cortical development (Hebert et al., 2003; Cheng et al., 2006). Although overexpression of a stabilized β -catenin, which is downstream of the WNT pathway, increases cortical size (Chenn and Walsh, 2002), the disruption of the WNT pathway affects the hippocampus rather than the cortex (Galceran et al., 2000). Thus, normal embryonic cortical development primarily depends on FGF signaling, and in order to better understand the mechanisms mediating these roles, several FGF receptor mutant models have been generated.

Mice that transiently overexpress a dominant negative *fgfr1* gene that interferes with normal functioning of all receptor types during early embryogenesis have a smaller cortex, particularly in the frontal and temporal regions, and reduced numbers of excitatory neurons (Shin et al., 2004). Furthermore, these mice exhibited hyperactivity. Specific receptor knockouts have subsequently shown the relative contribution of each FGF receptor to cortical development. In order to avoid embryonic lethality of *fgfr1* and *fgfr2* systemic gene knockouts, *fgfr* alleles containing loxP site have been recombined *in vivo* with a variety of Cre lines, including the *foxg1* knock-in Cre, *nestin*-Cre and *hgfap*-Cre lines. Mice lacking *fgfr1* in radial glial progenitors driven by *hgfap*-Cre (which targets the dorsal telencephalon and hippocampal anlage), exhibited severe reduction of hippocampal volume, almost complete absence of midline telencephalic commissures due to abnormal development of midline glia, and decreased inhibitory interneuron number in the cortex and hippocampus (Ohkubo et al., 2004; Smith et al., 2006; Muller Smith et al., 2008). In contrast, the number of cortical excitatory neurons was not decreased in mice lacking *fgfr1* alone (Muller Smith et al.,

2008). However, mice lacking *fgfr2* alone or in combination with *fgfr1*, via *hgfap*-Cre mediated recombination, showed a decrease in cortical excitatory neurons and volume, both of which were more pronounced in the medial prefrontal area of the cortex (Stevens et al., 2010). The mechanism of these abnormalities leading to a loss of cortical excitatory neurons resides in the ability of FGFR2 signaling to induce radial glial stem cells to re-enter the cell cycle, particularly in anterior regions. Therefore, FGFR2 support prefrontal cortical development by promoting the self-renewal or maintenance of cortical stem cells. These data converge with previous work demonstrating that PFC size is reduced by knockout of FGF17, a ligand for FGFR2 (Cholfin and Rubenstein, 2008).

Consistent with the decreased number of excitatory projection neurons in PFC in conditional knockouts for *fgfr2* driven by the *hgfap*-Cre transgene, glutamatergic synapses in the bed nuclei of the stria terminalis (BST), an area that receives projections from the PFC and in turn projects to the hypothalamus, were also reduced in these mice. A decreased number of GABAergic neurons in the BST was also noted in these animals, which is likely to be secondary to decreased glutamate input, as FGFR2 was not targeted in this region (Stevens et al., 2010). These changes may have important consequences for the correct functioning of limbic circuitry.

Mice constitutively lacking FGFR3 through the germline have skeletal defects but have not been reported to have abnormal cortical morphogenesis. (Colvin et al., 1996; Oh et al., 2003). On the other hand, mice with activating mutations of *fgfr3* have an increase in the rate of the cell cycle of cortical stem cells in early neurogenesis and an increase in the generation of TBR2+ IPCs at later stages, leading to increased cortical size and cortical cell number (Inglis-Broadgate et al., 2005; Thomson et al., 2007, 2009). The caudal and lateral areas of the cortex were most affected, reflecting the natural gradient of *fgfr3* expression. Thus, FGFR2 and FGFR3 both appear to influence the appropriate proliferation of stem cells in different regions of cortex (anterior and posterior, respectively), suggesting that the regulation of signaling by each of these receptors individually and in combination may be critical for the appropriate expansion of different cortical areas. Compound mutation for *fgfr1*, *fgfr2* and *fgfr3* in the early anterior neural tube (driven by *foxg1*-Cre) results in an almost complete agenesis of both dorsal and ventral telencephalic regions (Gutin et al., 2006; Hebert and Fishell, 2008).

