Autism as a Disorder of Neural Information Processing: Directions for Research and Targets for Therapy [1]

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Abstract

The broad variation in phenotypes and severities within autism spectrum disorders suggests the involvement of multiple predisposing factors, interacting in complex ways with normal developmental courses and gradients. Identification of these factors, and the common developmental path into which they feed, is hampered by the large degrees of convergence from causal factors to altered brain development, and divergence from abnormal brain development into altered cognition and behaviour. Genetic, neurochemical, neuroimaging and behavioural findings on autism, as well as studies of normal development and of genetic syndromes that share symptoms with autism, offer hypotheses as to the nature of causal factors and their possible effects on the structure and dynamics of neural systems. Such alterations in neural properties may in turn perturb activity-dependent development, giving rise to a complex behavioural syndrome many steps removed from the root causes. Animal models based on genetic, neurochemical, neurophysiological, and behavioural manipulations offer the possibility of exploring these developmental processes in detail, as do human studies addressing endophenotypes beyond the diagnosis itself.

The past several years of research on autism and brain development have produced a confluence of findings that point the way towards understanding this complex behavioural syndrome in terms of its developmental roots. Imaging and behavioural studies on one front and genetic and biochemical studies on the other are converging on a view of autism as the result of pervasive, early developmental abnormalities affecting neural information processing. Such dysfunctions may arise through the interactions of many determinants, each of which contributes differently to the final phenotypic profile. Examination of specific phenotypic components within the broad syndrome of autism promises to identify these underlying factors.

1 Autism and Abnormal Neural Dynamics

Key to the understanding of autism is its recognition as a developmental disorder – developmental not simply in terms of taxonomy but in terms of its detailed aetiology. The approach in most studies has been to attempt to dissect autism as if it were a lesion, a missing locus or capacity within an otherwise normal, fully developed brain in which all other factors have somehow been held constant. This approach is inappropriate to the study of developmental disorders because it assumes that the disorder is a function of a localised module, rather than an emergent property of developmental interactions between many brain regions and functions [129]. Cognitively, autism has been construed as a disorder involving fundamental deficits in central coherence [91], executive function [166], and theory of mind [21] or empathising [18] – these descriptions are neither mutually exclusive nor mutually independent, and a complete explanation will encompass all of them. Anatomically, abnormalities associated

with autism have been localised in cerebellum [74, 161, 73, 105], brain stem [105, 194], frontal lobes [42, 67, 215, 11], parietal lobes [69], hippocampus [12, 203] and amygdala [12]. While significant abnormalities are present in all these cognitive capacities and anatomical regions, it remains to be seen how these characteristics are related to each other and to autism's fundamental causes. Past research has focused on the leaves of the developmental tree – the collection of surface features that are diagnostic or most apparent in autism. In order to understand autism as a developmental syndrome it is necessary to explore development at its trunk and roots. It is in this way that the two fronts of autism will be joined, unifying abnormal structure and function with the underlying genetics and neurobiology, and providing specific targets for therapeutic intervention.

Looking beyond surface features is a challenge for autism research: primary dysfunctions can be masked by the evolution of compensatory processing strategies which normalise behaviour [200], and also by the induction of activity-dependent secondary dysfunctions [66, 2] which disrupt behaviour in new ways. There is thus a high degree of fan-out (divergence) from core dysfunctions in the developing brain to cognitive and behavioural symptoms in the developed brain. The sheer number of genetic susceptibility factors and loci that have been linked to autism implies that autism's core dysfunction admits a high degree of fan-in (convergence) from primary biasing factors to core dysfunctions. The 60% concordance for strictly diagnosed autism in identical twins [88] establishes a role for environmental interactions in this fan-in just as surely as it does for genetic predispositions.

