

## EXPERT REVIEW

# Toward a conceptual framework for early brain and behavior development in autism

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Studies of infant siblings of older autistic probands, who are at elevated risk for autism, have demonstrated that the defining features of autism are not present in the first year of life but emerge late in the first and into the second year. A recent longitudinal neuroimaging study of high-risk siblings revealed a specific pattern of brain development in infants later diagnosed with autism, characterized by cortical surface area hyper-expansion in the first year followed by brain volume overgrowth in the second year that is associated with the emergence of autistic social deficits. Together with new observations from genetically defined autism risk alleles and rodent models, these findings suggest a conceptual framework for the early, post-natal development of autism. This framework postulates that an increase in the proliferation of neural progenitor cells and hyper-expansion of cortical surface area in the first year, occurring during a pre-symptomatic period characterized by disrupted sensorimotor and attentional experience, leads to altered experience-dependent neuronal development and decreased elimination of neuronal processes. This process is linked to brain volume overgrowth and disruption of the refinement of neural circuit connections and is associated with the emergence of autistic social deficits in the second year of life. A better understanding of the timing of developmental brain and behavior mechanisms in autism during infancy, a period which precedes the emergence of the defining features of this disorder, will likely have important implications for designing rational approaches to early intervention.

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Studies employing the high familial risk for autism ‘infant sibling’ paradigm add substantially to our understanding of behavioral development in autism over the first few years of life.<sup>1</sup> Chief among these findings is the overarching idea that the defining behaviors of autism spectrum disorder (ASD) are not evident in the first 6 months of life, but emerge during the latter part of the first and second years. The diagnostic features of autism, in high-risk (HR) infant siblings, appear to consolidate between 18 and 36 months of age. Relevant findings from prospective, longitudinal brain imaging studies of HR infant siblings are now becoming available. Findings from these studies, when combined with recent discoveries related to genetic and environmental risks for autism, enrich our understanding of possible neurodevelopmental mechanisms underlying very early brain and behavior development in autism. In this paper we propose a conceptual framework for the early, post-natal development of autism that integrates behavioral and brain imaging findings from HR, prospective infant sibling studies of autism. This developmental framework postulates that early increased proliferation of neuroprogenitor cells leads to a non-uniform, hyper-expansion of cortical surface area that links to early deficits in visual receptive/visual attention abilities which alter subsequent experience-dependent neuronal development more broadly in the brain. Cortical overgrowth results in a disruption in the refinement of selected neural circuit development and is associated with the emergence of social deficits in autism. Better understanding of the timing of developmental brain and behavior mechanisms in

autism during infancy, a period which precedes the emergence of the defining features of this disorder, will likely have important implications for designing rational approaches to early intervention.

## THE ONSET OF THE DEFINING BEHAVIORS IN THE SYNDROME OF AUTISM

Genetic and environmental studies suggest that the pathophysiology of autism initiates pre-natally during mid-fetal development<sup>2,3</sup> and implicate excitatory neurons of the cerebral cortex.<sup>4,5</sup> However, there is now consensus in the field that the defining symptoms of autism emerge during the latter part of the first and second years of life. Several studies take a syndromic approach to assessing early manifestations of autism in infants employing the Autism Observation Scale for Infants (AOSI).<sup>1,6</sup> This direct behavioral assessment procedure revealed no differences at 6 months of age between HR infants who go on to be diagnosed with autism (HR-ASD), HR infants who are not later diagnosed as having autism (HR-negative) and low-risk (LR) infants.<sup>1,7</sup> Modest but significant differences on the AOSI were observed, however, in HR-ASD infants by 12 months of age in comparison to HR infants who do not go on to develop autism and low familial risk infants.<sup>1,7,8</sup>

Complementing the syndromic approach noted above, differences between select behavioral dimensions associated with autism were detected between groups at 12 months, but not

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**Box 1** Infant Sibling Studies: methodologic and conceptual challenges

Several recent reviews summarize findings from the infant-sibling paradigm.<sup>17–19</sup> Approximately 10–20% of younger siblings of probands with autism will meet diagnostic criteria for the disorder themselves.<sup>20–22</sup> In addition, a substantial proportion of high-risk siblings not diagnosed with autism show other developmental/clinical concerns.<sup>23–25</sup> Following the initial publication of results that tracked behavioral development from 6 to 24/36 months in a high familial risk cohort,<sup>1</sup> a number of research groups pulled together preliminary results for publication. This period, from 2005 to 2012, was appropriately a period of discovery for those working in this paradigm. However, subtle methodological/ conceptual decisions made during this period present challenges to summarizing the state of the field. Many papers have been published that do not include diagnostic outcome data or some other clinical stratification between 18–36 months of age. Unlike studies of unaffected family members during adolescence or adulthood, these studies cannot determine whether observed differences between HR and LR groups are due to a general familial factor inherited by HR children or a subgroup of individuals who will later meet diagnostic criteria for ASD or some other diagnostic outcome.<sup>23</sup> If there is no difference between groups, it cannot be determined whether a true disorder-specific effect is obfuscated by examining a HR group in aggregate.

