

Autism spectrum disorders: developmental disconnection syndromes

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Autism is a common and heterogeneous childhood neurodevelopmental disorder. Analogous to broad syndromes such as mental retardation, autism has many etiologies and should be considered not as a single disorder but, rather, as 'the autisms'. However, recent genetic findings, coupled with emerging anatomical and functional imaging studies, suggest a potential unifying model in which higher-order association areas of the brain that normally connect to the frontal lobe are partially disconnected during development. This concept of developmental disconnection can accommodate the specific neurobehavioral features that are observed in autism, their emergence during development, and the heterogeneity of autism etiology, behaviors and cognition.

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Introduction

Autism spectrum disorders (ASDs) form a heterogeneous, neurodevelopmental syndrome for which there is yet no unifying pathological or neurobiological etiology. It is defined by clinical assessment and onset of three core disturbances before three years of age: atypical social behavior; disrupted verbal and non-verbal communication; and unusual patterns of highly restricted interests and repetitive behaviors. However, across these core features there are significant differences in the extent and quality of symptoms; for example, although language problems are fundamental, delay in spoken language is observed in only half of ASD subjects [1,2]. Other associated, but non-core, features such as mental retardation are also variable, and current data suggest that <50% of all individuals who have autism present with significant cognitive impairment [3]. Social impairments can also

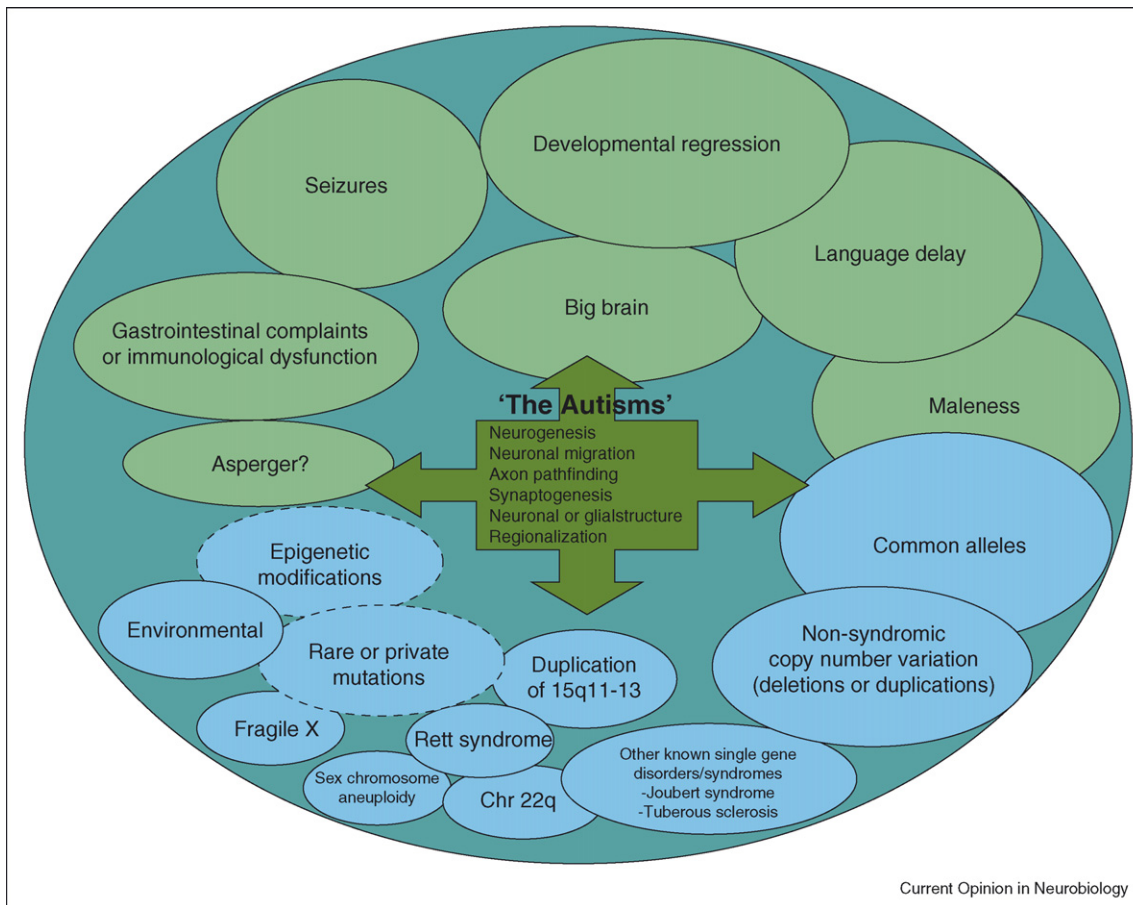
be expressed in different ways — some individuals who have ASD display an aloof style of social interaction, whereas others actively seek personal interactions, albeit in a socially odd manner [4,5]. Similarly, although onset before age three is mandatory in the current diagnostic scheme, there also are major differences in developmental course, with some children manifesting signs of the disorder from early infancy and others experiencing behavioral regression in the second or third year of life. Finally, as might be predicted from the clinical picture, treatment responsiveness also varies significantly among children with autism, and two children who appear the same at age three can show markedly different developmental trajectories at later ages.