The very breadth of autism's anatomical and functional abnormalities admits the possibility that its core dysfunctions may involve some pervasive alteration of neural processing. One route to such an alteration might be via abnormally low signal-to-noise in developing neural assemblies, a condition that may be produced by abnormal neural connectivity. The high incidence of epilepsy in autism [16] is consistent with this hypothesis, and there has been no shortage of relevant neuropathological findings. The numbers of Purkinje cells, and to a lesser extent granule cells, in cerebellar cortex are abnormally low [262, 192, 24, 25] – presumably leading to disinhibition of the cerebellar deep nuclei and consequent overexcitation of thalamus and cerebral cortex. Neurons in hippocampus, amygdala, and other limbic regions are abnormally densely packed [24, 25, 187], and a Golgi analysis of the hippocampus in two autistic brains [187] has revealed an abnormally low degree of dendritic branching. A recent photographic examination of neurons in several cortical regions suggests a reduction in the size of cortical minicolumns in the autistic brain, and an increase in cell dispersion within minicolumns – characteristics that could increase the total number of minicolumns and thus the degree of connectivity between minicolumns [44, 45]. It is important to note that a decrease in signal-to-noise can arise from abnormalities of connectivity in either direction: whereas an overconnected network passes so much noise that it swamps the signal, an underconnected network passes so little signal that it becomes lost in the noise. In either case, large segments of the network are constrained to either an all-on or an all-off state, and the network's information capacity is thereby reduced [54].

2 Neurophysiologic and Neuroanatomic Effects

2.1 Neurophysiological Consequences

Such a failure to delimit activation within an abnormally connected network may be observable as hyper-arousal in response to sensory input, and decreased ability to select among competing sensory inputs [29]. Cardiovascular, neuroendocrine and neurochemical indices of arousal in novel and stressful situations are consistent with this prediction [229, 124], as are physiological and behavioural observations of the extent and intensity of perceptual processing. Physiologically, functional imaging has demonstrated heightened activity in autism in brain regions associated with stimulus-driven, sensory processing, and decreased activity in regions that normally subserve higher-order processing: these results include abnormally high activity in ventral occipital visual areas during a visual task demanding separation of local features from global context (the Embedded Figures Test), even while prefrontal and parietal activations are abnormally low [190]; heightened activity during face processing in peristriate cortex [76], inferior temporal gyrus [205], and other areas outside the fusiform 'face area' [174] while fusiform activity is abnormally low; heightened activity in superior temporal gyrus during inference of mental state from pictures of eyes, while prefrontal and medial temporal activations are abnormally low [22]; and decreased connectivity between extrastriate visual areas and prefrontal and temporal areas associated with inference of mental state, while prefrontal and temporal activations are again abnormally low [48].

Supporting the idea of impaired selection of perceptual inputs, evoked potential and quantitative EEG studies reveal a pattern of abnormally distributed response in autism during tasks that demand selective attention. In adults with autism, the P1 evoked potential is either abnormally augmented in response to stimuli at the attended location, or abnormally generalised to stimuli distant from the attended location [233]. During shifts of attention between hemifields, the normal, spatiotopically selective augmentation of the visual steady-state evoked potential is absent, and instead both hemispheres activate indiscriminately during shifts of attention into either hemifield [27, 29]. In children with autism, the visual N2 to novel stimuli is augmented during task performance even when these stimuli are not relevant to the task [133]. When a response is required to an auditory stimulus, the P3 in these same children with autism is abnormally generalised to occipital sites overlying visual processing areas [134]. In general, both in children and in adults, perceptual filtering in autism seems to occur in an all-or-none manner, with little specificity in selecting for the location of the stimulus, for the behavioural relevance of the stimulus, or even for the sensory modality in which the stimulus appears.

