

Independent Effects of Paternal Age and Neuregulin1 Expression in Mice in
Relation to Schizophrenia

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ABSTRACT

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Heather El-Amamy

This thesis work is divided into two parts, both guided by the overwhelming evidence that hereditary factors influence neurodevelopment. The first section is focused on advanced paternal age, which may modulate an offspring's place on the continuum of normal behavior, as well as conferring increased risk for the development of certain disorders, such as schizophrenia. By using a mouse model to examine the difference between old and young father offspring, we have been able to flesh out this phenotype. Additionally, by examining the female and male offspring separately, we discovered gender-specific differences between the groups. Ongoing work is seeking to identify changes in methylation between the old and young father offspring that may explain these differences.

The second section deals with a specific gene that has been linked to schizophrenia, namely Neuregulin1. This gene plays several roles in neurodevelopment, notably including the proliferation of interneurons and their incorporation into the cortex and olfactory bulb. We used heterozygous mice to explore the effects of a change in gene expression of the proliferation of new neurons from the subventricular zone, their migration through the rostral migratory stream, and differentiation into various interneuron subtypes in the olfactory bulb. The heterozygotes appeared to have decreased turnover of a subset of calretinin-expressing interneurons of the granule cell layer. We also treated subgroups of these mice with clozapine, however this did not seem to have

any effect. We looked at the olfactory system in this work since this is a model of neurogenesis that continues into adulthood. Yet the regions that produce cortical interneurons during early development give rise to the subventricular zone. Therefore the findings related to subventricular zone neurogenesis may have similar implications for cortical development.

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CHAPTER 1: INTRODUCTION

One of the recurring themes of neuroscience is what the diseased brain reveals about normal brain function. Rather than being a simple input-output system, the central nervous system (CNS) has multiple parallel and interlocking systems covering systems as basic as breathing and blood flow, and as complex as specific declarative memory. The existence of schizophrenia provides a window into the functions that are required for normal behavior and cognition. On one hand, the gross anatomy and pathology of the brain was historically not thought to be disturbed in schizophrenia, in contrast to the large structural alterations found in dementia, degenerative movement disorders, tumor, stroke, and traumatic injury. However, as exploration of this syndrome has advanced, distinct recurring features of anatomy, cellular histology, and circuit function have revealed differences between the brain in schizophrenia and in normal controls. That these seemingly small differences result in such strong changes in behavior and cognitive function is surprising. Yet this has facilitated the exploration of brain mechanisms for understanding salient information from all the multiple stimuli present in the environment, as well as an exploration of which aspects of brain development are critical for these functions.

In this thesis, I will discuss biological mechanisms that add to inter-individual variability, but can also contribute to schizophrenia vulnerability in cases where they are dysfunctional. Schizophrenia is a severely debilitating, chronic psychiatric disorder that affects roughly 1% of the population worldwide and is characterized by an abnormal

perception of reality (D. A. Lewis & Lieberman, 2000). While features of the disorder may include hallucinations, delusions, social withdrawal, lack of motivation, disorganized thought or behavior, deficits in attention and memory, and difficulty processing information, there is a great deal of heterogeneity in the clinical presentation (van Os & Kapur, 2009). Patients will vary in the constellation of symptoms displayed and the severity and course of the disorder. Although these clinical symptoms do not appear until adolescence or early adulthood, there is now increasing evidence that schizophrenia may emerge from neurodevelopmental abnormalities that occur long before the onset of clinical symptoms that appear in adolescence or early adulthood. I will therefore address possible causes and impacts of genetic and epigenetic factors that may contribute to schizophrenia vulnerability. This introductory chapter will address two main aspects of schizophrenia etiology, namely, the epidemiological evidence for a neurodevelopmental origin of the disorder and the role of specific genetic alterations in causation of schizophrenia. In regards to the first, advanced paternal age will be explored as described in the literature and as modeled in animals, while the second will be explored as a historical concept and as related to the specifics of Neuregulin1 function. Modeling of mutant Neuregulin1 function in mice will then be described in Chapter 3.

EPIDEMIOLOGICAL ETIOLOGY OF SCHIZOPHRENIA

Several environmental factors that alter risk for schizophrenia have been identified through epidemiology, and epigenetic alterations are a probable mechanism for these environmental influences to modulate vulnerability by controlling gene expression. While the clinical phenotype of schizophrenia does not emerge until early adulthood,

environmental exposures that occur throughout development have been linked to the disorder. Risk factors that likely act prenatally include advanced paternal age, fetal hypoxia, nutritional deficiency, and maternal stress or infection (Brown et al., 2007; Brown & Susser, 2008; Khashan et al., 2008; Malaspina, 2001; Malaspina et al., 2001; Mittal, Ellman, & Cannon, 2008; Nicodemus et al., 2008; Perrin, Brown, & Malaspina, 2007; Susser et al., 1996; M. Q. Xu et al., 2009). During early life, childhood trauma, migration, an urban environment, chronic stress, and cannabis use can all contribute to schizophrenia risk (M. Cannon & Clarke, 2005; T. D. Cannon, Mednick, & Parnas, 1990; Cantor-Graae & Selten, 2005; Henquet, Di Forti, Morrison, Kuepper, & Murray, 2008; Howes et al., 2004; Krabbendam & van Os, 2005; Luzi, Morrison, Powell, di Forti, & Murray, 2008; Moore et al., 2007; Murray, Morrison, Henquet, & Di Forti, 2007; Nicodemus et al., 2008; Schreier et al., 2009; Tienari et al., 2004). As there is considerable heterogeneity in individual response to these risk factors, they are thought to represent gene-environment interactions. A person's vulnerability to these exposures is thought to depend on preexisting genetic or epigenetic differences (Caspi & Moffitt, 2006).

There is mounting evidence that schizophrenia is a developmental disorder. This is in part supported by evidence of congenital abnormalities suggestive of neurodevelopmental defects in schizophrenia. Minor physical anomalies (MPAs) are subtle malformations that indicate altered morphogenesis in the first or second trimester. These include reduced facial symmetry, lowered orbital landmarks and eye fissures, and asymmetrical ear shapes (M. F. Green, Bracha, Satz, & Christenson, 1994; Gaultieri, Adams, Shen, & Loiselle, 1982; O'Callaghan, Larkin, Kinsella, & Waddington, 1991;

Tarrant & Jones, 1999). As MPAs derive from the ectoderm, which shares its embryological origins with the brain, the above facial irregularities seem to be linked to brain abnormalities. (Ismail, Cantor-Graae, & McNeil, 1998; Sperber, 1992). In fact, these biological markers of developmental disturbance are not specific to schizophrenia, but have been linked to a broad range of mental disorders, including autism, hyperactivity, epilepsy, learning disabilities, poor motor coordination, mental retardation, attention deficit disorder, cerebral palsy, and affective disorders (Lloyd et al., 2008; Lohr & Flynn, 1993; J. J. McGrath et al., 1995; McNeil, Cantor-Graae, & Ismail, 2000).

The neurodevelopmental theory of schizophrenia asserts that abnormalities present in utero lead to pathological processes in early adulthood with the emergence of schizophrenia as the end result. Since brain development continues into young adulthood, Keshavan has built on the neurodevelopmental theory by proposing a “2-hit model” in which abnormalities occur in both early development and adolescence. Dysfunction at these two critical time points can combine to elicit the symptoms of schizophrenia (Keshavan & Hogarty, 1999). This view may explain the premorbid symptoms apparent in individuals who later go on to develop schizophrenia.

Neurodevelopmental defects, such as minor physical anomalies (MPAs) and neurological soft signs (NSS), are present not only in schizophrenia patients, but also in their relatives. A recent meta-analysis of MPAs in patients with schizophrenia and their unaffected first-degree relatives found that MPAs were more prevalent in schizophrenia patients than in their relatives. However, MPAs were, in turn, more prevalent in the first-degree relatives than in healthy controls (T. Xu, Chan, & Compton, 2011). A meta-analysis of NSS in unaffected first-degree relatives of schizophrenia patients showed the

same pattern. It found that NSS were significantly more common in these relatives than in controls. They were also more common in those with schizophrenia than in their relatives (Neelam, Garg, & Marshall, 2011). The presence of these developmental abnormalities in unaffected siblings, parents or children of individuals with schizophrenia may suggest a familial basis.

In fact, MPAs and NSS are not the only traits associated with schizophrenia that are more prevalent in the unaffected first-degree relatives of patients than in the general population. Several abnormalities in brain structure have been identified in schizophrenia. The most robust anatomical finding has been an increase in volume of the CSF-filled spaces of the lateral and third ventricles and the cortical sulci, as well as a reduction in cortical gray matter. White matter abnormalities have also been found, with evidence of increased orbitofrontal white matter in patients. Regional volume reductions are also seen in frontal lobes and temporal and limbic structures, possibly implicating dysfunction in circuitry that includes the cortex, thalamus, limbic areas, and basal ganglia in schizophrenic pathology (Barta, Pearlson, Powers, Richards, & Tune, 1990; Buchanan & Carpenter, 1997; Buchanan, Vladar, Barta, & Pearlson, 1998; T. D. Cannon, 1996; T. D. Cannon et al., 1998; Fan et al., 2008; Johnstone, Crow, Frith, Husband, & Kreel, 1976; Pearlson, Garbacz, Moberg, Ahn, & DePaulo, 1985; Pearlson & Marsh, 1999; Pfefferbaum & Marsh, 1995; Zipursky, Lambe, Kapur, & Mikulis, 1998; Zipursky et al., 1994). Some of these structural differences are also shared with family members to a less marked degree, such as gray matter reductions in the frontal and temporal lobes, decreased hippocampal volume, and increased white matter in the orbitofrontal area (T. D. Cannon et al., 1998; Diwadkar, Montrose, Dworakowski, Sweeney, & Keshavan,

2006; Fan et al., 2008; Job et al., 2003; McDonald et al., 2005; McIntosh et al., 2006; Staal et al., 2000; Whalley, Harris, & Lawrie, 2007).

Several studies have also found subtle cognitive deficits in nonpsychotic relatives of patients with schizophrenia. Cognitive impairment is one of the core features of schizophrenia, and these findings suggest that a similar but milder impairment is present in family members. These deficits included verbal memory, spatial working memory, language ability, attention, and response inhibition (Appels, Sitskoorn, Westers, Lems, & Kahn, 2003; Cosway et al., 2000; Faraone et al., 1995; Grove et al., 1991; Park, Holzman, & Goldman-Rakic, 1995; Scala, Lasalvia, Cristofalo, Bonetto, & Ruggeri, 2012; Snitz, Macdonald, & Carter, 2006). There is also some evidence that the symptoms apparent in family members may reflect the specific pathology of the proband. For example, the deficit subtype of schizophrenia is characterized by more severe negative symptoms, cognitive deterioration, and structural brain abnormalities (Amador et al., 1999; Buchanan, Kirkpatrick, Heinrichs, & Carpenter, 1990; Buchanan et al., 1994; Kirkpatrick & Galderisi, 2008; Tek, Kirkpatrick, & Buchanan, 2001). When comparing relatives of patients with deficit versus non-deficit schizophrenia, only relatives of the deficit subtype displayed impairment in executive functioning, increased levels of negative symptoms, and higher levels of social isolation (Kirkpatrick, Ross, Walsh, Karkowski, & Kendler, 2000; Scala et al., 2013).

These subtle traits associated with schizophrenia prompted Gottesman and Shields to coin the term “endophenotypes,” to describe internal or intermediate phenotypes that could only be discovered by a “biological test or microscopic examination” (Gottesman & Shields, 1973). Such intermediate phenotypes, called

endophenotypes, are defined as measurable biological traits that vary continuously in expression among individuals, but appear at higher rates in those at risk for the disorder than in the general population. They are typically functionally related to aspects of the clinical disorder, even though they manifest in individuals regardless of whether the illness is present. Endophenotypes that show abnormal expression in healthy relatives and are also perceptible before the onset of the first episode of psychosis are more likely to be a part of the causal path of the disorder. They can also transcend clinical categorizations and reveal shared mechanisms of causation in multiple disorders (T. D. Cannon & Keller, 2006; Gottesman & Gould, 2003; Preston & Weinberger, 2005). For example, this was apparent in the discussion of MPAs and NSS above, which have been associated with multiple developmental disorders. These endophenotypes have been exceedingly useful in exploring the still-unknown etiology of schizophrenia, a disorder where the clinical presentation can vary widely from patient to patient. The study of endophenotypes allows the exploration of biological mechanisms upstream of clinical symptoms that may modulate risk for schizophrenia. This is useful in assessing congenital risk factors, as the increased prevalence of endophenotypes in first-degree relatives who themselves do not display a clinical phenotype, and the tendency of the disorder and endophenotypes to cluster within families, suggest a degree of heritability.

DEVELOPMENTAL PROCESSES THAT CAN AFFECT ADULT FUNCTION

One possible type of developmental dysfunction, proposed by Feinberg in 1982, is that abnormal synaptic pruning may be involved in the etiology of schizophrenia (Feinberg, 1982). In the healthy human newborn, there is a dramatic increase in the

number of cortical synapses formed until synaptic density reaches its maximum between ages 2 and 4 (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997). After reaching roughly 150% the number of synapses seen in adulthood, there is then a decline in synaptic density until the late teens or early adulthood (Huttenlocher, 1979; Petanjek et al., 2011). Developing synapses are either stabilized by neuronal activity or pruned away (Hua & Smith, 2004). However, in schizophrenia, studies have found decreased presynaptic protein markers and decreased cortical spine density relative to controls, without a difference in neuronal density (Broadbent, Byne, & Jones, 2002; Faludi & Mernics, 2011; Garey, 2010; Glantz & Lewis, 2000; Kalus, Muller, Zuschratter, & Senitz, 2000). Returning to the “2-hit model,” if synaptic development is somewhat suppressed during development, the synaptic pruning and decreased plasticity that occurs in adolescence could exacerbate abnormalities, leading to the schizophrenic phenotype. However, synaptogenesis could alternatively be unimpaired during development, and accelerated pruning during adolescence could elicit the clinical phenotype.

Although abnormal synaptic pruning has not been proven to be a part of the etiology of schizophrenia, another area of focus is cortical development and migration of new neurons, particularly interneurons. The production of interneurons is a key developmental process in the formation of cortical circuitry. Interneurons form connections between other neurons and modulate the activity of excitatory neurons through the release of GABA and glycine (Dreifuss, Kelly, & Krnjevic, 1969; Fonnum & Storm-Mathisen, 1969; Somogyi, Freund, Wu, & Smith, 1983). They can make multiple synaptic connections with excitatory neurons and control activation through the use of feed-forward and feedback inhibition (Berger, Silberberg, Perin, & Markram, 2010;

Silberberg, Gupta, & Markram, 2002; Somogyi, Tamas, Lujan, & Buhl, 1998; Wang et al., 2004). In fact, these interneurons do seem to be impaired in schizophrenia, as schizophrenia is associated with a 45% decrease in GAD67, an enzyme that synthesizes GABA, in a subset of interneurons that express parvalbumin (Akbarian et al., 1995; T. Hashimoto et al., 2003; Volk, Austin, Pierri, Sampson, & Lewis, 2000).

GENETIC AND EPIGENETIC ETIOLOGIES OF SCHIZOPHRENIA

There is strong evidence of a genetic component of schizophrenia. The results of several family studies have illustrated that the risk of developing schizophrenia increases as the proportion of genes in common with a schizophrenic individual increases. In the general population, 1% of people suffer from schizophrenia. If a third-degree relative has schizophrenia, an individual's risk rises to 2%. If someone with schizophrenia is a second-degree relative, the risk rises to around 2-6%. For first-degree relatives, this risk increases further to between 6% and 17%. Identical twins share 100% of their DNA. If one twin develops schizophrenia, the risk of the other twin also having it is 48% (Gottesman & Erlenmeyer-Kimling, 2001).

Adoption studies also point to genetic inheritance. Offspring of schizophrenic parents show similar elevated risk whether they are raised with their biological parents or in an adoptive home, and regardless of whether parents developed the disorder before or after the adoption. Offspring of nonpsychotic biological parents also do not show an elevated risk if they are raised by schizophrenic adoptive parents (Heston, 1966; Higgins, 1976; Tienari, 1991; Tienari et al., 1985; Tienari et al., 1994; Wender, Rosenthal, Kety, Schulsinger, & Welner, 1974). This indicates that a genetic risk is conferred and the

increased incidence of schizophrenia is not simply due to environment. In fact, in monozygotic twins discordant for the disease, offspring of the unaffected twin show similar risk of developing schizophrenia as offspring of the schizophrenic twin (Gottesman & Bertelsen, 1989; Kringlen & Cramer, 1989). There seems to be a hereditary risk even in the absence of the disorder.

The high heritability of schizophrenia has motivated decades of research attempting to unravel the genetics of schizophrenia. Early researchers began a search for a major single gene that may be responsible for transmission. However, it became apparent that the disorder did not show a Mendelian inheritance pattern (Risch & Baron, 1984; Tsuang, Bucher, & Fleming, 1982). In fact, although a positive family history is a strong indicator of increased risk, most individuals with schizophrenia have no first-degree relatives who exhibit the disorder. This signifies a more complex genetic component (Kendler, 1987; J. Yang, Visscher, & Wray, 2010).

More recently, genome wide association studies (GWAS) or linkage studies have been used to discover possible candidate genes. These studies take advantage of the concept of linkage disequilibrium. Alleles from neighboring genetic markers tend to be inherited together. The entire genome can be systematically surveyed by doing a case-control comparison for single-nucleotide polymorphisms (SNPs), or base pair variations that occur throughout the genome. SNPs associated with a disorder indicate areas of the genome that may be relevant to its etiology (Hardy & Singleton, 2009; McCarthy et al., 2008). This allows multiple susceptibility loci to be identified at once without prior bias. In linkage studies, this analysis is performed between cases and controls in a family, while association studies compare cases and controls among the general population.

These studies detect common polymorphisms that show an association with schizophrenia, and several pertinent loci have been detected. Many of the implicated genes also have functions that could potentially be relevant to the etiology of schizophrenia. These include factors involved in neurodevelopmental (e.g. Nrg1, PTPN21, RELN, EFHD1, EML5, ANK3, VRK2, SHISA9, LNX2, TCF4, C1orf187), neuroendocrine (e.g. NRGN, PAM) and immune (e.g. HLA-DRB1, HLADQA1, SPA17, PTGS2, PLAA, PRSS16, TLR4, CSF2RA, IL3RA) systems. Although these can combine to make a substantial contribution to schizophrenia risk, all of these polymorphisms also presented small odds ratios individually. This indicates that, although these variants are common, they only have a weak effect on relative risk for schizophrenia. However, this may be expected, as the decreased reproductive fitness in schizophrenia would cause the negative selection of any risk alleles of large effect size, making them exceedingly rare (Alkelai et al., 2011; Alkelai et al., 2012; Athanasiu et al., 2010; J. Chen et al., 2011; Hosak, Silhan, & Hosakova, 2012; Ikeda et al., 2011; International Schizophrenia et al., 2009; Kirov, Zaharieva, et al., 2009; Lencz et al., 2007; X. Ma et al., 2011; Need et al., 2009; O'Donovan et al., 2008; Rietschel et al., 2012; Shi et al., 2009; Shifman et al., 2008; Stefansson et al., 2009; Sullivan et al., 2008; Walsh et al., 2008; Yamada et al., 2011).

Because of the pressure of negative selection, rare mutations that confer schizophrenia risk with higher penetrance are likely recent de novo mutations or older mutations of intermediate effect size that have not yet been selected out. Such mutations do seem to exist in the form of copy number variants (CNVs). CNVs are genomic insertions, duplications, translocations or deletions of sections of DNA that can be from a

few kilobases to several megabases in length. These structural variants can have effects on phenotype if, for example, the mutation occurs in dosage-sensitive genes or in regions containing regulatory sequences (Mulle, 2012; Owen, 2012). Whole genome scans have revealed that rare, large CNVs are three to eight times more frequent in cases with schizophrenia than in unaffected controls. There is evidence for the involvement of CNVs in the pathogenesis of other neurodevelopmental disorders, such as autism, mental retardation, epilepsy, and ADHD. These structural variants may be playing a similar role in schizophrenia (Kirov, Grozeva, et al., 2009; Walsh et al., 2008; B. Xu et al., 2008).

GWAS analyses have also identified specific CNV loci on several different chromosomes that, although not fully penetrant, confer a relatively high degree of risk for schizophrenia. Some structural variants associated with schizophrenia have also been linked to several different psychiatric disorders, indicating a possible etiological overlap. For example, the Neurexin1 (NRXN1) deletion has been strongly associated with schizophrenia, as well as autism, epilepsy, and mental retardation. NRXN1 encodes a presynaptic neuronal cell adhesion molecule that induces postsynaptic differentiation in dendrites, so its implication points to a potential role of synaptic dysfunction. While some of the CNVs linked to schizophrenia are confined to a single gene, others span multiple genes, making it difficult to determine which genes are involved in the pathogenesis. However, the use of pathway analysis on identified genes to determine whether genes from specific functionally defined pathways were overrepresented in the sample revealed that a disproportionate number of disrupted genes were involved in neurodevelopment or synaptic transmission in cases but not controls. One notable example is the Neuregulin1 signaling pathway. Neuregulin1 (Nrg1) binds to the ErbB4 receptor, and this complex

plays a role in the regulation of neurotransmitter receptor expression, myelination, synaptic plasticity, and neuronal survival, migration, and differentiation. ErbB4 interacts with MAGI2 at neuronal synapses, and both of these have been identified as structural variants associated with schizophrenia (Doherty, O'Donovan, & Owen, 2012; Duan, Sanders, & Gejman, 2010; Gejman, Sanders, & Kendler, 2011; International Schizophrenia, 2008; Kirov, Grozeva, et al., 2009; Kirov et al., 2008; Mulle, 2012; Need et al., 2009; Raychaudhuri et al., 2009; Stefansson et al., 2008; Sudhof, 2008; Tam, Redon, Carter, & Grant, 2009; Walsh et al., 2008; B. Xu et al., 2008).

In addition to genetic mutations, epigenetic mechanisms can regulate genomic functions, including gene expression, through the covalent modifications of DNA and histones. In chromatin, DNA is wrapped around histone cores to form nucleosomes. Epigenetic mechanisms then alter the access of transcription factors to DNA binding sites. In DNA methylation, DNA methyltransferases (DNMTs) attach a methyl group to the C5 position of the cytosine in a CpG dinucleotide, which generally promotes a closed, transcriptionally repressed state and leads to gene silencing. Histone modifications include methylation, acetylation, phosphorylation, ubiquitination, and sumoylation and can cause either gene activation or repression (Feng & Fan, 2009; Jenuwein & Allis, 2001).

These epigenetic mechanisms have been associated with the pathogenesis of schizophrenia. Aberrant methylation is present in numerous loci in the frontal cortex of schizophrenic individuals. These include several genes implicated in the disease etiology, such as those involved in neurodevelopment or glutamatergic and GABAergic neurotransmission (Mill et al., 2008). S-adenosylmethionine (SAM) is the methyl donor

used by DNMTs to transfer the methyl group to a cytosine residue. In the schizophrenic prefrontal cortex, levels of SAM are twice as high as healthy controls. This is also associated with an increase in DNMT1, which may contribute to the hypermethylation and downregulation of certain cortical genes (Guidotti et al., 2007). Global methylation patterns in the peripheral blood are also a marker for schizophrenia, with patients showing significant hypomethylation (Melas et al., 2012).

An analysis of copy number discordance between monozygotic twins discordant for schizophrenia found that these twins did not differ in their structural variants (Ono et al., 2010). However, monozygotic twins do differ in their peripheral blood methylation patterns based on whether they have the disorder. Genome-wide DNA methylation profiling has identified numerous differentially methylated CpG sites, mostly in regions containing promoters. These included methylation differences in genes that have previously been implicated in schizophrenia, such as the dopamine D2 receptor and the catechol-O-methyltransferase (COMT) gene. The affected twin also had a methylation pattern that was more similar to unrelated schizophrenic individuals than to the unaffected co-twin (Dempster, Mill, Craig, & Collier, 2006; Dempster et al., 2011; Kinoshita et al., 2013; Petronis et al., 2003). As the concordance rate of schizophrenia between monozygotic twins is only 48%, epigenetic factors could account for this difference.

DNA methylation is dynamic and there appears to be some correlation between levels of methylation and the severity of symptoms. In the early 1960s, schizophrenics were given high doses of methionine in an attempt to treat the disorder. This instead led to an exacerbation of their symptoms (Brune & Himwich, 1962; Pollin, Cardon, & Kety,

1961; Tremolizzo et al., 2002). Methionine is converted to SAM, and there is some evidence that high methionine can cause hypermethylation in specific regions of the genome, which may be responsible for the negative effects on schizophrenia (Dong et al., 2005; Waterland, 2006). Methionine is metabolized through removal of a C1 methyl group to homocysteine, which can be remethylated to methionine by the enzyme methionine synthase. Homocysteine levels are elevated in schizophrenia (Adler Nevo et al., 2006; Applebaum, Shimon, Sela, Belmaker, & Levine, 2004; Haidemenos et al., 2007; Levine, Sela, Osher, & Belmaker, 2005; Levine et al., 2002; Regland, Johansson, Grenfeldt, Hjelmgren, & Medhus, 1995; Susser, Brown, Klonowski, Allen, & Lindenbaum, 1998), and high homocysteine levels in pregnant women even increase the schizophrenia risk for their children (Brown et al., 2007). Plasma homocysteine levels also correlate positively with the severity of both positive and negative symptoms in schizophrenia, as levels rise during exacerbation of the illness and fall during remission (Petronijevic et al., 2008). This may be due to the fact that elevated homocysteine levels are associated with aberrant methylation in 1,338 CpG sites in the peripheral leukocytes of patients with schizophrenia. Significant positive correlations were observed at 580 sites, while negative correlations were seen at 758 sites. As areas with higher CpG content were more likely to show positive correlations, the effect of homocysteine on methylation may depend on CpG density (Kinoshita et al 2013). Given the association of high homocysteine levels with schizophrenia, studies have also investigated the possible ameliorating effects of decreasing homocysteine. Folic acid, vitamin B6, and vitamin B12 are all involved in the metabolism of homocysteine, and combined treatment with these vitamins has been shown effective at reducing plasma homocysteine levels (Spence et al.,

2001). Treatment of schizophrenic patients with these vitamins leads to a decrease in both homocysteine levels and clinical symptoms (Levine et al., 2006). These results suggest that hyperhomocysteinemia may play a role in schizophrenia pathogenesis through its impact on DNA methylation.

MODELING ADVANCED PATERNAL AGE AS A WINDOW TO SCHIZOPHRENIA PATHOLOGY

The effects of advanced paternal age have become increasingly relevant in recent years as the trend of older parenthood gains popularity. In England, for example, the percentage of fathers aged 35 to 54 grew from 25% in 1993 to 40% in 2003 (Bray, Gunnell, & Davey Smith, 2006). Over the past century, advanced paternal age has been increasingly linked to the development of genetic disorders in offspring. The first evidence of such a link came in 1912, when Wilhelm Weinberg observed that children with a later birth order were more likely to display a sporadic case of skeletal disorder achondroplasia (Crow, 2000b). It wasn't until 1957 that Penrose distinguished between the effects of birth order, maternal age, and paternal age, to show that the increased incidence of de novo achondroplasia was solely linked to paternal age (Penrose, 1957). We now know that this disease is caused by an autosomal dominant mutation in the FGFR3 gene that is inherited from the father (Rousseau et al., 1994).

Since Weinberg's finding, several other autosomal dominant disorders have been linked to advanced paternal age. Risch compared the distribution of parental ages in cases of these disorders with the distribution in the general population to calculate the ratio of observed to expected cases for each parental age range (Risch, Reich, Wishnick, &

McCarthy, 1987). In addition to achondroplasia, Apert, Crouzon, and Pfeiffer showed a strong paternal age effect in which incidence increased exponentially with increasing paternal age. Risk of the offspring having these mutations increased more sharply when the father was over 40 years old.

Penrose(Penrose, 1955) first introduced the copy-error hypothesis in 1955 to explain this paternal age effect. He posited that these mutations were due to mistakes in DNA replication. In males, gonadocytes divide 30 times before puberty to give rise to spermatogonial stem cells, which will then divide every 16 days during spermatogenesis. This adds up to 610 cell divisions by age 40 and 840 by age 50. Females, meanwhile, have only 24 cell divisions during oogenesis, and this number remains constant with increasing age (Crow, 1997). The copy error hypothesis would therefore predict a greater number of mutations to derive from the paternal cell line due to the greater number of cell divisions. The autosomal dominant disorders linked to paternal age are thought to be caused by nucleotide substitutions in hypermutable "hotspots" on the paternal chromosome. The FGFR3 nucleotide 1138 that is mutated in achondroplasia has one of the highest mutation rates, at 10^2 - 10^3 times the normal mutation rate (Wilkin et al., 1998).

Recently, more complex disorders have been linked to advanced paternal age. Alzheimer's Disease(Bertram et al., 1998), schizophrenia(Malaspina et al., 2001; Tsuchiya et al., 2005), bipolar disorder(Dalman, 2009), and autism spectrum disorders(Kolevzon, Gross, & Reichenberg, 2007; Reichenberg et al., 2006) all increase in frequency with increasing paternal age. These disorders are much more common than the autosomal dominant disorders, with a frequency on the order of 0.1-1%, as opposed to the 1/25,000 frequency of achondroplasia. They have also not been conclusively linked

to a single locus, and probably involve multiple genes. Given the relatively high rate of incidence and the observation that the incidence roughly triples with advanced paternal age(Croen, Najjar, Fireman, & Grether, 2007; Frans et al., 2008; Malaspina et al., 2001), the copy error hypothesis may be insufficient to explain this paternal age effect. A 2009 study has even linked increasing paternal age to decreasing intelligence, measured at 8 months, 4 years, and 8 years in children (Saha et al., 2009). If paternal age can affect a continuous trait like intelligence, a rare mutational mechanism seems an unlikely and inadequate explanation. Epigenetic mechanisms may therefore be a more likely explanation for the paternal age effect.