If one considers this clinical heterogeneity, the lack of correlation between occurrence of different deficits (including the core features) [6], and also the genetic heterogeneity [7,8], it might be more constructive to think of ASDs as 'the autisms' than as a unitary syndrome (Figure 1). Thus, research efforts have the multiple goals of explaining the etiology of ASDs and of understanding the syndrome-specific and non-specific factors that influence the variability in relative risk, in developmental course of symptom expression, in treatment responsiveness and in co-occurrence of medical and mental health dysfunctions in ASDs [9].

Research into the biological and genetic basis of the autisms is in its infancy, so current etiological viewpoints are necessarily primitive. Here, we provide a synthesis of data published mostly in the past two years that support the emerging hypothesis that the autisms result from disconnection of brain regions that are highly evolved in humans and that are involved in higher-order associations [10,11] (in other words, that ASDs form a 'developmental disconnection syndrome'). This hypothesis is analogous to the concept of focal disconnection syndromes put forth 40 years ago by Norman Geschwind, in which disruptions in connectivity between higher association and multimodal cortical regions lead to specific disorders of cognition [12,13]. However, owing to the developmental nature of the autisms, disconnection in the case of ASDs is not primarily a disruption of previously connected regions, as in the original disconnection syndromes, but rather is a failure of their normal development that might have diverse etiologies.

Thus, developmental disconnection in the ASDs could include a weakening of already formed connections, or a

Figure 1



Here we emphasize some of the many possible etiological features (genetic and environmental heterogeneity; blue circles) and the clinical or syndromic heterogeneity (green circles) within autism spectrum disorder, in addition to the myriad of neurodevelopmental processes that might be disrupted to cause disconnection (central arrowed box). Broken lines emphasize areas where the extent of the contribution to the disorder remains to be defined relative to the contributions made by other factors. Although we postulate that developmental disconnection is a unifying theme to explain the pathophysiology of the autisms, we need to emphasize that little is known about the specific relationship between etiologies, mechanisms and the resulting phenotypes. The enormous complexity and heterogeneity, from the causal-mechanistic levels to the observed phenotypes, needs to be clearly acknowledged; hence the need to reframe the syndrome of autism as 'the autisms'. Because the genetic architecture of the autisms is not yet known, we list known causes, such as genetic syndromes (Fragile X, Joubert and Timothy syndromes) in which ASD can be observed, and acknowledge the likely contribution to the autisms from many distinct forms of genetic variation (including common and rare variation) and from environmental factors. The term 'autisms' reflects not only that ASD is based on multiple etiologies but also that there are distinct clinical entities whose phenotypic overlap and etiologies remains to be defined. For example, what features define the ~1/5 of ASD subjects who have macrocephaly? Is it one relatively distinct pathway that is disrupted, or many molecular etiologies that converge on big brains? Furthermore, do those who have macrocephaly comprise a cohort enriched for seizures and regression, and are these other features related to specific etiologies? A similar set of questions can be applied to those who have developmental regression and other phenotypes. In addition, it remains to be determined whether the various clinical phenotypes relate not only to specific causal factors but also to specific intermediate developmental processes that underlie brain and behavior, such as neurogenesis, neuronal migration, axon pathfinding, synaptogenesis, synaptic plasticity and regionalization.

