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Genetic control of postnatal human brain growth

Laura I. van Dyck[1] and **Eric M. Morrow**[1,2,3,#]

[1]Department of Molecular Biology, Cell Biology and Biochemistry, and Brown Institute for Brain Science, Brown University

[2]Developmental Disorders Genetics Research Program, Emma Pendleton Bradley Hospital and Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University

[3]Hassenfeld Child Health Innovation Institute, Brown University

Abstract

Purpose of review—Studies investigating postnatal brain growth disorders inform the biology underlying the development of human brain circuitry. This research is becoming increasingly important for the diagnosis and treatment of childhood neurodevelopmental disorders, including autism and related disorders. Here we review recent research on typical and abnormal postnatal brain growth and examine potential biological mechanisms.

Recent findings—Clinically, brain growth disorders are heralded by diverging head size for a given age and sex, but are more precisely characterized by brain imaging, postmortem analysis, and animal model studies. Recent neuroimaging and molecular biological studies on postnatal brain growth disorders have broadened our view of both typical and pathological postnatal neurodevelopment. Correlating gene and protein function with brain growth trajectories uncovers postnatal biological mechanisms, including neuronal arborization, synaptogenesis and pruning, and gliogenesis and myelination. Recent investigations of childhood neurodevelopmental and neurodegenerative disorders highlight the underlying genetic programming and experience-dependent remodeling of neural circuitry.

Summary—In order to understand typical and abnormal postnatal brain development, clinicians and researchers should characterize brain growth trajectories in the context of neurogenetic syndromes. Understanding mechanisms and trajectories of postnatal brain growth will aid in differentiating, diagnosing, and potentially treating neurodevelopmental disorders.

Keywords

postnatal brain development; brain growth disorders; microcephaly; macrocephaly; connectivity; children; adolescents

[#]To whom correspondence should be addressed: Eric M. Morrow PhD MD, Brown University, Laboratories for Molecular Medicine, 70 Ship Street, Box G-E4, Providence, RI 02912, Tel: 401-863-9778, Fax: 401-432-1607, eric_morrow@brown.edu.

Conflicts of interest

None

Introduction

Prenatal attenuations in brain growth arise largely from disruptions in neurogenesis. Conversely, the postnatal period of human brain development involves a critical period of growth largely driven by experience-dependent formation of neuronal connections. Therefore, disorders of brain growth appearing postnatally offer an opportunity to understand genetic control and environmental input involved in neural circuitry development. Neurodevelopmental processes occurring during postnatal phases of human brain development appear to involve neuronal arborization, synaptogenesis and pruning, and gliogenesis and myelination. The following review describes recent progress regarding the biology underlying development of human brain circuitry through specific investigation of postnatal brain growth. We give examples of postnatal neurodevelopmental disorders that illustrate these aspects of human neurobiology.

Part 1: Clinical observations regarding postnatal brain development

The human brain undergoes dramatic changes in size and connectivity after birth. From birth to age 6, the brain increases in size by four-fold, reaching 90% of adult volume [1]. During normal development, the growth of head circumference (HC) is largely driven by growth of underlying brain tissue. Based on growth charts proposed by Rollins et al. [2] and data from Centers for Disease Control and Prevention [3], occipitofrontal circumference (OFC) at the 50^{th} percentile increases from 34.71 cm (females) and 35.81 cm (males) at birth to 45.20 cm (females) and 46.50 cm (males) at 1 year of age. After the first year, head growth continues more gradually into early adulthood.

OFC is a reliable predictor of brain volume in children younger than 6-years-old [4,5], therefore, clinicians can indirectly detect brain growth abnormalities through HC measurements. Abnormal brain size signaled by microcephaly and macrocephaly in early postnatal years is often indicative of disorders of neurodevelopment [6].

Infants with primary microcephaly exhibit small HC at birth. By contrast, infants with postnatal microcephaly present with normal HC at birth and display subsequent attenuations in HC growth. Microcephaly is defined as OFC $<3^{rd}$ percentile for sex, age, and ethnicity [2]. While both primary and postnatal microcephalies are generally caused by reduced brain growth, the distinction in trajectories of growth abnormalities may reflect different developmental mechanisms. Genetic insults disrupting neurogenesis often lead to primary microcephaly whereas defects in later-stage developmental mechanisms (connectivity or gliogenesis) often result in postnatal microcephaly (Figure 1). Postnatal microcephaly also may herald concern about an early-onset neurodegenerative process. Of course, many conditions may involve components of both prenatal and postnatal processes.