Epigenetic mechanisms such as DNA methylation alter the access of transcription factors to DNA binding sites. DNA methyltransferases attach a methyl group to the C5 position of the cytosine in a CpG dinucleotide, which generally promotes a closed, transcriptionally repressed state and leads to gene silencing (Feng & Fan, 2009). DNA methylation during spermatogenesis is an active process and a gradual loss of fidelity across replication cycles results in altered methylation patterns, which can be propagated to subsequent generations. It is possible that the effects of paternal age on offspring behavior are due to aberrant methylation patterns propagated from father to offspring. For some time, it was thought that total epigenetic reprogramming occurred during early embryogenesis. However, there is evidence that this erasure is not complete. One example of incomplete erasure comes from studies of the agouti viable yellow gene in mice, which encodes a yellow coat color. In a study by Chong et al, the level of methylation of a near-by transposon affects expression levels of the agouti gene (S. Chong et al., 2007). Female mice with one copy of the agouti viable allele were bred with

either wild-type males or males with heterozygous mutations of genes involved in epigenetic modification (Smarca5 or Dnmt1). Offspring of the heterozygotes that were wild-type for Smarda5 and Dnmt1 were genetically identical to the offspring of the wild-type males. However, the offspring of heterozygous fathers were more likely to be yellow. This suggests that disruptions of the male epigenome can be passed on through the germ line and go on to affect the phenotype of the offspring.

Even behavioral phenotypes can be transmitted epigenetically through the male germ line (Alter et al., 2009). In an inbred strain of Balb/cJ mice, paternal open field behavior was correlated with open field behavior of female offspring. Mice were genetically identical, and the fathers were removed after conception, making the inheritance of a mutation or an environmental impact on offspring behavior less likely. Presumably, all that was passed on from father to offspring in these mice was contained in the sperm, so the inheritance of some epigenetic modification that can cause reduced open field activity is the most likely explanation.

There is also some evidence that paternal age may affect males and females differently. One study on longevity showed an inverse relationship between paternal age and lifespan of female offspring but not male offspring (Gavrilov et al., 1997). Daughters showed a 4.4-year reduction in lifespan when their fathers were over 50 years old, suggesting that the paternal age effect might be stronger for female offspring. Consistent with this hypothesis is evidence that the male to female ratio for autism spectrum disorder decreases with increasing paternal age (Anello et al., 2009). Autism generally occurs in males at four times the rate seen in females. However, the rate is 6.2:1 for offspring of fathers under age 30, and 1.2:1 for offspring of fathers over age 45. Another possibility is

that multiple disease mechanisms are at work, and the mechanism linked to paternal age is less sensitive to gender differences. In either case, further comparison of the effects of paternal age on males and females would provide valuable insights into the processes at work and the implications of these findings.

The exploration of abnormal methylation patterns in neuropsychiatric disorders is just beginning. In 2008 Mill et al published the first whole-genome methylation profile of psychosis, analyzing the frontal cortex of schizophrenia and bipolar patients (Mill et al., 2008). They found methylation differences in over 100 loci, including several genes involved in glutamatergic and GABAergic signaling and others that were previously linked to these disorders. Interestingly, the psychosis-related methylation changes presented with vastly different patterns in male and female subjects. Given the sexual dimorphism in the frequency and presentation of these disorders, this finding is not completely unexpected.

In schizophrenia, for example, there are gender differences in the course of schizophrenia. These differences are even apparent during the premorbid phase of the disorder. Females exhibit higher levels of premorbid functioning, particularly in social interaction (Amminger et al., 2006; Childers & Harding, 1990; McGlashan & Bardenstein, 1990; V. A. Morgan, Castle, & Jablensky, 2008; Nordentoft et al., 2006; Norman, Malla, Manchanda, & Townsend, 2005; Shtasel, Gur, Gallacher, Heimberg, & Gur, 1992). The decreased premorbid functioning in males seem to be related to the significantly higher levels of negative symptoms also found in males (Chaves, Seeman, Mari, & Maluf, 1993; R. K. Willhite et al., 2008). In general, the course of schizophrenia appears to be milder in women, as they are less likely to be institutionalized, show higher

rates of remission and lower rates of relapse, and have a better treatment response to antipsychotics (Goldstein, Cohen, et al., 2002; Uggerby, Nielsen, Correll, & Nielsen, 2011; Usall, Ochoa, Araya, Marquez, & Group, 2003; Usall, Suarez, Haro, & Group, 2007).

There are also brain structural differences between the sexes in schizophrenia. Male schizophrenic patients have larger lateral and third ventricles, as well as decreased frontal and temporal lobe volumes, when compared to controls. However, female schizophrenic patients generally do not show this difference or display a much slighter effect (Andreasen et al., 1990; Gur et al., 2000; Reite et al., 1997). Sex-specific regional differences have also been identified, especially in corticolimbic structures. For example, in female schizophrenic patients relative to healthy female controls, there was a significant decrease in anterior cingulate volume determined by MRI. Male patients, though, did not show a difference from controls in this area (Goldstein, Seidman, et al., 2002; Takahashi et al., 2003). Also, the ratio of orbitofrontal cortex to amygdala volume was disturbed as men with schizophrenia had a higher ratio than healthy men, while women with schizophrenia had a lower ratio than healthy women (Gur et al., 2004).

Males are also 40% more likely to develop schizophrenia and display the clinical phenotype an average of 3 to 4 years earlier than females, with the peak incidence for females and males ages 20-29 years and ages 15-24 years, respectively (Aleman, Kahn, & Selten, 2003; Angermeyer & Kuhn, 1988; Hafner, Behrens, De Vry, & Gattaz, 1991; Hafner, Maurer, Loffler, & Riecher-Rossler, 1993; J. McGrath et al., 2004; Munk-Jorgensen, 1987). These sex differences may be due to a possible protective effect of estrogen. This is also supported by findings that earlier puberty in women is associated

with delayed age of onset (R. Z. Cohen, Seeman, Gotowiec, & Kopala, 1999). A smaller peak in age of onset is also seen from ages 45-54, only in women (Hafner et al., 1991; Hafner, Riecher-Rossler, et al., 1993; Munk-Jorgensen, 1987). This suggests that the higher estrogen levels between adolescence and menopause may play some protective role. In fact, there is evidence that the course of schizophrenia in women may fluctuate with levels of estrogen. Estrogen levels vary throughout a woman's menstrual cycle, and phases with lower estrogen have been associated with greater symptom severity (Bergemann, Parzer, Runnebaum, Resch, & Mundt, 2007; Hallonquist, Seeman, Lang, & Rector, 1993; Riecher-Rossler, Hafner, Stumbaum, Maurer, & Schmidt, 1994; L. H. Rubin et al., 2010). Women are also more prone to psychotic episodes during the estrogen withdrawal phases following childbirth, abortion, or termination of estrogen therapy (Bergemann et al., 2002; Kendell, Chalmers, & Platz, 1987; Mahe & Dumaine, 2001). Conversely, an improvement in psychotic symptoms can result from increased estrogen, whether the increase is due to pregnancy, postmenopausal estrogen replacement, or hormonal contraceptives (Felthous, Robinson, & Conroy, 1980; Kendell et al., 1987; Lindamer, Lohr, Harris, & Jeste, 1997). In sum, higher estrogen levels are associated with decreased lifetime incidence of schizophrenia, delayed onset, and reduced symptom severity. Because treatment with estrogen can alter the course of schizophrenia, it is likely that estrogen has a direct mitigating influence on psychotic symptoms. The mechanism for estrogen's effects is not entirely clear. Estradiol does interact with the dopaminergic, glutamatergic, and serotonergic systems, so it may function similarly to atypical antipsychotics (Hughes et al., 2009; Taylor, Maloney, Dearborn, & Weiss, 2009). It may also have epigenetic effects, as both testosterone and estradiol are ligands

for nuclear transcription factors that can recruit activator or repressor complexes to regulate DNA or histone methylation (Ceschin et al., 2011).

Both the genetic and epigenetic changes described can result in changes in gene expression that may contribute to complex disorders like schizophrenia, which have high heritability and are also susceptible to environmental modulation. Epigenetic modifications found in the parents can sometimes be passed on to the children, and even environmental influences on the epigenome can persist transgenerationally (Anway, Cupp, Uzumcu, & Skinner, 2005; Lane et al., 2003; H. D. Morgan, Sutherland, Martin, & Whitelaw, 1999; Rakyan et al., 2003). The epigenome is also especially sensitive to environmental insults during the prenatal period of rapid cell division, as epimutations can also be maintained through mitotic cell division (Dolinoy, Weidman, & Jirtle, 2007). Postnatally, people remain susceptible to social, psychological, and chemical stressors such as migration, urbanicity, and cannabis use, which modulate schizophrenia risk (Rutten & Mill, 2009; van Os, Kenis, & Rutten, 2010; van Os, Pedersen, & Mortensen, 2004). While this mechanism is not entirely clear, epigenetic misregulation is a possibility, since regulation of DNA methylation by such environmental factors continue in differentiated cortical neurons throughout life (Marutha Ravindran & Ticku, 2004; Numachi et al., 2007; Rampon et al., 2000; Siegmund et al., 2007).

NEUREGULIN 1 VARIATION AS AN ETIOLOGY FOR SCHIZOPHRENIA

One gene that has been associated with schizophrenia is Nrg1, which is widely expressed throughout the body and throughout life and has several roles in development. The human Nrg1 gene is roughly 1.4 megabases long, although less than 0.3% of this

encodes protein. The presence of multiple promoters and alternative splice sites allows for at least fifteen different Nrg1 isoforms to be produced from this gene (Falls, 2003). Nrg1 is classified into six types based on its extracellular N-terminal domain. Types I, II, IV, and V contain immunoglobulin-like domains and are collectively referred to as Ig-Nrg1. Type III contains a cysteine-rich domain and is sometimes referred to as CRD-Nrg1. The characteristic domain of Type VI is still unclear. All isoforms contain an epidermal growth factor (EGF)-like domain, which activates ErbB receptor tyrosine kinases. Alternative EGF-like splice variants produce α isoforms that are found in the mesenchyme β isoforms that are found in the nervous system. Downstream from these is a juxtamembrane region containing protease-cleavage sites, followed by a transmembrane domain and a cytoplasmic tail. Isoforms are further categorized based on the presence of a stalk before the transmembrane domain. Isoforms are labeled “1” if they have a stalk and transmembrane domain, “2” if they do not have a stalk but have a transmembrane domain, and “3” if they are truncated after the stalk and are synthesized as soluble isoforms without a transmembrane domain. This last form is directly released into the extracellular space. The carboxy tail is labeled either “a” or “b” form, depending on the exon. In Type III, the CRD also contains another transmembrane domain, so that this isoform remains attached to the membrane after cleavage (Buonanno & Fischbach, 2001; P. J. Harrison & Law, 2006; Mei & Xiong, 2008). Most Nrg1 isoforms are synthesized as pro-Nrg1s, which are anchored to the membrane with an extracellular EGF domain. Variants are generated by cleavage on the extracellular side of the transmembrane domain by such enzymes as tumor necrosis factor- α converting enzyme

(TACE, also called ADAM17), β -site of amyloid precursor protein cleaving enzyme 1 (BACE1), and meltrin beta (also called ADAM19) (Hu et al., 2006; Loeb, Susanto, & Fischbach, 1998; Montero et al., 2007; Willem et al., 2006; Yokozeki et al., 2007). The C-terminal fragment can also be cleaved on the internal side of the membrane by gamma secretase. This forms the intracellular domain (ICD), which can engage in back signaling to modify gene expression (Bao et al., 2004; Bao, Wolpowitz, Role, & Talmage, 2003). All of these possible combinations of types, EGF domains, stalks, and tails provide a great deal of diversity. These isoforms show differential regional and temporal expression, and likely have distinct functions.

Nrg1 signaling involves the stimulation of ErbB receptor tyrosine kinases, which are homologous to the EGF receptor (EGFR, also called ErbB1). Nrg1 induces ErbB to dimerize, leading to kinase activation and phosphorylation of the intracellular domain (Bublil & Yarden, 2007). Adaptor proteins or enzymes can then dock on the phosphorylated tyrosine residues, allowing for the activation of downstream signaling pathways. Nrg1 activity can be mediated by the heterodimers ErbB2-ErbB3, ErbB2-ErbB4, ErbB3-ErbB4, or ErbB4-EGFR, as well as the homodimer ErbB4-ErbB4. However, ErbB4 is the only ErbB protein that can interact with Nrg1 and display resultant tyrosine kinase activity (Bjarnadottir et al., 2007; Fu et al., 2001; Si, Wang, & Mei, 1999; Yarden & Sliwkowski, 2001). ErbB2 does not bind Nrg1, but instead functions as a co-receptor with an active kinase domain (Tzahar et al., 1996). ErbB3 can bind Nrg1, but has an impaired kinase domain and is catalytically inactive (Guy, Platko, Cantley, Cerione, & Carraway, 1994). The EGFR does not bind to Nrg1, but when forming a heterodimer with ErbB4 it can also activate signaling pathways more

commonly associated with the EGFR. Like Nrg1, ErbB4 has multiple isoforms that show variable temporal and regional expression (Mei & Xiong, 2008).

Several genetic linkage and association studies have pointed to Nrg1 as a probable candidate gene for schizophrenia. It was first implicated in an Icelandic linkage study in which a high-risk haplotype containing five SNPs and two microsatellite regions, named HAP_{ICE}, was significantly overrepresented among schizophrenic patients versus controls (Stefansson et al., 2002). Since then, many other studies have found an association between schizophrenia and HAP_{ICE}, or other haplotypes located in the Nrg1 gene. This finding has also been confirmed by meta-analysis (Badner & Gershon, 2002; Corvin et al., 2004; Hall, Gogos, & Karayiorgou, 2004; Hong et al., 2004; J. W. Kim et al., 2006; C. M. Lewis et al., 2003; Li et al., 2004; C. M. Liu et al., 2005; Munafò, Thiselton, Clark, & Flint, 2006; Petryshen et al., 2005; Stefansson et al., 2003; Tang et al., 2004; Thiselton et al., 2004; Williams et al., 2003; Zhao et al., 2004). In fact, the Nrg1 receptor ErbB4 has also been implicated, as studies have found associations between ErbB4 haplotypes and schizophrenia (Agim et al., 2013; Nicodemus et al., 2006; Norton et al., 2006; Silberberg, Darvasi, Pinkas-Kramarski, & Navon, 2006). There has even been an interaction between Nrg1 and ErbB4 variants identified that is also associated with schizophrenia (Norton et al., 2006). This suggests that the Nrg1 impact on schizophrenia pathology is likely mediated through ErbB4 signaling.

Genomic analysis can identify loci of interest, but the impact of relevant SNPs or CNVs is not always obvious. Some SNPs have functional relevance, as they can alter mRNA transcript stability, cause amino acid changes, or modify transcription factor binding affinity (Genomes Project et al., 2010). Even SNPs in non-coding regions can

affect gene splicing (Pagani & Baralle, 2004). However, others have simply been used as markers of specific loci and their functional consequences are not clear (Bush & Moore, 2012). CNVs can span several genes, so the gene of importance is also not always obvious. Studies of gene expression may therefore illuminate the biological consequences of identified genetic, epigenetic or environmental risk factors.

The theory that Nrg1 is involved in the pathogenesis of schizophrenia is bolstered by evidence that expression of both Nrg1 and ErbB4 are altered in schizophrenia. Schizophrenia is associated with an increase in specific mRNA transcripts of Nrg1 and ErbB4 in the frontal cortex and hippocampus (R. Hashimoto et al., 2004; Law, Kleinman, Weinberger, & Weickert, 2007; Law et al., 2006; Nicodemus et al., 2009; Nicodemus et al., 2006; Parlapani et al., 2010; Silberberg et al., 2006; Weickert, Tiwari, Schofield, Mowry, & Fullerton, 2012). In terms of protein expression, most studies have also reported an overexpression of specific splice variants of Nrg1 or ErbB4, and a shift in the ratios of various isoforms (V. Z. Chong et al., 2008; Hahn et al., 2006; R. Hashimoto et al., 2004; Law et al., 2007; Law et al., 2006; Parlapani et al., 2010; Silberberg et al., 2006; Weickert et al., 2012). Changes in levels of the enzymes that cleave Nrg1 are also associated with schizophrenia, as there is a positive correlation between ADAM17 and psychosis. The increase in ADAM17 is correlated with a decrease in full length Nrg1, and the ratio of Nrg1 N-terminal fragments to full length was increased in Brodmann's area 9 of the prefrontal cortex of schizophrenics (Marballi, Cruz, Thompson, & Walss-Bass, 2012). This overexpression of Nrg1 and region-specific imbalance of Nrg1 isoforms can be linked to phenotypic differences. For example, the high-risk HAP_{ICE} haplotype of Nrg1 is associated with increased Type III Nrg1 mRNA in postmortem

DLPFC of schizophrenics compared with controls, and this increase is also associated with an earlier age of onset of the disorder (Weickert et al., 2012). While there is strong evidence that Nrg1 is playing some role in the pathology of schizophrenia, it is difficult to pinpoint the relevant changes and effects. There is heterogeneity of Nrg1 expression throughout the brain, and studies have reported different effects of various isoform ratios. Also, this tissue is collected postmortem, so some changes could be due to antipsychotic treatment.

Examining the roles of Nrg1 in the brain may therefore illuminate its significance to schizophrenia. Although it does have actions in several organ systems, its roles in the central nervous system are most relevant. These include numerous developmental functions, beginning during embryogenesis. During prenatal and perinatal brain development, Nrg1 is involved in neuronal progenitor cell proliferation, neuronal migration in the cortex and cerebellum, and axon migration. It also controls the timing of astrogenesis. During the postnatal period of brain maturation, Nrg1 activity influences dendritic spine formation and pruning, as well as synaptogenesis. It also controls myelination in both the central and peripheral nervous system. Throughout adulthood, Nrg1 signaling is involved in modulation of neurotransmission, neuronal plasticity, and long-term potentiation (Buonanno, 2010; Corfas, Roy, & Buxbaum, 2004; Falls, 2003; P. J. Harrison & Law, 2006; Jaaro-Peled et al., 2009; Mei & Xiong, 2008; Rico & Marin, 2011; Schmitt, Parlapani, Gruber, Wobrock, & Falkai, 2008; Scolnick, Petryshen, & Sklar, 2006; Talmage, 2008).

Mutant mouse models have been very helpful in defining the functions of Nrg1 in development. Yet, due to the widespread expression and importance of Nrg1 during

development, Nrg1 knockout (KO) mice do not survive past birth. In complete Nrg1 KO mice, the EGF-like domain is disrupted, thereby preventing all Nrg1 isoforms from binding to ErbB receptors. These KO mice develop cardiac malformations and died in utero at E10.5. This point coincides with the time when embryos normally switch from relying on maternal circulation to their own circulation (Falls, 2003; D. Meyer & Birchmeier, 1995). These complete KO mice also show a dramatic reduction in cranial and sensory neurons, as well as a loss of peripheral myelination (Britsch et al., 1998; D. Meyer et al., 1997). However, due to the early demise of these mice, the effects of a total loss of Nrg1 in the central nervous system are not clear. Ig-Nrg1 KOs display a similar phenotype to complete Nrg1 KOs, and also do not survive past E10.5 due to cardiac defects. These mice have normal peripheral myelination, although they do show the reduction in cranial and sensory nerves seen in complete Nrg1 KOs (Britsch et al., 1998; Kramer et al., 1996; D. Meyer et al., 1997). On the other hand, mice with CRD-Nrg1 KOs do not have heart defects and survive until birth. Yet these mice die at birth because they lack functional neuromuscular synapses and are unable to breathe. They also have a reduction in myelination and cranial and sensory nerves (Wolpowitz et al., 2000). As homozygous Nrg1 KO mice are not viable, heterozygous mice that only have a 50% reduction in Nrg1 are used to further explore the phenotype (Duffy, Cappas, Scimone, Schofield, & Karl, 2008).

As Nrg1 has been linked to schizophrenia susceptibility, the effects of a change in Nrg1 expression have been viewed with an eye towards schizophrenia-related endophenotypes. While it is implausible to claim to reproduce such a complex cognitive disorder in mice, we can elicit behaviors that may reflect specific symptoms of

schizophrenia (Corbett et al., 1995; Duncan, Zorn, & Lieberman, 1999; Lipska & Weinberger, 2000; Smithies, 1993; Tarantino & Bucan, 2000). Pharmacological models of schizophrenia have been developed based on the discovery that certain drugs, such as amphetamine and ketamine, reproduce symptoms of schizophrenia in humans (Corbett et al., 1995; Duncan et al., 1999; Gainetdinov, Mohn, & Caron, 2001). When mice are treated with these drugs, they display distinct phenotypes that can be ameliorated by treatment with antipsychotics. The relevant behaviors include hyperactivity, decreased social interaction, reduced prepulse inhibition (PPI) indicating sensorimotor deficits, and cognitive or learning deficits. Treatment with antipsychotics may also attenuate the hyperactivity and improve PPI (Corbett et al., 1995; Coyle, 1996; Duncan et al., 1999; Sams-Dodd, 1998; Swerdlow & Geyer, 1998; Tamminga, 1998). Genetic animal models can be used to study certain features of schizophrenia, and might therefore replicate some but not all of these symptoms.

Several of these endophenotypes are detectable in Nrg1 EGF/- mice. These mice had a reduction in all known Nrg1 isoforms, as all need an EGF-like domain to activate ErbB receptors. Behavioral testing reveals that heterozygotes are hyperactive and show subtle deficits in PPI. The PPI deficit was not seen at baseline and was only apparent when mice were treated with MK-801, a noncompetitive NMDA receptor antagonist and a psychotomimetic(Duffy et al., 2008; Gerlai, Pisacane, & Erickson, 2000). Most Nrg1 proteins are synthesized with a transmembrane (TM)-domain, and Nrg1 TM/- mice display a similar phenotype. They also show PPI deficits and hyperactivity that is reversed by antipsychotic treatment, as well as increased aggression and a lack of the typical preference to investigate a novel conspecific over a familiar one (Boucher et al.,

2007; Karl, Duffy, Scimone, Harvey, & Schofield, 2007; O'Tuathaigh et al., 2007; O'Tuathaigh et al., 2008; O'Tuathaigh et al., 2006; Stefansson et al., 2002). Although the changes in Nrg1 expression in schizophrenia are more complex and subtle, the presence of these endophenotypes indicates that the heterozygous model is relevant for schizophrenia.

There is also evidence that cognitive deficits are linked to Nrg1 signaling in patients with schizophrenia. The n-back task is a test of working memory in which subjects must encode a series of stimuli while recalling previous stimuli in that series. For example, in a 1-back task, subjects respond to each stimulus by recalling the one presented just prior (Callicott et al., 1999). The DLPFC is involved in holding and manipulating information over a delay (J. D. Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997; E. E. Smith, Jonides, Marshuetz, & Koeppe, 1998), and increased working memory load leads to increased brain activation in this region (Braver et al., 1997; J. D. Cohen et al., 1997; Kammer et al., 1997). In patients with schizophrenia, those who were homozygous for risk SNPs in both Nrg1 and ErbB4 showed significantly higher levels of fMRI activation in the DLPFC during the n-back test, suggesting that changes in Nrg1 signaling may be associated with an increased cortical activation requirement to perform the task (Nicodemus et al., 2010).

INTERNEURON PRODUCTION DURING DEVELOPMENT AND ADULTHOOD

While Nrg1 also influences neurotransmission and myelination, one role that is of particular interest given its role in cognition is its functions in cortical circuitry

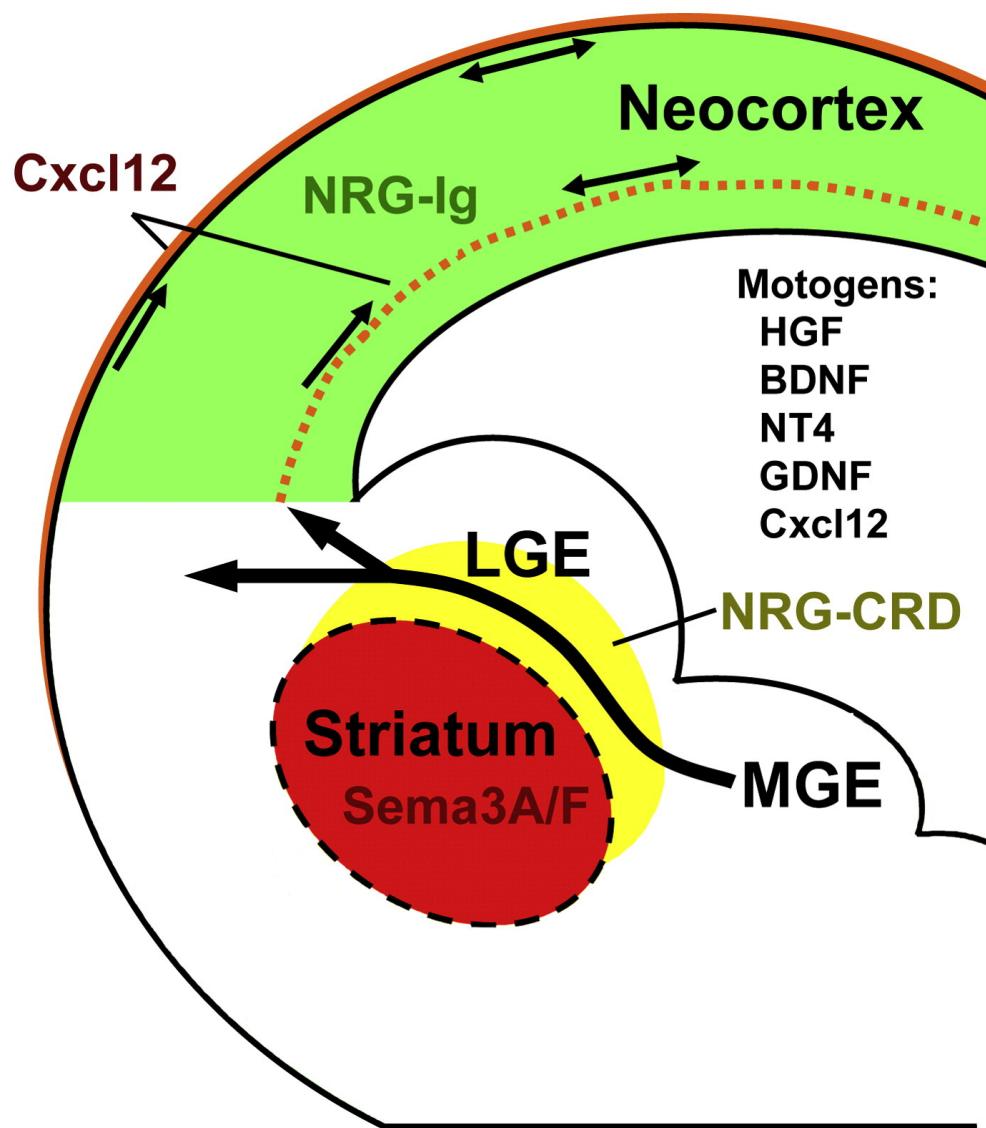
development and interneuron migration (Rico & Marin, 2011). Most cortical GABAergic interneurons are produced in the telencephalon during embryogenesis from around E12.5 until birth. This neurogenesis occurs in contiguous regions of the subpallial telencephalon called the lateral, medial, and caudal ganglionic eminences (or LGE, MGE, and CGE, respectively) (Flames & Marin, 2005). These areas are defined by their patterns of expression of various transcription factors. During early corticogenesis, the majority of neocortical interneurons originate in the MGE (Anderson, Marin, Horn, Jennings, & Rubenstein, 2001; Lavdas, Grigoriou, Pachnis, & Parnavelas, 1999; Marin, Anderson, & Rubenstein, 2000; Sussel, Marin, Kimura, & Rubenstein, 1999; Wichterle, Garcia-Verdugo, Herrera, & Alvarez-Buylla, 1999; Wichterle, Turnbull, Nery, Fishell, & Alvarez-Buylla, 2001). However, a smaller population appears to come from the LGE, which also produces olfactory interneurons. There is also a later wave of neurogenesis that begins around E15.5. During this stage of cortical development, interneurons mostly originate in the LGE, although some still arrive from the MGE (Anderson et al., 2001; Corbin, Gaiano, Machold, Langston, & Fishell, 2000; Pleasure et al., 2000; Toresson, Potter, & Campbell, 2000; Wichterle et al., 1999; Yun, Potter, & Rubenstein, 2001). The CGE also contributes interneurons to the cortex, most of which are produced during the later stages of corticogenesis (T. Ma et al., 2012). Interneurons predominantly arrive at their destinations in the cortex through tangential migration (Parnavelas, 2000; Parnavelas, Barfield, Franke, & Luskin, 1991; Polleux, Whitford, Dijkhuizen, Vitalis, & Ghosh, 2002). The diversity in embryonic origins of cortical interneurons yields a diversity in their ultimate fates, as different regions give rise to distinct subtypes (Valcanis & Tan, 2003; Wichterle et al., 2001; Q. Xu, Cobos, De La Cruz, Rubenstein, &

Anderson, 2004). The timing of an interneuron's birth also influences its fate.