The downstream targets that mediate FGF regulated cellular events are still under investigation. Relevant to the early patterning processes in the cortex, FGF8-mediated activation of FGFRs is known to repress genes that specify dorsal and posterior cell fate including *coup-tf1*, *emx2*, and *wnt8b* (Crossley et al., 2001; Garel et al., 2003; Storm et al., 2006). FGF and other signaling factors also induce RAS/MAPK pathways, supporting NSC proliferation and self-renewal, and PI3K/AKT pathways, supporting cell survival. Several transcription factor genes are also activated by FGF signaling in NSCs as well as neuronal progeny, including *pea3*, *erm* (*etv5*), and *er81* (*etv1*) some of which are anteriorly expressed (Hasegawa et al., 2004; Cholfin and Rubenstein, 2008) and may be involved in cell differentiation or fate. The multiplicity of targets demonstrates how master regulatory factors such as FGF may exert multifaceted roles in stem cells and their progenies.

CORTICAL INTERNEURON DEVELOPMENT

The ganglionic eminences of the ventral telencephalon give rise to the striatum which emerges from the lateral ganglionic eminence (LGE), and to cortical and hippocampal GABA interneurons which are born in the medial and caudal ganglionic eminences (MGE and CGE). Parvalbumin (PV)+ and somatostatin (Sst)+ interneurons arise from the MGE, while calretinin+ interneurons arise largely from the CGE (Wonders et al., 2008). The interneurons from the MGE and CGE travel to the cortex via tangential migration during embryogenesis and progressively integrate into the cortical circuitry. Postnatally they undergo a protracted maturation and develop into their mature interneuron subtypes through processes that are largely unknown.

FGFR1 and FGFR2 appear to regulate early patterning of the ganglionic eminences before neurogenesis (Gutin et al., 2006). We shown that loss of *fgfr1* or *fgfr2* in the cerebral cortex via *hgfap*-Cre mediated recombination, which does not target the ganglionic eminences, results in a decrease in PV+ and Sst+ interneurons within the cortex (Smith et al., 2008). Work in our lab suggests that this deficit develops postnatally, and does not arise from defects in the patterning or proliferation of stem cells and progenitors in the ventral telencephalon. FGFR1 may act in the developing postnatal neocortex to support the survival and maturation of GABA interneurons.

CLINICAL STUDIES

Biological mechanisms of neuropsychiatric disorders can be studied in clinical populations using multiple lines of inquiry. Structural brain imaging can reveal changes in brain region volume while functional imaging can demonstrate altered functioning of brain regions, both of which may originate in early developmental processes, particularly when found in patients presenting early in the course of illness or young subjects at high risk for psychiatric disorders. More specific mechanisms relevant to stem cell biology may be examined in the post mortem brain as well as genetic analysis of patients. Converging evidence from populations of patients with autism, schizophrenia and affective disorders suggests that stem cell biology is implicated in neuropsychiatric etiology and pathophysiology.

AUTISM

The brain structure of patients with autism spectrum disorders (ASD) including autism, Asperger's Disorder (AD) and pervasive development disorder not otherwise specified (PDD-NOS) has been found to be abnormal using several different approaches. It is now widely believed that at least some of the deficits are present very early in life and that abnormal embryonic brain development may be a contributor to later structural deficits.