Recent fMRI evidence suggests that the autistic brain may compensate for this deficit in selecting sensory inputs by suppressing any irrelevant sensory information at a later, less efficient stage of processing [29]. In other words, in the absence of a normally functional mechanism to bias sensory processing towards attended stimuli, all stimuli receive much the same degree of sensory evaluation, and the irrelevant stimuli must then be actively discarded

in a manner that creates a processing bottleneck. Perhaps because such a compensatory mechanism cannot be as quickly reset as the normal mechanism of selective attention, performance is impaired at tasks that demand rapid reconfiguration of perceptual resources [36]. An autistic deficit in rapid shifting of attention has been observed in cases of shifts between sensory modalities [71], between spatial locations [246, 247, 234, 236, 235, 104, 27], and between object features [72, 189]. Even when the demand for rapid shifting is eliminated and people with autism produce normal behavioural output, physiological measures remain abnormal, indicating the operation of compensatory processing: frontal negativities associated with sustained attention are reduced or absent in the autistic brain [68, 53], the frontal late positive component to peripheral visual stimuli is delayed [237], and the visual P3b is highly variable [68] with a somewhat low average amplitude [162, 53, 244, 237].

2.2 Developmental Connections

These abnormalities of perceptual processing point to a developmental explanation for higher-order abnormalities, an explanation that depends crucially on the idea of a developmental chain of abnormal function: when a developing brain is confronted with an abnormal constraint on information processing, it will evolve an abnormal organisation in order to accommodate that constraint [129]. It is via such a chain of dysfunction that a core deficit such as degraded neural signal-to-noise could fan out into a welter of autistic behavioural abnormalities. From the earliest months of infancy, the flood of input generated by over-aroused, under-selective primary processing would overload nascent higher-order cognitive processes [29] – systems whose development may be being independently sabotaged by the same neuropathology that affects primary regions. Such an effect may explain the extension of sensory and motor activations in adults with autism into territories that normally subserve later-maturing cognitive functions [160]. Depending on its timing, such an error of neurocognitive development might underlie loss of cognitive skills or failure to develop skills.

Faced with this bottleneck in higher-order cognition, the developing and plastic brain would likely evolve a cognitive style that avoids reliance on high-level integrative processing and instead emphasises low-level features – a pattern typical of autistic attention and perception which Frith has termed weak central coherence [91]. Central coherence, in Frith's definition, is the drive that causes fragmentary features to lose their identity as separate fragments once they are assembled into a single object; it is the effect of context on meaning. Weak central coherence is of especial interest as part of an explanatory framework since since it predicts not only autism's cognitive impairments in integrative tasks but also its cognitive advantages in tasks that demand attention to detail. People with autism perform better than normal on the Embedded Figures Test [206], a task that demands recognition of individual features within spatial arrangements. Unlike normal subjects, they are not aided by pre-segmentation of patterns in the Wechsler Block Design subtest, and when they make errors, these are more likely to be ones of global configuration rather than local detail [207]. In many high-functioning children with autism, lexical-to-phonological decoding

based on words' small-scale features outpaces comprehension, producing a condition known as hyperlexia [261]. Perhaps because they process faces as collections of individual features rather than as centrally coherent gestalts, children with autism are impaired at recognising unfamiliar faces [33, 136] and show a reduced or absent face-inversion effect [111, 224]. Again presumably because of intense processing of individual features, the normal levels-of-processing effect on memory is inverted in autism, with rote memory superior to normal, and memory for semantic associations impaired [228]. This piecemeal approach to perception is mirrored by a failure to generalise special skills to broader domains – *e.g.* the calendar calculator who has no interest in other forms of arithmetic calculation.

Autism's weakened central coherence may thus be a secondary property, emerging in the interaction of normal cognitive development with abnormal neural information processing – an interaction that encourages an unusual cognitive dependence on low-level processing of individual details. Indeed, the presence of low-level perceptual abnormalities in autism [181] has contributed to a recognition that many higher-level cognitive abnormalities may best be characterised as the effects of a surfeit of local processing rather than any specific impairment in global processing [180], and to an appreciation of the role of compensatory developmental changes surrounding altered perceptual functioning [159]. The possibility that some of autism's cognitive symptoms may develop as compensatory or accommodative changes raises the possibility of targeted behavioural and pharmacological interventions – one could, for example, imagine an early intervention aimed at preventing the developing brain from relying so exclusively on its intact processing of local features, in somewhat the same manner as an eye patch prevents a child at risk for amblyopia from relying on the intact eye.