Interneurons derived from the MGE follows an inside-out layering pattern when they are incorporated into the cortex, in which interneurons born at earlier stages preferentially occupy the deeper layers of the cortex (Miyoshi, Butt, Takebayashi, & Fishell, 2007). Those derived from the LGE and CGE follow the opposite pattern, and the earlier-born interneurons are incorporated into the superficial layers (Lee, Hjerling-Leffler, Zagha, Fishell, & Rudy, 2010; T. Ma et al., 2012; Miyoshi et al., 2010; Vucurovic et al., 2010).

ErbB4 is highly expressed in the interneuron precursors of the MGE and LGE, and Nrg1 signaling through ErbB4 is critical for interneuron migration and differentiation (Neddens, Vullhorst, Paredes, & Buonanno, 2009; Yau, Wang, Lai, & Liu, 2003). As shown in **Figure 1**, taken from Huang 2009, CRD-Nrg1 forms a permissive corridor through the LGE toward the cortex for the tangentially migrating interneurons. This corridor is bordered by the developing striatal mantle, where expression of Semaphorin3A and Semaphorin3F create an inhibitory territory that these migrating interneurons avoid (Flames et al., 2004; Marin, Yaron, Bagri, Tessier-Lavigne, & Rubenstein, 2001). There is also heterogeneous expression of Ig-Nrg1 in the cortex, and this seems to act as a diffusible chemoattractive gradient (Flames et al., 2004; Marin et al., 2003; Wichterle, Alvarez-Dolado, Erskine, & Alvarez-Buylla, 2003).

FIGURE 1: Production of Cortical Interneurons

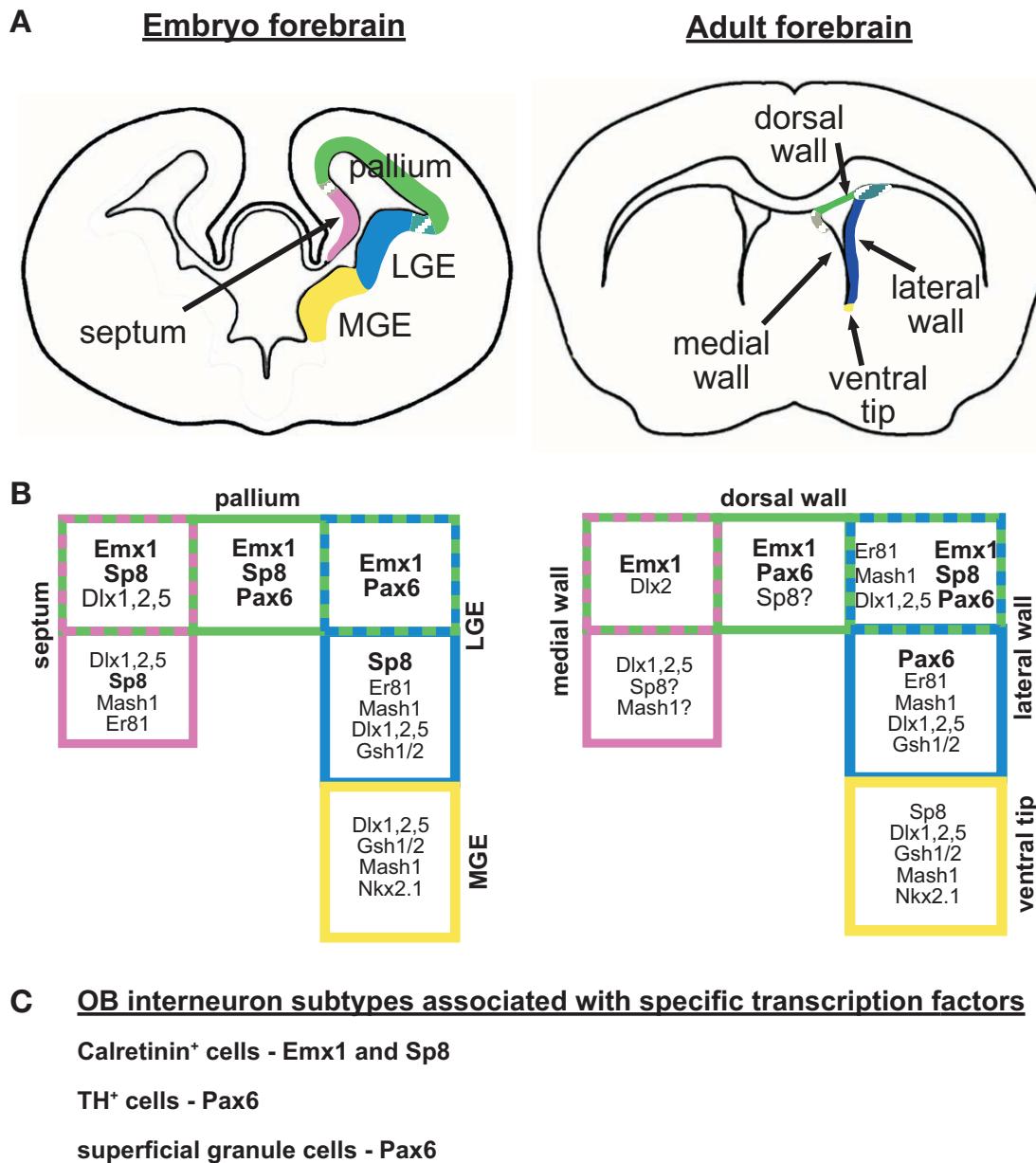


Extracellular signals control the migration of newborn interneurons from the medial and lateral ganglionic eminences (LGE, MGE) to the neocortex during development. CRD-Nrg1 forms a permissive corridor through which they migrate, bordered by chemorepellant signals from the striatum. Ig-Nrg1 forms a chemoattractive gradient in the neocortex.

(Huang, 2009)

After contributing to corticogenesis, all other regions of the telencephalic neuroepithelium contribute to the formation of the subventricular zone (SVZ) (Young, Fogarty, Kessaris, & Richardson, 2007). While the germinal zone regresses, neural stem cells do persist in the adult SVZ to form a neurogenic niche that provides new neurons to the olfactory bulb throughout life. The MGE, LGE, and embryonic cortex (also called the pallium) give rise to discrete areas of the SVZ. These regions express patterns of transcription factors that reflect their embryonic origins (Kohwi, Osumi, Rubenstein, & Alvarez-Buylla, 2005; Merkle, Tramontin, Garcia-Verdugo, & Alvarez-Buylla, 2004; Parmar, Sjoberg, Bjorklund, & Kokaia, 2003; Stenman, Toresson, & Campbell, 2003; Tamamaki, 2005; Ventura & Goldman, 2007; Willaime-Morawek et al., 2006; Young et al., 2007). This is shown in **Figure 2**, taken from Alvarez-Buylla 2008. The medial wall, dorsal wall, lateral wall, and ventral tip of the adult SVZ are homologous to the embryonic septum, pallium, LGE, and MGE, respectively (Alvarez-Buylla, Kohwi, Nguyen, & Merkle, 2008; Kohwi et al., 2007; Merkle, Mirzadeh, & Alvarez-Buylla, 2007; Stenman et al., 2003; Ventura & Goldman, 2007; Waclaw et al., 2006; Young et al., 2007). The region of origin of SVZ progenitors biases them to a specific interneuron fate upon differentiation, once the new neurons are integrated into the olfactory bulb (Brill et al., 2009; Brill et al., 2008; De Marchis et al., 2007; Kelsch, Mosley, Lin, & Lois, 2007; Kohwi et al., 2007; Merkle et al., 2007; Young et al., 2007). The diversity that was seen in the generation of cortical interneurons is once again seen when neurons from these regions populate the olfactory bulb.

FIGURE 2: SVZ Embryonic Origins



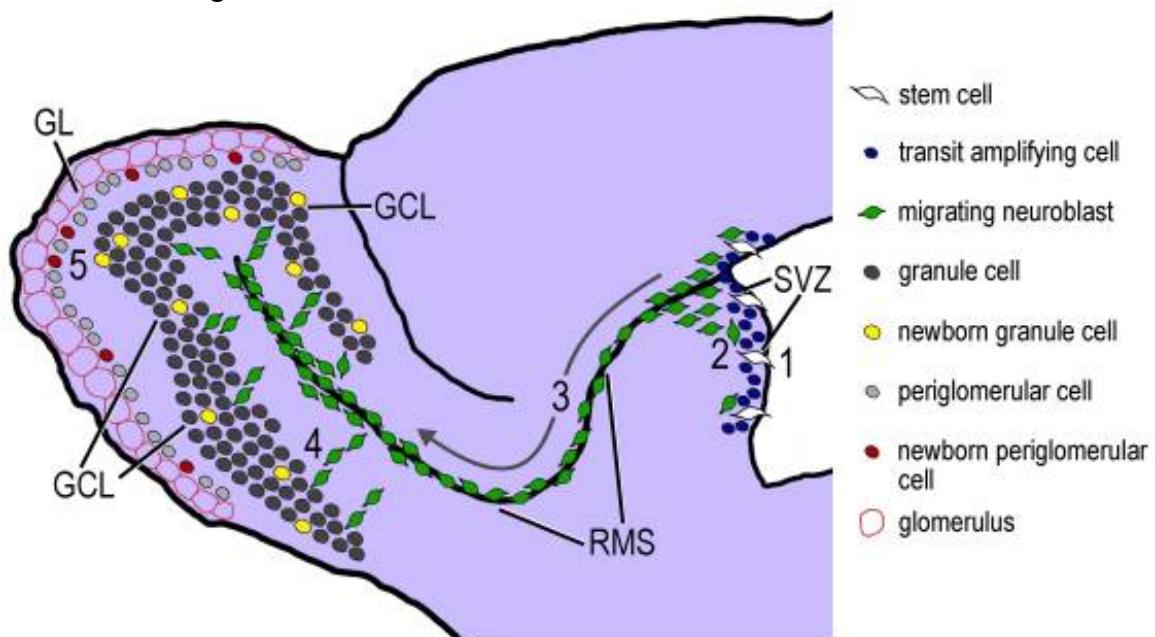
(A) Various regions of the SVZ derive from different embryonic germinal regions.

Homologous structures are color-coded. This diversity is reflected in the expressed transcription factors (B). Olfactory interneuron subtypes also express different transcription factors.

(Alvarez-Buylla et al., 2008)

An overview of SVZ neurogenesis, taken from Sui 2012, is shown in **Figure 3**. In SVZ proliferation, neural stem cells are the primary precursors, also called B cells, which have the capacity for self-renewal and are multipotent. These are astroglia cells that are derived from the radial glial cells that are the neural stem cells of the embryonic and early postnatal brain (Anthony, Klein, Fishell, & Heintz, 2004; Doetsch, Caille, Lim, Garcia-Verdugo, & Alvarez-Buylla, 1999; Imura, Kornblum, & Sofroniew, 2003; Laywell, Rakic, Kukekov, Holland, & Steindler, 2000; Merkle & Alvarez-Buylla, 2006; Miyata et al., 2004; Noctor, Martinez-Cerdeno, Ivic, & Kriegstein, 2004). B cells are generally in contact with the ventricle through small apical processes that are surrounded by ependymal cells (Mirzadeh, Merkle, Soriano-Navarro, Garcia-Verdugo, & Alvarez-Buylla, 2008). They divide slowly to give rise to transit-amplifying cells, also called C cells. C cells then divide quickly to produce neuroblasts, or A cells, which will travel to the olfactory bulb to be integrated into existing circuitry (Lledo, Merkle, & Alvarez-Buylla, 2008).

FIGURE 3: SVZ Neurogenesis



Stem cells and transit amplifying cells proliferate in the SVZ (1) and give rise to neuroblasts (2). These neuroblasts migrate tangentially through the RMS (3) to arrive at the olfactory bulb. They then migrate radially (4) into the GCL or GL, where they differentiate into olfactory interneurons and are incorporated into the existing circuitry.
(Sui, Horne, & Stanic, 2012)

Neuroblasts form a complex network of chains that span the length of the SVZ as they migrate anteriorly (Doetsch & Alvarez-Buylla, 1996; Lois, Garcia-Verdugo, & Alvarez-Buylla, 1996; Rousselot, Lois, & Alvarez-Buylla, 1995). These migrating neuroblasts join to form the rostral migratory stream (RMS) as they travel to the olfactory bulb (Doetsch & Alvarez-Buylla, 1996; Lois & Alvarez-Buylla, 1994). They assemble themselves into chains that cover the distance from the SVZ to the olfactory bulb, and crawl along each other in a process called chain migration (Lois et al., 1996; Wichterle, Garcia-Verdugo, & Alvarez-Buylla, 1997). These chains are formed exclusively from neuroblasts, although they are surrounded by tubes of specialized astrocytes (Doetsch & Alvarez-Buylla, 1996; Eom, Li, & Anton, 2010; Lois et al., 1996). It takes new neurons 2-5 days from their birth in the SVZ to reach the olfactory bulb, and another 5-10 days to complete their radial migration out of the RMS to reach their target destination. During this process, they differentiate into specific interneuronal subtypes, develop dendritic trees and synaptic spines, and become incorporated into the existing olfactory bulb circuitry (Carleton, Petreanu, Lansford, Alvarez-Buylla, & Lledo, 2003; Petreanu & Alvarez-Buylla, 2002).

The olfactory bulb is a layered structure containing the glomerular layer (GL), external plexiform layer (EPL), mitral cell layer (ML), internal plexiform layer (IPL), and granule cell layer (GCL), from most to least superficial. Olfactory sensory neurons (OSNs) are located in the olfactory epithelium in the posterior area of the nasal cavity. OSN axons form the olfactory nerve, which travels through the cribriform plate to reach the GL. In this region, OSNs synapse with projection neurons in structures called glomeruli, which are tangles of neuropil where OSN axons form synaptic connections

with projection neuron dendrites. Signaling from heterogeneous populations of inhibitory interneurons modulates this interaction. Projection neurons then send their axonal output to higher areas of the brain for processing (Whitman & Greer, 2009).

Signaling in the olfactory bulb starts with the OSN. Along with OSNs, the olfactory epithelium also contains supporting cells and basal cells, which are stem cells that regenerate OSNs throughout life. As OSNs only live for 30 to 60 days, these are continually being replaced. OSNs extend a dendritic process to the surface of the olfactory mucosa, where it branches into specialized cilia that provide a receptive surface for odorant molecules that are inhaled and dissolve in the olfactory mucosa (L. Buck & Axel, 1991; Firestein, 2001; Graziadei & Graziadei, 1979; Moulton & Beidler, 1967). Each individual OSN only expresses a single G protein-coupled odorant receptor out of the extensive multigene family of over 1000 different receptors (L. Buck & Axel, 1991; Chess, Simon, Cedar, & Axel, 1994; Mombaerts, 2001; Serizawa et al., 2003). The olfactory epithelium can be divided into four broad zones along the dorsoventral axis. OSNs that express the same receptor are contained in the same zone, although they may be widespread within this region (Ressler, Sullivan, & Buck, 1993; Vassar et al., 1994). Glial cells called olfactory ensheathing cells surround axonal projections from OSNs as they traverse the cribiform plate (Au, Treloar, & Greer, 2002; Doucette, 1984). They then converge in the olfactory bulb to form glomeruli, with each OSN contributing a single axon. Several thousand OSNs express the same odorant receptor, and these project to a few specific glomeruli that are exclusive to one receptor (L. B. Buck, 2000; Mombaerts, 2001; Mombaerts, Wang, Dulac, Chao, et al., 1996; Ressler, Sullivan, & Buck, 1994; Vassar et al., 1994; Wachowiak & Shipley, 2006). As receptors bind multiple odorants,

and odorants activate multiple receptors at varying degrees of efficiency, the pattern of glomerular activation acts as a signature for each odorant (Friedrich & Korschning, 1997; Koulakov, Gelperin, & Rinberg, 2007; Leveveau & MacLeod, 1966; Spors & Grinvald, 2002; Spors, Wachowiak, Cohen, & Friedrich, 2006).

In the glomerulus, OSN axons form glutamatergic synapses with the apical dendrites of mitral or tufted cells, two classes of excitatory projection neurons. The dendrites of these cells branch extensively, but each only receives input from a single glomerulus, maintaining the specificity of OSNs. Mitral cells have their cell bodies located in the ML and, in addition to their apical dendrites, extend several lateral dendrites into the deeper regions of the EPL to synapse with interneurons. The axons of mitral cells coalesce into the lateral olfactory tract and project to the piriform cortex, where higher olfactory processing occurs. Tufted cells can be located in the external, middle, or deep regions of the EPL. All but the external tufted cells also extend secondary lateral dendrites in the most superficial region of the EPL to synapse with interneurons. Tufted cells give rise to axons that give off collaterals in the IPL, which connect the glomeruli receiving input from OSNs that express the same odorant receptor. Tufted cell axons then join the lateral olfactory tract, and are thought to send projections to the anterior olfactory nucleus for processing (Belluscio, Lodovichi, Feinstein, Mombaerts, & Katz, 2002; Illig & Eudy, 2009; Lledo et al., 2008; Mombaerts, Wang, Dulac, Vassar, et al., 1996; Wachowiak & Shipley, 2006; Yan et al., 2008; Zou, Chesler, & Firestein, 2009).

The olfactory circuitry also contains interneurons that provide inhibitory input to this signaling pathway through their interaction with mitral and tufted cells. The majority

of these interactions are dendrodendritic. In these reciprocal synapses, glutamate is released from projection neurons to excite interneurons, which in turn releases GABA back onto the projection neurons to inhibit their signaling (Lledo, Saghatelyan, & Lemasson, 2004). The olfactory bulb contains a very high proportion of inhibitory neurons, as they are one hundred times more prevalent than the projection neurons (Nissant & Pallotto, 2011). As the excitability of projection neurons modulates the sensory information sent back to the cortex, inhibitory interneurons play an important role in encoding olfactory information (Lledo et al., 2008). Most interneurons reside in the GL and GCL of the olfactory bulb. The EPL contains far fewer cell bodies than other olfactory layers, however it does also contain interneurons. These form dendrodendritic synapses with mitral and tufted cells, however they are less well characterized. Interneurons are a heterogeneous population not only in terms of location, but also in their connectivity, firing patterns, morphology, and immunomarker expression (Crespo, Blasco-Ibanez, Marques-Mari, & Martinez-Guijarro, 2001; Kosaka & Kosaka, 2005; McQuiston & Katz, 2001; Pinching & Powell, 1971a; Price & Powell, 1970; Shipley & Ennis, 1996).

The periglomerular cells are interneurons of the GL. In the mouse, all of these are GABAergic, while some are also dopaminergic. They surround the glomeruli and project dendritic branches that interact with OSN axons and principle neuron dendrites (Kohwi et al., 2007; Kosaka & Kosaka, 2007). Most periglomerular cells are confined to one glomerulus, although a small number of them do have axonal projections to other nearby glomeruli (Pinching, 1970; Pinching & Powell, 1971a, 1971b). In glomeruli, OSN axons synapse with the dendrites of periglomerular cells, in addition to those of mitral cells.

These periglomerular cells then form dendrodendritic connections with the projection neuron of the same glomerulus. OSNs also activate external tufted cells, which form excitatory connections with a lateral network of superficial short axon cells. Short axon cells excite surrounding periglomerular cells, leading to more widespread inhibition of mitral cells through dendrodendritic synaptic connections. Thus, periglomerular cells provide local feedforward inhibition when activated by a local OSN, as well as broad inhibition of other mitral cells when activated by a network of excitatory connections (Aungst et al., 2003; Cleland, Johnson, Leon, & Linster, 2007; Linster & Cleland, 2009).

This is a mechanism for intraglomerular feedback inhibition as these interneurons can quickly begin to gate the activity of projection neurons after they are activated. Local inhibitory input can serve to enhance the contrast of odors. As mitral cells are receiving both excitatory and inhibitory input, they only overcome the inhibition and show a net activation when they are stimulated by odor ligands with a high affinity for their odor receptors (Cleland & Sethupathy, 2006). Meanwhile, the broader inhibitory signaling is thought to be involved in normalizing the signal intensity. Global mitral cell inhibition is delivered in proportion to sensory activation. Therefore, while OSN activation can show a large degree of variation depending on the odor concentration, mitral cell activation is more stable. This allows the olfactory system to recognize the identity of the odor regardless of its intensity (Aungst et al., 2003; Chalansonnet & Chaput, 1998; Cleland et al., 2007; Cleland & Sethupathy, 2006; T. A. Harrison & Scott, 1986; Meredith, 1986).

Granule cells make up approximately 95% of olfactory bulb interneurons. Their cell bodies are located in the GCL and they extend apical dendritic projections that branch extensively in the EPL (Nissant & Pallotto, 2011). There, they form

dendrodendritic synapses with mitral and tufted cells. Granule cells in the superficial GCL project to lateral dendrites of tufted cells in the superficial EPL, while those in the deep GCL synapse with lateral dendrites of mitral cells. There are also granule cells in the central zone of the GCL with dendrites that span the entire EPL. This segregation suggests that there may be parallel processing pathways for olfactory information through the mitral and tufted cell pathways (Greer, 1987; Imamura et al., 2006; Mori, 1987; Mori, Kishi, & Ojima, 1983; Orona, Scott, & Rainer, 1983). The lateral dendrites of mitral and tufted cells form reciprocal synapses with granule cells, as is seen with periglomerular cells. Upon depolarization, glutamate is released to activate granule cells, which then release GABA to inhibit mitral and tufted cells. The lateral dendrites of mitral cells can traverse great distances of up to 1 mm, and may contact granule cells along this entire length. It is possible for an action potential to spread along the length of the dendrite, and the spread may be blocked by focal stimulation of inhibitory granule cells along the way (Christie & Westbrook, 2003; Debarbieux, Audinat, & Charpak, 2003; J. Ma & Lowe, 2004; Margrie, Sakmann, & Urban, 2001; Xiong & Chen, 2002). Mitral cells can therefore interact with distant granule cells, which can then modulate this activity. This is an effective mechanism for lateral inhibition. Odors are not topographically represented in the olfactory bulb, in that glomeruli that are stimulated by similar odors do not neighbor each other and are instead widely distributed, although there are also foci of activation in specific regions of the GL and a degree of chemotopy in the olfactory bulb (Johnson, Woo, & Leon, 1998; L. Ma et al., 2012; Stewart, Kauer, & Shepherd, 1979; F. Xu et al., 2003; X. Yang et al., 1998). Granule cells also show a distributed pattern of activation in response to a stimulus (Shepherd, Chen, Willhite, Migliore, & Greer, 2007).

The olfactory bulb has a columnar organization that is maintained from the glomeruli through the GCL. Yet, as seen in the GL, there are distributed clusters of columnar activation in the GCL in response to a stimulus (D. C. Willhite et al., 2006). The ability of a mitral cell dendrite to activate granule cells at varying distances allows for the formation of a pattern of activation to identify odors. The clusters of granule cell activation may be involved in enhancing the contrast to assist with odor identification, as multiple inhibitory inputs onto a mitral cell will be more effective at suppressing its activity.

While periglomerular and granule cells both have reciprocal dendrodendritic interactions with projection neurons are involved in providing inhibitory input to both the activated projection neurons and those at variable distances, these interneurons have different effects on projection neuron firing. Periglomerular cells have stronger inhibitory effects on mitral cells and can reduce its firing frequency or even completely silence it independent of granule cell activity. The inhibitory effects of granule cells are activity-dependent. A granule cell cannot silence the mitral cell that activates it and, at most, can only have minimal effects on its firing frequency if the periglomerular inhibition is weak. However, if a granule cell is strongly activated it might silence other mitral cells through lateral inhibition. Increased granule cell activation also results in slight delays in the first spike time of the mitral cell. Thus, granule cells may be involved in controlling the synchrony of mitral cells (Arevian, Kapoor, & Urban, 2008; Arruda, Publio, & Roque, 2013; Davison, Feng, & Brown, 2003; Gire & Schoppa, 2009).

In addition to being spatially and embryologically distinct, interneuron subtypes vary in their temporal production throughout life. Interneuron production begins as early

as E14 and peaks during the first postnatal week in the mouse (Alvarez-Buylla & Lim, 2004; Wichterle et al., 2001). Interneurons that are born during this perinatal period are more likely to survive in the olfactory bulb long term, although it is not clear whether they are functionally different from those produced later in life (Lemasson, Saghatelyan, Olivo-Marin, & Lledo, 2005; Magavi, Mitchell, Szentirmai, Carter, & Macklis, 2005; Petreanu & Alvarez-Buylla, 2002; Winner, Cooper-Kuhn, Aigner, Winkler, & Kuhn, 2002). Periglomerular cells are all GABAergic and can be subdivided into three discrete populations based on their immunoreactivity to tyrosine hydroxylase (TH), an enzyme involved in dopamine synthesis, or to calcium binding proteins calretinin (CR) or calbindin (CB) (Parrish-Aungst, Shipley, Erdelyi, Szabo, & Puche, 2007). During early embryogenesis, almost all new periglomerular neurons are TH+. This is followed by a perinatal period with high levels of TH+ and CB+ newborn periglomerular interneurons. Postnatally, the majority of new periglomerular interneurons are CR+. Low levels of TH+ and vanishingly low levels of CB+ adult-born periglomerular interneurons are seen. Parvalbumin-expressing interneurons of the EPL are only produced perinatally through the first few weeks of life. Granule cells, the vast majority of which are CR+, show a peak in production during the early postnatal period, but continue to be produced at high levels throughout adulthood (Batista-Brito, Close, Machold, & Fishell, 2008).

Interneuron turnover is more common for adult-born neurons, although the exact rate of turnover is not well defined. On the low end, studies have estimated a turnover rate of roughly 15% of granule cells (Lagace et al., 2007; Ninkovic, Mori, & Gotz, 2007). Others have estimated that half of the superficial granule cells and the majority of deep granule cells are replaced continuously (Imayoshi et al., 2008; Valley, Mullen, Schultz,

Sagdullaev, & Firestein, 2009). In the GL, periglomerular cells seem to have a roughly 10% per month turnover rate (Sawada et al., 2011). Decreased neurogenesis leads to increased survival of interneurons in the olfactory bulb, indicating that olfactory turnover is being impaired (Lazarini et al., 2009; Mouret, Lepousez, Gras, Gabellec, & Lledo, 2009). This suggests that there are a certain number of interneurons necessary for the integrity of the olfactory circuitry to be maintained, and the increased survival may be a compensatory mechanism in response of the decreased supply of new interneurons.

Manipulation of SVZ neurogenesis has been useful in defining the role of adult-born neurons in olfaction. Deficits in SVZ neurogenesis during embryogenesis leads to impaired performance on olfactory discrimination tasks (Bath et al., 2008; Gheusi et al., 2000; W. R. Kim et al., 2007). However, most studies have not seen this in mice with deficits in adult SVZ neurogenesis (Breton-Provencher, Lemasson, Peralta, & Saghatelian, 2009; Imayoshi et al., 2008; Lazarini et al., 2009; Valley et al., 2009). It is possible that adult-born neurons are involved in olfactory discrimination, and this has simply been difficult to measure because these represent a relatively small proportion of neurons. In fact, while mice with blocked SVZ neurogenesis are still able to perform discrimination tasks, they show an increased reaction time in these tasks (Mouret et al., 2009). Increased reaction time in a discrimination task is generally associated with greater difficulty (Abraham et al., 2004; Uchida & Mainen, 2003; Wise & Cain, 2000), so there does seem to be a subtle discrimination deficit associated with decreased adult neurogenesis. There is also evidence that these neurons are used in other learning and memory tasks. Adult SVZ neurogenesis is necessary for fear conditioning and long-term memory of olfactory reward association learning (Lazarini et al., 2009; Sultan et al.,

2010; Valley et al., 2009). This indicates that there may be a critical role for new interneurons in providing circuit plasticity (Mouret et al., 2008; Nissant, Bardy, Katagiri, Murray, & Lledo, 2009). Decreased neurogenesis therefore has a negative effect on performance, as turnover is critical for optimization of olfaction.

Nrg1 and ErbB4 play an important role in neural development, and may be involved in the neurogenesis that continues into adulthood in the olfactory system. In addition to being expressed in the cortex, amygdala, hippocampus, medial habenula, reticular thalamic nuclei, hypothalamic nuclei, subthalamic nucleus, SNC and VTA, it is also seen along the ventral and medial border of the striatum/nucleus accumbens and in the subependymal zone along the lateral and olfactory ventricles (Steiner, Blum, Kitai, & Fedi, 1999). This last area is the rostral migratory stream (RMS), where ErbB4 presence suggests a role in cell proliferation and migration. Given the common origins of cortical and olfactory interneurons, abnormalities in the olfactory system may also be expected.

ErbB4 is expressed at high levels at P11 in the RMS and remains detectable as cells migrate into the olfactory bulb. Expression is maintained at reduced levels in the RMS and granule neurons into adulthood. Double-labeling in the adult RMS for ErbB4 and PSA-NCAM, a marker for migrating cells, revealed a very high level of colocalization. There was also limited colocalization with LeX, a marker of neural progenitor cells. It therefore seems that ErbB4 is being expressed on migrating neuroblasts. Conditional ErbB4 knockout mice were used to confirm the role of ErbB4 in migration. ErbB4-deficient mice demonstrated abnormal neuroblast chain organization and migration and deficits in placement and differentiation of olfactory interneurons. The neuronal precursors of mutant mice migrated more slowly and many more cells moved

back toward the SVZ or perpendicular to the RMS, as well as changing direction more frequently (Anton et al., 2004).

