Published in final edited form as:

J Autism Dev Disord. 2009 March ; 39(3): 511–520. doi:10.1007/s10803-008-0653-8.

Regulation of Cerebral Cortical Size And Neuron Number by Fibroblast Growth Factors: Implications For Autism

Flora M. Vaccarino^{*,¶}, Elena L. Grigorenko^{*,#}, Karen M. Smith^{*}, and Hanna Stevens^{*}

^{*} Child Study Center, Yale University School of Medicine

[¶] Department of Neurobiology, Yale University School of Medicine

[#] Department of Psychology, Yale University School of Medicine

Abstract

Increased brain size is common in children with autism spectrum disorders. Here we propose that an increased number of cortical excitatory neurons may underlie the increased brain volume, minicolumn pathology and excessive network excitability, leading to sensory hyper-reactivity and seizures, which are often found in autism. We suggest that Fibroblast Growth Factors (FGF), a family of genes that regulate cortical size and connectivity, may be responsible for these developmental alterations. Studies in animal models suggest that mutations in FGF genes lead to altered cortical volume, excitatory cortical neuron number, minicolumn pathology, hyperactivity and social deficits. Thus, many risk factors may converge upon FGF-regulated pathogenetic pathways, which alter excitatory/inhibitory balance and cortical modular architecture, and predispose to autism spectrum disorders.

Keywords

Fibroblast Growth Factors; excitatory pyramidal neurons; cerebral cortex; autism spectrum disorders; progenitor cells

Increased rate of brain growth in autism

Autism spectrum disorders (ASD) including autism, Asperger's Disorder, Pervasive Developmental Disorder (PDD), and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), encompass a spectrum of debilitating symptoms beginning early in childhood that can be classified into three broad categories: impairments in social communication and reciprocity; speech and language delay; stereotypic movements and circumscribed interests (American Psychiatric Association, 1994; Volkmar et al., 2004). It is often felt that social disability is at the core of the pathophysiology of these disorders. Despite this, individuals with autism spectrum disorders can vary greatly in the extent of their symptoms.

Although facial dysmorphology or other somatic features are present in rare forms of ASD, the more common non-syndromic form of these disorders does not appear to have grossly

Correspondence concerning this article should be addressed to: Flora M. Vaccarino Child Study Center, Yale University School of Medicine; 230 South Frontage Rd, New Haven, CT 0520; Telephone: 203-737-4147; flora.vaccarino@yale.edu.
 Flora M. Vaccarino: Yale University School of Medicine, New Haven, CT 0620, USA
 Elena Grigorenko: Yale University School of Medicine, New Haven, CT 0620, USA
 Karen M. Smith: Yale University School of Medicine, New Haven, CT 0620, USA
 Hanna Stevens: Yale University School of Medicine, New Haven, CT 0620, USA

altered phenotypic traits. However, in his seminal description of autism in 1943, Kanner noted that a large head circumference was a common finding in children with autism (Kanner, 1943). Subsequent studies have identified macrocephaly, which is a head circumference greater than 2 standard deviations above the population mean, to be present in approximately 20% of individuals with ASD (Davidovitch, Patterson & Gartside, 1996; Woodhouse et al., 1996; Fombonne et al., 1999; Miles, Hadden, Takahashi & Hillman, 2000). More recently, systematic studies have found that an abnormally elevated increase in head growth (assessed by cranial circumference) is present in a majority of children with ASD. Intriguingly, the larger head circumference is not present at birth, but develops within the first two years of life (Lainhart et al., 1997; Courchesne, Carper & Akshoomoff, 2003; Dementieva et al., 2005; Redcay & Courchesne, 2005), more specifically, at around the age of 4 months (Courchesne & Pierce, 2005; Redcay & Courchesne, 2005; Gillberg, 2002 #234}). In a meta-analytic study, Redcay and Courchesne (2005) have established a nonlinear dynamic of brain size fluctuation, with its relative proportion in individuals with autism changing from 13% smaller at birth, to 10% larger at 1 year of age, to 2% larger in adolescence when compared to control individuals. When the rates of change in head circumferences were compared among children with ASD and children from a normative sample, it was found that the rates were accelerated in the autism sample from birth to 12 months, but were no different from the normative sample from 12 to 36 months (Dawson et al., 2007). Similarly, a study carried out on a large sample of high-risk infants for the manifestation of ASD (the Baby Sibs Research Consortium), revealed increased growth velocity and decreased acceleration of head circumferences associated with ASD (Hodapp & Urbano, 2007). Specifically, though having started at approximately the same head circumferences, growth curves for children with ASD and for non-diagnosed children diverged early in the first year of life and remained divergent until about 28 months. Also, of note is the observation that children with autism have been reported to have increased body length and body weight as well. However, several studies, both retrospective and prospective, comparing individual growth curves from birth to 2–3 years, concluded that head circumference increases in autism were greater than expected for corresponding body height (Lainhart et al., 2006; Szatmari et al., 2007; Fukumoto et al., 2008). Hence, macrocephaly in autism cannot be attributed exclusively to an increase in body growth.

Macrocephaly in typically-developing children is most often attributable to an increased volume of cerebral spinal fluid with no associated brain volume increase. In contrast, macrocephaly in children with autism is due to an accelerated brain growth in the first months of life. Postmortem studies have found a larger total brain weight in individuals with autism (Palmen, van Engeland, Hof & Schmitz, 2004). Structural magnetic resonance imaging (MRI) studies have compared a large number of individuals with autism, of many different ages, to both typically-developing controls or non-autistic individuals with mental retardation (Piven et al., 1995; Piven, Arndt, Bailey & Andreasen, 1996; Courchesne et al., 2001; Aylward et al., 2002; Carper, Moses, Tigue & Courchesne, 2002; Boddaert et al., 2004; Courchesne, 2004; Herbert et al., 2004; Palmen & van Engeland, 2004; Carper & Courchesne, 2005; Hazlett et al., 2005; Palmen et al., 2005; Schultz et al., 2005; Hazlett et al., 2006); brain volume was found to be consistently enlarged. Furthermore, when the cerebrum was segmented into gray and white matter compartments, both were found to be enlarged, and the white matter compartment somewhat more enlarged (Courchesne et al., 2001; Herbert et al., 2003).