Even when clinical characterization strategies meet reproducible standards, challenges with interpretation can arise. Statistically significant main effects reported from group based analyses (with 3 or more groups) retain clinical meaning only after planned *post hoc* between-group analyses, controlling for family-wise error rate, have been described. For example, planned *post-hoc* comparisons that reveal group differences between LR and HR-ASD groups (for example, oculomotor function,<sup>26</sup> fixation duration,<sup>27</sup> motor development,<sup>7</sup> ERP components,<sup>28</sup>) provide minimal interpretable information if the HR-negative group falls at an intermediary position and doesn't statistically differ from either LR or HR-ASD groups. Indeed, there are very few studies that elucidate clear and interpretable evidence for a disorder-specific effect (that is, LR=HR-negative≠HR-ASD), a familial effect (that is, LR≠HR-negative=HR-ASD), or an endophenotypic effect (that is, LR≠HR-negative≠HR-ASD). Without planned between-group *post hoc* comparisons, accompanied by effect sizes, significant main effects of 'group' are especially difficult to include in a summary of HR infant siblings (for example, Elsabbagh, Mercure.<sup>29</sup>

Finally, a number of published reports revealed provocative results with fewer than 20 HR-ASD children.<sup>1,26,27,29–36</sup> While all of these data represent important preliminary results, they should be considered preliminary approaches to discovery science until sample sizes capable of representing the heterogeneity inherent in autism are ascertained, studied, and reported – and then these studies are replicated. The autism field is not immune to the reproducibility crisis<sup>37</sup> but with increased vigilance, researcher working within the infant-sibling paradigm holds great promise for elucidating reliable patterns of early development.<sup>38,39</sup>

earlier. For example, several studies reported that HR-ASD children differ from HR-negative and LR 12 month-olds in emerging language abilities,<sup>7,9–11</sup> aspects of social-cognition,<sup>12,13</sup> and repetitive behaviors.<sup>14–16</sup> With few exceptions, the majority of studies examining the early emerging ASD behavioral phenotype

are hindered by small sample sizes and methodological/conceptual variations in study design (Text Box 1).

**PRODROMAL FEATURES OF AUTISM**

Although observable behavior does not differentiate HR-ASD infants from their HR-negative and LR peers during the first six months of life, a number of preliminary studies highlight the importance of basic attentional operations and sensorimotor function in the early HR-ASD phenotype. Elison *et al*<sup>26</sup> postulated that many of the observable signs of ASD in 12-month-olds (for example, inconsistently orienting to one's name, diminished response to bids for joint attention, diminished spontaneous gaze to the face to extract social information, and inconsistently making eye contact), implicate behaviors associated with flexibly and efficiently allocating processing resources to salient or biologically relevant information in the environment. Indeed, several studies using eye tracking technology report that HR-ASD infants as young as 6 months of age allocate attentional resources to salient stimuli in a manner that differs from comparison groups in a disorder-specific fashion.<sup>26,30,36,40</sup> While the hypothesis stated above requires further exposition, visual orienting deficits have been identified in seven<sup>26</sup> and 12-month-old later diagnosed with ASD.<sup>31,41</sup> Further, in LR infants, Elison, Paterson<sup>26</sup> identified a specific association between visual orienting latencies and individual differences in organization of a white matter fiber bundle (the splenium of the corpus callosum) that projects through cortical areas important for visual and attentional processing,<sup>42</sup> including posterior parietal and occipital cortices.<sup>43</sup> This functional coupling was not observed in the HR-ASD group, suggesting atypical cortical function in this area that is critical for subsequent cognitive development.<sup>44,45</sup> The splenium also projects through the posterior hub of the default mode network, which has been characterized as early as the neonatal period,<sup>46</sup> suggesting that this may be an important target for subsequent research on its role in the very early development of autism.

Differences in fine and gross motor skills observed at 6 months of age in HR-ASD children<sup>7</sup> suggest that motor development in the first year of life may have a role in the development of autism.<sup>7,32</sup> The presence of increased motor stereotypes in HR-ASD infants<sup>14</sup> at 12 months of age also points to abnormal development of motor systems, suggesting that processes that regulate diminishing gross motor rhythmic stereotypes between 6 and 12 months may be abnormal. Indeed sensorimotor systems that integrate and transform visual and auditory information into motor commands during the infant period play a prominent role in a recent computational model of ASD emergence.<sup>47</sup> This model is augmented by preliminary evidence of abnormal neonatal brainstem function in graduates of the neonatal intensive care unit (NICU) who subsequently develop autism.<sup>48</sup> Sensorimotor deficits and accompanying brain changes in associated regions are widely reported in autism beyond the infant period,<sup>49–57</sup> as well as in first-degree relatives, supporting the sensorimotor domain as an endophenotype in autism.<sup>58</sup>