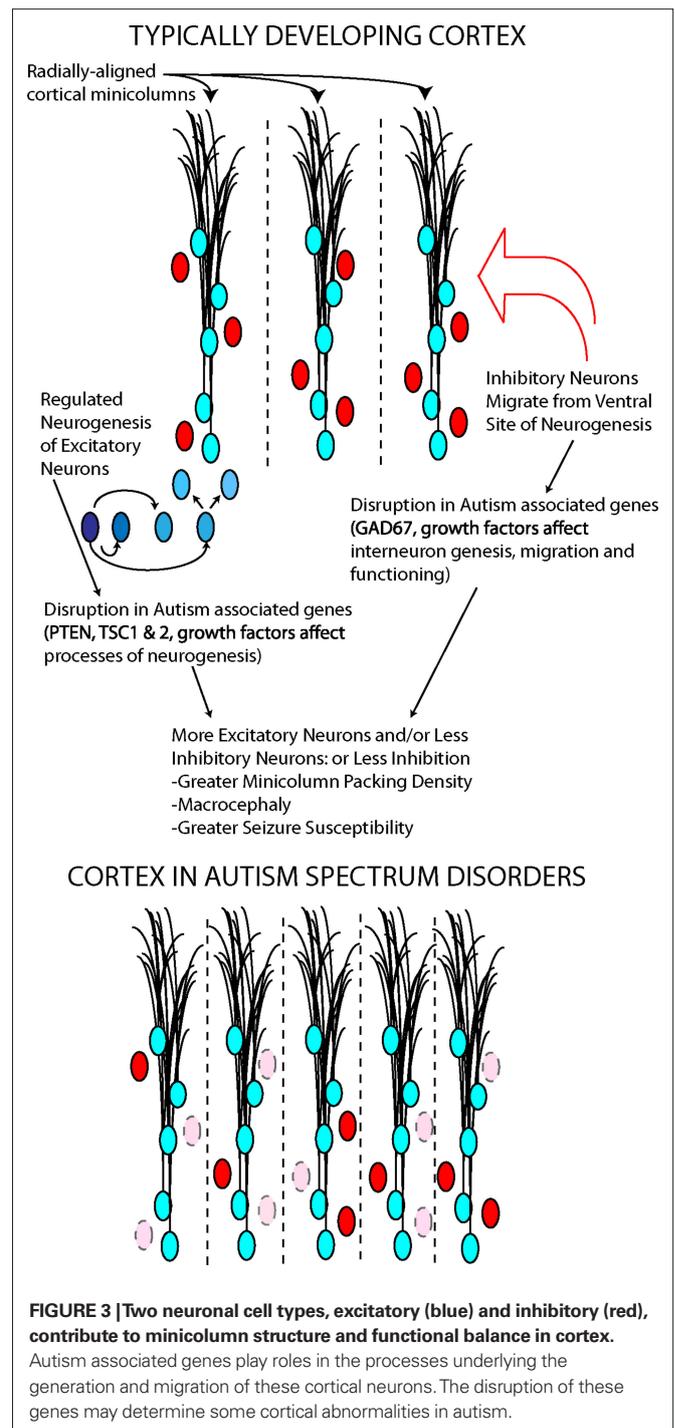
The head circumference of some patients with autism has long been known to be larger (Davidovitch et al., 1996; Woodhouse et al., 1996; Fombonne et al., 1999; Miles et al., 2000) because of abnormal acceleration in growth in early infancy (Courchesne et al., 2003). While no studies have been published on the neuroanatomy of high-risk individuals before a diagnosis of autism is made, retrospective data have shown that children with macrocephaly and autism do not have increased head circumference at birth (Lainhart et al., 1997; Courchesne et al., 2003; Dementieva et al., 2005; Redcay

and Courchesne, 2005) but begin to show larger head measures at about 4 months of age (Gillberg and de Souza, 2002; Courchesne et al., 2005; Redcay and Courchesne, 2005). These findings suggest that autism may be underlain by either problems in early postnatal life and/or processes of embryonic development on which these postnatal events depend. Structural imaging of individuals with autism has shown that differences in brain volume, including both white and gray matter, diminish after the age of 5 years (Hazlett et al., 2005), although some studies have reported increases in gray matter volume in adolescents and adults with ASD (Lotspeich et al., 2004; Palmen et al., 2005; Hazlett et al., 2006), particularly in PFC (Mitchell et al., 2009).

Although there is no clear mechanism accounting for the dysregulation in the trajectory of brain growth in ASD, one hypothesis stipulates that it is the consequence of altered regulation of neural stem cell proliferation or differentiation arising before birth (Vaccarino et al., 2009). Further evidence that early embryonic developmental events are implicated in the pathophysiology of autism comes from post mortem studies demonstrating a fundamental change in cortical structure. Patients with autism were shown to have an increased packing density of mini-columns, which are vertical (radial) assemblies of neurons thought to be anatomically and functionally interconnected (Casanova et al., 2003, 2006).

Several underlying mechanisms could explain macrocephaly and minicolumn pathology, all based on altered embryonic cortical development (Figure 3). The first is an increase in the number of radial units in the embryonic cerebral cortex, which in turn is thought to depend upon an increase in the number of “founder” NSCs in the cortical primordium (Rakic, 1995) (Figure 3). This mechanism is supported by the occurrence of mutations in *pten*, a gene that regulates embryonic stem cell proliferation (Eng, 2003) in a small number of autistic patients with macrocephaly (Butler et al., 2005). Abnormal expression of this gene in NSCs would likely result in an intrinsic alteration of stem cells. Interestingly, an animal model of *pten* mutations shows increased brain size and social deficits (Kwon et al., 2006), although this mutation was in differentiated neurons, not intrinsically affecting NSCs. In Fragile X syndrome, which frequently presents with symptoms of autism, fetal NSCs have been shown to differentiate into neurons at greater rates (Castren et al., 2005) and to misexpress multiple genes involved in proliferation and differentiation (Bhattacharyya et al., 2008). Mutant embryonic NSCs isolated from mice lacking the fragile X mental retardation protein (FMRP) due to a deletion in the *fmr1* gene differentiate in greater numbers into immature neurons (Castren et al., 2005). These findings are similar to those obtained in *Drosophila* germline stem cells lacking an ortholog of the *fmr1* gene (Yang et al., 2009). Thus, the *pten* and *fmr1* mouse models of ASD support the hypothesis that an intrinsic abnormality in NSC is responsible for features of these disorders. Two members of the *TF-II* family of transcription factors involved in Williams syndrome, another disorder with abnormal social behavior, have been shown in mice to regulate specific gene targets that may be involved in embryonic stem cell differentiation (Makeyev and Bayarsaihan, 2009).