Weak central coherence may in turn form the cognitive underpinning of a wide array of developmental behavioural disturbances, by impairing the use of contextual information in complex perceptual and executive tasks [93]. The executive deficit defined by this inability to use context may impact performance on theory-of-mind tasks [201], which depends on an ability to apply the context contained in one's inner model of another person's mental state. Such an exective deficit may also impede the development of joint attention and shared affect [137, 195], processes in which response to stimuli depends crucially on social context. The resulting poverty of early social cognitive experience may perturb or prevent the further activity-dependent development [66, 2] of specialised modules or capacities for such tasks as face processing, language, and complex social relations involving theory-of-mind and empathising. This failure to use context and to apply a theory of mind may result in a style of unsupervised learning founded on statistical associations rather than learning that is directed by the intentionality of others [92], and to a preference for ritualised, scripted, and repeatable interactions. Autism's surface symptoms might thus be understood as the developmental reaction of a normal human mind to abnormal neural hardware.

2.3 Anatomical Correlates

Partly because of the difficulty in recruiting people with autism who can tolerate task demands within the scanner environment, functional MRI has begun to be applied to autism only recently. Structural MRI, on the other hand, is an established technique. In adolescents and adults with autism, MRI morphometry has revealed volume deficits in cerebellum [74, 161, 73, 105], brain stem [105], and posterior corpus callosum [84]. As is the case with behavioural measures of autism, anatomical measures reveal subgroups: a minority of patients show increased rather than decreased cerebellar volume [70], and nearly half have a volume deficit in the parietal lobe [69] which is associated with a narrowing of the spatial focus of attention [233]. This anatomical heterogeneity likely reflects different convergent routes to, divergent routes from, or correlates of a common dysfunction. Studies of adult subjects say comparatively little about what this common dysfunction may be, since observations in adults take place long after the developmental pathology has run its course: although the underlying dysfunction may still exist in these adults, it can be expected to have been hidden by a forest of secondary dysfunctions and adaptive or compensatory changes.

Longitudinal studies using MRI volumetric and head circumference data point to the conclusion that autism involves transient postnatal macrencephaly [64]. Although non-standardised measurements of head circumference must be viewed with some caution, the data currently available on newborns later diagnosed with autism or PDD-NOS suggest that head size at the time of birth is normal or perhaps even slightly smaller than normal [65]. By 2 to 4 years of age, 90% of these children have MRI-based brain volumes larger than the normal average [42, 67, 215, 11], and group measures of head circumference have increased correspondingly. This abnormal brain growth is due primarily to excessive enlargement of cerebellar and cerebral white matter and cerebral grey matter [67, 108]. Even in older children, enlargement of superficial white matter tracts containing cortico-cortical fibres may persist, while internal capsule and corpus callosum are proportionately reduced [109]. Deviation from normal is so common and extreme that cerebellar and cerebral white matter volumes together with cerebellar vermis size accurately distinguish 95% of autistic toddlers and young children from normal children, and also accurately predict whether a young child with autism will have a low or high functioning developmental outcome [67]. These two-to-four-year-old autism patients show an anterior-to-posterior gradient of overgrowth, with frontal lobes being the largest [43]. This early abnormality creates a lasting legacy of increased head circumference throughout life, but, in most cases, not a lasting macrencephaly. By adulthood, then, macrencephaly is not typically present in autism, and brain volumes tend to be near normal. In sum, an abnormally rapid increase in brain volume in early life in autism is followed by abnormally slowed or prematurely arrested growth in cerebellar and cerebral regions. This early brain overgrowth takes place during a period which in normal development involves changes in synaptic density [117]. The increase in the volume of cortical grey matter matter may reflect a failure of synaptic pruning or a surfeit of synaptogenesis, and may thus be the earliest gross anatomical manifestation of a pervasive abnormality in the development of neural assemblies. Of equal potential importance, the increased volume

of local white matter projections suggests abnormality in the normal postnatal process of rapid myelination.