failure of certain connections to establish correct organization *de novo*. From a neurobiological perspective, the affected stages of development could include prenatally determined histogenic events such as neuronal migration and axon pathfinding, which establish proper positioning and patterning of basic connectivity, and postnatally regulated features of dendritic development, synaptogenesis and pruning. At these postnatal stages, even subtle disturbances in timing might influence connectivity and disconnectivity. Disrupting basic histogenic processes

across an extended period of development and maturation in humans, which begins *in utero* and extends well into childhood [14,15], provides an obvious point of convergence of interactions between genes and environmental factors that influence development. Studies in monkeys indicate that, although many developmental events such as neuron production and migration begin simultaneously across the cerebral cortex, differences in the duration of histogenesis between functional areas provide opportunities for differential disruptions that

depend on the timing of the environmental insult [16]. For example, neurons that form agranular association cortices in frontal regions are produced and migrate to their destinations in two-thirds of the time needed to assemble primary sensory granular cortices.

Heritability of the autisms

Based on twin and family studies, the autisms are among the most highly heritable common neuropsychiatric disorders [17–20]. The risk to a sibling born to a family in which there is already an autistic proband is estimated to be 25–100 times greater than the risk for the general population [21]. The severity of the three core disturbances varies across the autisms, but many of the core and associated features show familial clustering [1,22–24] and evidence of heritability [25]. Recent use of complex statistical models to examine a large cohort of twins from the general population whose autistic-like traits ranged from none to the extremely severe (i.e. ASDs) suggests that the three core traits are each highly heritable, albeit owing to different genes and modest non-shared environmental effects [26•]. The likely genetic heterogeneity among the three key components of the autisms suggests that examination of populations in which autistic-like traits are well characterized is a sound strategy for defining the underlying risk. The effects of such genetic risk factors are likely to converge on the modulation of inter-related neurodevelopmental events that broadly affect the physical and functional connectivity of higher-order association areas of the brain. Although we posit that development of the autisms requires a functional disconnection of these cortical regions from one another, it also is likely to include or be partially mediated by abnormalities in the development of subcortical regions that connect to these areas. In the remainder of this review, we focus on the cerebral cortex as a nexus that underlies the core disruptions observed in the autisms.

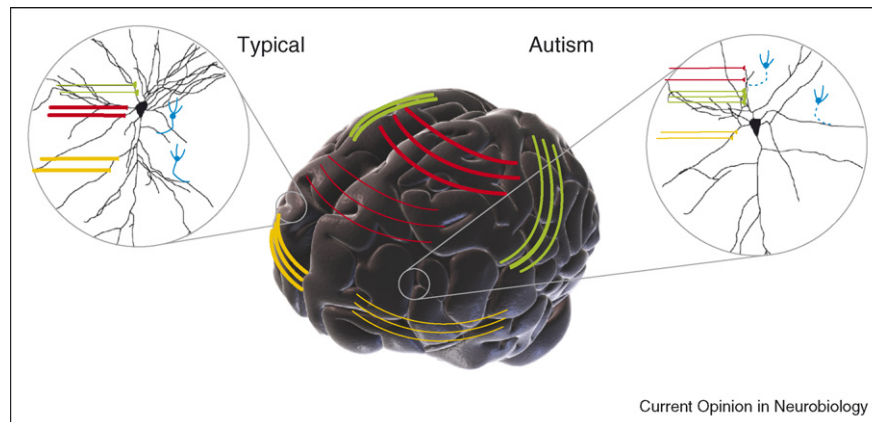
Limited clues regarding pathophysiology of the autisms