Significantly, at younger ages (2–3 years), the differences between individuals with ASD and controls seem most dramatic (Hazlett et al., 2005). After age 5, the volume differences between individuals with ASD and the comparison groups decline, concurrent with a deceleration of head growth in individuals with autism (Courchesne et al., 2001; Carper et al., 2002; Courchesne et al., 2003; Carper & Courchesne, 2005; Hazlett et al., 2005; Schultz et al., 2005; Hazlett et al., 2006). These findings suggest a substantially altered developmental trajectory of the cerebrum of individuals with autism, and therefore warrant further

investigation toward its causes and potential clinical significance. For example, could this increased rate of brain growth reflect an underlying altered neural structure responsible for altered information processing, a compensatory process, or rather an irrelevant epiphenomenon?

Developmental regulation of cortical growth and organization

Increases in cortical gray matter could be due to increases in neurogenesis resulting in larger numbers of neurons, or to increased gliogenesis, resulting in larger numbers of glia (McCaffery & Deutsch, 2005). The cerebral cortex is assembled through the contribution of two germinal layers, the neuroepithelium abutting the ventricular lumen, the ventricular zone (VZ), and the neuroepithelium just superficial to this, the subventricular zone (SVZ) (Noctor, Martinez-Cerdeno & Kriegstein, 2007). During embryogenesis, radial glial cells divide in the VZ, generating either neurons that directly migrate to the cortex, or intermediate progenitors that migrate to the SVZ (Figure 1a). The progenitors in the SVZ undergo a limited number of divisions producing cortical neurons. This number is likely to be genetically encoded and species-specific, as the larger the number of these neurogenic divisions, the greater the number of neurons generated and the greater the volume expansion of developing cortex (Noctor, Martinez-Cerdeno, Ivic & Kriegstein, 2004; Kriegstein, Noctor & Martinez-Cerdeno, 2006) (Figure 1b). Radial glia transform into astrocytes at the end of neurogenesis, by retracting their apical process and translocating to the cortex, and disappear shortly after birth (Levitt, Cooper & Rakic, 1981; Rakic, 2003). The processes responsible for the involution of radial glia and therefore the ending of neurogenesis are not precisely known, although a combination of increased differentiation into SVZ progenitors, increased transformation into astrocytes, and possibly cell death, are all likely to be contributing factors (Cameron & Rakic, 1991). In contrast, the SVZ persists postnatally, producing astrocytes and oligodendrocytes (Marshall & Goldman, 2002; Marshall, Suzuki & Goldman, 2003). This region remains a prominent source of neurons for the olfactory bulb throughout life, whereas its ability to generate cortical neurons becomes progressively limited, such as few cortical neurons are generated in the postnatal period (Ganat et al., 2006) and none in the adult mammalian cortex (Kornack & Rakic, 2001). The genetic and molecular events drive a neuron-to-glia switch in fate in the SVZ have been the source of recent studies (Vaccarino et al., 2007).

To better understand the cellular and molecular mechanisms underlying increased brain size in ASD, we must consider that the cerebral cortex is by far the largest structure in the primate brain, and that two types of neurons populate the cerebral cortex, the excitatory pyramidal cells, which secrete glutamate and send myelinated axons outside the cortical mantle, and the inhibitory interneurons, which secrete GABA and are intrinsic to the cortex (Jones & Peters, 1984). These neurons are organized into columns each comprising a core of excitatory neurons and a surrounding area of inhibition (Mountcastle, 1997). Neurons within each column are functionally related, that is they have similar response properties and represent a feature of sensory representation or analysis (i.e., left or right eye; orientation; color; position in space). An anatomical minicolumn has been defined as a core of pyramidal neurons ascending vertically through layers VI and II, surrounded by a peripheral neural space rich in dendrite arborizations and synapses and lined by GABAergic interneurons, thought to prevent the inappropriate spread of excitation (Peters, Cifuentes & Sethares, 1997).

The anatomically identifiable minicolumns may represent a mechanism to integrate or segregate inputs and outputs of a group of cells. These pyramidal cell modules are conserved in the mammalian kingdom and likely correspond to the functional minicolumns, identified by Mountcastle as the smallest units of cortical information processing (Mountcastle, 1997). Intriguingly, post mortem analyses of the brains of autistic individuals revealed an increased number of anatomically identified cortical minicolumns with a higher packing density and no

alteration in intra-column cell density (Casanova, Buxhoeveden, Switala & Roy, 2002; Buxhoeveden et al., 2006; Casanova et al., 2006). This increase in column number and density suggests that the number of excitatory neurons forming minicolumns may be increased, the inhibitory neurons that surround the minicolumns may be decreased, or both processes may be occurring at the same time.

Putative developmental mechanisms leading to altered cortical growth in ASD

Both VZ and SVZ produce the excitatory pyramidal neurons that form the basic minicolumn scaffolding of the cortex. An increase in the pool of progenitors in the VZ or SVZ could result in larger numbers of excitatory neurons, and, arising from these, minicolumns. In lower mammals, the inhibitory neurons surrounding the minicolumns arise almost exclusively from basal regions of the embryonic telencephalon, the medial and lateral ganglionic eminences. These neurons reach the cerebral cortex by a separate process of tangential migration (de Carlos, Lopez-Mascaraque & Valverde, 1996; Lavdas, Grigoriou, Pachnis & Parnavelas, 1999). In primates, however, these inhibitory neurons arise both from the ganglionic eminences and from the dorsal SVZ, from which they reach the cortex by radial migration (Letinic, Zoncu & Rakic, 2002). An absolute or relative decrease in inhibitory neuron production, migration, or survival may also be involved in the pathogenesis of autism, as it would produce a decreased distance between minicolumns and also explain the increased incidence of seizures in these children.

Although it is tempting to speculate that the increase in gray matter volume observed in neuroimaging studies in ASD may reflect an underlying increase in excitatory (pyramidal) neuron number, implicating the prenatal developmental mechanisms described above, it is important to note that we cannot exclude a postnatal trajectory in ASD pathogenesis. In particular, reduced pruning of connections between neurons, or decreased programmed cell death (McCaffery & Deutsch, 2005) may also lead to increased gray matter volume, although these mechanisms would be unlikely to generate an altered columnar structure.