In characterising this underlying abnormality, it is important to note that a general deficit in development may interact with normal developmental gradients to produce an anatomically and functionally specific pattern of deficits. Myelination, for example, is not uniformly controlled across the cerebral hemispheres, but instead develops in a posterior to anterior direction. The persistence of myelination into the third decade of life in frontotemporal but not occipitoparietal fibre tracts [264, 28] indicates that oligodendrocyte regulation differs regionally. Likewise, changes in the development of neuronal populations can arise in a regionally selective fashion: in a targeted mutation of the hepatocyte growth factor signalling system, for example, deficits of GABAergic neurons appear only in frontal and parietal cortices, and only in the parvalbumin-containing subpopulation of cells [184]. In terms of cellular and molecular relationships just as in the case of cognitive ones, it may be fruitful to view autism as a product of the interaction of normal development with abnormal contraints. Observations of abnormal patterns of early brain growth suggest that at least a portion of this interaction occurs postnatally. This postnatal time frame for pathogenesis offers hope of early biological interventions, if the genetic and neurochemical determinants of abnormal growth can be identified.

3 Neurobiological Bases

3.1 Genes

It has become increasingly clear that genetic factors are very significant determinants of autism pathophysiology. The risk that another sibling will be born with autism to parents who have already had an autistic child is approximately 4.5% [130]. Given recent estimates of population prevalence for autism (which have increased, partly as a result of more complete ascertainment) [50], this statistic represents a sibling recurrence risk over twenty times the risk for the general population. Moving from siblings in general to identical twins in particular, the increased risk of concordance for autism rises from twentyfold to over two hundredfold. Such a large differential suggests not only the involvement of multiple genes, but also a multiplicative effect among these genes. For example, if there were five genes involved, a twentyfold increase could be accumulated from risk multipliers as small as 1.8 for each gene. Although some estimates of the number of interacting genetic loci in autism are as low as two to ten [172], others range from over fifteen to over a hundred [191, 186].

This multiplicative mode of inheritance carries implications for the nature of the genetic factors involved, for the experimental discriminability of each individual factor, and for the potential of interventions targeting these factors. Multiplicative effects arise from interactions between individual genes, and the susceptibility factors for autism are therefore likely to influence gene expression or to encode subtle functional alterations in proteins that participate

in regulatory networks. Multiplicative inheritance also means that the small effect of each gene by itself will be difficult to identify and to confirm; each genetic variant is likely to act as "the straw that breaks the camel's back," innocuous by itself but pathological in concert. Although these small effect sizes will be difficult to discern, the advantage in terms of treatment is that intervening to restore regulation to a single gene or to a small set of genes may diminish the multiplicative effect enough to yield large preventative or therapeutic effects. This situation in which the disorder may be approached via any of several therapeutic targets stands in contrast to monogenic disorders where there may not be an obvious therapeutic strategy before decades of basic work (*e.g.* Huntington's disease).

A further consequence of the multiplicative model is that the prevalence of individual risk alleles in the general population will be high. Most if not all of these autism 'risk' alleles are likely to have some adaptive value, in cases where they do not lead to autism. In some cases this adaptive value would be obvious (*e.g.* enhancement of focused attention or other elements of neuropsychological function). In other cases the benefits to humanity of the existence of these alleles may be more difficult to determine, but are likely to be present.