The histopathology of the cerebral cortex in the autisms as observed to date indicates that there is only minor disruption to the fundamental radial and tangential organization of neurons and glia [27]. There are reports of altered packing density of cells, minor and highly variable disruption of dendritic orientation, reduced size and spacing of radial minicolumns of neurons in different cortical areas including the frontal lobe [28•,29], and selective reduction in cell number in some forebrain structures [30]. Whether or not disruption of the columnar organization of the cortex is the primary problem, the evidence, albeit based on small numbers, indicates that there are subtle (i.e. microscopic) but nonetheless widespread neuronal abnormalities throughout the cortex [22]. These limited studies together suggest that the autisms might be characterized by distributed atypical development.

The general trend of larger head size for individuals who have autisms is consistent with the concept of more widespread circuitry disturbances; macrocephaly is observed in ~20% of children who have ASDs [31–33], and some regions of the cerebral hemisphere can remain enlarged into adulthood [34]. Although the neuroanatomy of macrocephaly in the ASDs has not been finely delineated and findings vary, largely owing to small sample sizes, preliminary studies suggest that areas of both white matter and gray matter are abnormally large throughout many regions of the cortex, including frontal, temporal and parietal lobes [35–37]. However, the cortical changes are likely to be far more complex than simple increases in size: there can also be reduction of certain white matter tracts, depending on the age and subtype of autism represented in the studied population [38•]. The size of white matter tracts (which reflects axon arborization and myelination) and the neuron numbers, neuron densities and dendritic arborizations in gray matter all are features that might contribute to brain size, and that are developmentally regulated over an extended prenatal and postnatal time period. This period includes the most temporally extended processes in brain development: synapse formation, synapse pruning and myelination. The increase in brain size in typical children over time is due to early growth of gray matter followed by pruning of dendrites and synaptic structures, combined with major growth of white matter as it undergoes myelination. A recent study suggests that cognitive skills are more significantly correlated with the developmental trajectory of brain volumes over time than with static brain volume [39]. Thus, it will be important to delineate further the longitudinal pattern of specific brain volumes over time in the autisms. Finally, data from neurogenetic syndromic disorders, in which co-occurrence of autisms and alterations in synaptic organization are common [40], are consistent with a developmental disconnection model.

A model of disconnection, irrespective of the underlying developmental mechanisms, needs to account for the preservation or even enhancement of certain functions and for the specificity of deficits observed in the autisms. Although the syndromes often overlap, the autisms are not synonymous with global intellectual disability or mental retardation. Thus, as alluded to by Frith [10], we propose that to result in the autisms, the key disconnection must be between several frontal lobe and temporal lobe multimodal higher-order association cortices (Figure 2) — for example, a combination of frontotemporal, frontolimbic, frontoparietal and interhemispheric connections, as suggested previously by other authors [38•,41•,42–44]. From a developmental perspective, the model would include disruption of the initial architecture of connectivity and local circuits, which would change the influence of experience-dependent processes that occur subsequently and that are crucial for continued development and reorganization of connections. Specifically, disconnection of

Figure 2



Developmental disconnection in autism. Disconnection between cortical areas in the autisms can be heterogeneous and is represented by reduced size (illustrated by thinner lines) of certain callosal tracts (red) and frontotemporal connections (yellow). Overconnectivity (illustrated by thick green lines) between certain cortical areas might also lead to enhanced function in certain domains. At the level of local circuits (insets), the effects of disruption to long-range inputs can also be influenced by altered inhibitory input (blue broken lines), which is essential for the proper maturation and stabilization of connectivity.

dorsolateral prefrontal regions and anterior cingulate cortex from other regions necessary to develop joint attention in early infancy, which is the foundation of language and social behavior, would probably have widespread reverberations during development [44].