Increases in white matter such as those detected by MRI in the subcortical regions of the neocortex and cerebellum of adolescent patients with ASD (Courchesne et al., 2001) could reflect increases in oligodendrocytes, cells that ensheath axonal projections with myelin. However, MRI studies examining T2 relaxation have not detected increases in myelin density that would accompany such an excess of oligodendrocytes (Hendry et al., 2006). Alternatively, increases in white matter could reflect an increased neuron pyramidal neuron number, since these neurons are those that send myelinated axons outside the cortex. Thus, an increased number of cortical pyramidal neurons could explain both the increased gray and white matter volumes detected in neuroimaging studies in ASD, as well as the increased density of minicolumns.

Allometric models of cerebral development suggest that doubling the number of neurons supports a four-fold increase in neuronal connectivity, potentially generating a four-fold increase in white matter (Ringo, 1991). Thus, it can be predicted that subtle differences in neuron number, and therefore gray matter, could result in a larger, more-measurable difference in white matter volume (Casanova, 2004). Since the majority of myelination occurs postnatally, neonates born with increased numbers of pyramidal neurons and hence of minicolumns may have a normal brain size at birth, which will undergo accelerated growth postnatally due to the increased connectivity between minicolumns and the myelination of these connections, reflected in increased white matter volume. This hypothesis also implies that the primary pathogenic event leading to an increased number of minicolumns may substantially precede the manifestation of increased brain volume.

A recent imaging study (Herbert et al., 2004) has suggested that the WM increase in autism involves the outer, radiate compartment, which is composed of intrahemispheric cortico-cortical connections; indeed, several studies have shown that long-tract fibers such as the corpus callosum and internal capsule are not altered in ASD (Piven, Bailey, Ranson & Arndt, 1997; Manes et al., 1999; Hardan, Minshew & Keshavan, 2000). This important clue further suggests that the exuberant pyramidal neurons in ASD may be those that populate the upper cortical layers, which are those neurons that mostly form intrahemispheric and cortico-cortical connections. The formation of upper-layer cortical neurons occurs at the later stages of neurogenesis (Frantz & McConnell, 1996; Desai & McConnell, 2000) (Figure 2). An increase in later-developing upper layers pyramidal neurons and in their intrahemispheric connections could account for the larger proportion of subcortical radiate white matter and the relative decrease in long-range connections found in children with ASD (Herbert et al., 2003; Courchesne & Pierce, 2005).

Genes which affect cortical neuron growth and differentiation may be involved in ASD pathogenesis

Family and twin studies have determined that ASD are genetically complex, with some variation in expression due to environmental influences (Folstein & Rutter, 1977; Steffenburg et al., 1989; Bailey et al., 1995; Santangelo & Tsatsanis, 2005). Family studies of macrocephaly in autism suggest that this trait is heritable and that explorations of genetic factors affecting cell growth are warranted (Fidler, Bailey & Smalley, 2000; McCaffery & Deutsch, 2005). While a small percentage of ASD are inherited as monogenetic disorders, the majority of cases are due to the concurrent inheritance of several risk-conferring genetic variants (Santangelo & Tsatsanis, 2005). Although multiple genome-wide scans have been conducted, results generally have been inconsistent. Chromosomal regions 7q and 10p are supported by meta-analytic (Trikalinos et al., 2006) and high-resolution scanning studies carried by the Autism Genome Project (AGP) Consortium, respectively (Szatmari et al., 2007), but other regions may confer susceptibility to ASD.

Multiple candidate genes, including those controlling the growth of the cerebellum (Gharani et al., 2004) and glutamatergic and GABAergic synaptogenesis (Szatmari et al., 2007) also have been proposed to play a role. For example, the development or maintenance of synaptic connections may be affected in autism, and indeed, rare mutations have been reported in ASD for both neuroligins (Jamain et al., 2003; Laumonnier et al., 2004), the associated neurexins (Feng et al., 2006) and SHANK (Durand et al., 2007), molecules which are associated with both excitatory and inhibitory synapses.

Altered regulation of genes involved in the development of the GABAergic system is also likely to cause a dysequilibrium of the glutamate/GABA neuronal systems. Interestingly, the GABA receptor subunits, GABRB3, is strongly implicated in ASD by multiple association studies and is reduced in expression in human cerebral samples of ASD, particularly Rett and Angelman syndromes (Samaco, Hogart & LaSalle, 2005). Furthermore, a recent genetic study of over 700 ASD families has implicated the *MET* tyrosine kinase, a gene product that regulates the migration of GABA interneurons, with the disorder (Campbell et al., 2006).

In accordance with the hypothesis that genes regulating neuronal number are important candidates for study in ASD, mutations in *PTEN*, a gene product that down-regulates the phosphatidylinositol 3-kinase (PI3K) pathway and is involved in cell cycle regulation, have been found in a portion of autistic subjects with macrocephaly (Goffin et al., 2001; Butler et al., 2005). The PI3K pathway increases precursor cell proliferation and survival and is thought to be regulated in part by FGF receptor signaling (Ong et al., 2001). Recently, an animal model

for *PTEN* mutations was developed which showed macrocephaly and social phenotypes reminiscent of autism (Kwon et al., 2006).

In appreciation of this mosaic of findings, the consensus hypothesis is that the etiology of ASD is predominantly oligogenic and likely includes gene–gene and gene–environment interactions. These observations nevertheless suggest that in autism there may be convergence of genetic risk factors to pathogenetic pathways affecting developmental processes that regulate the balance of excitatory/inhibitory neurons and cortical architecture (Persico & Bourgeron, 2006).

A possible cause for the excess of glutamate-containing excitatory neurons and the minicolumn pathology in some ASD patients may be represented by variations in expression or function in the genes coding for *Fibroblast Growth Factors* (*FGF*). FGF-mediated signaling regulates the number of excitatory neurons and the growth of the cerebral cortex (Vaccarino, Schwartz, Hartigan & Leckman, 1995; Ortega et al., 1998; Vaccarino et al., 1999b; Vaccarino et al., 1999a) and may therefore be implicated in the etiology of autism. This hypothesis arises from several lines of accumulated evidence (McCaffery & Deutsch, 2005), and specifically animal models developed in several laboratories.