Although review of the current status of identifying genetic risk factors for autism is beyond the scope of this manuscript, several thorough reviews are available [59, 88, 143, 141, 60]. Two relatively small regions, on 15q11-q13 centred around the $GABA_A\beta_3$ receptor subunit gene (*GABRB3*) and near the serotonin transporter (*SLC6A4*) on 17q11.2, are locations where more than two, but not all, studies have shown family-based association with autism. In addition to 17q, several other regions of the genome including 2q and 7q appear to be involved in the larger syndrome based on convergence from several studies. Fine mapping of these regions should be a priority in addition to generating larger samples in which two or more siblings have autism in a family (*e.g.* the Autism Genetic Resource Exchange (AGRE) [95]). In Turner syndrome, an interesting finding of increased risk for autism after deletion of the paternal, but not maternal X chromosome, suggests that a protein expressed only when the paternal X chromosome is present may be protective from autism. Such a protein might be expressed only in the developing female brain, perhaps accounting in part for the approximate 4:1 ratio of males with autism to females with autism [212]. Another possible explanation is that some of autism's several 'risk' alleles are on the X chromosome.

At least four X chromosome loci have already been implicated in autism, including neuroligin 3 (*NLGN3*), neuroligin 4 (*NLGN4*), *FMR1* (see below), and *MECP2*. Although rare, a possibly functional missense mutation has been identified in *NLGN3* in an affected sibling pair, and a *de novo* nonsense mutation of *NLGN4* has been found in affected siblings and their unaffected mother [126]. Discrepancies between the affected status of the mother and offspring are somewhat difficult to interpret since, as the authors note, strong sequence conservation exists between *NLGN4* and *NLGN4Y*. Nevertheless, the association of neuroligins with autism is of great interest in light of the idea that autism's pathophysiology may begin with abnormal neural connectivity.

The first truncating mutations in an autism-related disorder were reported when mutations in *MECP2* were identified in Rett syndrome [5]. The function of *MECP2* is to turn off

several genes whose promoters have been methylated. Therefore, in addition to *FMR1* and *UBE3A* discussed below, mutations in *MECP2* contribute to neurobiological dysfunction due to dysregulation of networks of temporally and spatially regulated genes. The recent finding of 2 *de novo* mutations of *MECP2* in a screen of 69 females with autism [41] shows that MeCP2, and perhaps its regulatory targets, are likely to be a contributing factor in autistic pathology.

In summary of the current findings, there is as yet no confirmed genetic finding in autism that has been explained in terms of its specific relation to brain development. In order to understand what genetic factors may influence the developmental processes that lead to autism, it is useful to focus on syndromes whose symptoms overlap with those of autism and which may be more tractable in terms of our current knowledge of biological cause and effect.

3.2 Proteins that Regulate Gene Expression

One such symptomatically overlapping disorder is Fragile X syndrome (FXS). FXS is the most common inherited form of mental retardation and second only to Down syndrome overall. Its neurobehavioural phenotype is characterised by some combination of mild to severe cognitive impairment, attention deficit, anxiety, seizure susceptibility, communicative disorders, and stereotypic behaviours. In addition, recent reports have suggested that 25-40% of individuals with FXS also meet diagnostic criteria for autism [15, 196, 14]. Studies of children with autism have shown a concurrence of FXS with autism of approximately 2%, with one study finding the Fragile X mutation to be the most frequent chromosomal anomaly associated with diagnosed autistic cases [13, 256]. In many instances the behavioural profiles observed in FXS seem indistinguishable from those of idiopathic autism – although some studies have noted distinct differences especially in the realm of social and communicative skills [55].

FXS is caused by the silencing of a single gene (*FMR1*) [175] that codes for the Fragile X Mental Retardation Protein (FMRP), an RNA binding protein [9]. FMRP binds to numerous mRNA cargoes, including its own mRNA, and has been hypothesised to regulate the expression of a specific set of genes in neurons. When FMRP is absent, the expression of these genes is altered and the FXS phenotype is observed. A critical feature of FXS, therefore, is that what is in one sense a single-gene disorder is more proximally the result of a disruption of complex patterns of expression of many genes. Using a novel technique, Miyashiro *et al.* have recently demonstrated that multiple classes of mRNA molecules are bound to FMRP in neurons [158]. In light of the high incidence of autistic behaviours in FXS, the data set of approximately 80 genes whose mRNA's bind to FMRP was screened to reveal 15 that map closely to suspected autism susceptibility loci. It is interesting and reasonable to speculate that polymorphic variations in these genes, and perhaps others to be determined, may be related to the variable autistic phenotype observed in many patients with FXS.