Microcephaly during the first year is associated with intellectual disability at age 7 years [8]. Postnatal microcephaly is often accompanied by abnormal or absent language, social impairment, and epilepsy [9]. Many childhood brain and neuropsychiatric disorders exhibit postnatal microcephaly, for example, Angelman syndrome (AS), Rett syndrome (RTT), and Christianson syndrome (CS).

Postnatal macrocephaly results from exaggerated head growth after birth, whereby infants are born with normal HC and then exhibit abnormal head enlargement, often due to increased brain growth, or megalencephaly. Macrocephaly is diagnosed when OFC is >97th percentile for sex, age, and ethnicity [2,10]. Accelerated postnatal brain growth is associated with developmental delays of motor, language, and cognitive functions [10–12]. Examples of childhood brain and neuropsychiatric disorders that present with postnatal macrocephaly include monogenic PTEN Hamartoma Tumor Syndrome (PHTS), Tuberous Sclerosis Complex (TSC), and autism spectrum disorder (ASD).

Part 2: Potential biological mechanisms governing postnatal brain growth

Prior to birth, almost all neurons of the brain are generated. The first half of gestation observes birth and migration of neurons. By the second half of gestation, neuronal connectivity begins to develop into immature circuits. Formation and differentiation of glial progenitors have commenced. Yet, the brain will continue to undergo extraordinary developmental changes in connectivity and glial development over the first two decades of life.

The newborn brain is 36% the size of the adult brain. Within the first postnatal year, the brain grows to approximately 70% of its adult size [13,14]. This growth is due to a rapid increase in neuropil (axons, dendrites, and synapses) and glial cells. Remodeling and myelination of neural circuits extend throughout adolescence. During postnatal development, experience shapes brain connectivity and circuitry. Here, we will address biological mechanisms underlying postnatal brain development (Figure 2).

Axon and dendrite elaboration

Axonal and dendritic outgrowth increase during the second half of gestation [15,16], forming connections, or synapses, with other cells to give rise to early neural circuits. Elaboration of dendrites accelerates during early childhood [6,17]. Similarly, dendritic spine numbers increase in early childhood, followed by a gradual decline during late childhood and adolescence [18]. Regulation of axonal and dendritic branching is critical for functional organization of circuits. Increasing evidence implicates altered axonal and dendritic formation in a subset of intellectual and developmental disabilities [19–23].

Synaptogenesis and experience-dependent synapse remodeling

During early childhood, synaptic connectivity far exceeds that of an adult. While formation of synapses begins prenatally, the majority of synaptogenesis occurs in early childhood [24–26]. Postmortem studies show that synaptic density increases from birth until late childhood [6,27], followed by a gradual period of pruning (likely largely experience-dependent) that continues until early adulthood. Histological and neuroimaging studies in humans suggest that the time course of synaptogenesis follows a posterior-to-anterior pattern, peaking first in sensory and motor areas, followed by association cortices [26,28]. Subsequent synaptic pruning follows a similar pattern, with primary cortices undergoing synaptic remodeling first, followed by association cortices [6,29]. Synaptogenesis and synaptic pruning may be responsible for cortical thickening and thinning, respectively [28].

Gliogenesis and myelination

Beginning prenatally, the proliferation, migration, and differentiation of glial progenitor cells continues for an extended period after birth. Abundant progenitors migrate into neuron-populated areas and differentiate into various glial cells, such as astrocytes and oligodendrocytes. Together, these cells make up over half the cells of the human brain and regulate numerous functions of the developing and adult brain [30*]. The increase in number and size of glial cells are greatly responsible for early rapid brain and head growth.

Mature oligodendrocytes form myelin sheaths to increase axonal conduction [31], beginning at the end of the second trimester [15]. Myelination appears to be regulated by electrical activity of neurons, occurring in a posterior-to-anterior direction [6,32]. White matter fiber tract development rapidly increases in the 6-month to 24-month interval and gradually continues until late adolescence [33].

Part 3: Genetic syndromes exemplifying abnormalities in postnatal brain growth

A wide range of disorders are associated with abnormal postnatal brain growth. These disorders may arise from an attenuation or an exaggeration of growth, and from either monogenic or complex etiologies. In the following section, we will discuss a subset of postnatal brain growth disorders (Table 1).