That such deficits are present in the autisms is supported by an emerging literature on decreased functional connectivity that involves higher-order processing [45–47], and by data that link anatomical differences in key pathways between these regions to the behaviors and cognitive processes that they underlie (e.g. [36,44]). For example, the size of the genu of the corpus callosum, which carries reciprocal fibers connecting the left frontal and right parietal cortices, is positively correlated with functional connectivity in tasks that require the integration of language functions and visuospatial imagery [38*,45]. In addition, some people who have ASDs show distinct alterations in the frontal lobar asymmetries of multimodal language cortex, suggesting that there is disruption of the interhemispheric pathways and the perisylvian intrahemispheric distributed language system [35]. From a neurobiological perspective, differences in pathway connectivity could reflect subtle abnormalities in white matter tracts that reflect developmental alterations in axon number, axon pathfinding, synaptogenesis and subsequent axon elimination. Another instructive observation in this regard comes from Joubert syndrome, in which there is physical disconnection and misrouting of normally crossed and asymmetric sensorimotor systems, resulting in mis-wiring. Although Joubert syndrome is rare, ~25% of children with the syndrome have autism [48] (J Gleeson *et al.*, personal communication).

Intersection of the autisms with the development of functional connectivity

Recent basic neurodevelopmental studies have defined molecular mechanisms that regulate neuronal migration, axon pathfinding, synapse construction and synapse deconstruction, all of which contribute to the functional and structural connectivity that underlies higher cognitive functions. Perhaps most striking has been the discovery that the molecular systems involved in this complex process are pleiotropic: the transcription factors, cell adhesion molecules, extracellular matrix proteins, axon guidance cues and neurotrophins that are involved in the development of connectivity also participate in other processes. In neurodevelopmental disorders, the timing, location and degree to which gene expression is disrupted dictate the emergent phenotype.

A scaffold of basic connectivity is established prenatally in all mammalian species [14], with genetic mechanisms governing the process. Although the genetic output can be influenced greatly by features of the uterine environment (e.g. malnutrition, maternal stress, infections that challenge the immune system, or exposure to toxins or drugs of abuse), information from the outside world (i.e. experience) that stimulates patterned electrophysiological activity does not seem to be necessary for establishing the initial architecture of sensory and motor systems. However, spontaneous prenatal brain activity does contribute to the appropriate wiring of circuits [14,49].

By contrast, postnatal development of the systems that interpret extrinsic information to guide behavior depends greatly on experience, which interacts with the genetic network to build the fine details of interconnected circuits.

The hierarchical nature of the process of circuit formation is particularly acute in relation to social behavior, verbal communication and non-verbal communication, the development of each depending greatly on the capacity of earlier developing sensory, motor and internal homeostatic regulatory components [50]. Thus, the limits of the early-developing parts of a system as determined by genetics greatly influence the subsequent range of possibilities for the development of connectivity and, eventually, the level of function and degree of plasticity a particular circuit can exhibit [49]. As we have already noted, disruption of this developmental hierarchy at the level of disconnection would target certain higher-order association systems, such as those involved in joint attention previously mentioned. It is striking, however, that the development of certain pathways is spared, or even enhanced. This could occur by selective disruption of both long-range connections (which can be affected by changes in expression of axon guidance molecules) and local connections in GABAergic circuits (which serve as essential mediators of activity-dependent maturation of cortical circuits) [51,52]. This selectivity clearly does occur: cell-type-specific and regional disturbances of long-range circuits (reviewed by [53]) and interneuron development [54,55] have both been demonstrated in genetic animal models. This re-emphasizes that the vulnerability of certain systems might relate to the differential timing of circuit assembly in different cortical areas [16]. Whereas the neuronal populations that comprise primary sensory areas are generated over a longer period of time prenatally than the populations of association areas, connectivity of the association areas exhibits a more extended maturation process. Thus, the susceptibility to both very early and late perturbations might be greater in these areas than in other cortical regions. In this regard it is interesting that the left hemisphere in humans takes longer to develop and is more influenced by environmental factors than is the right hemisphere [56]. In addition to these area-specific changes in susceptibility over time, the heterogeneity in disruption of the autisms is also likely to be affected by differential expression patterns (both temporal and spatial) of genes that have been linked to vulnerability.