Taken together, this body of work indicates that the defining features of autism are not present at 6 months of age, but begin to emerge in the second year of life and appear to consolidate between 18 and 36 months. There is a striking paucity of data at 9–10 months of age, which may eventually alter what we currently know about the developmental emergence of defining characteristics of autism (but see refs. 29,59,60). To date, the majority of pre-symptomatic behavioral markers of autism, investigated in the first year of life, have been characterized with eye tracking technology. Attentional and sensorimotor functioning that supports basic information processing capacities, motor function, as well as flexibly and efficiently allocating processing resources to salient or biologically relevant information, represent critical

targets for further investigation. This behavioral evidence also points to relevant neural systems implicated or associated with these behaviors, including the precuneus,<sup>61,62</sup> the posterior cingulate cortex,<sup>42</sup> the intraparietal sulcus,<sup>63,64</sup> the corpus callosum<sup>26,65,66</sup> and the cerebellum.<sup>67</sup> Whether these structures play a foundational role in a cascade of downstream events, resulting in autism, is currently unclear.

### CORTICAL SURFACE AREA, BRAIN OVERGROWTH AND THE EMERGENCE OF AUTISTIC BEHAVIOR

One of the most consistent findings from studies of toddlers with autism has been a modest but significant increase in overall brain volume.<sup>68–70</sup> Findings from a retrospective head circumference and prospective brain imaging study of two year olds with autism, followed up at age four years, indirectly suggested that brain enlargement was not present at birth but emerged at the end of the first and second year of life.<sup>71</sup> Increased brain volume was associated with a stable increase in cortical surface area (but not cortical thickness) from two to four years of age.<sup>71</sup> The presence of an early increase in surface area in association with brain enlargement, was also recently reported by Ohta and Nordahl.<sup>72</sup>

Hazlett, Gu<sup>73</sup> prospectively assessed infants at high and low familial risk for autism, with brain imaging and cognitive-behavioral measures at 6, 12 and 24 months of age.<sup>73</sup> HR subjects who were diagnosed with autism at 24 months of age were observed to have significant brain enlargement in comparison to both HR children who did not develop autism and those at LR with typical development. Brain enlargement was not present at 6 or 12 months of age, indicating that brain overgrowth at 24 months of age was the result of an accelerated rate of brain growth in the second year of life. HR infants later diagnosed with autism also showed an increased growth rate of cortical surface area from 6 to 12, but not 12 to 24 months of age in comparison to both the HR without autism and LR groups. No group differences were seen in cortical thickness across the 6–24 month interval. Exploratory analyses revealed that the greatest differences in surface area growth rate in HR-ASD infants were observed in the right middle occipital gyrus and left cuneus in visual cortex. This developmental perspective on individual-level change in brain growth rate, over a specific time period, as opposed to the finding of cross-sectional brain enlargement, has implications for our understanding of the number of autistic individuals potentially affected by this phenomenon and its relevance to understanding etiologic heterogeneity and pathogenesis in this disorder (see Text Box 2).

Surface area growth rate from 6 to 12 months in HR-ASD infants was significantly correlated with total brain volume growth rate from 12 to 24 months of age. Change in total brain volume from 12 to 24 (but not 6 to 12) months of age was associated with increased severity of autistic-like social deficits at 24 months on the Autism Diagnostic Observation Schedule (ADOS).<sup>74</sup> Similar findings in severity of social deficits were observed at 12–24 but not 6–24 months of age, as measured on the Communication and Symbolic Behavior Scales.<sup>75</sup> No significant relationship was observed between brain volume and repetitive behavior on the ADOS.

### THE PATHOPHYSIOLOGY OF EARLY AUTISM

Taken together the findings described above suggest a temporal sequence of events in the developing brain of autistic individuals whereby hyper-expansion of surface area, beyond the non-uniform expansion of surface area noted in typically developing infants,<sup>82</sup> co-occurs temporally with a prodromal period of behavioral (that is, motor-sensory and visual orienting) differences from 6 to 12 months of age. Subsequent brain overgrowth occurs