Monogenic postnatal microcephalies

ANGELMAN SYNDROME (AS)—First described in 1965, AS is a classic postnatal microcephaly disorder. There is evidence of developmental delay by age 6–12 months, and in the majority of cases, decelerated growth in HC resulting in microcephaly by age 2 years [34]. AS arises from loss of expression of the maternally inherited allele of the imprinted ubiquitin protein ligase E3A (*UBE3A*) gene, most frequently due to a genomic deletion on chromosome 15q11q13 [66–68]. In mature neurons, *UBE3A* is expressed from the maternally inherited copy, whereas in most other tissues and cell types *UBE3A* is expressed from both alleles [66,69,70]. The biological role of *UBE3A* in AS remains poorly understood. *UBE3A* encodes E6-associated protein (E6-AP), an E3 ubiquitin ligase. E6-AP is believed to participate primarily in protein degradation in proteasomes via the ubiquitin pathway [34], functioning as a cellular quality control. E6-AP targets proteins involved in cell-cycle regulation and synaptic function and plasticity [71,72].

The majority of individuals with AS exhibit decelerated HC growth resulting in microcephaly [73]. Microcephaly is more frequent among patients with a deletion in chromosome 15q11q13 [74]. Microcephaly in AS may be caused by decreased brain volume arising from impaired connectivity. Mouse models exhibit reduced brain size, learning and memory impairment [75,76], and impaired synaptic transmission [77]. In addition, they show abnormal dendritic spine morphology and decreased dendritic spine density [21]. Finally, diffusion tensor imaging (DTI) studies reveal altered white matter pathways and connectivity in participants with AS [78]. Unlike neurons, mature oligodendrocytes express

UBE3A biallelically. Nonetheless, disruption to the maternal copy may compromise myelination in AS [69].

RETT SYNDROME (RTT)—RTT is an X-linked progressive neurodevelopmental disorder mainly affecting females. Classic RTT is characterized by typical early development until age 6–18 months, followed by gradual developmental regression, and in most cases, decelerated postnatal head growth [79]. The majority of RTT cases result from loss-of-function mutations in the X-linked gene *MECP2* [80]. *MECP2* encodes for methyl-CpG-binding protein 2 (MeCP2), a protein highly expressed in the brain that regulates transcription [37*]. MeCP2 can act as both a repressor and an activator of transcription through interacting with histone deacetylase-containing complexes and with promoter regions, respectively [81,82]. It is believed that RTT arises mainly from loss of transcriptional activation, rather than loss of repression [81]. For example, loss of *MECP2* leads to repression of several genes involved in brain development, including brain-derived neurotrophic factor (BDNF) [81,82]. MeCP2 is likely involved in neuronal maturation and maintenance, rather than in neuronal proliferation, demonstrated by increasing postnatal *MECP2* expression levels as neurons mature [83–85].

Postnatal deceleration of head growth resulting in microcephaly is found in the majority of RTT cases [35,36,86]. Decelerated head growth may result from a deficit in both development and maintenance of neuronal connectivity. Postmortem studies reveal a profound decrease in dendritic growth in cortex [87], corroborated by studies in RTT mouse models [19,88]. In addition, postmortem brain and mouse model studies demonstrate decreased dendritic spine density [19,89], particularly in later stages of development, suggesting an error in maintenance [88,90]. Decreased dendritic growth is at least in part due to *MECP2*-deficient glia, which are unable to support dendritic morphology of both wild-type and *MECP2*-null neurons [91–93]. In addition, RTT patients likely present with mild progressive white matter pathology [94,95].

CHRISTIANSON SYNDROME (CS)—CS is an X-linked neurodevelopmental disorder primarily affecting males [38]. Boys with CS exhibit severe intellectual disability, absent speech, ataxia, and epilepsy. The majority of patients display postnatal microcephaly [38–40]. CS arises from loss-of-function mutations in *SLC9A6* [40], which encodes for the Na +/H+ exchanger 6 (NHE6) protein. NHE6 localizes to early, recycling, and late endosomal membranes and transiently associates with the plasma membrane [96–98]. NHE6 regulates endosomal lumen pH by allowing for electroneutral exchange of proton ions out of the endosome for monovalent cations into the endosome [97,99]. Over-acidification of endosomal pH in absence of functional NHE6 may disrupt endosomal trafficking normally needed for growth of axonal and dendritic arbors, as well as for dendritic spines during long-term potentiation (LTP) [100] and neuronal development [101]. In the mouse model, loss of NHE6 results in over-acidification of endosomal compartments and reduced endosomal signaling by neurotrophins and their receptors, such as BDNF and TrkB, respectively [98].