A study by Ghashghaei et al built on this work by clarifying the role of Nrg1, which is expressed by immature neuroblasts in the SVZ and at high levels in the region around the RMS. An exogenous Nrg1 infusion into the SVZ leads to rapid aggregation of proliferating precursor cells and affects the organization of migration. To examine the initial effect of Nrg1 on cells leaving the SVZ, the cell tracker dye CMFDA was used to label newborn SVZ cells. After 7 days of infusing Nrg1 into the ventricle, there was increased proliferation in the Nrg1-treated brains compared to controls. However, only a few CMFDA cells had progressed through the RMS to the olfactory bulb, as compared to the large numbers migrating out of control brains. This suggests that Nrg1, in addition to having an effect on proliferation, may also be acting as a chemoattractant, as the exogenous excess prevented new cells from leaving the SVZ (Ghashghaei et al., 2006).

OLFACTION IS ABNORMAL IN SCHIZOPHRENIA, IS AFFECTED BY NEUREGULIN 1, AND PROVIDES INSIGHTS RELEVANT TO BRAIN DEVELOPMENT IN SCHIZOPHRENIA

For decades there has been growing interest in olfactory abnormalities in patients with schizophrenia. Several studies have confirmed deficits in odor identification(Brewer, Edwards, Anderson, Robinson, & Pantelis, 1996; Houlihan, Flaum, Arnold, Keshavan, & Alliger, 1994; Hurwitz, Kopala, Clark, & Jones, 1988; L. C. Kopala, Clark, & Hurwitz, 1993; L. C. Kopala, Good, & Honer, 1995; L. C. Kopala, Good, & Honer, 1994; L. Kopala, Clark, & Hurwitz, 1989; L. Kopala, Good, Martzke, &

Hurwitz, 1995; Malaspina et al., 1994; Moberg et al., 1997; Seidman et al., 1997; Serby, Larson, & Kalkstein, 1990; Wu et al., 1993) and odor memory (Dunn & Weller, 1989; Wu et al., 1993). Some have found sensitivity (Geddes, Huws, & Pratt, 1991), while others have reported an increase(Bradley, 1984; L. C. Kopala et al., 1993; L. Kopala et al., 1989) or decrease in this measure (Isseroff, Stoler, Ophir, Lancet, & Sirota, 1987; Serby et al., 1990). There also appear to be abnormalities in judging the hedonic value of odors. Most studies found that schizophrenic patients have more difficulty identifying pleasant odors, and rate these odors as being less pleasant, while showing no difference from healthy controls in rating unpleasant odors (Kamath, Turetsky, & Moberg, 2011; Moberg et al., 2003; Plailly, d'Amato, Saoud, & Royet, 2006; Strauss, Allen, Ross, Duke, & Schwartz, 2010). However, one observed the opposite pattern, and described schizophrenics as giving pleasant odors more positive ratings (Doop & Park, 2006).

There is some evidence to suggest that first-degree relatives of schizophrenics may share these deficits (L. C. Kopala et al., 2001; Roalf et al., 2006; Ugur, Weisbrod, Franzek, Pfuller, & Sauer, 2005). In one study, 19 psychotic patients, 27 nonpsychotic relatives, and 43 healthy controls were given the University of Pennsylvania Smell Identification Test (UPSIT), a scratch-and-sniff multiple choice test (L. C. Kopala et al., 2001). The performance of nonpsychotic subjects was intermediate to that of psychotic relatives and controls, as 58% of psychotic subjects, 34% of nonpsychotic subjects, and 9% of controls had an olfactory deficit. This may indicate that a genetic predisposition for schizophrenia is also related to the observed olfactory deficits.

Schizophrenics can display both negative and positive symptoms, however the negative symptoms have been more closely linked to olfaction deficits (Corcoran et al.,

2005; Geddes et al., 1991). In particular, blunted affect, apathy, and anhedonia show a correlation with poor performance on the UPSIT (Ishizuka et al., 2010). Social deficits in schizophrenia are often present long before the onset of psychosis, and are among the negative symptoms that are most resistant to treatment (Malaspina et al., 2000). As olfaction is closely related to social interaction in other mammals, Malaspina examined the relationship between olfactory deficits and social drive in schizophrenia (Malaspina & Coleman, 2003). Social drive was determined from medical records and patient and family interviews, and IQ was also measured. This study showed that, together, social drive and intelligence accounted for almost 50% of the variation in UPSIT scores. Poor self-care is also associated with both negative symptoms and poor olfactory discrimination (Brewer et al., 1996).

It has even been proposed that the olfactory deficit could be used as a diagnostic tool to predict development of schizophrenia. One study examined olfactory identification ability in people at ultra-high risk for schizophrenia, including those with attenuated or limited psychotic symptoms, or a genetic risk combined with a decrease in mental functioning. Patients who went on to develop schizophrenia or schizophreniform psychosis had significantly lower olfactory ability as compared to controls or patients who developed other psychotic disorders (Brewer et al., 2003). Similarly, adolescents with early onset psychosis also displayed smell identification deficits. These deficits were specifically associated with characteristics of schizophrenia, such as negative symptoms and cognitive deficits, and not typical features of bipolar disorder, such as grandiosity (Corcoran et al., 2005).

An olfactory deficit measured at the onset of a first psychotic episode may also

signify a poorer long-term prognosis. For example, results of the UPSIT test can predict symptom remission a year later. Patients without remission on negative or cognitive symptoms had shown an olfactory deficit. However, this was not the case for patients displaying positive or anxiety/depression symptoms a year later (Good, Whitehorn, Rui, Milliken, & Kopala, 2006). A 2010 study also used the UPSIT to test olfactory function in patients who met the criteria for a first episode of schizophrenia spectrum disorder and had less than 6 months lifetime exposure to antipsychotics. Subjects were then assessed an average of 41 months later, and patients who did not originally exhibit an olfactory deficit were better able to attend to their basic needs (Good et al., 2010).

Olfactory bulb abnormalities are also apparent. Schizophrenic patients show a 23% decreased olfactory bulb volume bilaterally(Turetsky et al., 2000) while their relatives showed a volume decrease only in the right olfactory bulb, when compared to healthy controls (Turetsky, Moberg, Arnold, Doty, & Gur, 2003). Despite having a decreased right bulb volume, the unaffected relatives in this study did not demonstrate the impaired olfactory ability seen in the schizophrenic patients.

While not much research has been done on the structure of the olfactory bulb in schizophrenic patients, there is some evidence to suggest that neurogenesis in the SVZ may play a role in the pathology of schizophrenia. Irradiation of the SVZ and SGZ in adult male rats has been proposed as a model for schizophrenia (Iwata et al., 2008). Three months after irradiation, the authors confirmed depleted neurogenesis and elicited several schizophrenia-related endophenotypes. Irradiated rats exhibited hyperactivity after a methamphetamine dose, as well as auditory sensory gating deficits, social interaction deficits, and working memory deficits. These results imply that dysfunction in

neurogenesis and cell migration from the SVZ might be somewhat responsible for these deficits.

While antidepressants cause neurogenesis mainly in the hippocampus, chronic antipsychotic use may also increase neurogenesis in the SVZ (Newton & Duman, 2007). Atypical antipsychotics such as olanzapine and risperidone have been used to effectively treat schizophrenia, and cause a 2- to 3-fold increase in neurogenesis in the adult rat SVZ (Wakade, Mahadik, Waller, & Chiu, 2002). The increased appearance of BrdU-positive cells in the anterior SVZ suggests that these drugs cause increased migration of neurons through the rostral migratory stream to the olfactory bulb. In contrast, the typical antipsychotic haloperidol did not stimulate neurogenesis, confirming the results of previous research (Malberg, Eisch, Nestler, & Duman, 2000). The ability of olanzapine(W. Green, Patil, Marsden, Bennett, & Wigmore, 2006) to stimulate SVZ neurogenesis after 3 weeks of treatment has been confirmed in rats. However, one study of risperidone(W. Green et al., 2006) and one of olanzapine(Kodama, Fujioka, & Duman, 2004) failed to show this effect on SVZ cell division.

There is clear evidence that schizophrenia patients exhibit structural and functional olfactory abnormalities, though we do not yet know the extent of the structural differences or the significance of the functional deficits. The presence of olfactory deficits in unaffected relatives suggests that a genetic mechanism might be responsible. Given the schizophrenia-related phenotype seen in Nrg1-deficient mice, the correlation between olfactory deficits and negative and cognitive symptoms, and the clear abnormalities in cell proliferation and migration, the olfactory system is a useful model to elucidate the mechanism of action of Nrg1 and its role in development.

CHAPTER 2: ADVANCED PATERNAL AGE EFFECTS ON MALE AND FEMALE OFFSPRING

INTRODUCTION

Our lab has set out to measure behavioral and genetic/epigenetic effects in old father offspring (OFO) and young father offspring (YFO). These groups had fathers aged 12 months or 3 months, respectively. Both old fathers and young fathers were bred to 3-month-old females. In previous studies, performed by Maria Milekic, only the male offspring were tested. These studies found decreased open field activity and decreased prepulse inhibition in OFOs. However, as there is evidence that the paternal age effect may be even stronger in females, we began to test both the female and male offspring in parallel. Mice were run through a battery of behavioral tests to determine the behavioral phenotype and whether any sex differences were present. The estrous cycle of female offspring was determined after each behavioral test, in the method described by Caligioni (Caligioni, 2009). The ultimate goal of this study was to determine whether behavioral differences between OFOs and YFOs could be attributed to genetic or epigenetic inheritance. By comparing OFOs and YFOs that showed the most extreme behavioral differences, we could attempt to identify differentially methylated regions or mutations that may be linked to advanced paternal age.

RESULTS

Open Field

The open field test is a widely-used measure of general activity and exploratory behavior, which assesses the response of a mouse to an unfamiliar environment. A decrease in the open field activity of OFOs is the most consistent finding seen in previous cohorts of male OFOs. In this study, the effect was replicated, but it was only significant for the male offspring (**Figure 4**). Male OFOs showed decreased total ambulatory distance ($p=0.0379$) and decreased ambulatory distance in the center ($p=0.0224$). There was also a near-significant trend toward decreased ambulatory distance in the periphery ($p=0.0606$).

Prepulse Inhibition (PPI)

When a noise is presented to a mouse, it will exhibit an unconditioned, reflexive startle response. When a much weaker noise precedes a strong stimulus the startle is attenuated as the nervous system has a chance to adapt its response to the stimulus. In humans, deficits in PPI signify impaired sensorimotor gating. We were particularly interested in PPI since several psychiatric disorders are associated with a reduction in PPI, including schizophrenia (Geyer, Swerdlow, Mansbach, & Braff, 1990), bipolar disorder (Giakoumaki et al., 2007), and autism spectrum disorder (Perry, Minassian, Lopez, Maron, & Lincoln, 2007).

Previous male OFO cohorts have shown a decrease in PPI, however this has been difficult to replicate. **Figure 5** shows the measurements of %PPI for this cohort when the

prepulse is 2db (**a**), 6db (**b**), 8db (**c**), 12db (**d**), or 16db (**e**) above the background noise. None of the measures of %PPI for either male or female offspring showed a significant effect of paternal age (**Figure 5**).

Fear Conditioning

In humans, we have seen an effect of paternal age on general intelligence of the offspring. To determine whether this would translate into a difference in learning and memory between our cohorts of old and young father offspring, we used a paradigm that paired a neutral stimulus and context with an aversive stimulus. The fear conditioning test takes places over 3 days. On the first day, mice learn that a tone is paired with a foot shock. They receive three trial of this pairing and learn to react to the tone with a fear response that includes freezing. On the second day, we cover the walls and floor of the chambers with plastic and change the lighting and scent of the test chambers. The mice then receive 3 tones without any shock pairings. The amount of freezing to the tone measures the strength of the tone-shock association in the mice. On the third day, the original appearance and scent of the chambers is restored. Mice are placed in the chambers, but again do not receive any shocks. The amount of freezing in this session measures the strength of the association between the context of the chamber and the shock. Fear conditioning is useful because there is a distinction between the roles of the amygdala and hippocampus in the learned fear responses. The amygdala is critical in learning to freeze to both the tone and the context, but the hippocampus is only involved in learning to freeze to the context.

Figure 6 shows the results of the fear conditioning tests, after mice had learned to

associate a tone with delivery of a shock. To test conditioning to the tone, mice were placed in a novel box, after which the tone was played and freezing behavior was measured. **Figure 6a** shows background levels of freezing to the novel box before the tone test is delivered. There was no paternal age effect on this behavior, although there was a gender effect. Males showed higher background levels of freezing ($p=0.0022$). Freezing behavior to the tone (**Figure 6b**) or to the context of the shock delivery box (**Figure 6c**) did not show any gender or paternal age effects.

Social Interaction

In the social interaction test, mice were introduced to a novel conspecific of the same gender in an open field. In one corner of the field, the novel mouse was contained in a box with a mesh screen to allow interaction. Another corner of the field contained an empty novel box. This allowed us to control for interest in novelty and specifically assess novel social interaction. Some paternal age-related psychiatric disorders, most notably autism spectrum disorders, are notable for deficits in social interaction. We were therefore interested in any patterns of abnormal social interaction our old father offspring might demonstrate.

Figure 7 shows the results of this test. There was no paternal age effect on time spent with the novel mouse (**Figure 7a**), time spent with the novel box (**Figure 7b**), or the ratio of time spent with the novel mouse divided by the total time spent with either the novel box or the novel mouse (**Figure 7c**). This last measure is an assessment of the percentage of time that included social interaction out of the time spent investigating novel objects. The only significant effect found in this test is one of gender, as male mice

spent more time than females in the quadrant with the unfamiliar mouse ($p=0.0257$).

Light-Dark Test

In the light-dark test, mice are allowed to explore an open area that contains one brightly lit side and one darkened side. The task makes use of the conflict between a mouse's instinct to avoid the mildly threatening, bright, open area and the tendency to explore the novel environment (Bourin & Hascoet, 2003; Crawley & Goodwin, 1980). Therefore an increase in time spent in the light compartment is considered an indicator of decreased anxiety. In fact, this test has been used to determine whether drugs are anxiolytic or anxiogenic (Bourin & Hascoet, 2003).

In this test, there was a paternal age effect specific to the female offspring. Female OFOs spent significantly more time in the light, with $p=0.0201$ (**Figure 8a**). The light-dark test was also the only test that showed an effect of estrous in the females. Females in estrus at the time of the test spent more time in the light than those in other stages of the estrous cycle.

Food Neophobia

Due to the finding that female OFO spent more time in the light compartment during the light-dark choice test, we were interested in testing whether female OFOs also displayed decreased neophobia. As female OFOs were less deterred by their aversion to light in their exploration of the compartment, this might indicate a reduced level of anxiety in response to novelty. To determine whether this effect could also be seen in relation to a novel food, we food-deprived mice for 24 hours after weighing them. They

then had access to both a novel food and a familiar food in their home cages. We measured latency to eat each food, and the amount of each consumed. Blueberry Nutri-Grain bars were used for the novel food, as mice prefer this over a range of other palatable foods and will consume it even when they are not food-deprived (Swank & Sweatt, 2001).

Mice were weighed before food deprivation. In addition to a gender effect that showed males weighing more than females ($p<0.0001$), there was also an effect of paternal age on weight for the male OFOs. Male OFO weighed less than YFO, with a p-value of 0.0424 (**Figure 9a**). While there was no significant paternal age effect on latency to eat either food or in familiar food consumed, the female OFO consumed more of the novel food than their YFO counterparts ($p=0.0480$), as shown in **Figure 9f**.

DISCUSSION

Estrous Cycle

As changes in estrogen levels may effect such behavioral elements as activity and emotionality (M. A. Morgan & Pfaff, 2001), the estrous cycle must be taken into account when performing behavioral tests on female mice. However, the findings in this area have been very inconsistent. Various studies have reported either an anxiolytic or anxiogenic effect of estrogen, as measured by the open field or elevated plus maze (Mora, Dussaubat, & Diaz-Veliz, 1996; Nomikos & Spyraki, 1988; Palermo-Neto & Dorce, 1990). It has also been shown to either facilitate or reduce learning in learned fear tasks

(Diaz-Veliz, Soto, Dussaubat, & Mora, 1989; Diaz-Veliz, Urresta, Dussaubat, & Mora, 1991; Gibbs, Burke, & Johnson, 1998; Mora et al., 1996; Sfikakis, Spyraki, Sitaras, & Varonos, 1978; Shors, Lewczyk, Pacynski, Mathew, & Pickett, 1998; Singh, Meyer, Millard, & Simpkins, 1994). It has been more reliably associated with an increase in running wheel activity (M. A. Morgan & Pfaff, 2002; Ruiz de Elvira, Persaud, & Coen, 1992; Thomas, Storlien, Bellingham, & Gillette, 1986; Wade & Zucker, 1970). In this study, the estrous cycle did not have a large effect on behavior. The only significant finding was that mice in estrus spent more time in the light compartment during the light-dark test. Thus signifies some minor support for an anxiolytic effect of estrogen.

Behavioral Phenotype

Previous cohorts have shown decreased open field activity, sometimes accompanied by decreased PPI, in male OFO. In this study, the decreased locomotor activity was replicated in male OFOs, although we did not reproduce the PPI deficit. In addition, we observed that there seems to be an effect of paternal age on weight for the male OFOs. Male OFOs weighed significantly less than the YFOs of this cohort.

However, the female OFOs displayed a different phenotype. Female OFOs did not show a significant difference in open field activity. Instead, female OFOs spent increased time in the light during the light-dark test, as well as consuming more of the novel food during the food neophobia test. Weight cannot account for the change in consumption, as this measure did not differ between the female OFOs and YFOs. There are therefore two measures that indicate reduced anxiety and less aversion to novelty in female OFOs. This appears to run counter to the reduced exploratory behavior in the

males, however the decreased locomotor activity in the males might also be interpreted as a state of decreased arousal. In sum, paternal age does seem to have disparate effects on male and female offspring in our study.

Still, we cannot draw that conclusion lightly. While it is true that the fathers were characterized by disparate ages, this is not the only difference between the groups. Notably, the old fathers were drawn from retired breeders while the young fathers were virgins at the start of the study. The difference in experience and hormonal status of the old and young fathers may also have heritable genetic or epigenetic effects. This highlights the difficulty in interpreting studies of environmental influences. Animal research has the advantage of allowing an impressive amount of control over experimental factors. However, certain variables, such as age, are harder to isolate. We can therefore only say that advanced paternal age is correlated with the observed behavioral phenotype.

Individual Differences

Further statistical analysis of the data has revealed the presence of individual effects of father on offspring behavior. These litter effects could not be explained by age of the father. This suggests that there may be other paternal variables that have an effect on the inheritance of the described behavioral phenotype. In future studies, behavioral testing should be run on the fathers to determine whether individual paternal effects on the offspring are linked to a specific paternal phenotype.

Genetic and Epigenetic Inheritance

One possible explanation for the behavioral differences between OFOs and YFOs is the accumulation of copy error mutations in the germ cell lines of older fathers. Spermatogenesis involves the perpetuation of mitotic divisions throughout life. During each of these divisions, the entire genetic sequence must be replicated, carrying the possibility of de novo mutations. In fact, point mutations, microsatellite repeats, and copy number variations that result from mitotic copy errors have all been associated with advanced paternal age (Crow, 2000a; Goriely & Wilkie, 2012; Hehir-Kwa et al., 2011; Sun et al., 2012).

These were originally thought of as random mutations that would amass as the number of mitotic cycles increased. However, more recent studies have put forth a “selfish spermatogonial selection” hypothesis (Goriely, McGrath, Hultman, Wilkie, & Malaspina, 2013). This is based on the observation that mutations in germ cells that affect proliferation can lead to selective expansion of that clonal cell line. These mutations will then be preferentially enriched within the sperm cell population. Of note, several of the risk genes linked to schizophrenia and other neurodevelopmental disorders associated with advanced paternal age are involved in cellular proliferation pathways. In fact, some of these candidate genes are also linked to cancer, highlighting their proliferative advantage. Nrg1 is among these, as it has been implicated in breast cancer, multiple myeloma, and B cell leukemia/lymphoma (Britsch, 2007; Emamian, 2012).

This could explain why paternal age seems to produce a consistent phenotype in the offspring. If the paternal age effect were simply due to random mutations, each

mutation would be responsible for a different phenotypic effect and we would not see a significant group-wide shift. However, if we consider that selfish selection could be behind the relevant mutations, genes that are involved in proliferative pathways would be expanded. We could then expect to see distinct phenotypes and disease risks emerge as a result of advanced paternal age.

Another plausible mechanism is the inheritance of epimutations from old fathers. Our studies, and others that examined paternal age effects (Auroux, 1983; Foldi, Eyles, McGrath, & Burne, 2010; Garcia-Palomares et al., 2009; R. G. Smith et al., 2009), observed a population-wide quantitative shift in behavior. If the advanced paternal age effects were due to an increase in rare mutations, as was originally proposed, we would expect to see the mouse model result in rare outliers instead of the generalized effects we have described. Thus, the buildup of epigenetic changes over time that can be passed down through the germ line, creating an accumulation of subtle changes, is more fitting with the evidence.

This is also consistent with recent studies identifying changes in DNA methylation that are linked to advanced paternal age. Epigenetic changes have been identified in the male germ line, and these sperm methylation patterns show both intra- and inter-individual variability (Flanagan et al., 2006). These changes appear to be passed on to the offspring, as human infants show CpG methylation levels in umbilical cord blood that are correlated with parental age (Adkins, Thomas, Tylavsky, & Krushkal, 2011). Maria Milekic has also been analyzing the changes in methylation seen in the male OFO mice described here, and her findings also support these studies. She has identified a list of differentially methylated genes associated with paternal age in the male

offspring.

Methylation analysis has not been performed on the female offspring. Yet there is reason to believe that the female and male OFOs would show disparate epigenetic effects, in the same way that they display distinct behavioral phenotypes. In human newborns, parental-age related methylation changes do show gender differences. While most of these gender-specific methylation differences are located on the X chromosome, this is also the case for some autosomal CpGs (Adkins et al., 2011). However, as the behavioral phenotype seen in female OFOs is not as robust as that observed in males, the female methylation analysis of this cohort may be of less value.

FIGURE 4: Open Field Activity

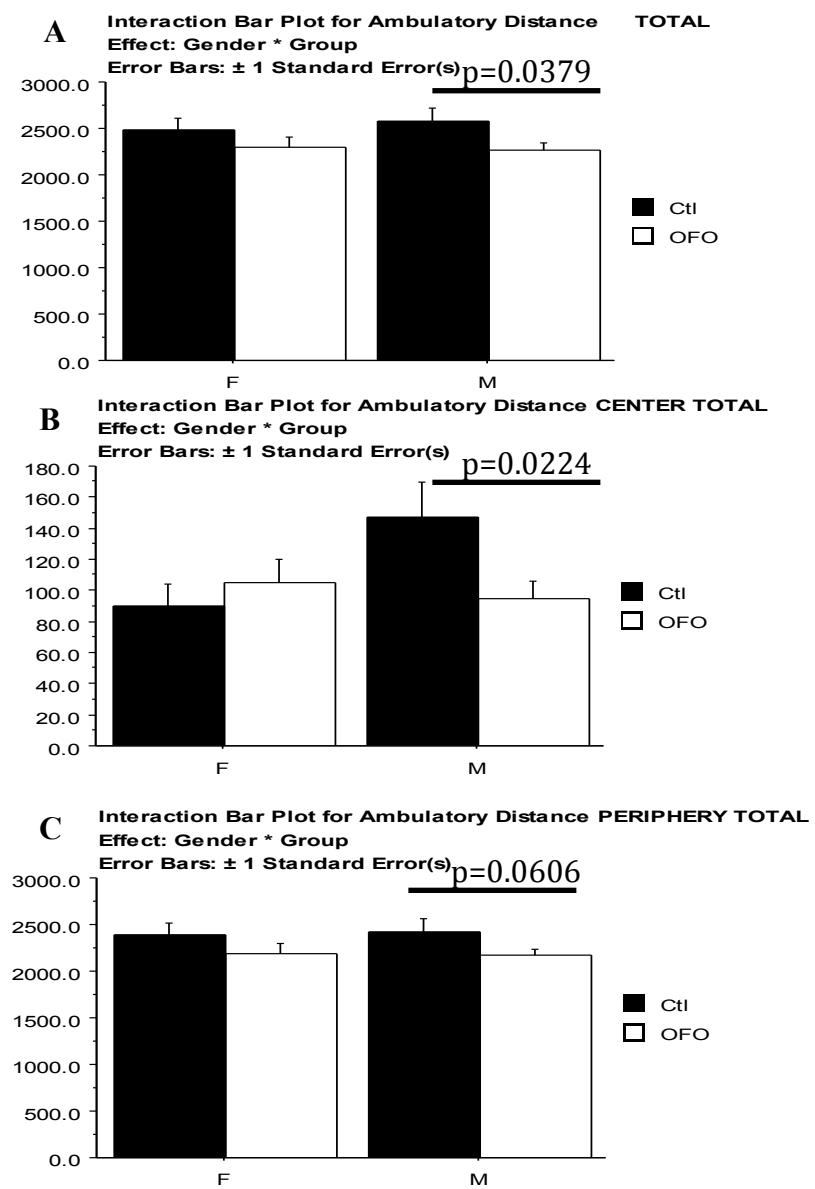


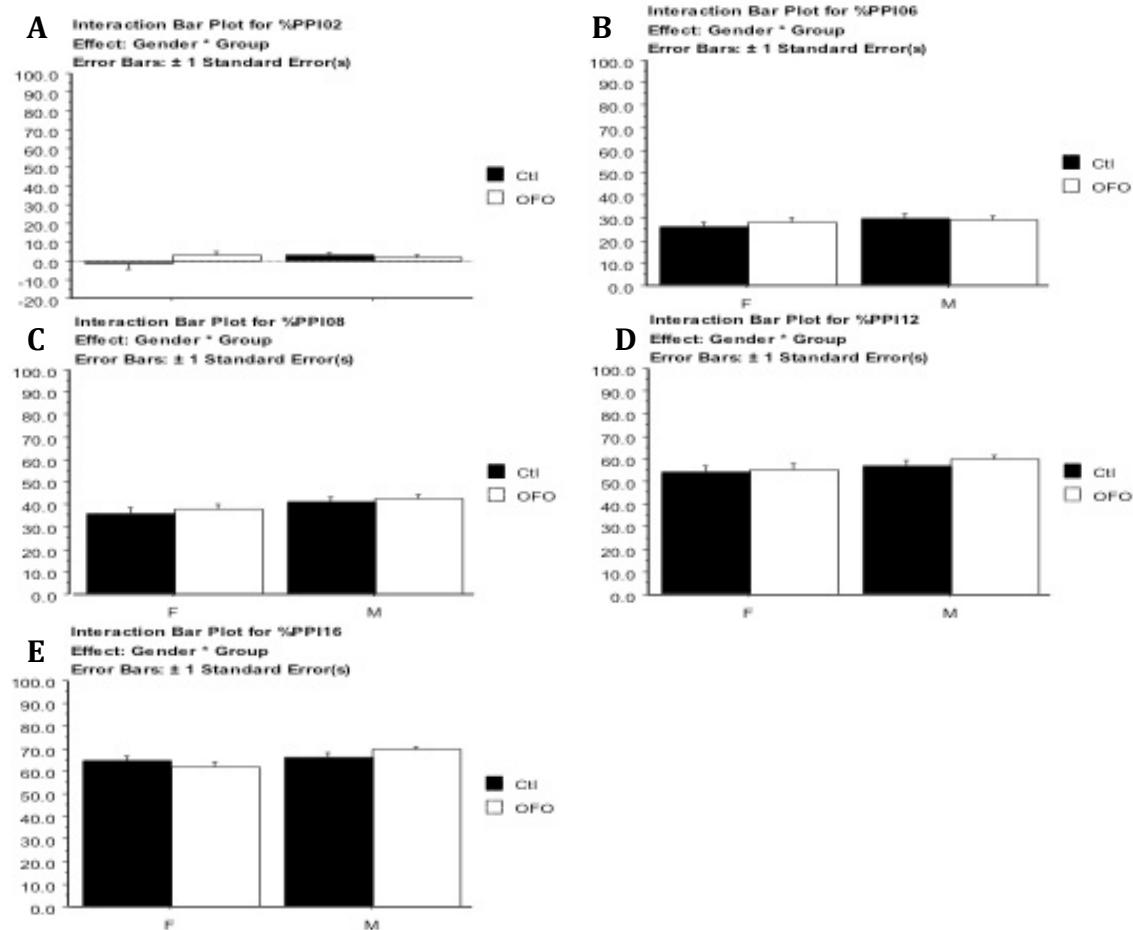
FIGURE 4: Open Field Activity

(A) Total ambulatory distance traveled during the open field test. Male OFOs showed decreased activity ($p=0.0379$), but there was no paternal age effect in females.

(B) Ambulatory distance traveled in the center of the open field. Male OFOs showed decreased activity ($p=0.0224$), but there was no paternal age effect in females.

(C) Ambulatory distance traveled in the periphery of the open field. Male OFOs showed a trend towards decreased activity ($p=0.0606$), while there was no paternal age effect in females.

FIGURE 5: Prepulse Inhibition



Percent prepulse inhibition for prepulse 2db (**A**), 6db (**B**), 8db (**C**), 12db (**D**), or 16db (**E**)

over background. There was no significant change in %PPI for any of these groups.