The receptors for FGFs are present on neural stem cells and cortical neuron progenitors *in vitro* and *in vivo* (el-Husseini, Paterson & Shiu, 1994; Wuechner et al., 1996; Wilke, Gubbels, Schwartz & Richman, 1997; Vaccarino et al., 1999b; Vaccarino et al., 1999a; Blak et al., 2005). FGF binding to these receptors maintains neuronal progenitors in a proliferative state and therefore promotes their expansion (Vaccarino et al., 1995; Vaccarino et al., 1999a; Tanaka et al., 2001; Ohkubo et al., 2004). One of the FGF ligands, *Fgf2*, increases the genesis of cortical pyramidal neurons (Vaccarino et al., 1995; Vaccarino et al., 1999b) and of granule neurons in cerebellum and hippocampus (Tao, Black & DiCicco-Bloom, 1996; Wagner, Black & DiCicco-Bloom, 1999; Cheng, Black & DiCicco-Bloom, 2002). A single intraventricular injection of *Fgf2* in rat embryos increases the genesis of excitatory pyramidal neurons in the neocortex, leading to a permanent increase in the number of cortical neurons and astroglial cells and enlarged cortical size (Vaccarino et al., 1999b) (Figure 3). In contrast, disruption of the *Fgf2* gene decreases cell proliferation in the VZ during development and leads to a loss of cortical pyramidal neurons and astrocytes, without any change in the number of inhibitory neurons (Vaccarino et al., 1999b; Raballo et al., 2000). Significantly, the excitatory neuron loss is more prominent in anterior cortical regions (Korada et al., 2002).

There are 4 FGF receptor genes, *Fgfr1-Fgfr4*, of which *Fgfr1*, *Fgfr2*, *Fgfr3* are expressed in the developing brain. *Fgfr1* is enriched in dorsomedial regions, which include the hippocampal primordium. Consistently, the conditional deletion of the *Fgfr1* gene from radial glial cells results in lifelong hippocampal atrophy (Ohkubo et al., 2004) and altered midline connectivity (Smith et al., 2006) but no significant alterations in cerebral cortical development.

Functionally disrupting all *Fgf* receptors during brain development by overexpressing an inactive *Fgf* receptor does disrupt cerebral cortical development. Inactive *Fgf* receptor overexpression results in a smaller neocortex with loss of glutamatergic pyramidal neurons in both frontal and temporal regions, emphasizing the importance of global *Fgf* signaling for excitatory neuron development (Shin et al., 2004). Recent data suggest that *Fgfr2* may be the crucial receptor in this respect. The selective deletion of *Fgfr2* in radial glial progenitor cells results in decreased cortical volume and decreased pyramidal cell number and density in the neocortex, more pronounced in medial prefrontal (mPF) cortical regions; furthermore, the volume of subcortical white matter is dramatically reduced due to decreased number of axonal fibers (unpublished data). To visualize cortical minicolumns in the *Fgfr2* mutants, we immunostained the apical dendritic bundles with an antibody to the microtubule-associated

protein MAP2. The data show a decrease in density of minicolumns in both mPF and cingulate cortical regions, consistent with the decrease in density of pyramidal cells (Figure 4).

Thus, the deletion of *Fgfr2* in radial glial cells mimics in part the phenotype of *Fgf2* null mice, in that the *Fgfr2* mutants have a concomitant decrease in cortical volume, excitatory neurons, and astrocytes, with preservation of cortical layer architecture.

Mutations in *Fgf17*, a ligand for *Fgfr2*, also result in reduced mPF cortical areas (Cholfin & Rubenstein, 2007). Furthermore, mice lacking *Fgf17* have deficits in social interactions without changes in cognitive abilities (Searce-Levie et al., 2007). Mouse pups lacking *Fgf17* have fewer ultrasonic vocalizations (an important component of mother-infant social interaction in rodents) when separated from their mothers. In adult, opposite-sex pairs of *Fgf17* mutant mice spend less time interacting than opposite-sex pairs of control mice (Searce-Levie et al., 2007). These social deficits, which mimic autistic features, may be attributed to the decreased activation of the prefrontal cortex in mutant mice. In conclusion, converging evidence suggest that FGF signaling may be controlling the modular (columnar) expansion of the cortex in mammals. Therefore, FGF ligands and receptors are an important class of candidate genes for mediating the accelerated brain growth evident in ASD.

The human *FGF8* (10q24) and *FGFR2* (10q26) genes are in proximity to previously identified broad autism linkage peaks on chromosome 10q, supporting the plausibility that these genes may be contributing risk for autism. As noted above *FGFR2* binds *FGF2*, *FGF17* and *FGF8*, which interact with the D3 immunoglobulin-like domains and the D2-D3 linker region of this receptor (Olsen et al., 2003). Like *Fgf2*, the *Fgf8* gene regulates cortical volume (Meyers, Lewandoski & Martin, 1998) and, like *Fgf17*, plays a role in the patterning of neocortical areas and in the development of intracortical connections (Huffman, Garel & Rubenstein, 2004). These data are intriguing, considering that a “disconnection” between prefrontal cortex and other cortical areas is thought to underlie the social disability in ASD patients (Geschwind & Levitt, 2007).

Conclusions and Future directions

In line with the genetic heterogeneity of ASD, there are likely to be many genetic determinants of the excitatory/inhibitory imbalance in the brain. The contributions of an exuberance of pyramidal neurons is in accordance with some of the symptoms and difficulties of patients with ASD. The excitatory overactivity may cause disruptions in cortical rhythms and seizures. Interestingly, seizures are found in approximately 30% of children with ASD, indicating that cortical development must be disrupted in ways that eventually alter the excitatory/inhibitory balance. Depending on the regional extent of this phenomenon, exuberant pyramidal neuron number and connectivity may cause noisy neuronal processing, or impaired long-range interactions among cortical areas and cortical-subcortical regions, which in turn may lead to diverse symptoms such as decreased attentional focus to socially relevant situations, inability to process global features, language deficit, perseveration, and poor impulse control. Future research will reveal whether the exuberance in neuron number is more prominent in certain regions of the cortex and how it may lead to different forms of autism.