#### Box 2 Accelerated brain growth rate, brain enlargement and etiologic heterogeneity

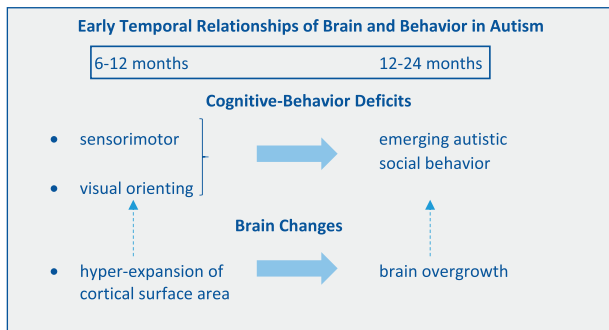
Etiologic heterogeneity is well documented in the behaviorally defined syndrome of autism.<sup>76</sup> Cross-sectional studies of brain volume in autistic individuals suggest that brain enlargement is present in a small subgroup of children with autism and thus may have relevance for understanding pathogenesis in that subgroup alone. This determination is based on using a statistical cutoff for defining enlargement of greater than 1.5 standard deviations beyond the mean of a non-autism comparison group.<sup>77–79</sup> As would be expected by using such a statistical cutoff, some studies have identified that brain enlargement is present in ~15% of autistic children. This approach to understanding the overall significance of the phenomenon of brain overgrowth is reminiscent of the use of a threshold of head circumference greater than the 98th percentile to define macrocephaly, a standard measurement in pediatric clinical practice.<sup>80</sup>

Individual rather than group level, prospective studies suggest an alternative way of conceptualizing this phenomenon and its relevance for understanding heterogeneity in autism. Accelerated brain growth rate in autism (that is, increased rate of brain growth between 12 and 24 months as described by Hazlett and Gu<sup>73</sup> suggests that rather than cross-sectional volumes, it is change over time in brain volume, in an individual relative to themselves, across a specific interval of time, that may be most relevant to understanding the pathogenesis of autism and its relationship to the unfolding symptoms and cascading brain changes over time. As an illustration, a substantial change from an initial brain volume in the 30th percentile of the population to brain volume in the 60th percentile would not identify an individual as having brain enlargement or megalencephaly, yet this two-fold accelerated rate of brain volume growth over time is substantial and may be of greater significance than absolute volume viewed cross-sectionally. Data from Hazlett *et al*<sup>73</sup> and corresponding pre-clinical studies by Fang *et al*<sup>81</sup> suggest that substantial change over time (rather than cross-sectional measures of enlargement that may or may not be due to an accelerated growth rate in infancy) may adversely affect development of neural circuitry and result in the appearance of the social deficits characteristic of autism. This developmental perspective on the significance of brain overgrowth complicates interpretations of the relevance of brain enlargement over time with respect to etiologic heterogeneity in autism and may indicate that this mechanism is relevant to a greater proportion of affected individuals than would be observed with a statistical cutoff defining cross-sectional brain enlargement.

in the second year of life, at a time when autistic social deficits are emerging and becoming more robust<sup>13</sup> (Figure 1).

#### Hyper-expansion of surface area and brain volume

Early expansion of cortical surface area was initially thought to be due to the symmetrical, proliferation of neuronal progenitor cells, according to the radial unit hypothesis of Rakic.<sup>83</sup> More recent refinements relevant to gyrencephalic mammals suggest that a specialized type of progenitor cell, exclusive to mammals with a folded cerebral cortex and referred to as the intermediate radial glia cell, is generated in the outer subventricular zone. Fan-like expansion of these radially migrating neurons is thought to drive tangential surface area growth and play a fundamental role in the ontogenetic and evolutionary expansion of the mammalian cerebral cortex.<sup>84–87</sup> The production of neurons through intermediate progenitor cells may precede development of the



**Figure 1.** Early temporal relationships of brain and behavior in autism.

subventricular zone such that expanded numbers of intermediate progenitor cells that later lead to an increase in cortical surface area occurs before the onset of neurogenesis and without increasing the size of the ventricular zone.<sup>85,88</sup>

Studies in mice have identified molecular contributors to progenitor cell proliferation and cortical surface area expansion such as  $\beta$ -catenin,<sup>89,90</sup> ARHGAP11B<sup>91</sup> and FGF signaling.<sup>92</sup> Although it should be noted that mechanisms underlying surface area expansion in the gyrencephalic brains of humans may not fully correspond to those contributing to surface area expansion in the lissencephalic brains of rodent models; and thus rodent models of cortical surface area growth may not model all aspects of human neocortical brain development. Non-human primate models may prove especially important in this regard.

The genetic architecture of surface area has been described in humans,<sup>93</sup> and differs from that underlying changes in cortical thickness.<sup>94–96</sup> Genes involved with regulation of neuronal proliferation have also been linked to autism,<sup>97,98</sup> including a relationship to the social and stereotypical behaviors of autism in a mouse model dysregulating the  $\beta$ -catenin/*Brn2/Tbr2* transcriptional cascade that results in expansion of basal neural progenitor cells.<sup>99</sup> Indeed in a review of the genetics and post-mortem literature, Packer<sup>100</sup> recently suggested that proliferation of neural progenitor cells potentially plays a central role in the pathogenesis of autism.