GABA interneurons surround each minicolumn, and some genetic evidence and post mortem data suggest a GABAergic abnormality in ASD (Fatemi et al., 2002). Multiple genes involved in the



development and function of the GABAergic system, including *dlx5*, have been involved in Rett syndrome, a developmental abnormality with autistic features (Horike et al., 2005); furthermore, alterations in the development of GABAergic neuron circuitry have been found in mice lacking the *Methyl-CpG binding protein 2 (MeCP2)* gene, whose mutations are responsible for Rett syndrome (Medrihan et al., 2008; Zhang et al., 2010). Lastly, a large number of synaptic-related genes have been implicated in small subsets of patients with ASDs (in total, accounting for probably less than 3–4% of the cases)

(Buxbaum, 2009; Radyushkin et al., 2009). Thus, it appears that abnormalities in both the early-determined size and scaffolding of the cerebral cortex and later developing synaptic connections may play a role in individual cases of autism.

SCHIZOPHRENIA

In schizophrenia, retrospective studies have suggested that head circumference is decreased at birth and developmental delays are present in early childhood, both of which implicate prenatal and early postnatal alterations in forebrain development (Cannon et al., 2002). The occurrence of prodromal symptoms in the majority of cases (Hafner et al., 1994), as well as the presence both prior to and after onset of illness of neuropsychological deficits (Crespo-Facorro et al., 2007) also implicates disruption of forebrain development. Neuropsychological dysfunction implicates the PFC in patients with schizophrenia, the cortical region that has expanded most extensively in mammalian evolution and that has been suggested to rely on key evolutionary developments in stem cell function (Martinez-Cerdeno et al., 2006).

Altered hippocampal development has also been implicated in the pathogenesis of schizophrenia (Kobayashi, 2009). Total brain gray matter and hippocampal volumes are reduced at the time of first episode in schizophrenia (Ohnuma et al., 1997; Gur et al., 1999) and at times later in the disease course, volume reductions have been observed in PFC, hippocampus and temporal lobe (Shenton et al., 2001). Longitudinal studies with structural imaging show that both the PFC and the medial temporal lobe become progressively smaller during the period when psychosis develops and that dorsal prefrontal regions experience even more loss as illness progresses, consistent with a neurodegenerative process (Pantelis et al., 2007). Post mortem studies of the cerebral cortex of patients with schizophrenia have shown reductions in neuropil (Selemon et al., 1998), as well as in GABAergic cells expressing PV and reelin (Guidotti et al., 2000; Fatemi et al., 2001; Hashimoto et al., 2008). Post mortem analysis of the hippocampus also shows evidence for an abnormal GABAergic system and suggests that important signaling pathways are altered, including WNT and TGFbeta (Benes et al., 1998, 2007; Todtenkopf and Benes, 1998; Arnold et al., 2005). While these post mortem findings may reflect changes in the adult brain due to disease progression and medication effects, alterations in cortical neurodevelopmental processes could also create vulnerabilities that develop later in life.

Genes that are implicated in stem cell regulation, including *neuregulin*, *disc-1*, *wnt* related genes, *bdnf* and *fgfr1*, have been associated with schizophrenia in genetic association and post mortem studies, suggesting NSCs dysregulation in at least some cases. Mouse models lacking *fgfr1* embryonically have smaller hippocampi and cortical interneuron deficits similar to those in patients with psychosis (Ohkubo et al., 2004). Similarly, deficient *bdnf*, *neuregulin* and *disc-1* genes in mice mimic various aspects of the disorder (Ayhan et al., 2009; Brandon et al., 2009; Meyer and Morris, 2009). Conversely, mutations found in some patients with schizophrenia have significant effects on cortical stem cell development. Mice lacking the genes within the 22q11 mutation (velocardiofacial syndrome, a known chromosomal abnormality predisposing to schizophrenia) have abnormal neurogenesis, specifically affecting upper cortical layers (Meechan et al., 2009). As in autism, patients

with schizophrenia are likely heterogenous, with pathology in some determined by a component of neuronal functioning that arises postnatally and in others, determined by earlier disruptions of patterning and neurogenesis.