FIGURE 6: Fear Conditioning

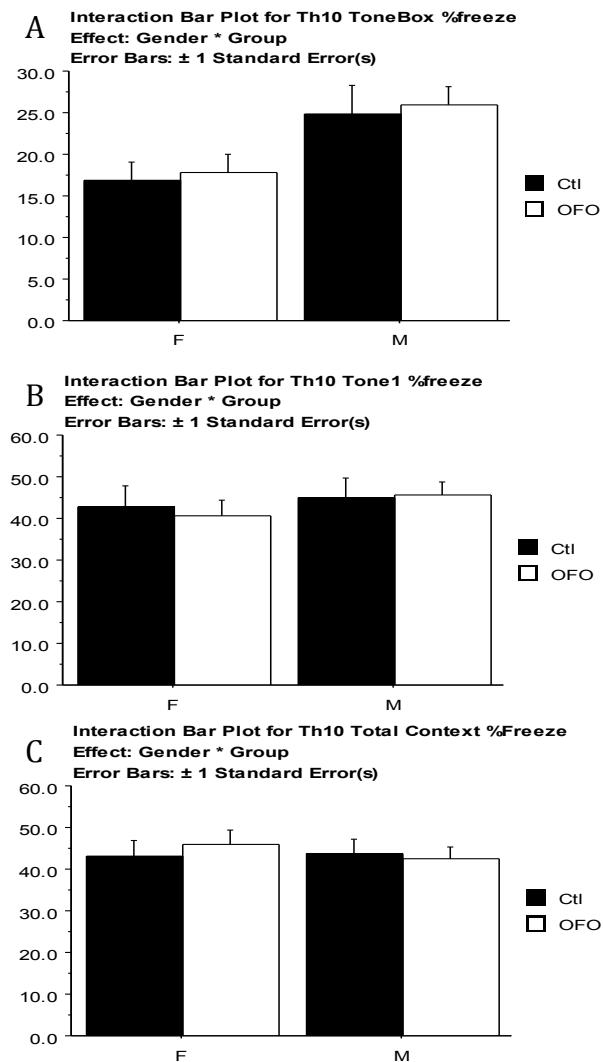


FIGURE 6: Fear Conditioning

In the fear conditioning paradigm, mice were trained to associate a tone with the delivery of a shock. They were then tested on their association of either the tone or the shock-delivery box with the shock by measuring the percent of time spent frozen. **(A)** shows levels of freezing to the novel box before the tone test was administered. **(B)** shows %freezing to the tone delivery. **(C)** shows the freezing to the context of the shock-delivery box. None of these measures showed any effect of paternal age, although males showed significantly more baseline freezing to the box where the tone test was given ($p=0.0022$).

FIGURE 7: Social Interaction

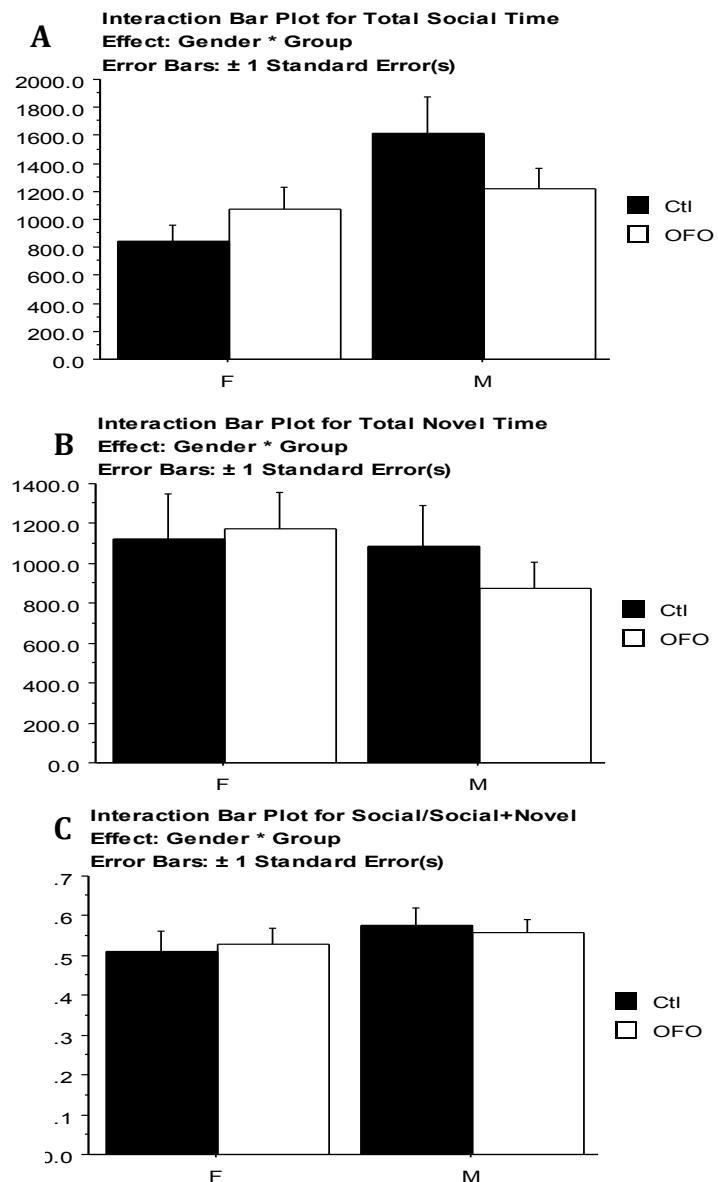
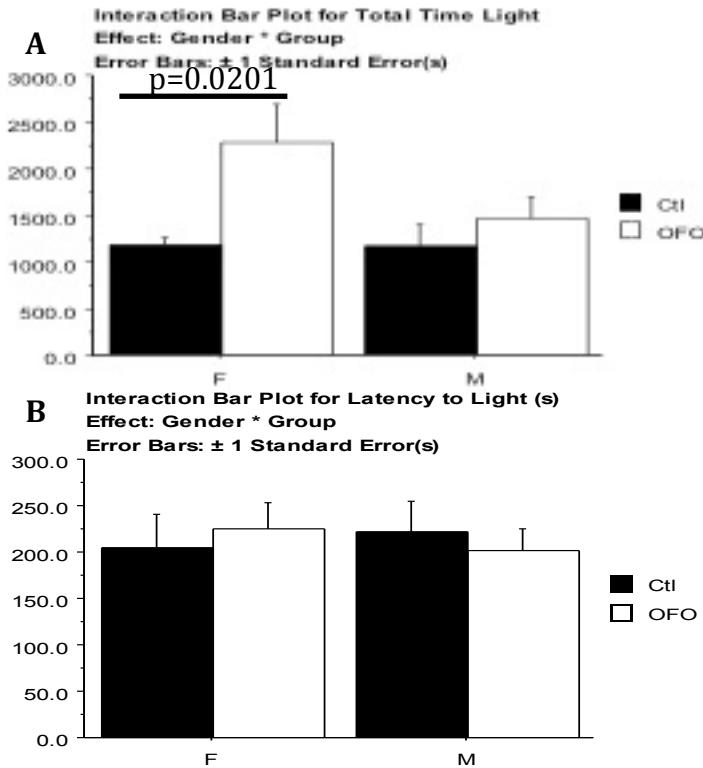


FIGURE 7: Social Interaction

In the social interaction test, mice were placed in an open field that contained a novel mouse in a box with a mesh screen, allowing for interaction, in one corner. Another corner just contained a novel box. There was no paternal age effect on **(A)** time spent in social interaction, **(B)** time spent investigating the novel box, or **(C)** the ratio of social session time to social plus novel session time. However, there was a gender effect on total social time, as males spent more time engaging in social interaction.

FIGURE 8: Light-Dark Test



(A) In this task, an open field chamber was split in two, with one side brightly lit and the other side darkened. This graph shows the total time spent in the light portion of the chamber for both male and female OFOs and YFOs. The female OFOs spent significantly more time in the light half of the chamber ($p=0.0201$). Male offspring did not show an effect of paternal age.

(B) This graph shows the latency to enter the light portion of the chamber when mice were placed in the dark half. There was no difference between groups.

FIGURE 9: Food Neophobia

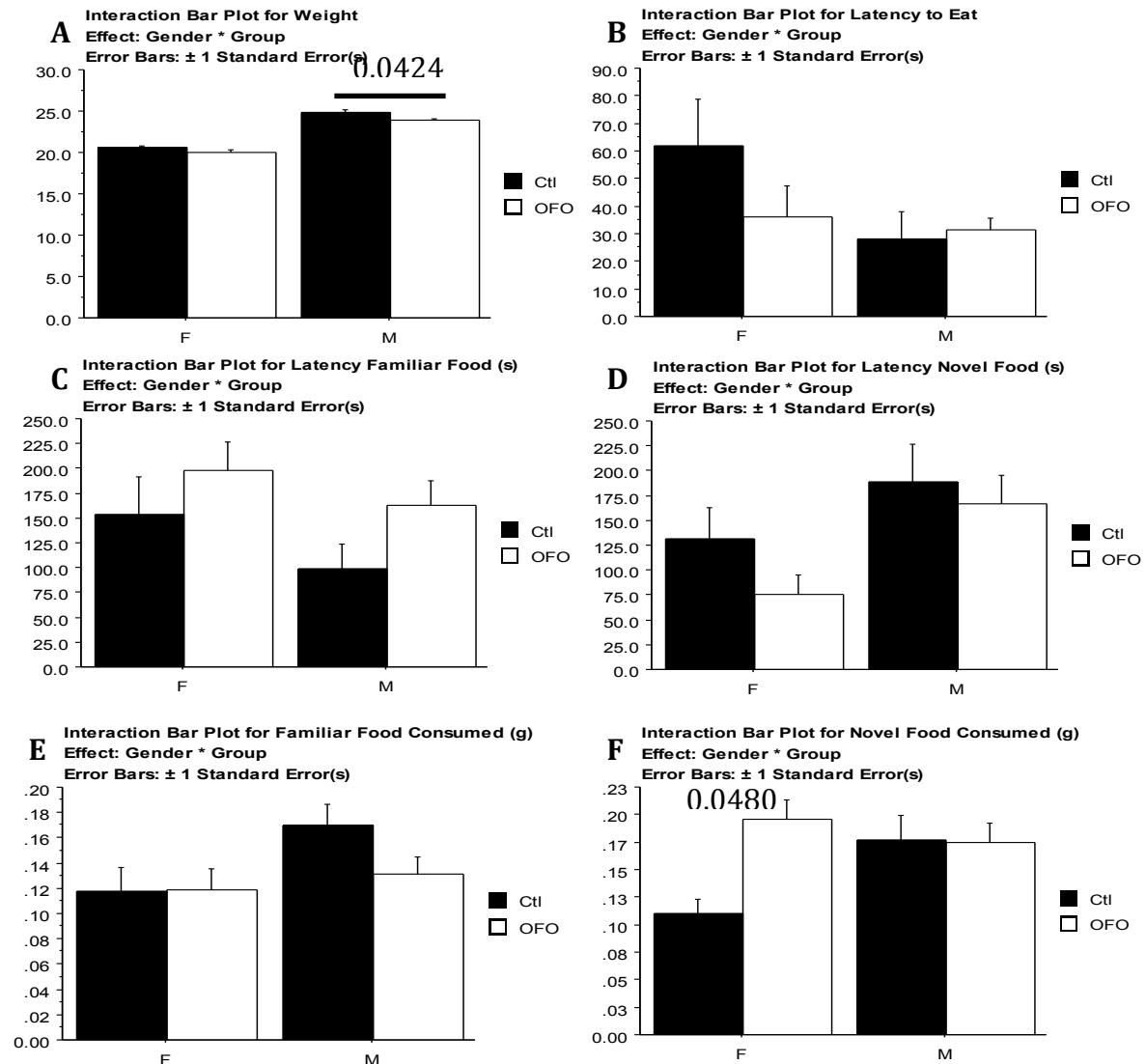


FIGURE 9: Food Neophobia

- (A)** Measurements of weight before food deprivation showed an effect of gender, as males weighed more than females ($p<0.0001$). There was also a significant paternal age effect only for the male offspring. Male OFOs weigh less than YFOs ($p=0.0424$)
- (B)** The latency to eat either food was not dependent on group.
- (C)** The latency to eat the familiar pellet was not significantly changed in any group.
- (D)** The latency to consume novel food was not different between the groups for males or females.
- (E)** Grams of familiar food consumed did not differ among the groups for males or females.
- (F)** Female OFOs consumed significantly more of the novel food than YFOs ($p=0.0480$). This difference was not seen in the male offspring.

CHAPTER 3: The Role of Ig-Nrg1 in SVZ Neurogenesis and Behavior

Introduction

Migration is one of the neurodevelopmental roles associated with Nrg1, and it has been implicated in tangential migration of cortical interneurons during embryogenesis. The Nrg1 receptor ErbB4 is also highly expressed in the migrating neuroblasts of the SVZ and RMS, as well as in the olfactory bulb, and is found in all periglomerular, mitral, and tufted cells, as well as a subset of granule cells. Nrg1 is also expressed in the SVZ, around the RMS, and throughout the olfactory bulb (Anton et al., 2004; Bovetti et al., 2006; Lindholm, Cullheim, Deckner, Carlstedt, & Risling, 2002; Oberto et al., 2001; Perroteau, Oberto, Ieraci, Bovolin, & Fasolo, 1998; Perroteau et al., 1999). It is possible that the Nrg1-ErbB4 interaction is playing a similar role in the integration of adult-born interneurons into the olfactory bulb as is seen in the developing cortex. This theory is especially attractive given that the SVZ is derived from areas that give rise to cortical interneurons during development.

All six types of Nrg1 are found in the brain, and show different patterns of expression at different ages reflecting their distinct roles in neurodevelopment. Of these,

types I, II, and III are the best characterized and show the highest levels of expression. In both humans and rodents, types III and II are the most prevalent, while types IV and VI combined make up less than 1% of the total Nrg1 (X. Liu et al., 2011). These isoforms are thought to have distinct functions, including playing differing roles in cortical migration. CRD-Nrg1 forms a permissive corridor allowing the passage of ErbB4-expressing interneurons from the ganglionic eminences to the cortex. Meanwhile, Ig-Nrg1 is secreted to form a chemoattractive gradient (Anton et al., 2004; Flames et al., 2004). In this way, Nrg1 can have both short-range and long-range actions.

The SVZ yields newborn interneurons that migrate to the olfactory bulb through adulthood. As there is reason to suspect that this process may show similarities to cortical interneuron neurogenesis, it provides a useful model to examine circuitry dysfunctions that may be relevant to the broader clinical phenotype of schizophrenia. We have been using hypomorphic Nrg1 mice to investigate the functions of this gene in neurogenesis, shedding light on its roles in neuronal proliferation, migration, and differentiation, in addition to exploring its behavioral phenotype. Some endophenotypes seen in Nrg1 heterozygotes are seen in all mutants, while others are associated with certain isoforms. By examining mice that are heterozygous for the Ig-domain, we can separate out the effects of specific isoforms.

PRELIMINARY DATA

Behavioral Phenotype of Nrg1^{Ig/-} Mice

Previous studies from the Gingrich lab have also used Nrg1Ig/- mice to explore the role of Ig-Nrg1 in SVZ neurogenesis and behavior. Hyperactivity is one of the most common schizophrenia-related endophenotypes used to assess mutant mouse models, and it has also been seen in Nrg1 mutants (Gerlai et al., 2000; Stefansson et al., 2002). The results of this test are shown in **Figure 10a**. During an open field session lasting 60 minutes, Nrg1Ig/- mice displayed higher levels of activity than Nrg1+/+ mice. Hyperactivity is thought to be associated with the positive symptoms of schizophrenia, as it is sensitive to treatment with clozapine (Stefansson et al., 2002).

In addition to locomotor activity, mutant animals had altered social interaction, which is an endophenotype associated with the negative symptoms of schizophrenia. Mice were introduced to an intruder in their home cages for six minutes, during which they were allowed to interact. This interaction mainly consists of anogenital investigations (AGI), in which the resident mouse follows and olfactorily explores the intruder. **Figure 10b** shows the latency to first AGI as well as the time spent in AGI, broken down into 2-minute intervals. This test showed a significant effect of genotype. While Nrg1+/+ mice showed high levels of AGI during the first 2 minutes before habituating, Nrg1Ig/- mice had low levels of AGI throughout the session.

As social interaction in mice is closely linked to olfaction, performance was assessed in the olfactory discrimination task illustrated in **Figure 11a**. Mice were trained to distinguish between two odor-infused dishes of digging material to locate a food reward. In the first task, they were trained to discriminate between cinnamon and paprika. Although both groups of mice needed the same number of trials to reach the criterion of six correct choices in a row (**Figure 11c**), Nrg1Ig/- mice took longer to make their choice

(**Figure 11b**). As this subtle difference was apparent in a high contrast test of two spices, a more difficult test was used to tease out any deficits in the mutant mice. Mice were therefore trained to distinguish between carvone stereoisomers. While mice are able to distinguish between these two odors (Slotnick & Bisulco, 2003), the task is thought to be more difficult because the patterns of glomeruli activated by each stereoisomer have a high degree of overlap (Linster et al., 2001; B. D. Rubin & Katz, 1999, 2001). As shown in **Figure 11d**, Nrg1Ig/- did need a greater number of trials to reach criterion for the low contrast discrimination.

SVZ Neurogenesis

As the incorporation of newborn neurons into the olfactory bulb is necessary for optimal olfactory performance (Mouret et al., 2009), Merker and Gingrich wanted to determine whether impaired SVZ neurogenesis could explain the olfactory deficits seen in Nrg1Ig/- mice. The first group of mice was sacrificed 24 hours after receiving injections of BrdU. Slices were taken from the SVZ, and were stained for BrdU. This would yield a snapshot of levels of proliferation occurring in the germinal region of the SVZ for both Nrg1+/+ and Nrg1Ig/- mice. As shown in **Figure 12a**, there was no effect of genotype on total SVZ BrdU counts per mm². When he then looked at BrdU+ cells that had been integrated into the GCL of the olfactory bulb, there was a significant decrease in BrdU staining in the Nrg1Ig/- mice at both 21 days and 60 days after BrdU injections (**Figure 12b, 12c**). However, while it was clear that changing levels of Ig-Nrg1 caused a decrease in adult-born olfactory neurons, it was not clear whether this was due

to changes in survival, migration, or differentiation, or whether there was any heterogeneity in the SVZ proliferative zones or in the layers or regions of the olfactory bulb. The subsequent project set out to answer those questions.

RESULTS

Experimental Design

This experiment is an expansion of our lab's previous experiments on Nrg1^{-/-} mice bred on a C57Bl/6 background. As described, these mice show a subtle olfactory deficit in addition to decreased BrdU staining in the GCL of the olfactory bulb. However, the significance of this result is not clear. Examining BrdU staining from the SVZ through the RMS and into the olfactory bulb at three different time points, as well as staining for various olfactory interneuron markers in different layers of the olfactory bulb, would reveal the effects of altered Ig-Nrg1 expression on neuronal proliferation, survival, migration, and differentiation in adult neurogenesis. Additionally, mice were treated with either clozapine or vehicle as described in the methods section at a dosage of 10mg/kg. As there is evidence that antipsychotic treatment can enhance neurogenesis and may change Nrg1 expression, we wanted to determine whether this would ameliorate any of the phenotypic or anatomical effects of the mutation.

The experimental design of this study is illustrated in **Figure 13**. Male mice were treated with either clozapine or vehicle in their drinking water for 21 days. Mice then received a behavioral assessment, which included tests of locomotor activity in an open

field as well as social interaction. After behavioral testing, they received four injections of BrdU over six hours. They were divided into three groups that were sacrificed 24 hours, 21 days, or 60 days after the BrdU injection, and continued to receive either clozapine or vehicle until the time of sacrifice.

Behavioral Phenotype

Open Field Activity

Locomotor activity in an open field is a common schizophrenia-related endophenotype, which was altered in our lab's previous cohort of Nrg1Ig/- mice. We therefore assessed this measure in our cohort, as shown in **Figure 14**. The test was run over 60 minutes, and **Figure 14a** shows the average distance traveled by each of the four groups, broken down into 10-minute bins. **Figures 14b, 14c, and 14d** show the total distance traveled over the 60-minute session throughout the entire open field, in the center, and in the periphery, respectively. We were able to replicate the previously described finding of hyperactivity in Nrg1Ig/- mice (**Figure 9a**). The heterozygotes showed an increase relative to controls in total distance traveled ($p=0.0004$), as well as higher activity in the periphery ($p=0.0083$). However, we did not see any significant effect of clozapine in this test.

Social Behavior

The resident-intruder task was used to measure social interaction. In this test, mice were housed individually and had a male intruder mouse introduced into their home cages for six minutes. Mice were scored on time spent in AGI with the novel mouse. Time spent sniffing the intruder as well as time spent chasing the intruder and attempting to sniff were both included in the measure of social interaction. The results are shown in **Figure 15**. **Figure 15a** shows the latency to the first AGI. **Figures 15b** and **15c** show the total time in which the mice engaged in AGI with the intruder, with this information broken down into 2-minute bins in **15c**. Although the previously described cohort did show a decrease in social interaction in the heterozygotes during the first 2 minutes of a resident-intruder task (**Figure 9b**), we did not replicate that finding in this cohort. There was no significant effect of either genotype or treatment on latency to AGI or total time spent in AGI.

SVZ Neurogenesis

We then went on to examine olfactory neurogenesis, beginning in the SVZ. We compared total BrdU staining in Nrg1^{+/+} and Nrg1^{Ig/-} mice treated with either vehicle or clozapine. **Figure 16a** shows an example of BrdU staining around the entire SVZ. This entire germinal region was outlined and the area was calculated using the ImageJ program. This value was used to calculate the BrdU counts per mm² 24 hours after BrdU injections, shown in **Figure 16b**. This shows the baseline rates of proliferation for each of the four groups. The previous study did not show any change in BrdU staining in the SVZ after 24 hours (**Figure 12**). This finding was confirmed in the current cohort.

There was no effect of either genotype or treatment on overall BrdU staining in the SVZ after 24 hours.

However, the SVZ is diverse composition including regions derived from different embryonic structures and expressing different transcription factors (Lledo et al., 2008). Taking advantage of these naturally occurring divisions, the SVZ can be divided into five distinct regions defined in **Figure 17**. These include the dorsal wall, medial wall, lateral wall, dorsal tip, and ventral tip. Dividing the SVZ into regions revealed that this diversity is also apparent in the rates of proliferation in each subregion. As shown in **Figure 18**, at 24 hours after BrdU injections, the highest levels of BrdU staining were seen in the lateral wall and dorsal and ventral tips of the SVZ, while the dorsal and medial walls showed lower levels of staining. There was also a significant decrease in BrdU staining in the Nrg1Ig/- mice specifically in the lateral wall of the SVZ (**Figure 18d**). This was not seen in any of the other regions. This indicates that Ig-Nrg1 may have a more dramatic influence on proliferation in this region of the SVZ. Clozapine did not show an effect on any of the SVZ subdivisions.

Figure 19 shows SVZ staining in mice sacrificed 21 days after BrdU injections. At this time point, the majority of the BrdU+ cells had migrated out of the SVZ. Therefore, all measures of BrdU per mm² were lower relative to those seen after only 24 hours. Once again, no significant effect of either genotype or treatment was seen in total SVZ BrdU staining (**Figure 19a**). The subdivisions also showed no effect of clozapine. However, the decrease in BrdU staining in the lateral wall of the SVZ in Nrg1Ig/- mice was maintained at 21 days post-BrdU, with p=0.002 (**Figure 19d**). Additionally, there was a decrease in the medial wall of the Nrg1Ig/- mice at 21 days

post-BrdU (**Figure 19e**), which was not seen at the earlier time point. This suggests that there is also a decrease in survival associated with the genotype, or there may be an increase of migration out of the SVZ.

RMS

In following the migratory path from the SVZ to the olfactory bulb, we then looked to the RMS. An example of BrdU staining in this region can be seen in **Figure 20a**. As shown in **Figure 20b**, there was a significant effect of genotype on BrdU counts per mm² measured in the RMS at 21 days post-BrdU. Nrg1Ig/- mice showed lower levels of BrdU staining, with a p-value of 0.0003. Given this finding, it may be more likely that the emergence of a decrease in BrdU staining in the medial wall of the SVZ at this time point is due to a survival deficit rather than an increase in migration.

Olfactory Bulb

Adult-born neurons produced in the SVZ migrate into the olfactory bulb and are incorporated into either the GL or GCL. Most adult-born neurons in the GCL express CR. In the GL, distinct populations of interneurons express tyrosine hydroxylase (TH), calretinin (CR), or calbindin (CB). CB+ interneurons are mainly produced perinatally, while CR+ and low levels TH+ GL interneurons are produced during adulthood (Batista-Brito et al., 2008; Parrish-Aungst et al., 2007). We therefore stained the olfactory bulb with TH, CR, and BrdU. An example of this staining can be seen in **Figure 21**. In the

GL, we counted cells in that were double-stained with BrdU and either TH or CR, while in the GCL we counted cells double-labeled with CR and BrdU.

Glomerular Layer and Granule Cell Layer BrdU Staining

Figure 22 shows BrdU staining in the GL of the olfactory bulb at 21 days and 60 days post-BrdU. Total BrdU measurements are shown in **Figures 22a** and **22b**. Cells per mm² that were double-stained with BrdU and CR (**Figure 22c, 22d**) or BrdU and TH (**Figure 22e, 22f**). The majority of the BrdU+ cells were stained with CR, while less than 25% were TH+. The number of BrdU+ cells in the GL also decreased from 21 days to 60 days, indicating that adult-born neurons continue to experience turnover after they are added to the olfactory circuitry. However, there was no effect of either genotype or treatment on numbers of BrdU+ cells or the numbers of newborn TH+ and CR+ interneurons.

BrdU staining in the GCL of the olfactory bulb at 21 days and 60 days post-BrdU can be seen in **Figure 23**. Total BrdU staining is shown in **Figure 23a** and **23b**, while double-staining of BrdU and CR in the GCL is shown in **Figure 23c** and **23d**. These sets of graphs are almost equivalent as the vast majority of new GCL neurons were CR+. As was seen in the GL, there was a decrease in BrdU staining from 21 days to 60 days, indicating that turnover was also occurring in the GCL. In contrast to the BrdU staining in the GL, the GCL did show an effect of genotype, although there was still no effect of clozapine. Nrg1Ig/- had fewer newborn neurons in the GCL at both 21 days and 60 days

post-BrdU. This confirms the previous finding of decreased BrdU staining at both of these time points (**Figure 11b, 11c**). However, as the previous study did not look at the GL, we can now say that changes in Ig-Nrg1 expression preferentially alter levels of newborn neurons entering the GCL.

Glomerular Layer and Granule Cell Layer Interneuron Distribution

In addition to measuring the number of BrdU+ cells in the GL and GCL, we also looked at total numbers of interneurons, both newborn and existing, at both 21 days and 60 days post-BrdU. These measurements are displayed in **Figure 24** for GL CR+ neurons (**Figure 24a, 24b**) and TH+ neurons (**Figure 24c, 24d**), and GCL CR+ neurons (**Figure 24e, 24f**). There was no significant effect of either genotype or treatment on levels of any of these interneurons. Since there was a reduction in BrdU+CR+ granule cells with no reduction in total CR+ granule cells, this indicates that there is decreased turnover in the GCL of Nrg1Ig/- mice. The GCL appears to adapt to decreased proliferation by increasing the survival length of existing interneurons.

Olfactory Bulb Heterogeneity

An interesting fact was also revealed when olfactory bulb staining was broken down by Bregma level from Bregma 2.8 at the caudal end and Bregma 3.6 at the rostral end. In the GL, there was still no apparent difference between the groups at either 21 days or 60 days post-BrdU in BrdU staining (**Figure 25a, 25b**), or double-staining with BrdU

and TH (**Figure 25c, 25d**), or BrdU and CR (**Figure 25e, 25f**). Total TH+ (**Figure 26a, 26b**) or CR+ (**Figure 26c, 26d**) interneurons did not show significant variance along the rostral-caudal axis. However, this was not the case in the GCL. We reported a decrease in BrdU+ cells in this region at both 21 days and 60 days post-BrdU. This decrease appears to be specific to new neurons in the region of the GCL contained from Bregma 3.2 to Bregma 3.4 (**Figure 27**).

DISCUSSION

Antipsychotics

In this study, we did not see a significant effect of clozapine treatment on either the behavioral phenotype or SVZ neurogenesis. Given the lack of any effect, we must consider the possibility that the clozapine treatment was ineffective. However, this seems unlikely, as we were able to measure clozapine in the blood of sample animals that experienced this protocol. By dissolving clozapine into the drinking water and measuring the amount consumed each week compared to the average weight of the animals, we could calculate the clozapine dosage at 10mg/kg per day for each animal. Two animals were sacrificed to assess the efficacy of the treatment by measuring whole blood clozapine levels. One animal had a norclozapine level of 59ng/ml after three weeks, while another had a level of 237ng/ml after two weeks. This is lower than the clinical dosage in humans of around 300ng/ml.

A more likely explanation is that, even though this dosage is below the clinically effective range, it is too high to see the effects previously reported. Other studies have seen a decrease in locomotor activity in Nrg1 mutant mice treated with clozapine at a

dosage of only 1mg/kg (Rimer, Barrett, Maldonado, Vock, & Gonzalez-Lima, 2005; Stefansson et al., 2002). As we did not see the reduction in activity that has previously been reported with clozapine in Nrg1 mutants, it would be worth repeating the clozapine at a lower dose to determine whether we can replicate this finding. At least in the dentate gyrus, it also seems a lower dose is more effective at stimulating neurogenesis. Chronic clozapine treatment with 5mg/kg or 20mg/kg did not alter rates of neurogenesis in the dentate gyrus, although a very low dose of 0.5mg/kg was responsible for a temporary increase in proliferation in this region (Halim, Weickert, McClintock, Weinberger, & Lipska, 2004; U. Meyer, Knuesel, Nyffeler, & Feldon, 2010). Perhaps the SVZ neurogenesis that has been reported with the use of similar antipsychotics (W. Green et al., 2006; Wakade et al., 2002) could also be seen with a lower dose of clozapine.