A recent large-scale, longitudinal, brain imaging study in human infants<sup>101</sup> observed that early, post-natal surface area expansion in infancy is a principal driving factor in the growth of cortical volume at two years of age in the general population. Increased numbers of pre-frontal cortical neurons are reported in one post-mortem study<sup>102</sup> of older children and adolescents with ASD, although differences in neuron number are not reported in others.<sup>103,104</sup> While proliferation of neural progenitor cells is not the only factor affecting cortical dimensions, it is considered a major early determinant. According to the “radial unit model” of Rakic<sup>83</sup> cortical surface area is directly related to the number of radial units or so-called, “cortical mini-columns”. The report of an increased number of narrow, cortical mini-columns in the brains of autistic individuals is consistent with the above suggestion of an early increase in number of neurons in the brain in autism.<sup>105</sup> However, these findings were not confirmed in a larger post-mortem study, where mini-columns in autistic subjects were found to be wider than controls, with more robust differences being found at younger ages.<sup>106</sup>

The early post-natal period in human brain development is also noted to be a time for sculpting of neuronal processes through pruning and apoptosis, largely beginning at the end of the first year.<sup>107</sup> Decreased post-natal spine pruning resulting in an increased number of spines, was reported in a recent post-mortem study of ASD,<sup>108</sup> suggesting this as a potential contributor

to brain overgrowth and refinement of neural circuitry. Spine density was correlated with the hyper-activated mechanistic target of rapamycin (mTOR) and decreased neuronal autophagy. An autism mouse model of over-activated mTOR resulted in decreased postnatal spine pruning and autism-like social deficits that was corrected by the mTOR inhibitor rapamycin.<sup>108</sup> The mTOR signaling pathway has been implicated in a number of genetically defined autistic syndromes such as PTEN-associated ASD (or Cowden Syndrome), a condition associated with macrocephaly and altered brain growth trajectory.<sup>94,109</sup> Kwon, Luikart<sup>110</sup> demonstrated that inactivation of PTEN led to reduced social interaction and hyper-responsiveness to sensory stimuli in mice. PTEN mutants also have neuronal hypertrophy and macrocephaly. Conditional deletion of PTEN in lineages that generate interneurons increases the ratio of parvalbumin to somatostatin interneurons.<sup>111</sup> Intriguingly, PTEN+/- mice show macrocephaly and an excess of cortical neurons at birth, and early brain overgrowth is driven by excess Wnt/ $\beta$ -catenin signaling.<sup>94</sup>

Other manipulations that alter Wnt/ $\beta$ -catenin pathway activity drive cortical overgrowth. The small molecule WNT pathway inhibitor XAV939 induced a transient amplification of intermediate progenitors, when injected into the developing neocortex of embryonic mice, followed by excessive production of excitatory pyramidal neurons in neocortical layers 2/3, and autism-like behaviors.<sup>81,112</sup> The excess of excitatory neurons impaired dendrite and spine development and affected the laminar distribution of interneurons. Dysregulation of neuronal development consequently altered excitatory and inhibitory synaptic connections and strength, causing an imbalance between synaptic excitation and inhibition, consistent with the Excitatory/Inhibitory Imbalance Theory of autism.<sup>113,114</sup> Mice exhibited autistic-like behavioral changes in social interaction and repetitive behaviors, suggesting a mechanistic link between early over-proliferation of cortical neurons and development of neuronal processes that impacts functional circuitry and produces an autistic-like behavior profile. Likewise, *in utero* exposure to the anti-epileptic valproic acid, known to increase risk for autism in humans<sup>2</sup> and a well-recognized animal model of autistic behaviors,<sup>115</sup> leads to expansion of upper layer cortical neurons.<sup>116</sup>

Consistent with the hypothesis that brain enlargement in autism is due to altered progenitor cell proliferation leading to network dysregulation are the recent findings by Marchetto, Belinson<sup>117</sup> examining induced pluripotent stem cells, neural progenitor cells and neurons from individuals with ASD who demonstrated early brain overgrowth on MRI. ASD-derived neurons showed abnormal neurogenesis and reduced synaptogenesis, leading to functional deficits in neuronal networks. This process was reversed with administration of insulin-like growth factor 1 (IGF-1) suggesting a potential underlying cellular mechanism for targeted intervention.

#### Converging evidence from studies of genetically defined autistic conditions

Etiological heterogeneity is ubiquitous in autism. The framework put forward in this paper derives largely from findings in HR infant sibling studies and is therefore defined by the subset of infants who presumably have ‘idiopathic’ autism and a high familial liability for this condition. While etiologies differ in autistic individuals, there is likely to be more convergence at a mechanistic level with at least some other subgroups of autistic individuals.