The majority of CS patients exhibit decelerated postnatal head growth. In a cohort of twelve independent pedigrees, 92% of CS participants displayed postnatal microcephaly with decelerated head growth [39]. Postnatal microcephaly is likely due to a deficit in

development and maintenance of connectivity, as supported by the CS mouse model. *Slc9a6*-null mouse neurons exhibit diminished axonal and dendritic branching, decreased synapse number and spine density, and a greater number of immature spines [98]. In addition, a subset of CS patients shows brainstem and cerebellar atrophy, as evidenced by magnetic resonance imaging (MRI), presenting after 12 months of age [38,102] and particularly after the first decade [39]. Clinical findings are corroborated by findings in the CS mouse model demonstrating Purkinje cell loss with age [103].

Monogenic postnatal macrocephalies

***PTEN*-RELATED DISORDERS—**Mutations in phosphatase and tensin homolog (*PTEN*) are implicated in various distinct disorders with concomitant macrocephaly, including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome, and Proteus-like syndrome [41]. These disorders, and other conditions with germline heterozygous loss-of-function mutations in *PTEN*, share a predisposition of tumors, and therefore are collectively referred to as PHTS (PTEN Hamartoma Tumor Syndrome). *PTEN* mutations are also described in patients with ASD with pronounced macrocephaly [56,57].

PTEN encodes a widely expressed tumor suppressor phosphatase. PTEN's lipid-phosphatase activity inhibits the phosphoinositide 3-kinase (PI3K)-AKT pathway, which activates mammalian target of rapamycin (mTOR) signaling. The PI3K-AKT-mTOR pathway is involved in cell functions such as survival, proliferation, and cellular architecture (reviewed in [42]). In the brain, the PI3K-AKT pathway is implicated in functions including neuronal survival, outgrowth, synaptic plasticity, learning, and memory. In addition, PTEN acts as a protein phosphatase involved in regulation of various cell-survival pathways, for example, in mediation of growth suppression via the mitogen-activated protein kinase (MAPK) pathway [104]. Therefore, in the context of loss of PTEN protein or function, cell signaling and growth lack regulation.

In a cohort of 161 patients with pathogenic germline *PTEN* mutations, 94% of PHTS individuals presented with macrocephaly [105], supported by MRI studies [106]. In addition, mouse models show a gene dose-dependent increase in brain weight and macrocephaly, which increases from birth to adulthood [22,105,107**]. Brain overgrowth is likely due to abnormalities in proliferation and connectivity. *PTEN* haploinsufficiency in a mouse model leads to hyperplasia, specifically an excess neuronal population at birth and an excess glial population in adulthood, suggesting a role of PTEN in controlling cell number [107**]. Furthermore, neurons exhibit hypertrophy of neuronal soma and dendritic arborization and increased dendritic spine density [22]. In addition, MRI revealed white matter abnormalities and dilated perivascular spaces in patients with *PTEN* mutations [106]. This suggests that loss of PTEN protein or function disrupts neurodevelopmental events occurring prenatally (i.e., neurogenesis) and postnatally (i.e., gliogenesis, dendritic growth, myelination).

TUBEROUS SCLEROSIS COMPLEX (TSC)—TSC is an autosomal dominant disorder characterized by hamartomas in multiple organ systems and variable symptom presentation. Common neurological manifestations include epilepsy, cognitive disability, and an ASD phenotype [43,44]. TSC results from heterozygous germline mutations in either *TSC1* or

TSC2 [43]. Tumors likely develop from a "second hit," in which disruption to the functional allele or other TSC protein leads to uncontrolled cell growth. Indeed, several downstream protein cascades are disrupted in TSC, particularly the mTOR signaling pathway [46]. *TSC1* and *TSC2* encode for hamartin and tuberin, respectively, which form a heterodimer complex [108]. Loss of a functional hamartin-tuberin complex leads to increased activation of mTOR signaling and subsequent unregulated cell growth and proliferation. The hamartin-tuberin complex is implicated in neurodevelopment, specifically in the regulation of somatic size, dendritic arborization, dendritic spine formation and morphogenesis, axon specification and guidance, astrocyte proliferation, and cortical lamination [46].

Neurological pathology associated with TSC includes macrocephaly [109], hamartomatous brain lesions, cellular cytomegaly, lamination defects, astrogliosis, and white matter abnormalities [45,110]. While several TSC neurological abnormalities arise prenatally, many occur postnatally. For example, there is increasing evidence of abnormal neuronal connectivity [111], which experiences large changes after birth. Postmortem studies of TSC individuals show multipolar neurons, shortened dendrites, abnormal spine morphology, and decreased dendritic spine density of projection neurons in tubers [112,113], corroborated by rodent models [114]. Furthermore, recent brain imaging studies show diffuse white matter abnormalities, structurally compromised axons, and altered structural connectivity in TSC [78,110,115**,116,117].