Linking neurodevelopmental etiology and the genetics of the autisms

Connecting the neurobiological components that build and modify connectivity to the genetic etiologies of the autisms remains a significant challenge, in part owing to moderate-to-weak genetic associations, the likely involvement of multiple genes, and the difficulties of replication in heterogeneous clinical populations [57]. It is becoming clear that the genetics of idiopathic autisms is complex, involving multigenic interactions and potentially multiple, rare genetic variants, or mutations. In addition, any specific genetic risk element is probably related to specific impairments in aspects of cognition or behavior such as social behavior [58], language [1,59] or

repetitive behaviors [60], rather than to the traditional clinical diagnosis of the autisms [6].

Despite the challenges that remain, there has been progress. Analysis of non-syndromic cases in families in which multiple children are affected have revealed rare mutations that disrupt the genes encoding Neuroligin 3 and Neuroligin 4, which are implicated in basic mechanisms of synaptogenesis such as clustering of synaptic glutamate receptors (see also review by Craig and Kang, in this issue) [61]. Neuroligins interact with a family of proteins called β -neurexins during synaptogenesis and there is emerging evidence that rare variations in copy number and common variations within the genes encoding Neurexin 1 and Neurexin 3 contribute to ASD susceptibility [62]. However, particular mutations in neuroligin genes can cause different phenotypes, including autism and mental retardation without autism, within the same family [63]. Similarly, in the Amish population, mutations in the gene encoding contactin-associated protein-like 2 (*CNTNAP2*), which has high homology to the neurexin genes, can cause a rare neuronal migration disorder that results in seizures, language delay, intellectual disability and, in nearly two-thirds of patients, an ASD [64]. Using data from the Autism Genetic Resource Exchange (AGRE; <http://www.agre.org/>), we have identified a common variation in *CNTNAP2* in a large cohort of subjects who have idiopathic autism (M Alacron *et al.*, unpublished data) demonstrating that this gene contributes to non-syndromic ASDs. A rare mutation of *SHANK3*, which encodes a protein involved in dendritic development, was also identified in a few patients who have ASDs [65]. Certain rare syndromic disorders in which ASDs occur, such as Timothy syndrome, are characterized by mutations in Ca^{2+} or other ion channels that affect cell excitability and signaling cascades that influence axon growth, synapse formation and dendritic maturation (see also review by Krey and Dolmetsch, in this issue). Dendritic structure is a key modulator of synaptic function, and is one of the primary aspects of the brain to be affected in Fragile X syndrome [66]. A variant in the 5' regulatory region of *Reelin*, which encodes a protein that is essential for establishing the subplate (a key transient structure involved in afferent axonal patterning [67]) and for establishing basic laminar organization of the cerebral cortex, exhibits a modest association with ASDs in several studies [68–70], although not in all reports (e.g. [71]).

These genetic findings in idiopathic ASDs and non-syndromic mental retardation emphasize the overlap between the autisms and more general disruption of brain development, as is also suggested by the multitude of syndromic causes of the autisms, including Fragile X syndrome, Joubert syndrome and, rarely, Rett syndrome [40]. These data suggest that a salient contribution from stochastic events, such as the precise quantity and topology

of neuronal migration deficits, or suboptimal function of synapses on malformed dendrites, determine whether a child will have mental retardation, severe autism or a milder form of ASD such as Asperger syndrome or pervasive developmental disorder not otherwise specified (PDD-NOS). In other words, which systems are functionally disconnected, and how severe and widespread the disconnection is, will contribute to the ultimate phenotype. In addition, primary involvement of the prefrontal cortex and anterior cingulate gyrus are predicted to disrupt early developing processes such as joint attention, which are necessary antecedents to further development of language and social cognition. Thus, there is an enormous role for modulation of the salience of the social and other environmental stimuli that will effect the development of these systems.