Several genetically defined autism syndromes (for example, 16p11 deletion, PTEN, and *Chd8* mutations) are associated with increased brain volume and macrocephaly<sup>118,110,119</sup> Qureshi, Mueller<sup>119</sup> reported brain volume enlargement and expanded cortical surface area (but not cortical thickness) in individuals with deletion 16p11, a copy number variant associated with autism;<sup>120</sup>

whereas brain volume and surface area were decreased in those with duplication 16p11. Examination of a murine model of human 16p11 deletion revealed enhanced neuro-progenitor cell proliferation and premature cell-cycle exit.<sup>121</sup> Wang and Lin<sup>122</sup> examined *Chd8* in induced pluripotent stem cells (iPSCs) to better mimic the loss-of-function status that would exist in the developing human embryo prior to neuronal differentiation. Genome-wide association studies by these investigators identified seven of the twelve genes associated with human brain volume or head size were dysregulated in *Chd8* (+/-) neural progenitors and neurons, as well as finding differential expression of  $\beta$ -catenin signaling. Transcriptomic profiling revealed that *Chd8* regulates multiple genes implicated in ASD as well as brain volume. Finally, *Chd8*-deficient mice showed slight activation of Wnt/ $\beta$ -catenin signaling embryonically, an enlarged brain and autism-like phenotypes,<sup>123</sup> while *Chd8* knockdown early in cortical development (E13) impaired progenitor proliferation and led to depletion of the progenitor pool, which would ultimately reduce neuron number.<sup>124</sup> Future studies will be needed to evaluate the cellular basis for brain overgrowth in *Chd8* mutant mice, and to evaluate developmental stage and cell context-dependent effects of WNT signaling on brain overgrowth.<sup>125</sup>

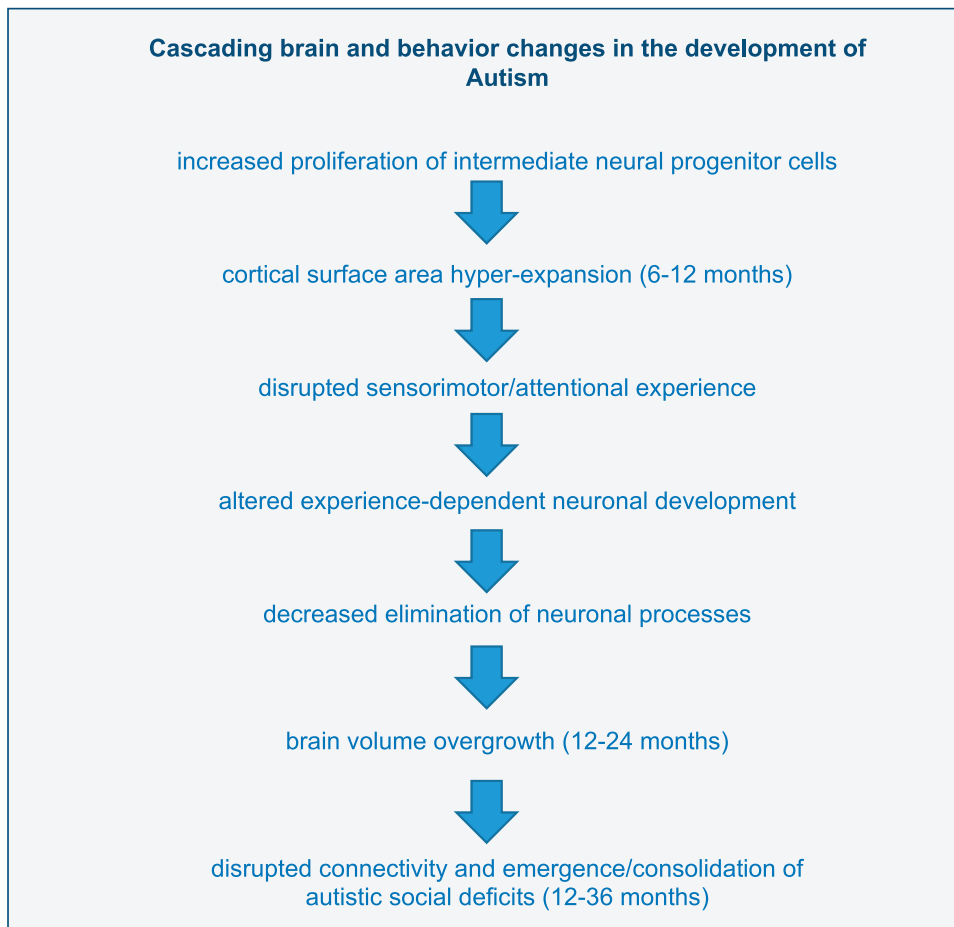
Considered together these studies suggest a potential cellular mechanism underlying brain overgrowth in autism – a primary increase in intermediate neural progenitor cells, possibly driven by abnormal Wnt pathway activation, leading to an increase in cortical neuron number, an increase in brain volume and an imbalance in neural connectivity.<sup>126</sup> There is increasing recognition that some high confidence autism-linked mutations, like *DYRK1*, cause microcephaly.<sup>127</sup> Consistent with the clinical and

etiologic heterogeneity known to be present in the behaviorally defined syndrome of autism, and consistent with the above referenced study showing decreased cortical surface area and brain volume in duplication 16p11, it should be emphasized that a primary increase in intermediate neural progenitor cells, may not be an underlying mechanism seen in autistic individuals who show no signs of macrocephaly or increased rate of brain growth and instead are microcephalic.<sup>119</sup>