NEURODEGENERATIVE DISORDERS—While postnatal microcephaly usually results from abnormal neurodevelopment, this clinical finding can also herald an early-onset neurodegenerative process. A heterogeneous group of neurodegenerative disorders cause regression and progressive loss of neurological function in children. Pathologic hallmarks of neurodegeneration include neuronal loss and gliosis in the nervous system. Many neurodegenerative disorders are due to neurometabolic disease, related to synthesis, metabolism, transport, or storage of biochemical compounds [118]. For example, Cockayne syndrome is a childhood autosomal recessive disorder arising from abnormal nucleotide excision repair [49]; it is characterized by both postnatal growth failure and degeneration [48]. Cockayne syndrome is generally caused by mutations in *ERCC6* or *ERCC8*, genes involved in DNA damage repair mechanisms. HC is typically normal at birth, followed by postnatal decelerated brain growth resulting in microcephaly. In addition, de novo mutations in *KIF1A*, which encodes for a microtubule-based motor protein involved in axonal transport of synaptic vesicle precursors, have been described in patients with a severe and progressive neurodegenerative syndrome presenting within the first months of life [50*]. The majority of patients exhibit microcephaly, potentially as a result of brain atrophy and cerebral white matter reduction.

Complex disorders

AUTISM SPECTRUM DISORDER (ASD)—ASD comprises genetically and clinically heterogeneous disorders of atypical neurodevelopment characterized by impaired communication and social interactions and stereotyped behaviors [51,52]. A subset of ASD appears to be associated with larger HC and brain volume [60**], perhaps with most rapid increase in head and brain size during the earliest stages of postnatal development [60**,

119–121]. A variety of subphenotypes exist within ASD depending on genetic etiology. For example, high rates of macrocephaly are found in *PTEN*-associated ASD [56,57]. Also, postmortem ASD brains show increased spine density in frontal, parietal, and temporal lobes [101,122], likely due to a defect in postnatal pruning and associated with hyperactivated mTOR and impaired autophagy [122]. However, some cohorts describe ASD populations with microcephaly [123]. For example, ASD patients carrying *DYRK1A* mutations present with microcephaly [61*]. In addition, there are examples of genetic reciprocity in ASD. Duplications within chromosome 16p11.2 are associated with decreased brain volume and HC, whereas deletions are associated with the mirror pattern of increased brain volume and macrocephaly [59]. Additionally, reciprocal deletions and duplications within 1q21.1 are associated with microcephaly and macrocephaly, respectively [58]. Interestingly, extreme HC (small or large) is associated with lower IQ and higher autism symptom severity in ASD patients from the Simons Simplex Collection (SSC) [124].

SCHIZOPHRENIA—According to the widely accepted neurodevelopmental model, schizophrenia may arise in part from abnormal brain growth beginning years before symptom onset [62]. A number of MRI studies describe reduced brain and gray matter volume and increased extracerebral cerebral spinal fluid (CSF) in schizophrenia (reviewed in [64]). Also, typical back-to-front gray matter loss is exaggerated, predominantly in prefrontal and temporal cortices [125–127]. Greatest reduction has been noted 3 months following onset of psychosis, advancing into most of the frontal cortex by one year after onset [128]. Postmortem studies indicate that loss of cortical gray matter is due to reduced dendritic complexity and synaptic density, rather than from decreased neuron number [63]. Given its complexity, identification of potential genetic etiologies for observed brain matter changes in schizophrenia is an ongoing area of research. As an example, results from a recent study revealed an association between schizophrenia and altered expression of complement component 4 (*C4*) genes, the encoded proteins of which are involved in synapse elimination during postnatal development [65**]. Finally, abnormal functional and structural connectivity and altered white matter integrity are observed in schizophrenia [129–132].

Conclusions

In conclusion, the study of brain growth disorders illustrates that postnatal neurodevelopment is supported by regulation of neuronal arborization, synaptogenesis and pruning, and gliogenesis and myelination. However, our understanding of biological events underlying typical and pathological brain development in the postnatal period is still incomplete. Additional longitudinal studies will be important in correlating gene and protein function with brain growth trajectories. Understanding the pathogenesis of childhood neurodevelopmental disorders will help in differentiating and diagnosing neurogenetic syndromes, as well as in developing interventions to normalize divergent postnatal brain growth trajectories.