AFFECTIVE DISORDERS

Patients with major depression have been found to have smaller hippocampi (Videbech and Ravnkilde, 2004) and smaller anterior cingulate cortical regions (Caetano et al., 2006). Connectivity and functioning of prefrontal and cingulate cortices have also been shown to be abnormal in individuals with major depression (Drevets, 2000; Grimm et al., 2008; Vasic et al., 2009). A recent longitudinal study of people at high familial risk for developing depression show thinning of the cerebral cortex, particularly in right-sided frontal and parietal areas (Peterson et al., 2009). This thinning was present even in children and adolescents prior to the onset of any mood episode, suggesting that structural changes that result from abnormal early cortical pruning during infancy or adolescence may be a predisposing factor in depression. In patients with bipolar disorder with psychotic symptoms, neuroanatomical and neuropsychological findings are similar to those found in patients with schizophrenia (Murray et al., 2004). In non-psychotic bipolar disorder, patients presenting at the first episode of illness have shown decreased volume in prefrontal and temporal cortex (Hirayasu et al., 1999; Strakowski et al., 1999; Kasai et al., 2003). Bipolar disease progression is associated with ventricular enlargement and stronger reductions of the PFC which correlate with impaired functioning during manic episodes (Bearden et al., 2001; Blumberg et al., 2003).

Post mortem studies have demonstrated that prefrontal cortical regions have abnormal densities of pyramidal, GABAergic and glial cells in patients with depression. Medium to large pyramidal neurons appear to be lower in density and smaller in soma size (Rajkowska et al., 1999, 2005; Law and Harrison, 2003) while smaller neurons and those in layers III, V may be increased in density (Chana et al., 2003; Rajkowska, 2003). Glial cell density in patients with depression appears significantly reduced (Ongur et al., 1998; Rajkowska et al., 1999; Cotter et al., 2001, 2002; Uranova et al., 2004). These findings suggest that abnormal prenatal development of stem/progenitor cells that generate the neurons populating different cortical layers and abnormal development of glial elements may account for structural brain abnormalities in depression.

Post mortem work has also examined the levels of signaling factors in patients with depression. In frontal cortical regions, FGF ligand and receptor levels as well as BDNF receptor levels were shown to be altered in patients with depression. Findings generally show reduced expression (Evans et al., 2004; Sibille et al., 2004) but some point to upregulated receptor levels (Tochigi et al., 2008). Altered gene expression in the mature cortex may suggest a role for FGF and other important mediators of neuronal growth in mood disorders in the adult brain. However, they may also reflect a genetic defect that may have contributed to an earlier altered developmental trajectory. Parallel findings in model animal systems (Chen et al., 2008) and patients with mood disorders (Rajkowska et al., 2001; Valentine and Sanacora, 2009) suggest a role for FGF in both embryonic and mature brain functions (**Figure 4**).

ADULT NEURAL STEM CELLS

Neural Stem Cells in the adult brain are present in regions around the ventricles, specifically in the SVZ, which gives rise to neurons that migrate to the olfactory bulb via the rostral migratory stream. A region in the hippocampal dentate gyrus (DG), the subgranular zone (SGZ), also contains NSCs which generate DG granule cells. Interestingly, over 80% of the interneurons in the olfactory bulb and 10% of granule cells in the DG are replaced by this mechanism in the period of about 1 year, suggesting that a portion of these neurons are under constant turnover (Lemasson et al., 2005; Ninkovic et al., 2007; Imayoshi et al., 2008).

The contribution of adult stem cells to regeneration and neuroplasticity in adult patients with mental illness has received relatively more attention than the role of embryonic NSCs in these disorders. Interestingly, as more is understood about the intrinsic and extrinsic regulation of both embryonic and adult NSCs, common mechanisms are being identified which may underlie disruption in both types of NSCs in disease states (Bordey, 2006).