### A CONCEPTUAL FRAMEWORK FOR EARLY BRAIN AND BEHAVIOR DEVELOPMENT IN AUTISM

#### Integrating brain and behavior

In typically developing infants, expansion of cortical surface area in the first year of life is most robust in visual cortex.<sup>82</sup> Surface area expansion in this same region is even more robust in infants later diagnosed with autism.<sup>73</sup> Hyper-expansion of surface area in visual cortex during the latter part of the first year may underlie the sensorimotor and visual orienting deficits observed during this period in infants later diagnosed with autism.<sup>26</sup> These sensory/attentional deficits may alter experience-dependent neuronal development resulting in decreased sculpting of neuronal processes and brain overgrowth and disruption of selected brain connections, which in turn leads to the development of autistic-like social deficits (see Figure 2). Alternatively, a primary increase in intermediate neural progenitor cells leading to an increase in neuron number, may directly result in a downstream increase in brain volume. Increases in neuron number may reduce efficient sensorimotor and attentional functioning observed in the first year of life. As suggested by the work of Fang *et al*<sup>81</sup> and Marchetto



**Figure 2.** Cascading brain and behavior changes in the development in autism.

et al,<sup>117</sup> abnormal brain overgrowth could disrupt synapse function and contribute to the emergence of autistic-like social and cognitive deficits in the early post-natal period.<sup>7</sup>

#### Other brain characteristics in autism during infancy

The above conceptual framework describes a sequence of events in the pathogenesis of brain overgrowth and the emergence of social deficits in autism. While we have built a story around two key findings newly emerging in the HR infant sibling brain imaging literature, other early brain differences have been identified in HR infant siblings in infancy. In HR-ASD infants generalized (multiple fiber tracts throughout the brain) abnormalities in white matter organizational structure have been reported<sup>65,128</sup> as early as 6 months of age. Aberrant white matter organizational structure has been observed by 6 months of age in the genu of the corpus callosum<sup>65</sup> and white matter organization in the genu and cerebellar peduncles is significantly associated with sensory hypo- and hyper-responsivity at 24 months of age.<sup>129</sup> In addition, other reports have demonstrated that increased extra-axial cerebrospinal fluid volume (EA-CSF) is present by 6 months of age in HR infants who are later diagnosed with autism at 24 months of age.<sup>38,39</sup> Enlargement of the extra-axial fluid compartment suggests diminished uptake and flow of cerebrospinal fluid (CSF) with accumulation of brain metabolites (for example,  $\beta$ -amyloid and pro-inflammatory cytokines).<sup>130,131</sup> Increased extra-axial fluid volume in infancy has been linked to motor deficits<sup>39,132–134</sup> as well as over-proliferation of neuronal progenitor cells.<sup>135</sup> This latter observation led Lehtinen, Zappaterra<sup>135</sup> to suggest that CSF composition may have critical relevance to the pathogenesis of neurodevelopmental disorders and is consistent with the findings by Hazlett, Gu<sup>73</sup> suggesting early post-natal hyper-proliferation in autism.

In a small study, disrupted connectivity measured via quasi-resting electroencephalography (EEG) differentiated HR in 14-month-old infants later diagnosed with autism from a HR-negative group and LR controls.<sup>136</sup> Interestingly, oscillations in the alpha wave are thought to reflect processes related to visual and/or attentional engagement. While source localization of scalp recorded electrophysiological activity remains an enduring challenge, EEG and ERP studies have the potential to elucidate processing differences in the early autism phenotype. Indeed, there is a growing body of work comparing HR and LR infants (Text Box 1), yet there are very few EEG/ERP studies that directly compare processing between outcome groups (HR-ASD, HR-negative and LR) in the first year of life.<sup>29,137</sup>

The potential for time-dependent pathophysiological mechanisms to instantiate cascading neurobiological processes is consistent with the theoretical framework for neurobehavioral development, 'Interactive Specialization'.<sup>138</sup> This model presumes that instantiating pathophysiology is transient<sup>99</sup> and/or likely to be obfuscated by subsequent cascading neurobiological effects or disease progression. ASD imaging studies have revealed decreasing cortical thickness but no change in surface area, in older autistic individuals,<sup>139,140</sup> suggesting a protracted period of dynamic, neurobiological development in autism, throughout childhood and into the adult years. The impact of the intersection of life experiences and accumulating effects of autistic social, cognitive and sensory impairments must be considered as perhaps having an additional, intermediate and long-term role in experience-dependent brain development at later ages.<sup>141</sup>