In conclusion, in autistic children, the balance between growth and regression critically important to brain development may be biased in favor of growth, particularly in the first year of life. A dysregulation in amount or timing of FGF gene expression may conceivably be responsible in some patients for aberrantly regulated brain growth and altered ratio of different neuronal subtypes, ultimately resulting in altered cortical modularity and connectivity. A clarification of their potential role in this syndrome may lay the foundations for understanding how aberrant brain growth could be treated or reversed.

Acknowledgments

This work was supported by NIH grants MH067715, Autism Speaks and the NARSAD Foundation. We thank Shawna Ellis for technical assistance and all members of the Vaccarino lab for helpful discussions.

References

- American Psychiatric Association. DSM-IV. 4. Washington (DC): American Psychiatric Association; 1994. Diagnostic and statistical manual of mental disorders.
- Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. *Neurology* 2002;59:175–183. [PubMed: 12136053]
- Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med* 1995;25:63–77. [PubMed: 7792363]
- Blak AA, Naserke T, Weisenhorn DM, Prakash N, Partanen J, Wurst W. Expression of Fgf receptors 1, 2, and 3 in the developing mid- and hindbrain of the mouse. *Dev Dyn* 2005;233:1023–1030. [PubMed: 15830353]
- Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet MH, Barthelemy C, Mouren MC, Artiges E, Samson Y, Brunelle F, Frackowiak RS, Zilbovicius M. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *Neuroimage* 2004;23:364–369. [PubMed: 15325384]
- Butler MG, Dasouki MJ, Zhou XP, Talebizadeh Z, Brown M, Takahashi TN, Miles JH, Wang CH, Stratton R, Pilarski R, Eng C. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet* 2005;42:318–321. [PubMed: 15805158]
- Buxhoeveden DP, Semendeferi K, Buckwalter J, Schenker N, Switzer R, Courchesne E. Reduced minicolumns in the frontal cortex of patients with autism. *Neuropathol Appl Neurobiol* 2006;32:483–491. [PubMed: 16972882]
- Cameron RS, Rakic P. Glial cell lineage in the cerebral cortex: a review and synthesis. *GLIA* 1991;4:124–137. [PubMed: 1827774]
- Campbell DB, Sutcliffe JS, Ebert PJ, Militerni R, Bravaccio C, Trillo S, Elia M, Schneider C, Melmed R, Sacco R, Persico AM, Levitt P. A genetic variant that disrupts MET transcription is associated with autism. *Proc Natl Acad Sci U S A* 2006;103:16834–16839. [PubMed: 17053076]
- Carper RA, Courchesne E. Localized enlargement of the frontal cortex in early autism. *Biol Psychiatry* 2005;57:126–133. [PubMed: 15652870]
- Carper RA, Moses P, Tighe ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage* 2002;16:1038–1051. [PubMed: 12202091]
- Casanova MF. White matter volume increase and minicolumns in autism. *Ann Neurol* 2004;56:453. author reply 454. [PubMed: 15349878]
- Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Minicolumnar pathology in autism. *Neurology* 2002;58:428–432. [PubMed: 11839843]
- Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, Hof PR, Trippe J, Stone J, Schmitz C. Minicolumnar abnormalities in autism. *Acta Neuropathol (Berl)* 2006;112:287–303. [PubMed: 16819561]
- Cheng Y, Black IB, DiCicco-Bloom E. Hippocampal granule neuron production and population size are regulated by levels of bFGF. *Eur J Neurosci* 2002;15:3–12. [PubMed: 11860501]
- Cholfen JA, Rubenstein JL. Patterning of frontal cortex subdivisions by Fgf17. *Proc Natl Acad Sci U S A* 2007;104:7652–7657. [PubMed: 17442747]
- Courchesne E. Brain development in autism: early overgrowth followed by premature arrest of growth. *Ment Retard Dev Disabil Res Rev* 2004;10:106–111. [PubMed: 15362165]
- Courchesne E, Pierce K. Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *Int J Dev Neurosci* 2005;23:153–170. [PubMed: 15749242]

- Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. *Jama* 2003;290:337–344. [PubMed: 12865374]
- Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology* 2001;57:245–254. [PubMed: 11468308]
- Davidovitch M, Patterson B, Gartside P. Head circumference measurements in children with autism. *J Child Neurol* 1996;11:389–393. [PubMed: 8877607]
- Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. Rate of head growth decelerates and symptoms worsen in the second year of life in autism. *Biol Psychiatry* 2007;61:458–464. [PubMed: 17137564]
- de Carlos JA, Lopez-Mascaraque L, Valverde F. Dynamics of cell migration from the lateral ganglionic eminence in the rat. *J Neurosci* 1996;16:6146–6156. [PubMed: 8815897]
- Dementieva YA, Vance DD, Donnelly SL, Elston LA, Wolpert CM, Ravan SA, DeLong GR, Abramson RK, Wright HH, Cuccaro ML. Accelerated head growth in early development of individuals with autism. *Pediatr Neurol* 2005;32:102–108. [PubMed: 15664769]
- Desai AR, McConnell SK. Progressive restriction in fate potential by neural progenitors during cerebral cortical development. *Development - Supplement* 2000;127:2863–2872.
- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsater H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni MC, de Mas P, Bieth E, Roge B, Heron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet* 2007;39:25–27. [PubMed: 17173049]
- el-Husseini, Ae-D.; Paterson, JA.; Shiu, RP. Basic fibroblast growth factor (bFGF) and two of its receptors, FGFR1 and FGFR2: gene expression in the rat brain during postnatal development as determined by quantitative RT-PCR. *Mol Cell Endocrinol* 1994;104:191–200. [PubMed: 7527353]
- Feng J, Schroer R, Yan J, Song W, Yang C, Bockholt A, Cook EH Jr, Skinner C, Schwartz CE, Sommer SS. High frequency of neurexin 1beta signal peptide structural variants in patients with autism. *Neurosci Lett* 2006;409:10–13. [PubMed: 17034946]
- Fidler DJ, Bailey JN, Smalley SL. Macrocephaly in autism and other pervasive developmental disorders. *Dev Med Child Neurol* 2000;42:737–740. [PubMed: 11104344]
- Folstein S, Rutter M. Infantile autism: a genetic study of 21 twin pairs. *J Child Psychol Psychiatry* 1977;18:297–321. [PubMed: 562353]
- Fombonne E, Roge B, Claverie J, Courty S, Fremolle J. Microcephaly and macrocephaly in autism. *J Autism Dev Disord* 1999;29:113–119. [PubMed: 10382131]
- Frantz GD, McConnell SK. Restriction of late cerebral cortical progenitors to an upper-layer fate. *Neuron* 1996;17:55–61. [PubMed: 8755478]
- Fukumoto A, Hashimoto T, Ito H, Nishimura M, Tsuda Y, Miyazaki M, Mori K, Arisawa K, Kagami S. Growth of head circumference in autistic infants during the first year of life. *J Autism Dev Disord* 2008;38:411–418. [PubMed: 17647099]
- Ganat YM, Silbereis J, Cave C, Ngu H, Anderson GM, Ohkubo Y, Ment LR, Vaccarino FM. Early postnatal astroglial cells produce multilineage precursors and neural stem cells in vivo. *J Neurosci* 2006;26:8609–8621. [PubMed: 16914687]
- Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Curr Opin Neurobiol* 2007;17:103–111. [PubMed: 17275283]
- Gharani N, Benayed R, Mancuso V, Brzustowicz LM, Millonig JH. Association of the homeobox transcription factor, ENGRAILED 2, 3, with autism spectrum disorder. *Mol Psychiatry* 2004;9:474–484. [PubMed: 15024396]
- Goffin A, Hoefsloot LH, Bosgoed E, Swillen A, Fryns JP. PTEN mutation in a family with Cowden syndrome and autism. *Am J Med Genet* 2001;105:521–524. [PubMed: 11496368]
- Hardan AY, Minshew NJ, Keshavan MS. Corpus callosum size in autism. *Neurology* 2000;55:1033–1036. [PubMed: 11061265]
- Hazlett HC, Poe MD, Gerig G, Smith RG, Piven J. Cortical gray and white brain tissue volume in adolescents and adults with autism. *Biol Psychiatry* 2006;59:1–6. [PubMed: 16139816]

- Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, Gilmore J, Piven J. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. *Arch Gen Psychiatry* 2005;62:1366–1376. [PubMed: 16330725]
- Hendry J, DeVito T, Gelman N, Densmore M, Rajakumar N, Pavlosky W, Williamson PC, Thompson PM, Drost DJ, Nicolson R. White matter abnormalities in autism detected through transverse relaxation time imaging. *Neuroimage* 2006;29:1049–1057. [PubMed: 16214373]
- Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr. Localization of white matter volume increase in autism and developmental language disorder. *Ann Neurol* 2004;55:530–540. [PubMed: 15048892]
- Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, Hodgson J, Adrien KT, Steele S, Makris N, Kennedy D, Harris GJ, Caviness VS Jr. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain* 2003;126:1182–1192. [PubMed: 12690057]
- Hodapp RM, Urbano RC. Adult siblings of individuals with Down syndrome versus with autism: findings from a large-scale US survey. *J Intellect Disabil Res* 2007;51:1018–1029. [PubMed: 17991009]
- Huffman KJ, Garel S, Rubenstein JL. Fgf8 regulates the development of intra-neocortical projections. *J Neurosci* 2004;24:8917–8923. [PubMed: 15483110]
- Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, Bourgeron T. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* 2003;34:27–29. [PubMed: 12669065]
- Jones, EG.; Peters, A. Cellular components of the cerebral cortex. New York: Plenum; 1984. Cerebral cortex.
- Kanner L. Autistic disturbances of affective contact. *Nervous Child* 1943;2:217–250.
- Korada S, Zheng W, Basilico C, Schwartz ML, Vaccarino FM. Fibroblast growth factor 2 is necessary for the growth of glutamate projection neurons in the anterior neocortex. *J Neurosci* 2002;22:863–875. [PubMed: 11826116]
- Kornack DR, Rakic P. Cell Proliferation Without Neurogenesis in Adult Primate Neocortex. *Science* 2001;294:2127–2130. [PubMed: 11739948]
- Kriegstein A, Noctor S, Martinez-Cerdeno V. Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion. *Nat Rev Neurosci* 2006;7:883–890. [PubMed: 17033683]
- Kwon CH, Luikart BW, Powell CM, Zhou J, Matheny SA, Zhang W, Li Y, Baker SJ, Parada LF. Pten Regulates Neuronal Arborization and Social Interaction in Mice. *Neuron* 2006;50:377–388. [PubMed: 16675393]
- Lainhart JE, Piven J, Wzorek M, Landa R, Santangelo SL, Coon H, Folstein SE. Macrocephaly in children and adults with autism. *J Am Acad Child Adolesc Psychiatry* 1997;36:282–290. [PubMed: 9031582]
- Lainhart JE, Bigler ED, Bocian M, Coon H, Dinh E, Dawson G, Deutsch CK, Dunn M, Estes A, Tager-Flusberg H, Folstein S, Hepburn S, Hyman S, McMahon W, Minshew N, Munson J, Osann K, Ozonoff S, Rodier P, Rogers S, Sigman M, Spence MA, Stodgell CJ, Volkmar F. Head circumference and height in autism: a study by the Collaborative Program of Excellence in Autism. *Am J Med Genet A* 2006;140:2257–2274. [PubMed: 17022081]
- Laumonnier F, Bonnet-Brilhault F, Gomot M, Blanc R, David A, Moizard MP, Raynaud M, Ronce N, Lemonnier E, Calvas P, Laudier B, Chelly J, Fryns JP, Ropers HH, Hamel BC, Andres C, Barthelemy C, Moraine C, Briault S. X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. *Am J Hum Genet* 2004;74:552–557. [PubMed: 14963808]
- Lavdas AA, Grigoriou M, Pachnis V, Parnavelas JG. The medial ganglionic eminence gives rise to a population of early neurons in the developing cerebral cortex. *Journal of Neuroscience* 1999;19:7881–7888. [PubMed: 10479690]
- Letinic K, Zoncu R, Rakic P. Origin of GABAergic neurons in the human neocortex. *Nature* 2002;417:645–649. [PubMed: 12050665]
- Levitt P, Cooper ML, Rakic P. Coexistence of neuronal and glial precursor cells in the cerebral ventricular zone of the fetal monkey: an ultrastructural immunoperoxidase analysis. *J Neurosci* 1981;1:27–39. [PubMed: 7050307]