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Key points

- Postnatal brain development is supported by genetic programming with experience-dependent remodeling.
- Correlations between gene and protein function and postnatal brain growth trajectories illuminate underlying biological mechanisms of neurodevelopment.
- Postnatal brain growth involves neuronal arborization, synaptogenesis and pruning, and gliogenesis and myelination.
- Investigation of the pathogenesis of brain growth disorders can teach us about typical postnatal neurodevelopment and help in the development of interventions to correct aberrant trajectories in brain development.

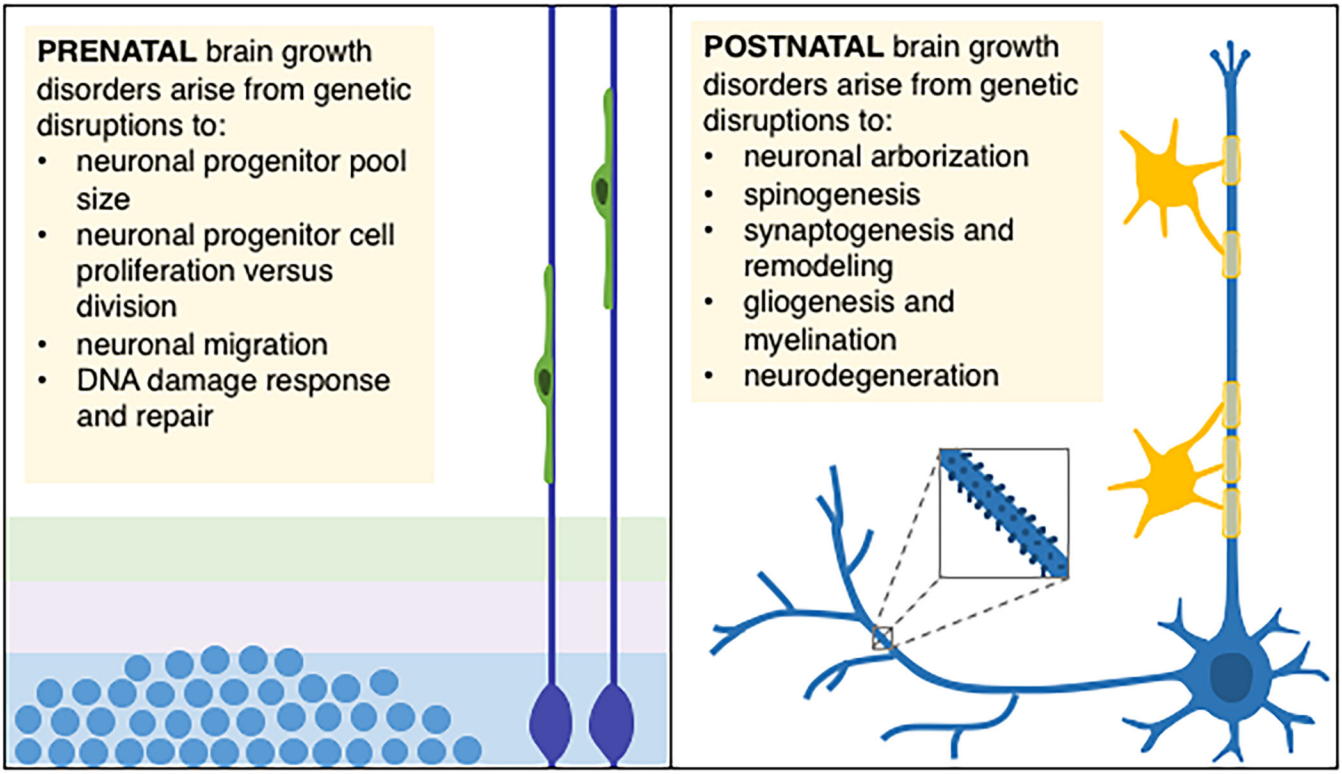

Figure 1.

Biological mechanisms underlying prenatal versus postnatal brain growth disorders. **(Left panel)** Prenatal brain growth disorders commonly arise from genetic causes associated with centrosomal abnormalities. Disruptions to centrosomal proteins may impact neuronal progenitor cell proliferation and differentiation, neuronal migration, and DNA repair responses (reviewed in [7]). **(Right panel)** Conversely, postnatal brain growth disorders mainly arise from genetic causes associated with disrupted connectivity (i.e., elaboration of axons and dendrites, spinogenesis and maturation, synaptogenesis and remodeling, and gliogenesis and myelination). Postnatal brain growth disorders may also result from childhood neurodegeneration.