Behavioral Phenotype

While several studies have examined the phenotype of Nrg1 heterozygous mice with a mutation in the TM-domain or EGF-domain, in which levels of both Ig-Nrg1 and CRD-Nrg1 are altered, the Nrg1Ig/- phenotype has yet to be fully characterized. Hyperactivity is a schizophrenia-related endophenotype that has been measured in other Nrg1 mutants (Gerlai et al., 2000; Stefansson et al., 2002). Although one previous study did not see hyperactivity in Nrg1Ig/- mice (Rimer et al., 2005), hyperactivity was apparent in the previous cohort and the current study confirms his finding. Given the normal locomotor activity seen in Type III Nrg1 heterozygotes (Y. J. Chen et al., 2008), these results indicate that changes in Ig-Nrg1 expression are responsible for the observed

hyperactivity. On the other hand, we did not replicate the previous finding of decreased social interaction in Nrg1^{Ig/-} mice. Further investigation is necessary to determine whether Ig-Nrg1 plays any role in this behavior.

Nrg1^{Ig/-} also showed mild olfactory deficits. Heterozygotes showed an increased latency to choose between cinnamon and paprika in an olfactory discrimination reward paradigm, yet were able to learn the task in the same number of trials as Nrg1^{+/+} mice. They also needed a higher number of trials to reach criterion on the more difficult discrimination task in which they had to distinguish between the two enantiomers of carvone. This mild impairment in olfactory acuity points to a deficit in the function of interneurons, which enact lateral inhibition to boost the contrast between similar odors and enhance the capacity for olfactory discrimination (Luo & Katz, 2001; Schoppa & Urban, 2003; Yokoi, Mori, & Nakanishi, 1995). This hypothesis is backed up by the neuroanatomical findings discussed below.

SVZ Neurogenesis

BrdU is a thymidine analog that is incorporated into a dividing cell's DNA, thereby marking proliferating cells. At 24 hours after BrdU staining, the SVZ showed no difference in proliferating cells between Nrg1^{+/+} and Nrg1^{Ig/-} mice. This finding confirmed what was seen in the previous cohort. Although there is an extensive neurogenic region surrounding the lateral ventricles that can generate neuroblasts and contribute new interneurons to the olfactory bulb, the majority of these are derived from the anterior SVZ (Alvarez-Buylla et al., 2008; Menezes, Smith, Nelson, & Luskin, 1995).

However, the SVZ is a heterogeneous structure with various regions deriving

from different embryological origins and expressing different transcription factors. This variability is maintained as the fate of a neuroblast appears to be set by its region of origin (Lledo et al., 2008). Subtle regional aberrations may be missed if this diversity is not taken into account. I therefore divided the SVZ into five regions based on their embryological origins. These were the dorsal, medial, and lateral walls, and the dorsal and ventral tips. When comparing BrdU staining between Nrg1^{+/+} and Nrg1^{Ig/-} mice in each of these areas, a decrease in BrdU staining was apparent in the lateral wall of the heterozygous mice.

This suggests that a decrease in Ig-Nrg1 expression is responsible for a baseline region-specific decrease in proliferation. Interestingly, the lateral wall is also the region of the SVZ that shows the highest levels of Nrg1 expression, particularly in the anterior SVZ. Thus it is not unexpected that the lateral wall was most impacted by changes in Nrg1 levels. Nrg1 expression in this region for the most part colocalizes with the expression of polysialylated neural cell adhesion molecule (PSA-NCAM), which is a transient marker of newly generated cells (Anton et al., 2004; Ghashghaei et al., 2006; Sato et al., 2001). After cleavage, Ig-Nrg1 is released extracellularly. The receptor ErbB4 is also expressed in PSA-NCAM migrating neuroblasts (Ghashghaei et al., 2006), so the relevant Nrg1-ErbB4 interactions may be autocrine, juxtacrine, or paracrine in nature.

Evidence of a decrease in proliferation is in line with previous research that has identified Nrg1 as a mitogen. In cultures of neural stem cells isolated from embryonic mouse telencephalon, treatment with the EGF domain of Nrg1 induced a four-fold increase in BrdU-labeled cells (Y. Liu, Ford, Mann, & Fischbach, 2005). This indicates that the proliferative effects of Nrg1 are likely due to an interaction with ErbB4, instead

of through back signaling of the ICD, as these effects were present after external application of Nrg1. One possible mechanism for this effect is the activation of phospholipase C (PLC). PLC has an interaction with ErbB4, and Nrg1 stimulation leads to a signaling cascade that is critical for stem cell proliferation (Gallicano, Yousef, & Capco, 1997; Lai & Feng, 2004; Montcouquiol & Corwin, 2001; Noh, Shin, & Rhee, 1995; Quinlan, Faherty, & Kane, 2003). However, the mechanism for Nrg1-induced proliferation has yet to be confirmed.

The results of this study also point to a role of Nrg1 signaling in survival of neuroblasts. After 21 days, BrdU staining in the SVZ shows a large overall reduction due to the migration of neuroblasts out of the SVZ through the RMS and into the olfactory bulb. Additionally, the reduction in BrdU+ cells seen in the lateral wall of Nrg1^{Ig/-} mice at 1-day post-BrdU was even more dramatic at 21-days post-BrdU. This was accompanied by a reduction in BrdU staining in the medial wall, which had not been seen at the earlier time point. There are two possible explanations for this reduction. The Ig-Nrg1 deficit could result in decreased survival of neuroblasts, or there could also be increased migration out of the SVZ. As there was also a decrease in BrdU+ cells in the RMS and olfactory bulb of the heterozygotes, impaired survival of neuroblasts seems more likely.

Other studies have also identified a role for Nrg1 signaling in survival. As previously described, Nrg1 signaling can include both the release of an extracellular domain, and the cleavage of an intracellular domain which can also engage in back signaling. Extracellular binding of ErbB receptors or depolarization can induce ICD cleavage. The ICD may then translocate to the nucleus to regulate gene expression. Its

functions include promoting cell survival and repressing regulators of apoptosis (Bao et al., 2004; Bao et al., 2003; Talmage, 2008). However, thus far ICD back signaling has only been associated with CRD-Nrg1. It is therefore possible the decreased survival described in Nrg1Ig/- mice is due to compensatory changes in expression of CRD-Nrg1. There might also be as yet unknown Ig-Nrg1 signaling mechanisms that influence survival, or previously undiscovered back signaling by these isoforms. However, this is speculative and needs further study.

The decrease in proliferation specifically in the lateral wall of the SVZ has implications for the composition of new olfactory bulb interneurons. In general, the lateral wall of the SVZ contribute periglomerular cells that express calbindin, which are produced perinatally, as well as deep granule cells. The dorsal SVZ produces TH+ periglomerular cells, while the medial SVZ produces CR+ periglomerular cells. Both of these regions also contribute superficial granule cells (Batista-Brito et al., 2008; Ihrie & Alvarez-Buylla, 2011; Lledo et al., 2008; Young et al., 2007). Since Nrg1Ig/- mice showed a decrease in proliferation in the lateral wall of the SVZ, a reduction in BrdU+ granule cells would also be expected.

As predicted, there was a decrease in new granule cells in the olfactory bulb at both 21-days and 60-days post-BrdU, most of which were CR+. NrgIg/- mice did not show a change in BrdU staining in the GL for either TH+ or CR+ periglomerular cells. This indicates that the regional specificity of Ig-Nrg1 on proliferation is reflected in a specific reduction in olfactory interneurons derived from that region. These findings suggest that the diversity of the olfactory bulb can be attributed to their origins in the SVZ, and can be traced back even further to the regional differences in SVZ embryologic

origins.

Interestingly, although there was a reduction in BrdU+ cells in the olfactory bulb of Nrg1Ig/- mice, there was no change in total counts of interneurons. This was true for both the GCL and all subtypes measured in the GL. Reduced proliferation and incorporation of new GCL interneurons into the olfactory bulb, combined with an equal number of overall cells, implies that the end result of this genetic manipulation is a decrease in GCL turnover. It seems there may be niche in the olfactory bulb that needs to be filled to maintain the circuitry, and the reduction in available migrating neuroblasts leads to fewer older GCL interneurons being replaced.

There is evidence that reduced SVZ proliferation increases the survival of olfactory bulb interneurons (Sui et al., 2012). Dopaminergic innervation modulates proliferation in the LGE during development, and continues to innervate this region as it is incorporated into the SVZ during adulthood (Abrous, Koehl, & Le Moal, 2005; Emsley, Mitchell, Kempermann, & Macklis, 2005; Freundlieb et al., 2006; Hoglinger et al., 2004; Lie, Song, Colamarino, Ming, & Gage, 2004; Ming & Song, 2005; Ohtani, Goto, Waeber, & Bhide, 2003). Dopamine induces proliferation of transit amplifying cells in this region, and depletion of dopaminergic fibers decreases proliferation (Baker, Baker, & Hagg, 2004; Freundlieb et al., 2006; Hoglinger et al., 2004; Kippin, Kapur, & van der Kooy, 2005; Winner et al., 2009). The relevant study used dopaminergic depletion to decrease SVZ proliferation and showed an increase in BrdU+ cells in the SVZ 15 days later and an increase in BrdU+ cells in the olfactory bulb 42 days later. They also saw equivalent numbers of total mature olfactory bulb interneurons (Sui et al., 2012). This matches what was seen in the Nrg1Ig/- mice. The genetic manipulation

resulted in reduced proliferation with no change in the total number of olfactory interneurons. A compensatory increase in survival, and consequently decreased turnover, is therefore a plausible mechanism for these findings.

A recent study has pointed to a role for olfactory turnover in optimizing olfactory performance. For example, one study blocked turnover by infusing the caspase inhibitor zVAD into the olfactory bulb and administered a battery of olfactory tests to determine the effects. This did not affect turnover of OSN, but did increase the survival of olfactory interneurons. While these mice were still able to perform olfactory discrimination tests as well as control mice, they showed an increased discrimination time when performing the task. They also spent more time exploring new odors than the control mice (Mouret et al., 2009). This provides evidence that the decrease in turnover leads to a longer processing time and less efficient functioning of the olfactory bulb circuitry. The decreased turnover seen in this study could therefore be responsible for the subtle olfactory deficits we have described. It seems reductions in turnover, whether by genetic or chemical means, can still result in this decreased efficiency of olfactory identification.

One novel finding of this study was that there also seems to be heterogeneity along the anterior-posterior axis of the olfactory bulb in terms of the rates of incorporation of new neurons. The decrease in BrdU+ cells in the GCL was specific to the area of the olfactory bulb from Bregma 3.2 to Bregma 3.4. This may have functional implications. While odorants activate a distributed pattern of glomeruli in the olfactory bulb, it has been thought that the glomeruli are arranged according to the chemical properties of the odorants that activate them (Johnson & Leon, 2007), although this theory has been recently disputed (L. Ma et al., 2012). If this is the case, a chemotopic

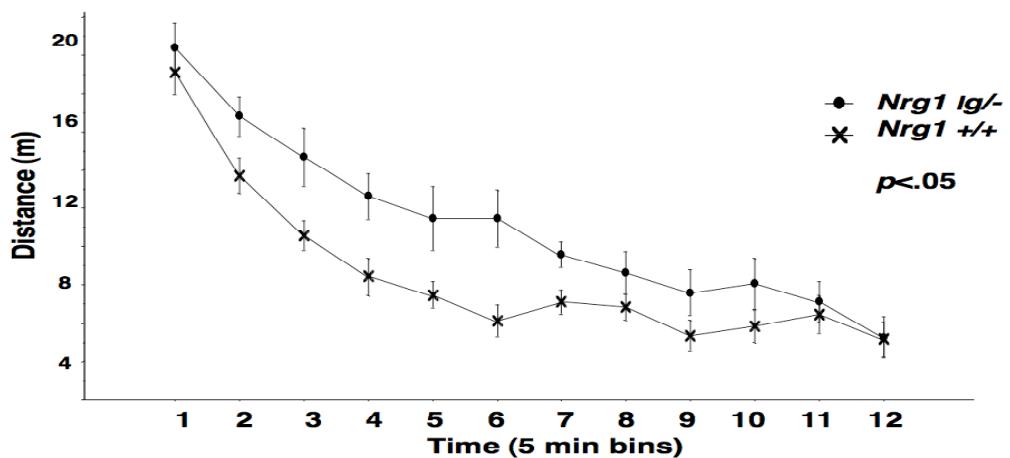
mapping of the olfactory bulb may elucidate the functions of glomeruli in that region, and Nrg1Ig/- mice should have greater difficulty discriminating between odors that activate the glomeruli in question.

Interestingly, in analyzing BrdU staining along the anterior-posterior axis of the olfactory bulb, it was apparent that the Nrg1+/+ mice showed increased BrdU+ cells in the region from Bregma 3.2 to Bregma 3.4, while the Nrg1Ig/- had somewhat even BrdU+ levels throughout. This suggests that the Nrg1+/+ had increased turnover specifically in that region. Since we were not training this cohort to discriminate between certain smells, it is likely that this area of the olfactory bulb is activated by relevant smells in the laboratory environment. Because Nrg1Ig/- mice did not show a similar increase, it is possible that they have an impaired ability to increase turnover in response to significant olfactory stimuli. Such a deficit would likely confer a disadvantage in adaptation to new stimuli.

This becomes increasingly relevant when we recall that the regions of the brain that give rise to the SVZ are also responsible for contributing cortical interneurons during early development. These cortical circuits also undergo pruning and neuronal turnover. One can imagine that, if the same mechanisms are in place during neurodevelopment, cortical circuitry may have less plasticity. This would have implications far beyond olfaction.

FIGURE 10: Nrg1Ig/- Behavioral Phenotype

A. Locomotor Activity in Nrg1Ig/- Mice



B. Social Interaction

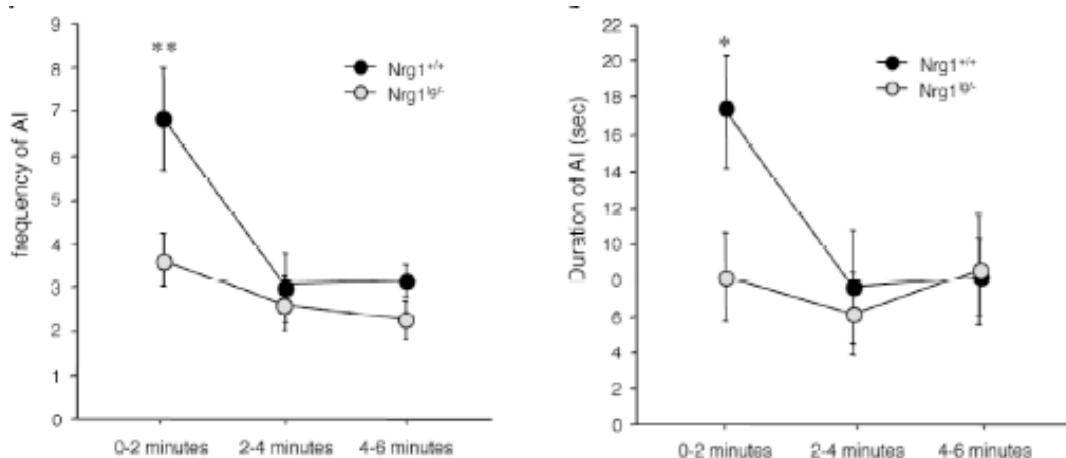
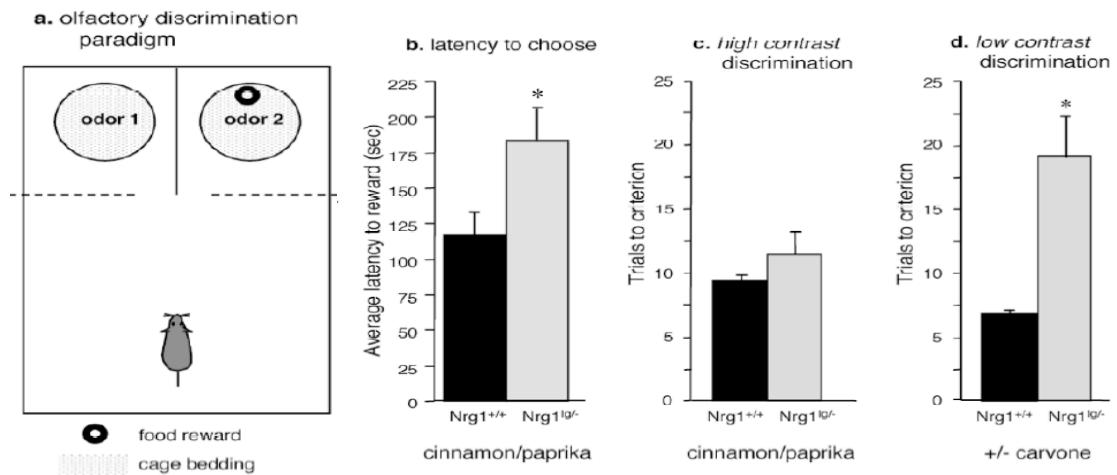


FIGURE 10: Nrg1Ig/- Behavioral Phenotype

(A) Locomotor Activity: Mice were run in a darkened novel open field for a period of 60 minutes. The graph shows mean distance traveled for each group, broken down into 5-minute intervals.

(B) Social Interaction: Mice were introduced to a novel conspecific and allowed to interact with the unfamiliar mouse for 6 minutes. The graphs show number and duration of anogenital investigations, broken down into 2-minute intervals.

FIGURE 11: Olfactory Discrimination



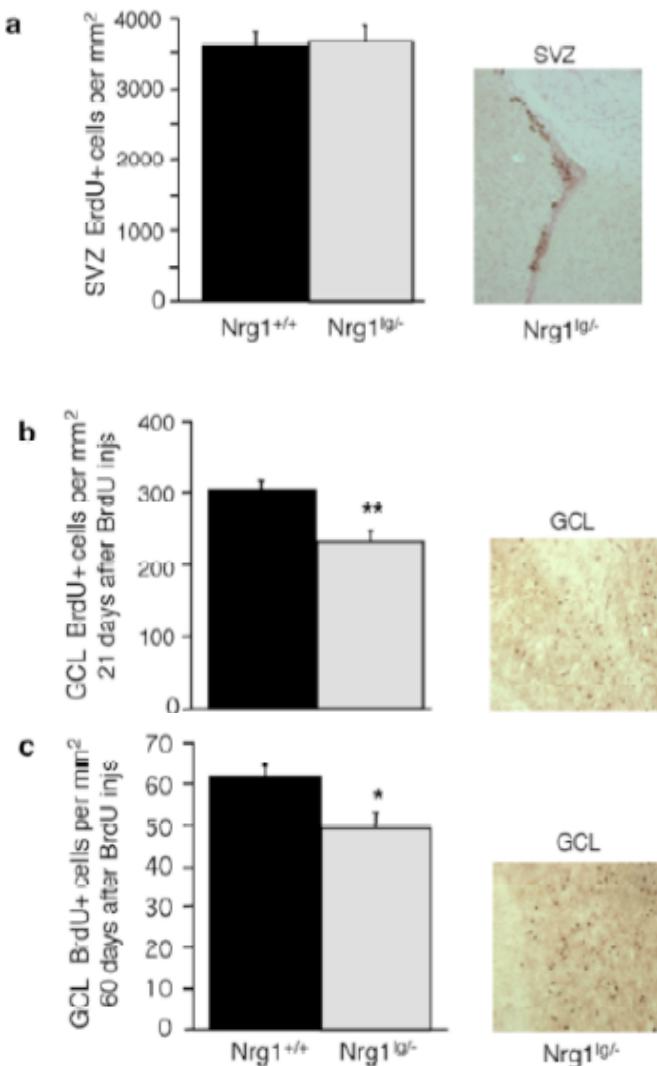
(A) Discrimination Paradigm: This is a schematic of the odor discrimination test. Mice were trained to distinguish between two odor-infused dishes of digging material in order to locate a food reward.

(B) Latency to Choose: Measure of the average time taken by mice in each group to make a choice in the odor discrimination task.

(C) High Contrast Discrimination: Number of trials required for the mice to be able to perform a correct discrimination between cinnamon and paprika six times in a row.

(D) Low Contrast Discrimination: Number of trials required for the mice to be able to perform a correct discrimination between the two enantiomers of carvone six times in a row.

FIGURE 12: SVZ and Olfactory Bulb BrdU Staining

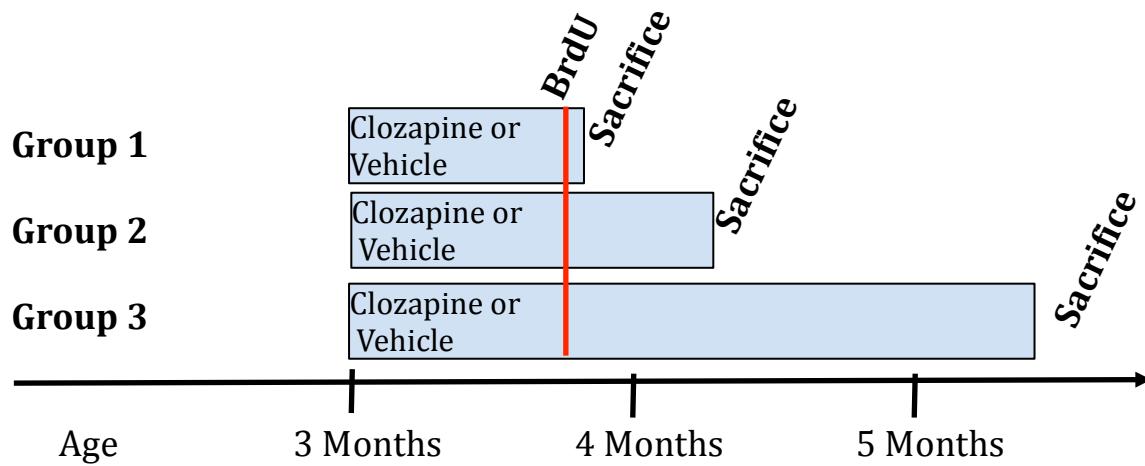


(A) SVZ BrdU Staining: Mice were sacrificed 24 hours after BrdU injection. BrdU+ cells were counted in the SVZ.

(B) GCL Olfactory Bulb BrdU Staining: Mice were sacrificed 21 days after BrdU injection. BrdU+ cells were counted in the GCL of the olfactory bulb.

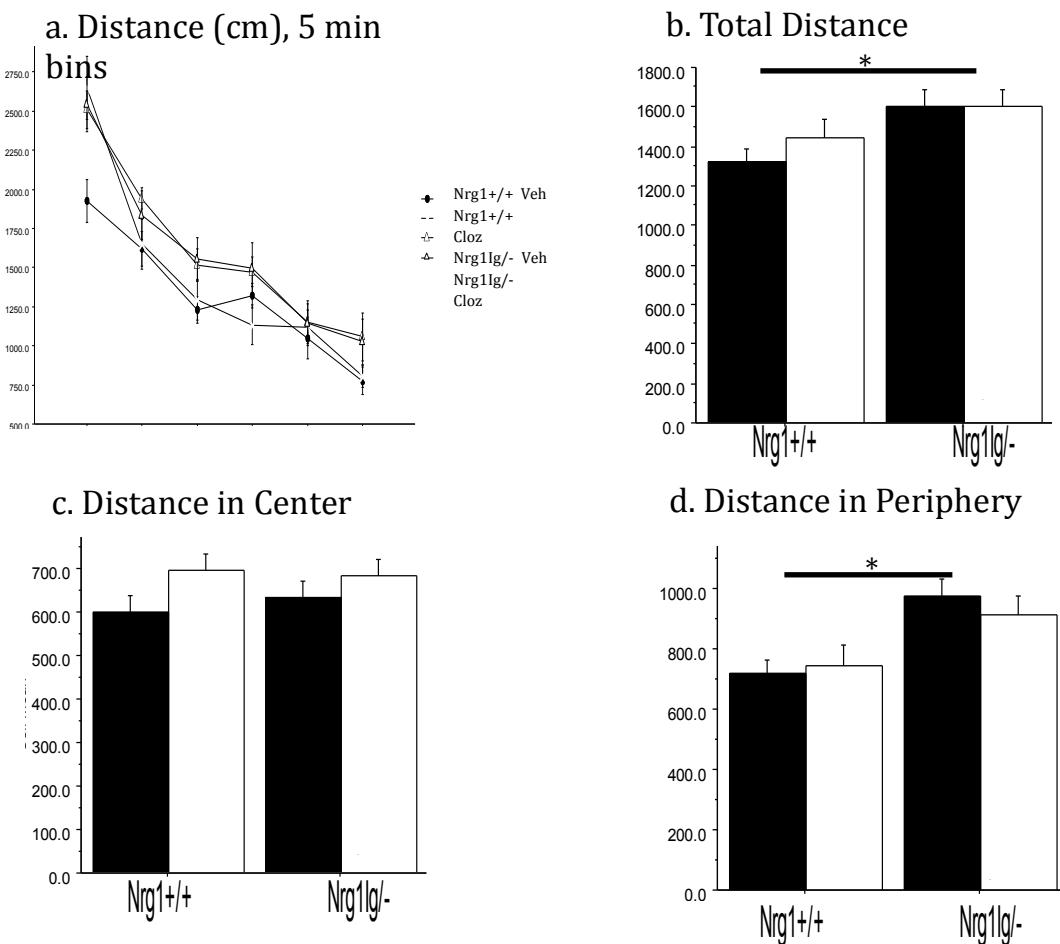
(C) GCL Olfactory Bulb BrdU Staining: Mice were sacrificed 60 days after BrdU injection. BrdU+ cells were counted in the GCL of the olfactory bulb.

FIGURE 13: Experimental Design



At age 3 months, mice were treated with either clozapine or vehicle in their drinking water. Those in the clozapine group received a dosage of roughly 10 mg/kg. After 21 days of treatment, mice were given an injection of BrdU every two hours for a total of four doses. Group 1 was sacrificed 24 hours after BrdU injections. Group 2 was sacrificed 21 days after BrdU injections. Group 3 was sacrificed 60 days after BrdU injections. Mice continued to receive clozapine treatment until they were sacrificed.

FIGURE 14: Open Field Locomotor Activity



Black bars indicate vehicle treatment, and white bars indicate clozapine treatment.

(A) Distance traveled in a novel darkened open field over 30 minutes, broken down into 5-minute intervals.

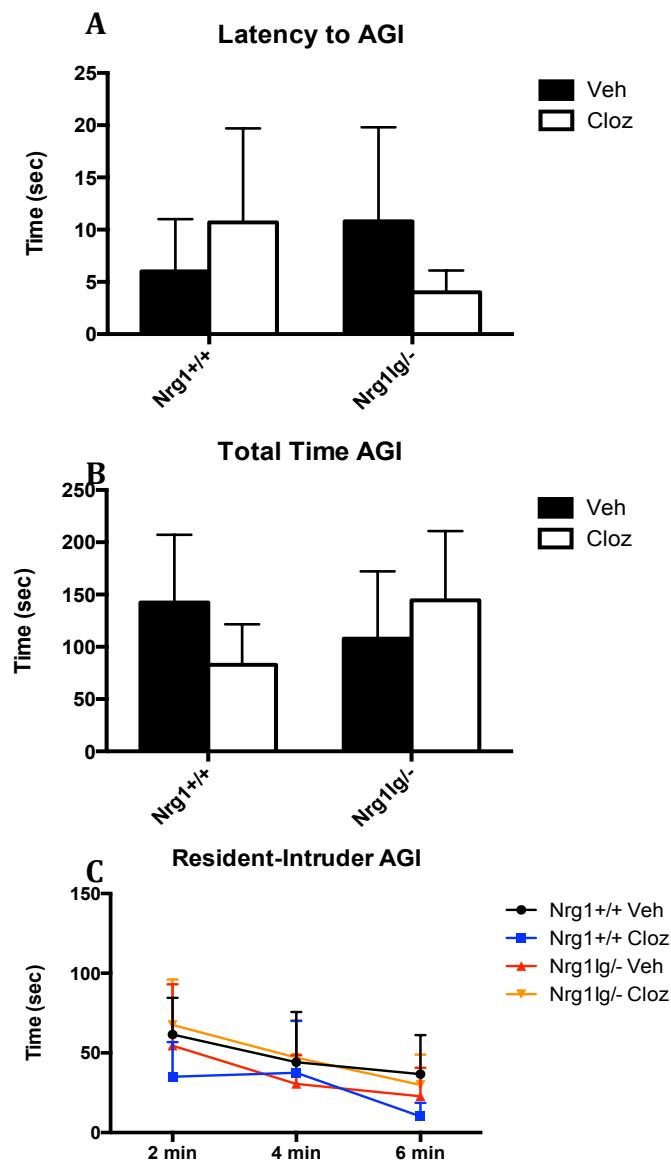
(B) Total distance traveled in novel open field over 30 minutes.

(C) Distance traveled in the center of the open field over 30 minutes.

(D) Distance traveled in the periphery of the open field over 30 minutes.

* indicates p<0.05.