- Manes F, Piven J, Vrancic D, Nanclares V, Plebst C, Starkstein SE. An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. *J Neuropsychiatry Clin Neurosci* 1999;11:470–474. [PubMed: 10570760]
- Marshall CA, Goldman JE. Subpallial dlx2-expressing cells give rise to astrocytes and oligodendrocytes in the cerebral cortex and white matter. *J Neurosci* 2002;22:9821–9830. [PubMed: 12427838]
- Marshall CA, Suzuki SO, Goldman JE. Gliogenic and neurogenic progenitors of the subventricular zone: who are they, where did they come from, and where are they going? *Glia* 2003;43:52–61. [PubMed: 12761867]
- McCaffery P, Deutsch CK. Macrocephaly and the control of brain growth in autistic disorders. *Prog Neurobiol* 2005;77:38–56. [PubMed: 16280193]
- Meyers EN, Lewandoski M, Martin GR. An Fgf8 mutant allelic series generated by Cre-and Fbp-mediated recombination. *Nature Gen* 1998;18:136–141.
- Miles JH, Hadden LL, Takahashi TN, Hillman RE. Head circumference is an independent clinical finding associated with autism. *Am J Med Genet* 2000;95:339–350. [PubMed: 11186888]
- Mountcastle VB. The columnar organization of the neocortex. [Review]. *brain* 1997;120:701–722. [PubMed: 9153131]
- Noctor SC, Martinez-Cerdeno V, Kriegstein AR. Contribution of intermediate progenitor cells to cortical histogenesis. *Arch Neurol* 2007;64:639–642. [PubMed: 17502462]
- Noctor SC, Martinez-Cerdeno V, Ivic L, Kriegstein AR. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nat Neurosci* 2004;7:136–144. [PubMed: 14703572]
- Ohkubo Y, Uchida AO, Shin D, Partanen J, Vaccarino FM. Fibroblast growth factor receptor 1 is required for the proliferation of hippocampal progenitor cells and for hippocampal growth in mouse. *J Neurosci* 2004;24:6057–6069. [PubMed: 15240797]
- Olsen SK, Garbi M, Zampieri N, Eliseenkova AV, Ornitz DM, Goldfarb M, Mohammadi M. Fibroblast growth factor (FGF) homologous factors share structural but not functional homology with FGFs. *J Biol Chem* 2003;278:34226–34236. [PubMed: 12815063]
- Ong SH, Hadari YR, Gotoh N, Guy GR, Schlessinger J, Lax I. Stimulation of phosphatidylinositol 3-kinase by fibroblast growth factor receptors is mediated by coordinated recruitment of multiple docking proteins. *Proc Natl Acad Sci U S A* 2001;98:6074–6079. [PubMed: 11353842]
- Ortega S, Ittmann M, Tsang SH, Ehrlich M, Basilico C. Neuronal defects and delayed wound healing in mice lacking fibroblast growth factor 2. *Proc Natl Acad Sci USA* 1998;95:5672–5677.
- Palmen SJ, van Engeland H. Review on structural neuroimaging findings in autism. *J Neural Transm* 2004;111:903–929. [PubMed: 15206006]
- Palmen SJ, van Engeland H, Hof PR, Schmitz C. Neuropathological findings in autism. *Brain* 2004;127:2572–2583. [PubMed: 15329353]
- Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lohuis BE, Kahn RS, Van Engeland H. Increased gray-matter volume in medication-naïve high-functioning children with autism spectrum disorder. *Psychol Med* 2005;35:561–570. [PubMed: 15856726]
- Persico AM, Bourgeron T. Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends Neurosci* 2006;29:349–358. [PubMed: 16808981]
- Peters A, Cifuentes JM, Sethares C. The organization of pyramidal cells in area 18 of the rhesus monkey. *Cereb Cortex* 1997;7:405–421. [PubMed: 9261571]
- Piven J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: a magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 1996;35:530–536. [PubMed: 8919716]
- Piven J, Bailey J, Ranson BJ, Arndt S. An MRI study of the corpus callosum in autism. *Am J Psychiatry* 1997;154:1051–1056. [PubMed: 9247388]
- Piven J, Arndt S, Bailey J, Haverkamp S, Andreasen NC, Palmer P. An MRI study of brain size in autism. *Am J Psychiatry* 1995;152:1145–1149. [PubMed: 7625461]
- Raballo R, Rhee J, Lyn-Cook R, Leckman JF, Schwartz ML, Vaccarino FM. Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *J Neurosci* 2000;20:5012–5023. [PubMed: 10864959]