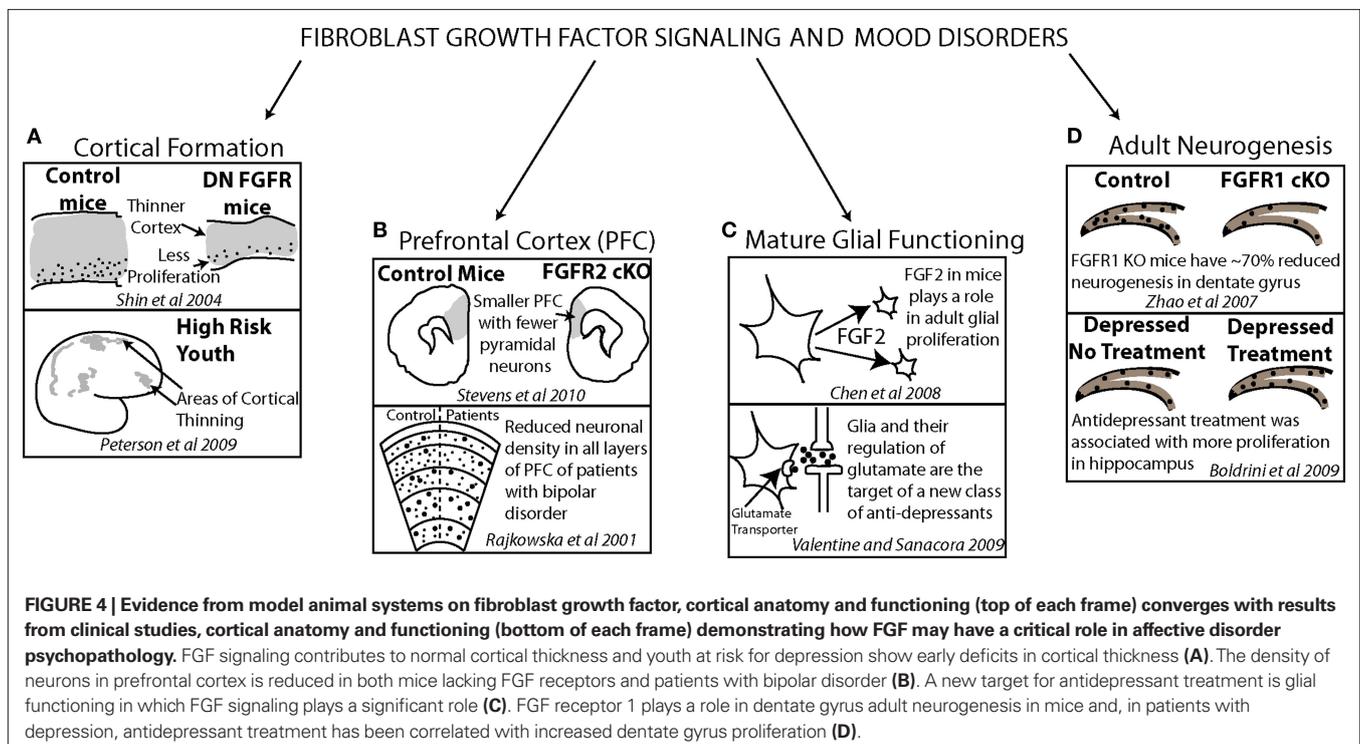
While the identity of NSCs in the adult brain is not clearly documented, it appears likely that they have many features characteristic of astroglia (Imura et al., 2003; Alvarez-Buylla and Lim, 2004; Liu et al., 2006). Like embryonic radial glia, adult SVZ NSCs have GABA_A receptors which limit their proliferation in response to GABA released by neuroblasts, suggesting negative feed-back regulation *via* non-synaptic GABAergic signaling between neuroblasts and GFAP-expressing NSCs (Liu et al., 2005).

Neuronal stem cells in the adult brain pass through several stages from quiescent multipotent cell (astroglial in nature, slowly dividing) to amplifying neural progenitors which rapidly proliferate and generate immature neurons, which finally mature into

granule cells or olfactory interneurons (Ma et al., 2009a). A large proportion of postnatally generated neurons die and only some are incorporated into the existing circuitry. It has been proposed that this pace may be adaptive in order to enhance the sensitivity of the system while the new neurons fully integrate. Environmental and activity-dependant factors may be critical for regulating how these cells pass appropriately through these stages and hence how newly born neurons will participate in normal brain functioning and potentially compensate for pathological states.