FIGURE 15: Social Interaction

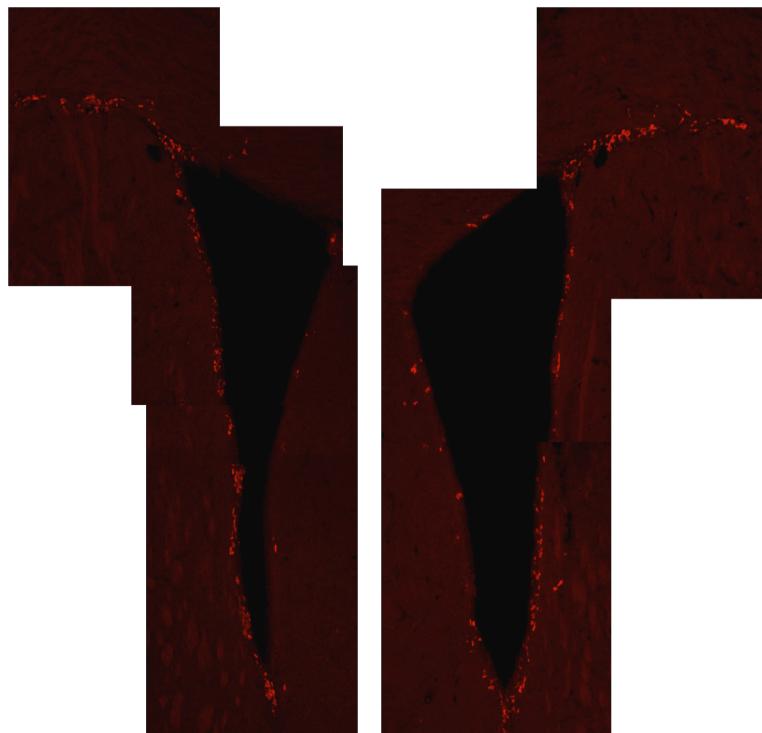


- (A) Mice were introduced to a novel conspecific for a total of 6 minutes. The latency to initiate anogenital investigation of the unfamiliar mouse was recorded.
- (B) Total time spent in anogenital investigations with an unfamiliar mouse was recorded over 6 minutes.
- (C) Time spent in anogenital investigations with an unfamiliar mouse was broken down

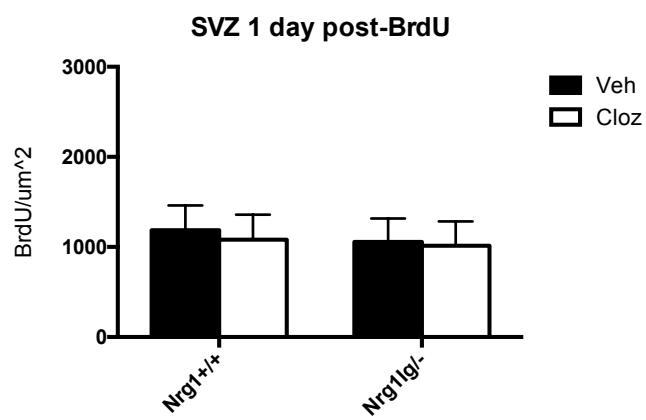
into 2-minute intervals.

FIGURE 16: SVZ BrdU Staining after 24 hours

A. Sample SVZ BrdU Staining



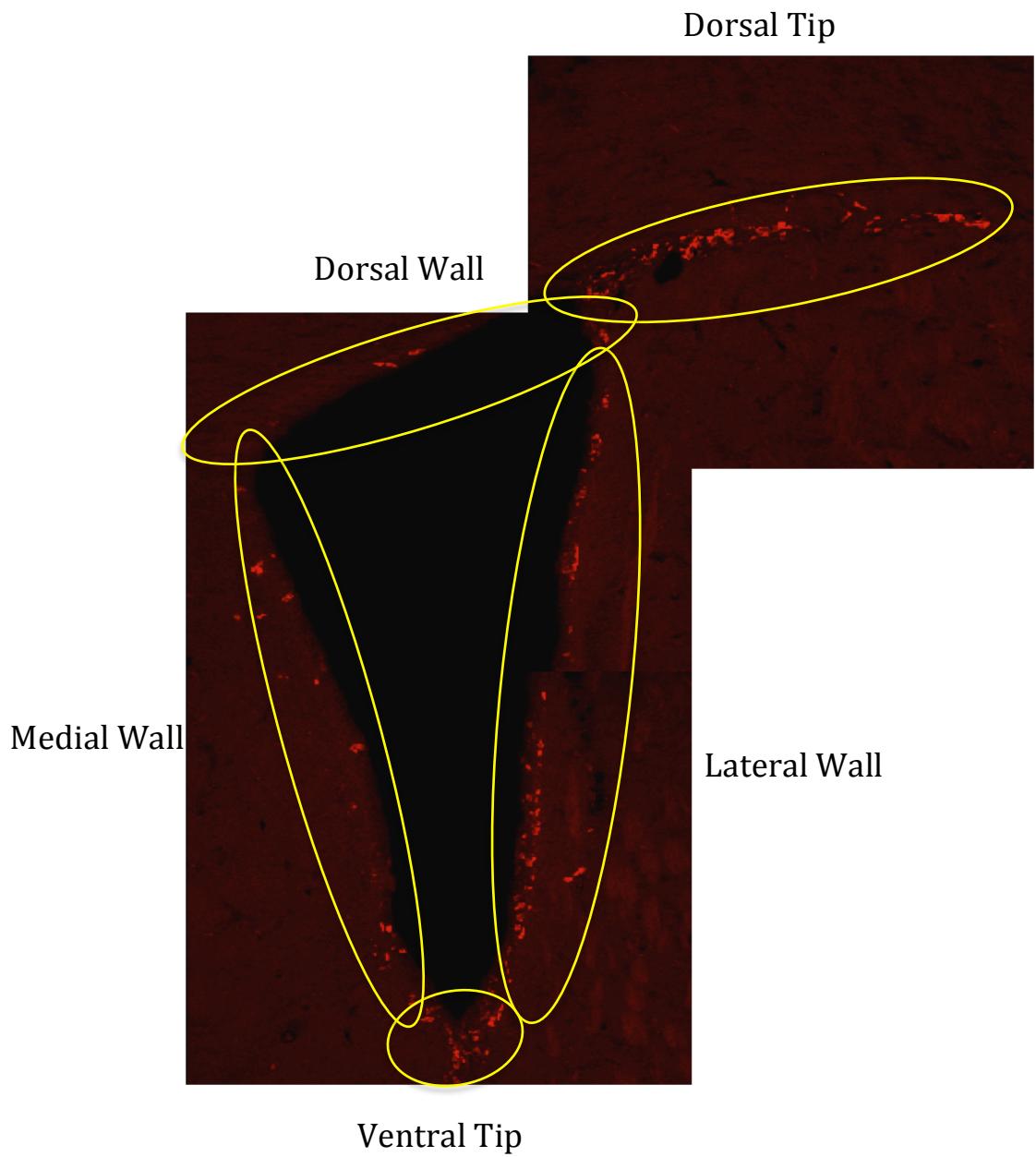
B. SVZ BrdU Counts



(A) Sample staining of the SVZ 24 hours after BrdU injection. Images were captured using a confocal microscope at 20x magnification and combined to show an entire coronal slice of the SVZ.

(B) Total BrdU counts per mm² from the entire SVZ, 24 hours after BrdU injection.

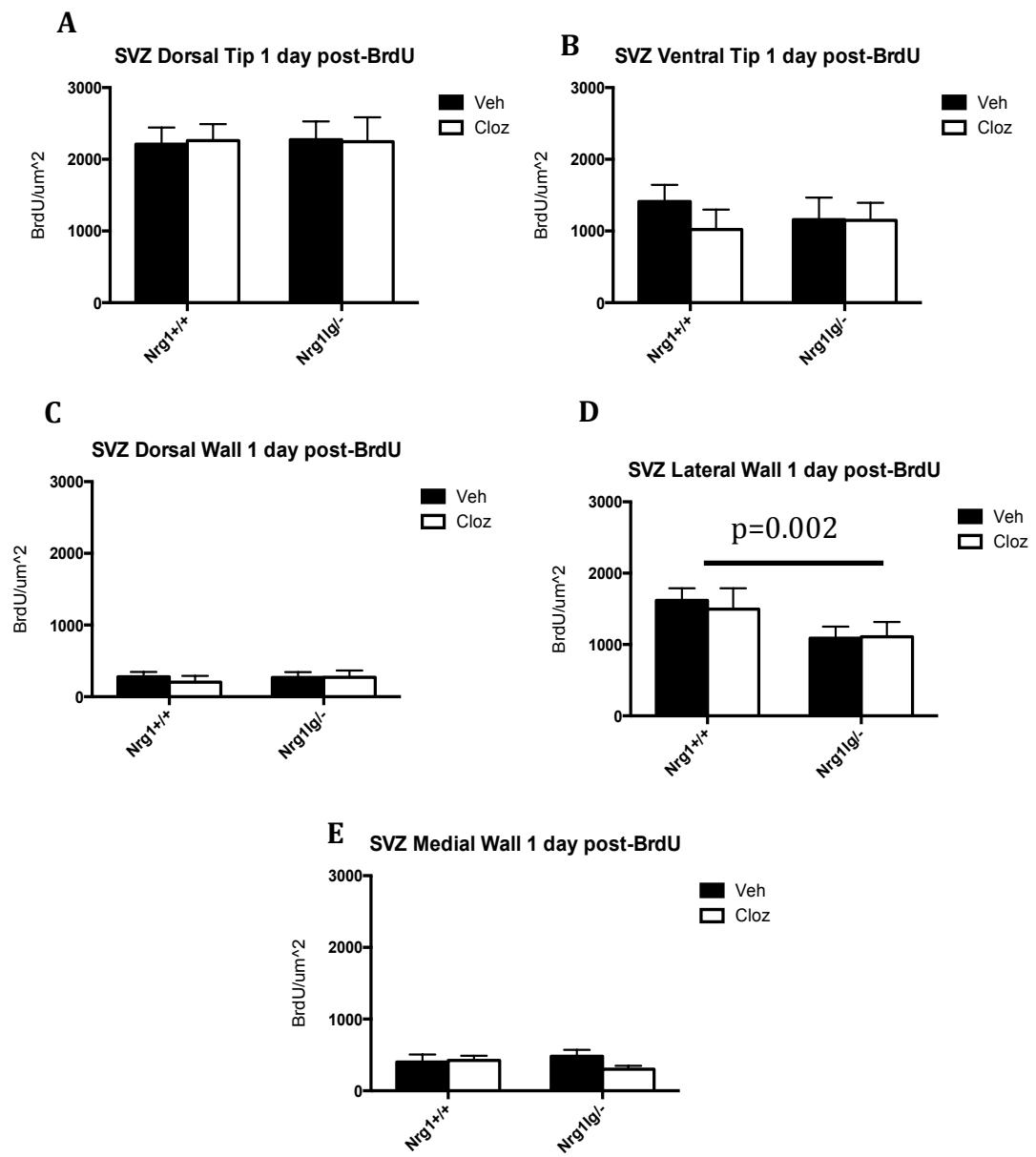
FIGURE 17: SVZ Subdivision



SVZ subdivisions include the dorsal and lateral tips, and the dorsal, medial, and lateral walls. These divisions were based on the embryonic origins and expressed transcription factors of different regions of the SVZ, as shown in the Lledo et al (2008) paper

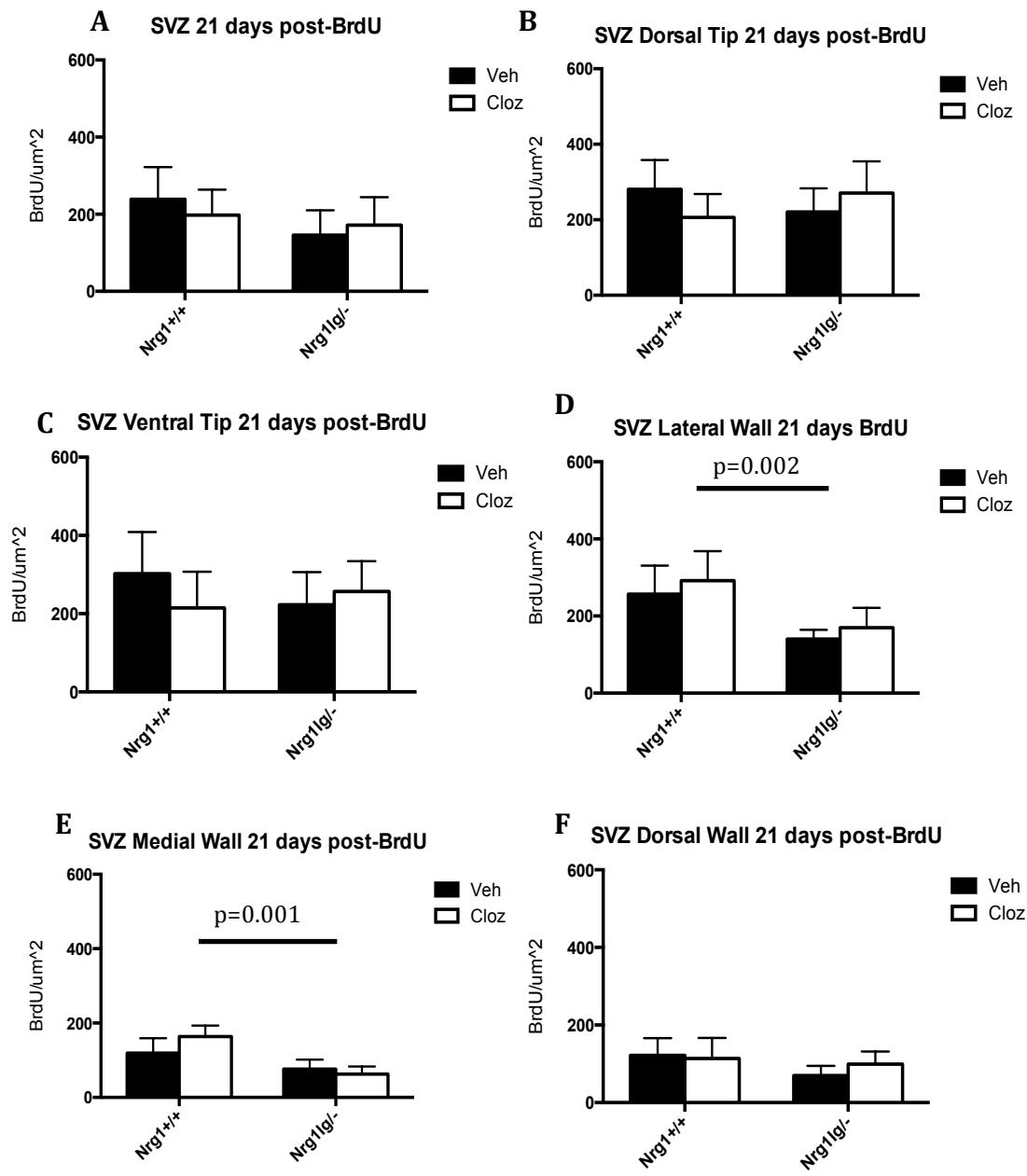
referenced in **Figure 2**.

FIGURE 18: SVZ Subdivision BrdU Staining after 24 hours



The SVZ was subdivided into five previously described regions. Total BrdU+ cells per mm^2 were counted in the dorsal tip of the SVZ (A), the ventral tip of the SVZ (B), the dorsal wall of the SVZ (C), the lateral wall of the SVZ (D), and the medial wall of the SVZ (E).

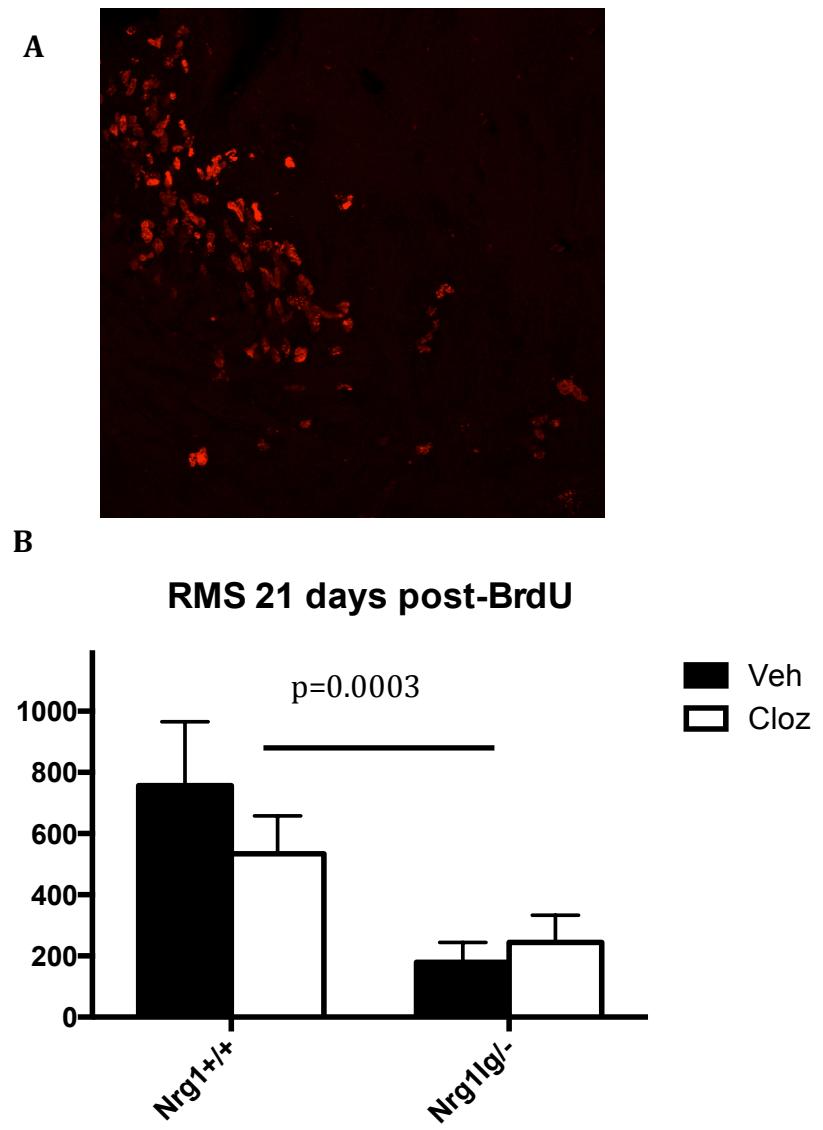
FIGURE 19: SVZ BrdU Staining after 21 days



(A) Total SVZ+ cells

per mm² were counted for the entire SVZ 21 days after BrdU injections. SVZ was then divided into previously described subregions to calculate BrdU+ cells per mm² for the dorsal tip (B), ventral tip (C), lateral wall (D), medial wall (E), and dorsal wall (F).

FIGURE 20: RMS BrdU Staining after 21 days

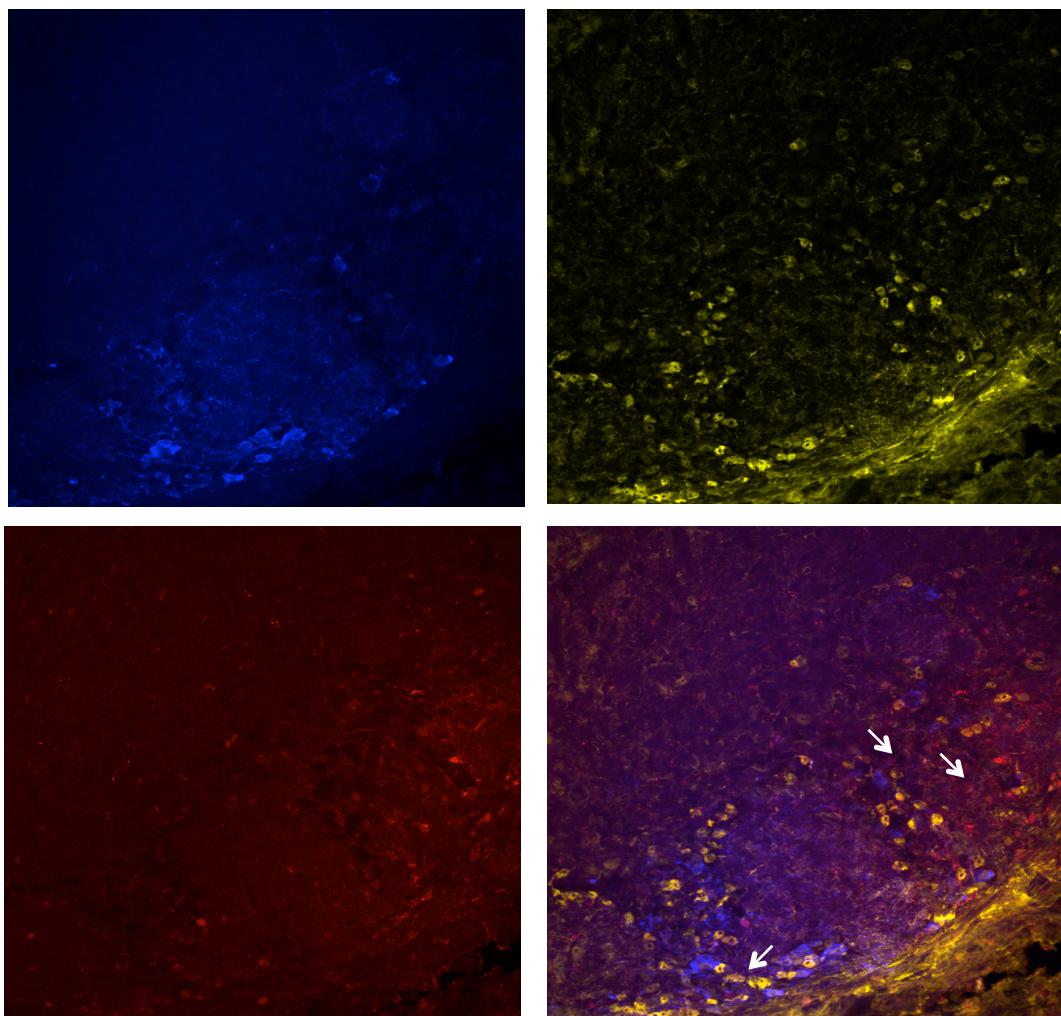


(A) Sample BrdU staining of the RMS at 40x magnification.

(B) Counts of BrdU per mm² in the RMS 21 days after BrdU injection.

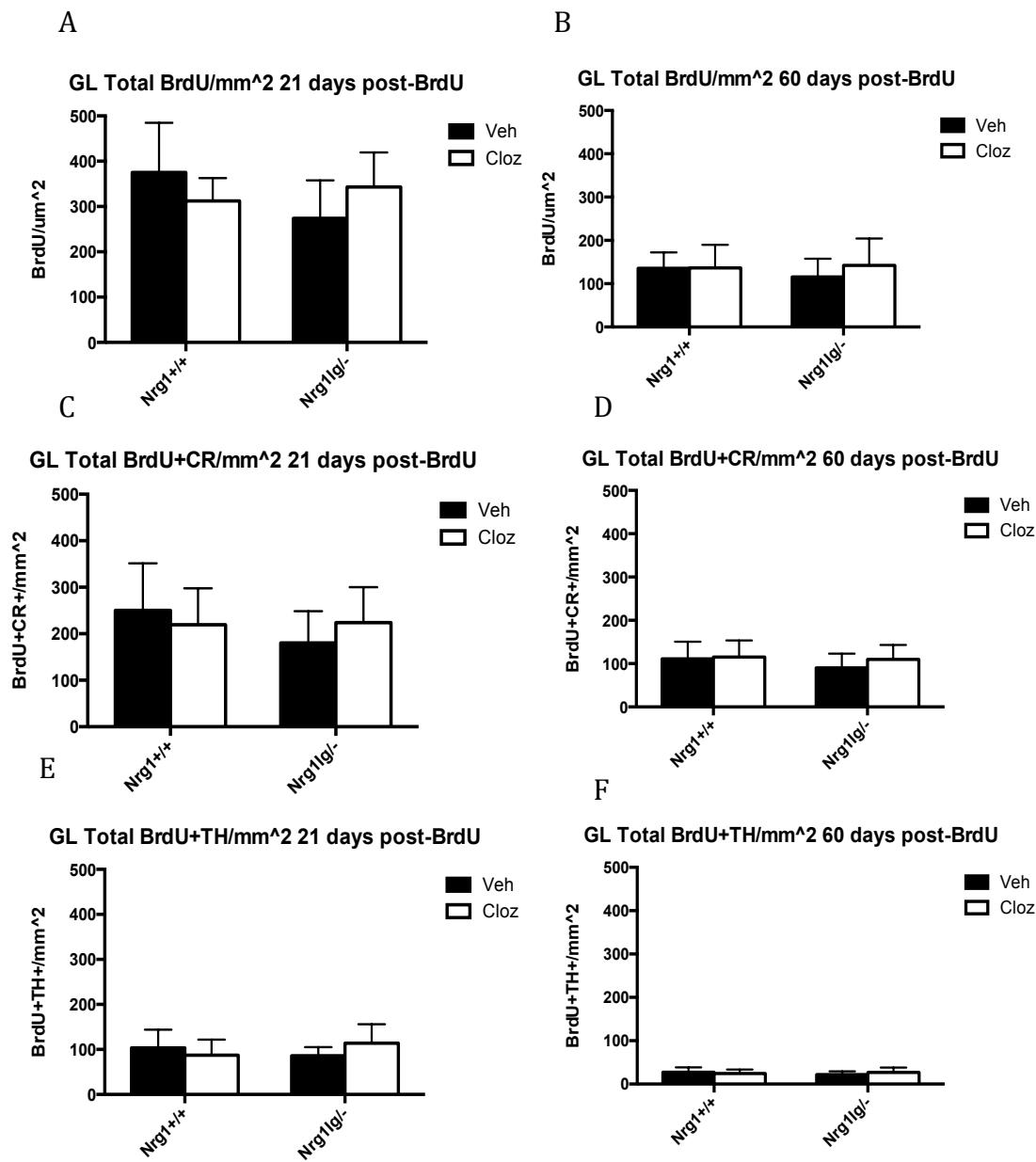
FIGURE 21: Olfactory Bulb Staining

TH/CR/BrdU



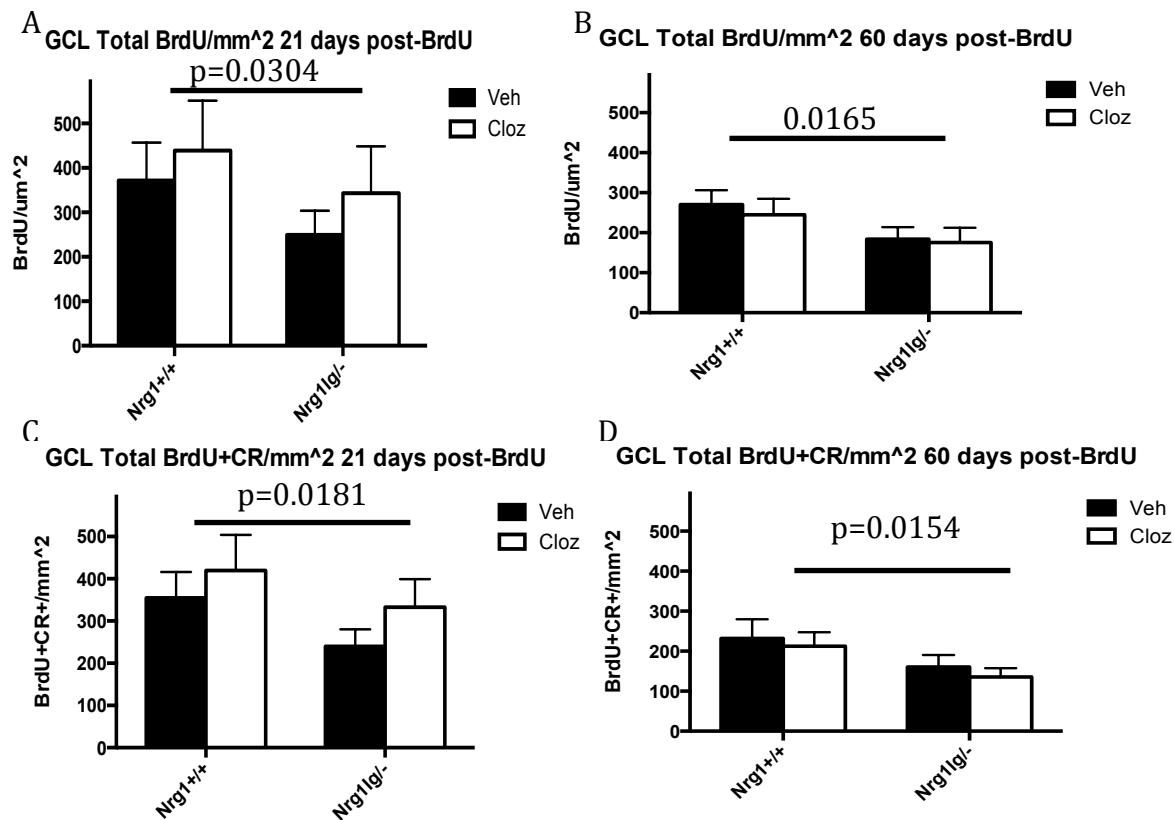
This is a sample immunostain from the GL of the olfactory bulb. TH+ cells are colored blue, CR+ cells are colored yellow, and BrdU+ cells are colored red. White arrows indicate examples of double-labeled cells.