- Rakic P. Developmental and evolutionary adaptations of cortical radial glia. *Cereb Cortex* 2003;13:541–549. [PubMed: 12764027]
- Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biol Psychiatry* 2005;58:1–9. [PubMed: 15935993]
- Ringo JL. Neuronal interconnections as a function of brain size. *Brain Behav Evol* 1991;38:1–6. [PubMed: 1657274]
- Samaco RC, Hogart A, LaSalle JM. Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. *Hum Mol Genet* 2005;14:483–492. [PubMed: 15615769]
- Santangelo SL, Tsatsanis K. What is known about autism: genes, brain, and behavior. *Am J Pharmacogenomics* 2005;5:71–92. [PubMed: 15813671]
- Scearce-Levie K, Roberson ED, Gerstein H, Cholfen JA, Mandiyan VS, Shah NM, Rubenstein JL, Mucke L. Abnormal social behaviors in mice lacking Fgf17. *Genes Brain Behav*. 2007
- Schultz, RT.; Win, L.; Jackowski, A.; Klin, A.; Staib, L.; Papademetris, X.; Babitz, T.; Carter, E.; Klaiman, C.; Feiler, A.; Volkmar, F. Brain Morphology in Autism Spectrum Disorders: An MRI Study; International Meeting for Autism Research (IMFAR); Boston, MA. 2005.
- Shin DM, Korada S, Raballo R, Shashikant CS, Simeone A, Taylor JR, Vaccarino F. Loss of glutamatergic pyramidal neurons in frontal and temporal cortex resulting from attenuation of FGFR1 signaling is associated with spontaneous hyperactivity in mice. *J Neurosci* 2004;24:2247–2258. [PubMed: 14999075]
- Smith KM, Ohkubo Y, Maragnoli ME, Rasin MR, Schwartz ML, Sestan N, Vaccarino FM. Midline radial glia translocation and corpus callosum formation require FGF signaling. *Nat Neurosci* 2006;9:787–797. [PubMed: 16715082]
- Steffenburg S, Gillberg C, Hellgren L, Andersson L, Gillberg IC, Jakobsson G, Bohman M. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry* 1989;30:405–416. [PubMed: 2745591]
- Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, Liu XQ, Vincent JB, Skaug JL, Thompson AP, Senman L, Feuk L, Qian C, Bryson SE, Jones MB, Marshall CR, Scherer SW, Vieland VJ, Bartlett C, Mangin LV, Goedken R, Segre A, Pericak-Vance MA, Cuccaro ML, Gilbert JR, Wright HH, Abramson RK, Betancur C, Bourgeron T, Gillberg C, et al. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet* 2007;39:319–328. [PubMed: 17322880]
- Tanaka A, Kamiakito T, Hakamata Y, Fujii A, Kuriki K, Fukayama M. Extensive neuronal localization and neurotrophic function of fibroblast growth factor 8 in the nervous system. *Brain Res* 2001;912:105–115. [PubMed: 11532426]
- Tao Y, Black IB, DiCicco-Bloom E. Neurogenesis in neonatal rat brain is regulated by peripheral injection of basic fibroblast growth factor (bFGF). *J Comp Neurol* 1996;376:653–663. [PubMed: 8978476]
- Trikalinos TA, Karvouni A, Zintzaras E, Ylisaukko-oja T, Peltonen L, Jarvela I, Ioannidis JP. A heterogeneity-based genome search meta-analysis for autism-spectrum disorders. *Mol Psychiatry* 2006;11:29–36. [PubMed: 16189507]
- Vaccarino FM, Schwartz ML, Hartigan D, Leckman JF. Basic fibroblast growth factor increases the number of excitatory neurons containing glutamate in the cerebral cortex. *Cereb Cortex* 1995;5:64–78. [PubMed: 7719131]
- Vaccarino FM, Schwartz ML, Raballo R, Rhee J, Lyn-Cook R. Fibroblast growth factor signaling regulates growth and morphogenesis at multiple steps during brain development. *Curr Top Dev Biol* 1999a;46:179–200. [PubMed: 10417880]
- Vaccarino FM, Fagel DM, Ganat Y, Maragnoli ME, Ment LR, Ohkubo Y, Schwartz ML, Silbereis J, Smith KM. Astroglial cells in development, regeneration, and repair. *Neuroscientist* 2007;13:173–185. [PubMed: 17404377]
- Vaccarino FM, Schwartz ML, Raballo R, Nilsen J, Rhee J, Zhou M, Doetschman T, Coffin JD, Wyland JJ, Hung YT. Changes in cerebral cortex size are governed by fibroblast growth factor during embryogenesis. *Nat Neurosci* 1999b;2:246–253. [PubMed: 10195217]
- Volkmar FR, Lord C, Bailey A, Schultz RT, Klin A. Autism and pervasive developmental disorders. *J Child Psychol Psychiatry* 2004;45:135–170. [PubMed: 14959806]

- Wagner JP, Black IB, DiCicco-Bloom E. Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. *J Neurosci* 1999;19:6006–6016. [PubMed: 10407038]
- Wilke TA, Gubbels S, Schwartz J, Richman JM. Expression of fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3) in the developing head and face. *Dev Dyn* 1997;210:41–52. [PubMed: 9286594]
- Woodhouse W, Bailey A, Rutter M, Bolton P, Baird G, Le Couteur A. Head circumference in autism and other pervasive developmental disorders. *J Child Psychol Psychiatry* 1996;37:665–671. [PubMed: 8894947]
- Wuechner C, Nordqvist AC, Winterpacht A, Zabel B, Schalling M. Developmental expression of splicing variants of fibroblast growth factor receptor 3 (FGFR3) in mouse. *Int J Dev Biol* 1996;40:1185–1188. [PubMed: 9032024]

Figure 1.

Schematic outline of the generation of cortical neurons during embryogenesis. A, radial glial progenitor cells spanning the entire cortical wall (yellow) undergo sequential divisions, generating at each step neuronal progenitors that further divide in the SVZ and populate a specific cortical layer. B, the number of divisions that the SVZ progenitors undergo will amplify the number of cortical neurons generated for a specific cortical layer.

Figure 2.

Neuronal circuitry in a cortical column within the cerebral cortex. Excitatory neurons in green, axons in brown and dendrites in black. Afferent fibers from thalamus in blue. Stellate neurons in layer 4 receive thalamic input and relay it to other neuronal dendrites within the column. Pyramidal neurons in layer 6 and 5 project to thalamus and brainstem or spinal cord, respectively (long-range projections). Pyramidal neurons in layer 3 project to near-by cortical areas.

Figure 3.

A single microinjection of the growth factor Fgf2 (about 75 ng) in the ventricles of rat embryos will induce an increased cerebral cortical size (A), an increased cellular density within the cerebral cortex (B), and an increased number of glutamate-containing neurons in the cortex (C). B shows cresyl violet staining in cortex and C stereological quantification of glutamate- or GABA-immunoreactive cortical neurons in the adult rat neocortex. For more details, see Vaccarino et al, *Nature Neuroscience* (1999)2:246–253.

Figure 4. Coronal sections illustrating MAP2 immunostaining in cingulate and medial prefrontal (mPF) regions of the mouse cerebral cortex. Left, wild type mice; right, mice lacking the *Fgfr2* gene in radial glial cells (*Fgfr2* cKO). Note the bundles of apical dendrites putatively arising from distinct cortical columns. The intercolumn distance (red arrows) appears to be greater in the *Fgfr2* cKO.