#### Regional surface area hyper-expansion, sensory deficits and excitatory/inhibitory imbalance

Hazlett, Gu<sup>73</sup> observed the most robust and significant surface area hyper-expansion in HR-ASD infants to occur in right middle occipital gyrus (Brodmann Area 18) and the left cuneus (Brodmann Area 17), both involved with visual processing. Increased surface

area in primary visual cortex has been linked to increased GABA concentration in medial occipital cortex.<sup>142</sup> Mariani et al<sup>143</sup> conducted whole genome sequencing on iPSC lines derived from macrocephalic individuals with ASD and detected significantly perturbed transcriptomic signatures involving regulation of cell proliferation and neuronal differentiation that appeared to be due to a decrease in cell-cycle length. Further analyses suggested a greater proportion of GABAergic neurons in cortical organoids from ASD-derived neurons. These authors concluded that there is an early increase in proliferation of GABAergic neuronal progenitor cells in ASD-derived organoids that give rise to an increased proportion of mature GABAergic interneurons.

Experience during critical periods in early postnatal life refines cortical circuitry. Critical periods are regulated by the balance of excitatory and inhibitory (E/I) neurotransmission in the brain during development.<sup>144</sup> Rubenstein and Merzenich<sup>113</sup> first proposed an E/I imbalance in autism. More recently, it has been proposed that alteration of the expression and/or timing of critical period circuit refinement in primary sensory brain areas may significantly contribute to autistic phenotypes, including cognitive and behavioral impairments.<sup>145</sup> The timing and location of surface area changes in the early development of autism suggests that regional hyper-proliferation of neural progenitor cells leading to brain overgrowth and disruption of vulnerable neural circuits may play a fundamental role in the development of autism. Consistent with the role of sensory experiences in the development of autism,<sup>146</sup> Angelman syndrome model mice deficient in Ube3a, were observed to have profound impairments in neocortical plasticity in visual cortex, however plasticity was preserved during dark rearing. Altered early sensory experience may indeed be a primary deficit in autism resulting in downstream changes that we more traditionally associate with the defining features of autism e.g., social deficits. Understanding the impact of aberrant sensory function and experience in the first year of life may provide insights relevant to early intervention. Indeed a small, pilot study employing the Early Start Denver behavior intervention model, an approach that is heavily based on reinforcing and synchronizing selected sensory inputs in infants with autism as well as those at risk for autism, suggested that this type of very early intervention may be particularly beneficial.<sup>147</sup> Wass, Porayska-Pomsta<sup>148</sup> employed a gaze-contingent eye tracking paradigm and demonstrated ability to train attentional control in 11-month-old infants. Given the findings by Elison, Paterson<sup>26</sup> and others regarding altered early visual orienting in infants who later demonstrate the defining features of autism, this approach offers a plausible avenue for targeted prodromal intervention in autism.

#### CAVEATS AND FUTURE DIRECTIONS

Findings regarding accelerated growth rate of cortical surface area and brain volume require replication. As discussed in Text Box 2, the concept of increased brain growth rate within individuals has implications for understanding the etiologic heterogeneity in autism and specifically the number of affected individuals for whom this mechanism is relevant. Future studies will also need to examine the specificity of increased brain growth rate to autism versus other neurodevelopmental disorders both in etiologically (for example, Fragile X Syndrome) and phenotypically (for example, language and learning disorders) defined conditions. Large-scale prospective studies will provide additional insights into risk and protective factors in the cascading brain and behavior changes that result in autism in 2–3 years old infants, including the effects of genes, exposure to environmental toxins and experience. Finally, links to mechanisms require further exploration e.g., examination of the relationship between findings from induced pluripotent stem cells and cellular development to more refined phenotypes such as hyper-expansion of cortical surface area in the first year of life.

In summary, a conceptual framework for the early, post-natal development of autism is proposed that integrates behavioral and brain imaging findings from HR, prospective infant sibling studies of autism. These findings are consistent with brain and behavior studies about autism at older ages, post-mortem studies, as well as findings from genetically defined autistic syndromes and corresponding mouse models. This developmental framework postulates that early increased proliferation of neuro-progenitor cells leads to a non-uniform, hyper-expansion of cortical surface area that leads to early deficits in visual receptive/visual attention abilities that alter subsequent experience-dependent neuronal development more broadly in the brain. Cortical overgrowth results in a disruption in the refinement of selected neural circuit development and is associated with the emergence of social deficits in autism. Thus autism appears to primarily be a disorder of early sensory-motor-attention impairment, associated with hyper-proliferation of neuronal progenitor cells; and secondarily resulting in the defining features of autism and, in particular, social deficits. Better understanding of the timing of developmental brain and behavior mechanisms in autism during infancy, a period which precedes the emergence of the defining features of this disorder, will likely have important implications for designing rational approaches to early intervention.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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