FIGURE 22: Olfactory Bulb GL BrdU Staining at 21 days and 60 days after BrdU



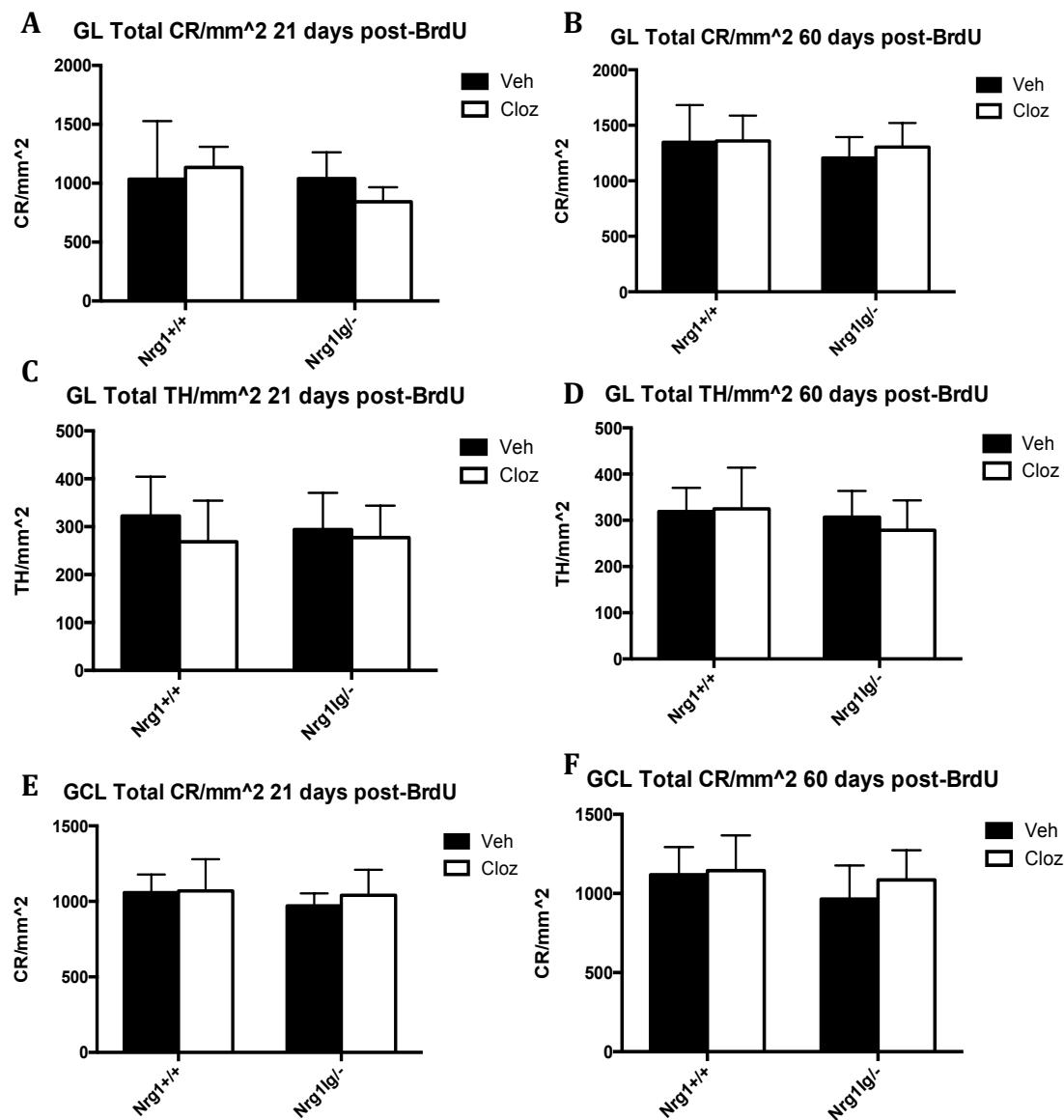
The olfactory bulb was immunostained with BrdU, calretinin (CR) and tyrosine hydroxylase (TH). BrdU+ cells per mm² were counted in the GL of the olfactory bulb at 21 days (**A**) and 60 days (**B**) after BrdU injection. Counts for cells double-labeled for BrdU and CR (**C, D**) or BrdU and TH (**E, F**) were also obtained.

FIGURE 23: Olfactory Bulb GCL BrdU Staining at 21 days and 60 days after BrdU



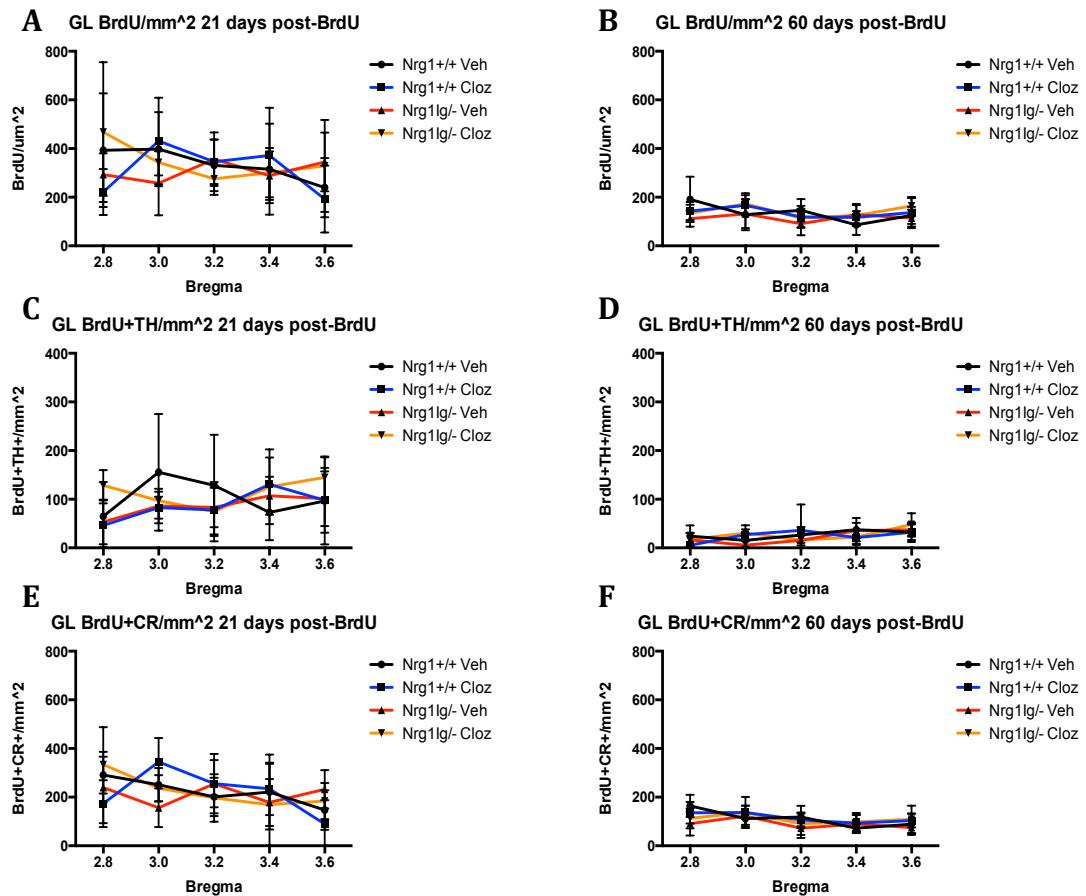
The olfactory bulb was immunostained with BrdU, calretinin (CR) and tyrosine hydroxylase (TH). BrdU+ cells per mm² were counted in the GCL of the olfactory bulb at 21 days (**A**) and 60 days (**B**) after BrdU injection. Counts for cells double-labeled for BrdU and CR (**C, D**) were also obtained.

FIGURE 24: Olfactory Bulb Staining at 21 days and 60 days after BrdU



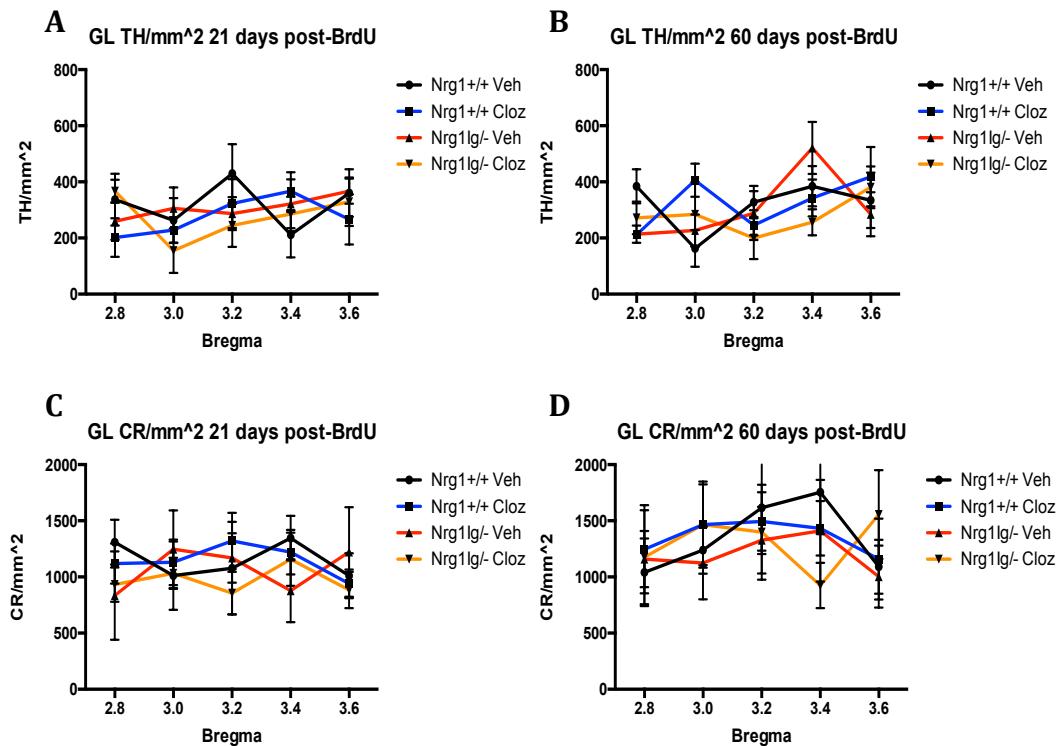
The olfactory bulb was immunostained with BrdU, calretinin (CR) and tyrosine hydroxylase (TH). In the GL of the olfactory bulb, counts per mm² of total interneurons expressing CR (**A, B**) or TH (**C, D**) were measured at 21 days (**A, C**) and 60 days (**B, D**) after BrdU injection. In the GCL of the olfactory bulb, counts per mm² of interneurons expressing CR at 21 days (**E**) and 60 days (**F**) were also measured.

FIGURE 25: Olfactory Bulb GL BrdU Staining by Bregma Level



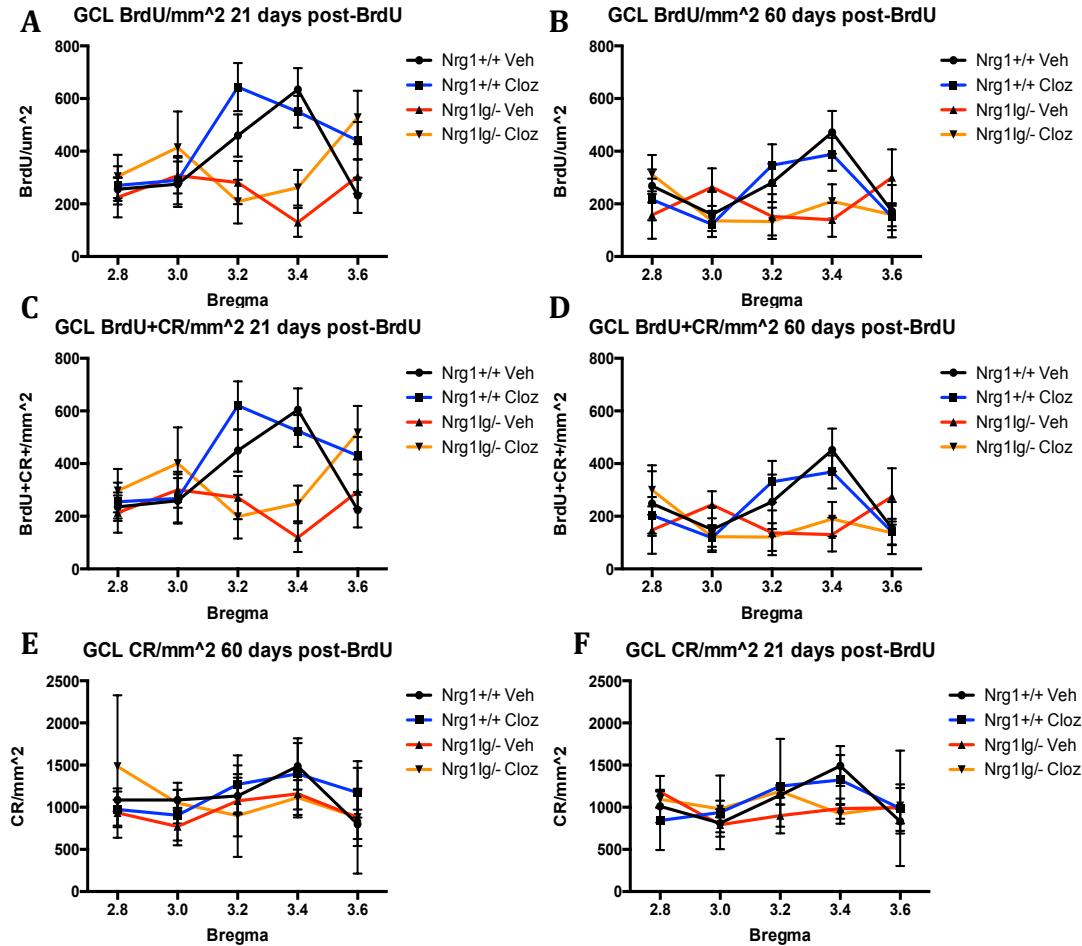
The olfactory bulb was immunostained with BrdU, calretinin (CR) and tyrosine hydroxylase (TH). BrdU+ cells per mm² were counted in the GL of the olfactory bulb at 21 days (**A**) and 60 days (**B**) after BrdU injection. Counts for cells double-labeled for BrdU and CR (**C, D**) or BrdU and TH (**E, F**) were also obtained. These measurements are broken down along the rostral-caudal axis from Bregma level 2.8 at the caudal end to Bregma 3.6 at the rostral end.

FIGURE 26: Olfactory Bulb GL Staining by Bregma Level



The olfactory bulb was immunostained with BrdU, calretinin (CR) and tyrosine hydroxylase (TH). BrdU+ cells per mm² were counted in the GCL of the olfactory bulb at 21 days (**A**) and 60 days (**B**) after BrdU injection. Counts for cells double-labeled for BrdU and CR (**C, D**) were also obtained. These measurements are broken down along the rostral-caudal axis from Bregma level 2.8 at the caudal end to Bregma 3.6 at the rostral end.

FIGURE 27: Olfactory Bulb GCL Staining Broken Down by Bregma Level



The olfactory bulb was immunostained with BrdU, calretinin (CR) and tyrosine hydroxylase (TH). In the GL of the olfactory bulb, counts per mm^2 of total interneurons expressing CR (**A, B**) or TH (**C, D**) were measured at 21 days (**A, C**) and 60 days (**B, D**) after BrdU injection. In the GCL of the olfactory bulb, counts per mm^2 of interneurons expressing CR at 21 days (**E**) and 60 days (**F**) were also measured. These measurements

are broken down along the rostral-caudal axis from Bregma level 2.8 at the caudal end to Bregma 3.6 at the rostral end.

CHAPTER 4: CONCLUSION

In this thesis, I have discussed two methods of adaptation that modulate the normal range of development and performance. Epigenetic factors regulate gene expression at the genetic level, while interneurons that modify neuronal activity at the neurocircuitry level. Both of these are influenced by environmental factors, allowing for a developmental response to external conditions. However, dysfunctions in either of these mechanisms can cause various vulnerabilities. While these effects may be subtle, they can also contribute to such devastating disorders as schizophrenia.

Interactions between genes and the environment can have wide-ranging effects throughout life, and epigenetic changes are thought to be a key mechanism through which the external influences achieve their effects. Early experiences during critical periods of development can have a lasting impact on an individual. The heritability of epigenetic effects may also be responsible for the transmission of traits across generations. One classic example involves the effect of maternal care on offspring methylation patterns. Rat dams can display high or low levels of licking and grooming (LG) behavior towards their offspring. Low LG leads to increased methylation of the estrogen receptor α promoter in the offspring hypothalamus, which results in female offspring displaying the same maternal care pattern as their mothers (Champagne, 2008). LG levels are also a

mechanism for the transmission of response to stress from mother to offspring in rats. High LG behavior causes a signaling cascade in the offspring that results in the hypomethylation of the glucocorticoid receptor promoter and this receptor's increased expression in the hippocampus. This produces a less fearful phenotype (Weaver et al., 2004; Weaver et al., 2007). Such changes may have adaptive value in the offspring. Dams living in a more threatening environment would have less time for LG behavior. The offspring born into such an environment might gain a survival advantage by being more fearful (Youngson & Whitelaw, 2008). Thus, the diversity and flexibility of a species may be maintained, transmitted, and expanded through the epigenome.

In addition to experience-dependent epigenetic inheritance, epigenetic states can also be transmitted to through the germ line. For example, imprinting occurs during gametogenesis in both the male and female germ line. Once the previous methylation patterns are, for the most part, erased, new methylation is added that is specific to the parent of origin. This allows either the maternal or paternal allele to be silenced, so that certain genes show only monoallelic expression (Verona, Mann, & Bartolomei, 2003).

While epigenetic regulation normally allows for adaptation, errors in this system can have disastrous consequences. Imprinting errors may be due to abnormal erasure, establishment, or maintenance of methylation. The epigenetic processes of spermatogenesis seem to break down with time, and epigenetic abnormalities have been observed. The spermatozoa of older rats show aberrations in chromatin packaging and integrity (Zubkova & Robaire, 2006), as well as ribosomal DNA hypermethylation (Oakes, Smiraglia, Plass, Trasler, & Robaire, 2003). Many imprinted genes are involved in brain development (Gregg et al., 2010), so abnormalities in methylation could result in

cognitive deficits. Malfunctions in the epigenetic regulation of the germ line in aging males may therefore contribute to the broad range of neurodevelopmental disorders that have been linked to advanced paternal age.

At the level of the brain, adaptations to the external environment are also occurring. This adaptation in response to experience can take several forms, including modulating synaptic strength, altering membrane excitability, or the formation of new synapses or dendritic branches. While these changes can occur quickly, the remodeling of circuitry by the integration of new neurons occurs over days or weeks and may indicate a more enduring type of adaptation (Sahay, Wilson, & Hen, 2011). Newborn granule cells seem to be selected for survival based on exposure to an activating odor. These adult-born interneurons improve olfactory acuity by using lateral inhibition to enhance pattern separation between glomeruli that respond to similar stimuli. Because of this adaptive capacity of the brain, exposure to new odors is associated with increased ability to discriminate that odor as compared to other similar odors (Moreno et al., 2009; Rochefort, Gheusi, Vincent, & Lledo, 2002; Rochefort & Lledo, 2005). Conversely, odor deprivation impairs discrimination and reduces survival of adult-born granule cells (Mandairon & Linster, 2009; Wilson & Sullivan, 1995; Yamaguchi & Mori, 2005). Thus, individual organisms can respond to variable environments by adapting to external stimuli in ways that are of maximum benefit.

As Graziella Di Cristo said of interneurons: “*We may compare GABAergic function of interneurons to that of the music director of a symphony orchestra, whose role is to structure and coordinate the overall musical performance and interpretation of the individual players. Without proper direction, the ensemble cannot produce the right*

melody. "(Di Cristo, 2007) GABAergic interneurons play an important and multifaceted role in modulating brain activity of brain circuitry. They act to modulate excitatory transmission, generate temporal synchronicity, increase brain plasticity, and allow the brain to respond to experience (Di Cristo, Pizzorusso, Cancedda, & Sernagor, 2011). We are only beginning to understand their diverse functions in brain activity and development, as the purpose of the impressive heterogeneity of interneuron subtypes is still unclear.

Interspecies differences in the production of new interneurons may even expose a form evolutionary adaptation. In rodents, the SVZ continues to produce interneurons throughout the adult life, which are supplied to the olfactory bulb and have been shown to improve olfactory acuity. However, proliferation in the SVZ of humans drops to a negligible level after 18 months of age (Sanai et al., 2011). On the other hand, the human SVZ shows high rates of proliferation during early postnatal life. In addition to supplying new neurons to the olfactory bulb, humans develop a medial migratory stream (MMS) that splits off from the RMS to supply the ventromedial prefrontal cortex (VMPFC). This appears to be specific to humans and has not been detected in other vertebrates (Sanai et al., 2011). These differences reflect the differences in specialization between rodents and humans. Olfactory cues remain a critical aspect of rodent life and play a large role in social interaction. The richness of their olfactory world is enhanced by their superior ability in this area. In humans, however, olfactory discrimination does not have the same meaning or significance in daily life. While the function of the MMS has not yet been fully characterized, the VMPFC of the adult is thought to have functions in visual memory and contextualization and the emotional processing of visual cues (Longe,

Senior, & Rippon, 2009; Szatkowska, Szymanska, & Grabowska, 2004). This is in line with our increased reliance on visual information over olfactory cues and the greater cognitive complexity of human life.

The roles of epigenetic modulation and brain plasticity and adaptation are also linked, as epigenetic changes cause altered gene expression that can have complex repercussions in an organism's neurobiology and behavior. In this thesis, we have explored the developmental implications of altered expression of a subset of isoforms of a single gene. While Nrg1 has several neurodevelopmental functions, including roles in neurotransmission and myelination, the scope of this study was to examine its effects on SVZ neurogenesis. We did this by tracking SVZ proliferation, the migration of immature neurons from this region, and their differentiation and integration into the olfactory bulb. Our findings revealed the Nrg1 has effects on proliferation in a subdivision of the SVZ as well as a possible impact on survival. This resulted in decreased turnover of interneurons in the GCL of the olfactory bulb, which had the functional consequence of impaired olfactory discrimination. This deficit in olfactory discrimination is similar to that seen in individuals with schizophrenia, a disorder that has also been linked to altered Nrg1 expression. This may have wider functional relevance as the ganglionic eminences produce cortical interneurons during development and also give rise to the SVZ. It is therefore possible that this change in gene expression is linked to dysfunction of the ganglionic eminences, yielding impaired interneuron development in both the cortex and olfactory bulb. However, this is an oversimplification as several genes have been linked to schizophrenia susceptibility and interneuron development is only one function of Nrg1. Schizophrenia is likely to involve an accumulation of vulnerabilities, which may show as

much heterogeneity among affected individuals as is seen in the clinical phenotype. This would also explain the appearance of subclinical symptoms during the prodromal phase and the presence of schizophrenia-related endophenotypes in healthy individuals who have some genetic risk. Yet this study gives us a glimpse of the ways altered gene expression may have broad developmental impacts.

METHODS

Open Field: Mice were placed in the center of a MedAssociates locomotor arena (17 x 17 x 12 inches) for 60 minutes and activity was tracked photocell beam measurements and calculated with MedAssociates software. The testing room was brightly lit for the duration.

Prepulse Inhibition: Mice were placed in sound-dampening chambers and allowed to acclimate for 10 minutes. Background noise was at 70db during the acclimation phase and the trials. A 120db startle stimulus lasting for 40ms was presented either by itself or preceded by a 15msec prepulse 100msec before the trial. The prepulse could be 2, 6, 8, 12, or 16 db above background. The startle was measured by changes in the force on the floor and occurred between 30msec and 70msec after the startle stimulus.

Social Interaction: Mice were placed in a MedAssociates arena for 60 minutes. This arena contained two novel boxes with mesh screens. An unfamiliar mouse of the same gender was placed in one of the boxes, while the other was left empty. Activity and time spent in each quadrant was measured with MedAssociates software.

Fear Conditioning: The fear conditioning protocol took place over 3 days. During the first day, mice were trained to associate a tone with the delivery of an aversive, mild foot shock. The second day tests the conditioning of mice to the tone. The walls and floors of the fear conditioning boxes were covered with an unfamiliar material and a different odor, so the mice would not associate this environment with the shock delivery. Freezing

behavior was measured before the first tone, to provide a background value. Freezing after the delivery of the first tone was used to assess conditioning to the tone. On day 3, mice were placed back in the environment used on day 1. Freezing behavior was used as a measure of conditioning to the shock context.

Light-Dark Test: In this task, MedAssociates arenas were divided into two compartments. One of these was dark and enclosed while the other side was open and lit. Mice were placed in the dark compartment at the start of the session. The latency to enter the light, and time and activity in each compartment was measured with MedAssociates software.

Food Neophobia: Mice were food-deprived for 24 hours before the test, with free access to water. Mice were then individually placed in their home cages and allowed six minutes of simultaneous access to a familiar food pellet and a piece of Kellogg's blueberry Nutri-Grain bar. Both food options were weighed before and after the test to determine grams consumed. The latency to taste each food was also recorded.

Social Investigation Paradigm. Male mice were housed individually in standard laboratory cages for one week prior to testing. A single group-housed male intruder was introduced in the home cage of the individually housed test subject and their behavior was recorded for 6 min. The test mouse was scored for behaviours related to AGI of the intruder (number of AGI events; total time spent in AGI). An AGI event was defined as any sniffing and grooming of the intruder near the tail, rump, or general anogenital area.

A trained observer (blind to genotype) scored the test mice for investigatory behaviors.

Olfactory discrimination paradigm. Olfactory discrimination was measured using a three-chambered box. In one chamber, a food reward was buried in a dish of “digging media” infused with a distinct spice while another dish containing digging media with a different odor (without a reward) was placed in the other arm. Mice were placed in the starting chamber and allowed to find the food reward through exploratory digging. A correct choice was scored if the mouse began digging in the chamber where the food reward was buried. Trials were continued until the test subject recorded 6 correct choices in a row. *NrgI*^{+/+} and *NrgI*^{lg/-} mice were tested in this paradigm using the following odor pairs: cinnamon/paprika (“high-contrast”) and (+)/(-) carvone (“low contrast”). The “correct” odor was randomized between mice and between trials the reward was randomly assorted between each chamber. Each odor was tested at a 1:100 (w/v) dilution into digging material.

Drug treatment was provided orally by dilution in drinking water. Clozapine (Sigma) was prepared as follows: 200 mg of clozapine was dissolved in 6.5 ml of 1N HCl and subsequently diluted to a stock concentration of 5 mg/ml in .033 N HCl. The pH of this solution was 5.9-6.6. A vehicle control HCl stock solution was prepared and pH adjusted to 6.0 with NaOH. Stock and vehicle were diluted to equivalent of .07 mg clozapine/ml in tap water and this was given to animals as sole source of water in darkened bottles. After confirmation of minimal degradation of clozapine in this aqueous solution solutions were changed weekly (all assays performed by Thomas Cooper, Analytical

Psychopharmacology Laboratory, Nathan Kline Institute). The amount of water consumed each week was measured and compared with the average weights of animals in each cage with an estimated dosage of 10 mg/kg per animal per day. Two animals were sacrificed to determine whole blood clozapine levels (samples processed as above by APL at NKI). After 3 weeks, a c57Bl/6 animal showed 59 ng/ml of norclozapine and after 2 weeks, a 129 strain animal showed a blood level of 237 ng/ml of norclozapine (therapeutic human levels are approximately 300 ng/ml).

BrdU treatment: Mice were injected intraperitoneally with the thymidine analog 5-bromo-2'-deoxyuridine (BrdU) (75 mg/kg, Sigma) once every two hours for a total of four doses each, and then sacrificed at either 24 hours or 21 days after the injections. Mice were anesthetized with xylazine/ketamine and intracardially perfused with ice-cold saline followed by 4% paraformaldehyde in phosphate buffer (PB). Brains were post fixed overnight at 4°C, and cut serially in 40um coronal sections cryostatically.

Fluorescent Staining: Day 1: Wash 3X in PBS. Block 1hr in 10% Normal Donkey Serum (NDS). Free-float sections overnight at 4°C with all primary antibodies except BrdU (Rabbit Anti-Caltretinin Millipore 1:200, Chicken GFAP Abcam 1:1000, Mouse Anti-NeuN Millipore 1:100, Chicken Anti-TH Aves 1:1000). Day 2: Wash slices 3x in PBS-T. Mount slices on slides and dry in hood for 1hr. Treat with secondary antibodies (405 Donkey anti-Chicken, 647 Donkey anti-Rabbit, 488 Donkey anti-Mouse, Jackson Immuno 1:200). Fix in 4% PFA 15 min at room temperature. Wash 3x in PBS-T. Treat with 4N HCl for 30min. Wash 3x in PBS-T. Fix in 4% PFA 5 min. Block in 10% NDS

for 30 min. Stain with anti-BrdU overnight at 4°C (Rat anti-BrdU AbD Serotec 1:100). Day 3: Wash 3x in PBS-T. Stain with secondary antibody (Cy3 Donkey anti-Rat, Jackson Immuno 1:200). Wash 3x in PBS-T. Mount with ProLong Gold (Invitrogen) and store slides at -20°C.

Image Collection: Scan on Olympus confocal microscope using FluoView 1000 software. Every sixth SVZ section was scanned and matched by Bregma level. ImageJ (NIH) was used for data collection. The area around the SVZ was selected and measured, and all BrdU+ cells were counted.

Statistics: Data was analyzed using 2-way ANOVAs and t-tests, and graphs were produced with Statview and Prism.

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