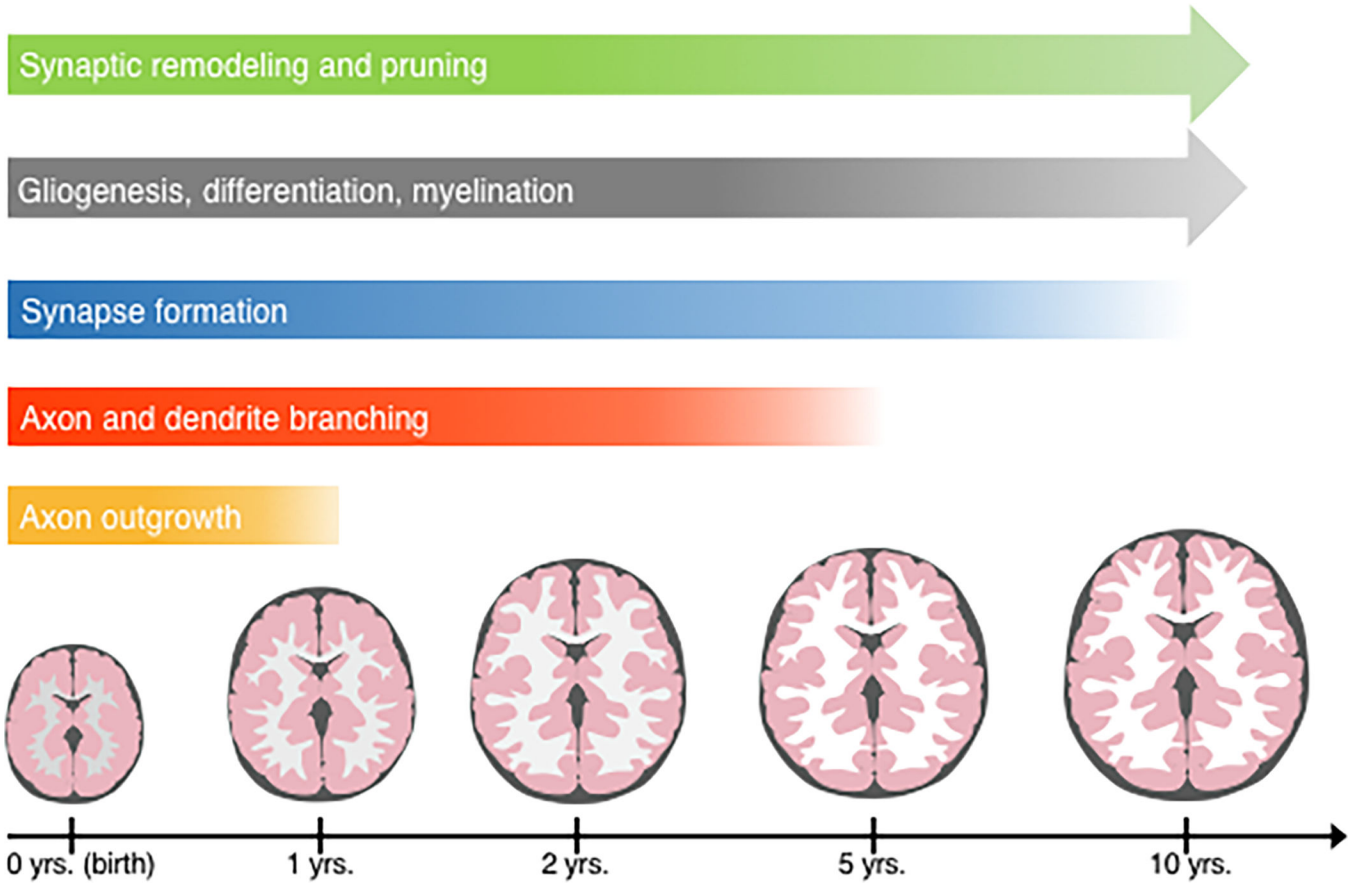

Figure 2.

Postnatal brain and head growth and underlying neurodevelopmental stages. The human brain and head size increase rapidly during the first and second postnatal years, followed by a more gradual increase into early adulthood. The increase in brain and head size largely results from elaboration of connectivity. Axon and dendrite growth and arborization continue after birth into early postnatal years. Synaptogenesis continues after birth, peaking at various points during childhood (depending on brain region). Synapses mature and remodel to form appropriate connections, and then undergo gradual pruning into early adulthood. Gliogenesis continues after birth, and glial cell differentiation and myelination continue into early adulthood.

Table 1

Genetic neurodevelopmental disorders associated with abnormal postnatal brain growth.