Like embryonic NSCs and radial glial cells, adult astroglial NSCs and progenitor cells in the SVZ and SGZ express several RTKs including *fgfr1*, *fgfr2* and *fgfr3*, *bmpr-1a/alk3* as well as *egfr*, and have active SHH and Notch signaling systems. Adult NSC maintenance and self-renewal depends on secreted FGF, BMP, SHH, and EGF, acting in conjunction with the cell-attached Notch signaling system (Machold et al., 2003; Zheng et al., 2004; Lie et al., 2005; Mira et al., 2010). For example, the number of proliferating cells in the adult SVZ is reduced by 40% in *fgf2* KO mice (Zheng et al., 2004). FGF2 increases cell cycle re-entry and BMP promotes quiescence in adult NSCs, and thus, as in the embryo, the balance of these 2 extrinsic factors is likely to be important for proper regulation of adult NSC proliferation and differentiation (Ming and Song, 2005; Mira et al., 2010).

Much evidence has been found linking major neuropsychiatric disorders to altered regulation of adult NSCs and to the molecular systems involved in their maintenance and differentiation. The SGZ of the DG has been the region of the most research focus. DG functioning underlies mood, memory, and reward, which are impaired in schizophrenia, major depression and bipolar disorder. In animal models of depression, schizophrenia, and bipolar disorder, the activity of SGZ stem cells is reduced. For example,



chronic stress leads to a depression-like phenotype in rodents, suppresses neurogenesis in the SGZ and reduces FGF2 expression in hippocampus (Warner-Schmidt and Duman, 2006). Findings from post mortem studies have demonstrated that numbers of proliferating cells in the DG are decreased in psychotic disorders (Reif et al., 2006); furthermore, abnormal FGF expression has been documented in the post mortem hippocampus of depressed and schizophrenic patients (Gaughran et al., 2006). In this study, neither antidepressant treatment nor the presence of affective disorders were found to be correlated with altered numbers of hippocampal dividing cells. However, other post mortem work has demonstrated that patients who received antidepressant treatment did show a greater number of neural progenitor and dividing cells in the DG than untreated patients with depression (Boldrini et al., 2009). Furthermore, antidepressant treatment increases hippocampal neurogenesis in both rodents (Malberg et al., 2000) and non-human primates (Perera et al., 2007). Chronic antidepressant administration to rodents has been shown to increase FGF2 expression in astrocytes and neurons within and outside of the hippocampus, suggesting that FGF signaling may be involved in the neurogenic action of antidepressants. In support of this idea, the infusion of FGF2 into the ventricles of adult rats increases cell proliferation and reduces depression-like behavior in rodents (Turner et al., 2008). Also, conditional knockout of *fgfr1* in neuronal stem cells by *nestin*-Cre results in reduced proliferation and neurogenesis in the adult DG (Zhao et al., 2007). New data suggest FGF2 may be specifically involved in the modulation of anxiety/fear behavior in rodents (Perez et al., 2009). However, it is currently controversial whether ongoing hippocampal neurogenesis is required for the therapeutic action of antidepressants. Some have proposed that hippocampal neurogenesis may be limited to mediating the beneficial action of antidepressants on cognition. One problem is the limitations of animal models of depression in which behavior may rely on mechanisms that are peripheral to human disease (Santarelli et al., 2003; Sahay and Hen, 2007; Holick et al., 2008; David et al., 2009). Hence, the specific role of FGF2 on the development and function of systems that subserve affective and cognitive functions in humans is still somewhat unclear.

Gene products implicated with neuropsychiatric illnesses *via* association studies have been shown to affect hippocampal neurogenesis, most likely by working intrinsically within stem and progenitor cells. The gene with the strongest association to schizophrenia, *disc-1*, has been shown to regulate the maturation of newborn neurons in the mature brain. When expression of *disc-1* is suppressed, neurons mature too quickly (Kim et al., 2009). This may involve a disruption of the balance between those signaling pathways that maintain neuronal stem cells, such as FGF, and those that advance their differentiation into neurons, such as BMP2/4. A role in progenitor cell maintenance and neuronal differentiation within hippocampal NSCs has been also identified for systems that regulate gene expression by methylating or acetylating specific histone proteins in stem and progenitor cells (Wu and Sun, 2009; Yu et al., 2009). A gene that has been associated with some forms of autism, *gadd45b*, may also play a role in these pathways as it increases progenitors in the DG after electroconvulsive treatment, perhaps by controlling *fgf* gene expression by DNA methylation

(Ma et al., 2009b). In summary, neuropsychiatric disorders may have links to stem cell biology in the mature as well as the developing brain.