Common risk alleles of autism candidate genes that influence connectivity

To explore the contribution of genes that regulate connectivity, Geschwind and colleagues performed an association study on a single, large cohort in which ~35 genes are involved in axonal pathfinding and neuronal migration [62]. This demonstrated conclusive association of ASDs with the genes encoding Neurexins 1 and 3 (*NRXN1* and *NRXN3*) and the GABA receptor $\beta 3$ (*GABRB3*), and suggestive association with *SLIT1* and with an overall significant over-representation of single-nucleotide polymorphisms (SNPs) in all of the genes that comprise this functional grouping [62]. Furthermore, strong and specific genetic evidence for the role of such general biological events comes from association of the hepatocyte growth factor (HGF) receptor proto-oncogene *MET* [72**] with ASDs. *MET* tyrosine kinase signaling participates in multiple aspects of neocortical and cerebellar neuronal growth [73] and maturation, particularly related to cortical interneuron development [55,74,75] and pyramidal cell dendritic growth [76]. In mice, hypomorphic expression states of *MET* and its ligand HGF result in intermittent seizures, anxiety and atypical social behavior [55,77]. On the basis of neurobiological data and location within a region of chromosome 7q31 that contains autism candidate genes, *MET* was considered a viable candidate for genetic investigation. Levitt and colleagues performed genetic association analyses on an original family cohort and a large replication group of families. The study [72**] documented a strong association of a common 'C' allele in the promoter region of the *MET* gene in multiplex families (those in which more than one child has autism). The 'C' variant causes a twofold decrease in *MET* promoter activity and altered binding of specific transcription factor complexes, implicating reduced *MET* gene expression in autism susceptibility. The findings represent the first connection of a genetic variant in idiopathic autism with a potential functional alteration at a molecular level. Given the pace of genetic discovery,

the identification of a more complete set of such variants is likely to occur rapidly, providing a fertile ground for neurobiological exploration in humans and model systems.

Conclusions

Moving from genes to modeling the autisms in experimental systems is challenging for several reasons. Here, we have explored only a few key developmental issues. First, the autisms are disorders in which complex information processing might be disturbed at different levels of development, introducing substantial heterogeneity. Fundamental to this core feature of the hypothesis is the detailed characterization of circuit development that is hierarchical, progressing from first-order pathways to complex higher-order connections [49,50]. Beyond timing issues, fundamental differences in the underlying neurodevelopmental disruptions probably lead to the heterogeneity in both symptoms and developmental course that are characteristic of the ASDs. This is evident in neurogenetic syndromes of known etiology, such as Fragile X, Rett, Smith–Opitz–Lemi and Down syndromes, in which there is a far greater prevalence of ASD diagnosis than in the typical population. Yet the cellular basis for dysfunctional circuits is poorly understood in the autisms compared with the syndromic neurogenetic disorders. This is due in large part to there being limited neuropathological material available for analysis, and the fact that structural imaging data across childhood that provide clues regarding developmental trajectory have been accumulated only recently. Lastly if, as the evidence supports, the autisms are caused by developmentally regulated disconnection of higher-order association areas from one another and from other areas, the circuitry will need to be better understood, and animal studies will need to be interpreted in the context of evolutionary differences in brain function, especially when considering human specializations such as joint attention and language. Although mouse models are a powerful tool for exploring synaptic or cellular physiology, ultrastructure and biochemistry, results from them cannot yet be translated to the highly evolved level of human behavior that relates to higher-order association cortex [78]. Alterations in social behavior result from distinct neural systems and environmental interactions in different species; will asocial ants help us to understand and develop treatments for the autisms? These issues will require careful consideration as the genetic and environmental contributions to the autisms are uncovered and we attempt to understand their neurobiology. As a final point of emphasis, resolving the genetic components of the autisms more completely will provide an essential substrate for shortening the long list of environmental factors that have been hypothesized to cause or contribute to the autisms. It will be most relevant to examine susceptibility to such factors in the context of known genetic vulnerability.

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