Disorder	Clinical Description	Genetic Description	Postnatal Disruptions	References
Monogenic Postnatal Microcephalies				
Angelman Syndrome (AS)	Characterized by severe intellectual disability, absent speech, seizures, postnatal microcephaly, movement disorder, developmental delay, and a behavioral profile that includes a happy demeanor and hyperactivity	Loss of expression of the maternally inherited allele of *UBE3A*	Decreased dendritic spine density and abnormal spine morphology, white matter pathology, and altered connectivity	[34]
Rett Syndrome (RTT)	Characterized by typical early development followed by regression, which involves loss of acquired skills and language, intellectual disability, gait abnormalities, stereotypic hand movements, postnatal microcephaly, and seizures (mainly affects females)	Loss-of-function mutations in the X-linked gene *MECP2* (however, can be associated with mutations in *CDKL5* and *FOXG1*)	Decreased dendritic growth and spine density, fewer spines, white matter pathology, and compromised glial function	[35,36,37*]
Christianson Syndrome (CS)	Characterized by severe intellectual disability, absent speech, ataxia, and epilepsy Frequently presents with postnatal microcephaly, craniofacial dysmorphology, eye movement abnormalities, progressive neurologic dysfunction, and loss of early acquired motor skills (mainly affects males)	Loss-of-function mutations in the X-linked gene *SLC9A6*	Decreased axonal and dendritic arborization, decreased spine density, and gray matter atrophy (most notable in cerebellum and brainstem)	[38–40]
Monogenic Postnatal Macrocephalies				
PTEN Hamartoma Tumor Syndrome (PHTS)	Characterized by a predisposition of tumors Often associated with Lhermitte-Duclos disease, developmental disabilities, macrocephaly, and autism spectrum disorder (ASD)	Germline heterozygous loss-of-function mutations in *PTEN*	Excess glial population, hypertrophy of dendritic arborization, increased dendritic spine density, and white matter abnormalities	[41–42]
Tuberous Sclerosis Complex (TSC)	Multi-system disease commonly presenting with dermatological, renal, and neurological manifestations Neurological manifestations include	Heterozygous loss-of-function mutations in either *TSC1* or *TSC2*	Astrogliosis, white matter abnormalities, structurally compromised axons, and altered structural connectivity Projection neurons within cortical tubers exhibit	[43–46]

Disorder	Clinical Description	Genetic Description	Postnatal Disruptions	References
	epilepsy, cognitive disabilities, behavioral problems, autism, and macrocephaly		shortened dendrites, abnormal spine morphology, and decreased dendritic spine density	
Neurodegenerative Disorders				
Cockayne Syndrome	Neurodegenerative disorder characterized by severe motor and cognitive developmental delays, intellectual disability, microcephaly, multi-organ degeneration, progessive hearing loss, retinopathy, and sun sensitivity	Autosomal recessive mutations in *ERCC6* (also known as *CSB*) or *ERCC8* (also known as *CSA*)	Neurological manifestations include neuronal loss, gliosis, demyelination, and axonal degeneration	[47–49]
KIF1A-associated Neurodegenerative Syndrome	Neurodegenerative disorder characterized by severe developmental delay, hypotonia, microcephaly, cortical visual impairment, ataxia, epilepsy, and movement disorders	De novo (likely dominant-negative) mutations in *KIF1A*	Progressive brain atrophy and cerebral white matter reduction, likely caused by impaired axonal synaptic vesicle transport	[50*]
Complex Disorders				
Autism Spectrum Disorder (ASD)	Genetically and clinically heterogeneous neurodevelopmental disorder characterized by impaired communication and social interactions, and stereotyped behaviors	Ongoing area of research, but examples include: *PTEN* mutations (associated with macrocephaly) *DYRK1A* mutations (associated with microcephaly) 16p11.2 (duplications associated with microcephaly and deletions with macrocephaly) 1q21.1 (deletions associated with microcephaly and duplications with macrocephaly)	Increased cortical thickness and spine density, decreased diffusion and resting state connectivity, and widespread reductions in white matter tract integrity (however, may be limited to right inferior longitudinal fasiculus after matching for head motion)	[51–53,54**,55–59,60**,61*]
Schizophrenia	Criteria include positive symptoms (i.e., hallucinations, delusions, disorganized behavior) and negative symptoms (i.e., blunted affect, lack of motivation)	Ongoing area of research, but examples include: Altered expression of *C4* genes (i.e., *C4A* and *C4B*)	Exaggerated parieto-frontal-temporal gray matter loss (predominantly in prefrontal and temporal cortices), reduced spine density and neuropil in deep layer III and layer V of prefrontal cortex, abnormal functional and structural connectivity, and altered white matter integrity	[62–64,65**]