THE FUTURE OF STEM CELLS AND INTERVENTIONS: INTEGRATING HUMAN AND ANIMAL KNOWLEDGE

Work in animal models reveals fundamental processes of brain development that are important to generate and test hypotheses concerning the pathogenesis of human mental disorders. This opens the possibility of manipulating stem cells in clinical populations. Avenues of research are utilizing general knowledge about stem cells to (1) use manipulated stem cells in a rehabilitative capacity in patients and (2) use stem cells from patients to understand pathophysiology and test candidate drugs for reversing abnormal cellular functions. We will review briefly here how knowledge about stem cell biology from both humans and animal models is being applied to develop these new research directions.

Research on the use of stem cells for rehabilitation was originally motivated by the potential for direct development of new neurons from stem cells that might replace lost neurons that are at the center of pathophysiology. For example, in degenerative illnesses such as Parkinson's disease and Amyotrophic Lateral Sclerosis, specific populations of neurons, dopaminergic cells and spinal motor neurons respectively, are progressively lost. Stem cell research has sought to use either embryonic or other types of stem cells to generate replacement neurons that could be transplanted and incorporated into the CNS of patients (for a Review, see Hynes and Rosenthal, 2000). This work has required knowledge acquired from animal models of the transcription and signaling factors that determine dopaminergic and spinal motor neuron fate and maturation. As researchers have pursued this goal, it has been shown that stem cells in animal model transplant recipients may have an indirect trophic role, i.e., reducing cell death, increasing metabolic functions and protecting remaining neurons from insults (Jung et al., 2004; Rafuse et al., 2005; Yasuhara et al., 2006). These findings may hold promise for future application of stem cell-derived therapies to neuropsychiatric disorders. Disorders such as schizophrenia and depression may have a neurodegenerative component, similar to neurological disorders for which the supportive role of stem cells has been demonstrated. The regions of the brain involved may be different for major affective and psychotic disorders than degenerative motor diseases – e.g., cortex and hippocampus – but these regions may be even better candidates for the application of stem cell support therapy given their nearby neurogenic zones. Extrinsic factors that influence the stem cell niches, like FGF and BMPs, will likely have an important role to play in these potential therapies.

Induced pluripotent stem cells (iPSCs) also hold great promise in their application to neuropsychiatric disorders. These pluripotent stem cells can be derived from skin fibroblasts or blood lymphocytes by introducing a combination of genes that confer stem cell like properties, essentially reprogramming the differentiated cells to behave like embryonically derived stem cells (Takahashi et al., 2007; Yu et al., 2007; Muller et al., 2008). Takahashi and colleagues reported the first generation of human iPSCs in 2007. They achieved this by introducing the *oct3/4*, *sox2*, *klf4*, and *c-myc* genes into fibroblasts with retroviral vectors. As iPSCs reproduce the essential features of human embryonic

stem cells (hESC) they can be coaxed to give rise to neurons. It has already been shown that hESC lines can give rise to mature, physiologically active neurons using different protocols, and many of these protocols have already been successfully applied to iPSC (Johnson et al., 2007; Chambers et al., 2009; Kriks and Studer, 2009; Soldner et al., 2009). Furthermore, by using different combinations of secreted patterning gene products such as FGFs, SHH and WNTs, different subtypes of neurons can be generated such as forebrain specific neurons, midbrain dopaminergic or GABAergic neurons (Yan et al., 2005; Eiraku et al., 2008; Chambers et al., 2009). Here again, decades of animal research in neurodevelopment is paying off, in that the accumulated knowledge in patterning and cell fate specification events in normal development will aid in the development of *in vitro* differentiation paradigms for generating specific neuron subtypes. More needs to be done and human and animal research must proceed in parallel.

Our inability to examine the direct consequences of gene sequence variations in the living CNS at the transcript and biological levels is a formidable challenge to the investigation of the genetic pathophysiology of psychiatric disorders. The derivation of iPSCs may allow us to investigate basic neurobiological aspects of neuropsychiatric disorders using patient-derived cell lines. For the first time, scientists will be able to use patient-derived cells to investigate developmental properties of the nervous system, such as neural stem cell proliferation, neural differentiation, and synapse formation either *in vitro* by using cell culture techniques, or *in vivo* by transplantation into a host animal, such as the developing rodent brain. One of the most promising aspects of iPSCs is the potential to examine the effects of specific human gene variants upon neural differentiation and function, by creating iPSCs from patients with particular genetic mutations. Furthermore, the gene expression profiles of neurons derived from such patients-derived neural stem cell lines can be examined. One potential complication of such studies is the large number of genetic variants present in the human genome.

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