An examination of FMRP's expression and association with polyribosomal machinery in the brain leads to three important concepts. First, some of the protein synthesis that involves FMRP occurs at synapses in response to Group I metabotropic receptor activation [257]. (Since not all FMRP-expressing cells receive synaptic input, though, it is likely that not all protein synthesis involving FMRP is synaptic.) Second, FMRP itself is synthesised in response to activation of metabotropic glutamate receptor subtypes 1 and/or 5. Third, this process requires FMRP, since synaptic activity dependent protein synthesis is greatly reduced in the FraX knockout mouse [99]. An interesting *in vivo* correlate of this observation is that the proportion of dendritic spines that contain polyribosomal aggregates is reduced in the cortices of knockout mice. Therefore, one physiologically based hypothesis is that FMRP regulates the local expression of a subset of genes by controlling their translation in response to neuronal activity.

Behavioural exposure to a complex environment increases FMRP expression in rat visual cortex [121], as do physical activity in the case of somatomotor cortex [121] and whisker stimulation in the case of barrel cortex [227]. Knockout of the *FMR1* gene in mice increases dendritic spine density in visual cortex [56]. Similarly, in barrel cortex, a natural process of developmental dendritic regression fails to occur in the knockout mouse [94]. Taken together, these findings provide strong evidence for a critical role of FMRP in protein syntheses involved in activity-dependent brain development, and specifically in the patterning of neural circuitry. Anatomically, in FXS there is an overabundance of long, thin dendritic spines and a relative reduction in the number of short, thicker spines in cortical regions examined (*e.g.* [110, 56, 122]). Although the FXS patients from which these microanatomical results arise were not specifically diagnosed with autism, the symptomatic and possible aetiological overlap between FXS and autism makes these observations relevant to the understanding of autistic neuropathology. The alteration in spine morphology suggests an abnormally large proportion of immature synapses. The fact that there are more long, thin spines, and more spines overall, may reflect a failure of the synapse elimination that would normally occur during early development. A study of the hippocampal formation in idiopathic autism [187] described reduced dendritic field size in pyramidal neurons in the Ammon's horn region, a result that contrasts with the FXS findings (in other brain regions) and suggests either a failure to fully reach adult form (the authors' interpretation) or an increase in the amount of pruning in the autistic cases, the opposite of what is reported in barrel cortex [94]. Either sort of change, an abnormal abundance of dendritic connections or an abnormal lack of them, could lead to difficulty in information processing due to reduced signal-to-noise. The difficulty in differentiating these two scenarios suggests that other methods are needed to converge on the capacity of structurally-altered brain regions for information processing.

The question remains as to why 25-40% of FXS cases have symptomatic similarity to autism and why other disorders such as Rett syndrome, Prader-Willi syndrome, and Angelman syndrome may have similar symptoms as well. This neurobehavioural similarity suggests something common to the aetiology or something common to the outcome in each disorder. One example of an aetiological commonality is that of interacting genetic factors, such as the FMRP cargo genes that map to loci associated with autism. The broad range

of severities and features in the FXS phenotype may reflect interaction with polymorphisms in such genes.

Common outcomes are perhaps more challenging to understand, but the possibility exists of relatively stable or "trapping" end points that may be reached via fan-in from multiple pathways and, once entered, are very difficult to overcome. For example, one might imagine that the autistic symptoms exhibited in FXS and in idiopathic autism serve a purpose with respect to their neurobehavioural contexts by reducing, say, high levels of anxiety. Thus any attempt to overcome these symptoms serves to increase anxiety and hence elicits opposition and persistence of symptoms. It is also possible that symptoms such as chronically repeated stereotypic movements offset some tension at the neural level rather than the cognitive or behavioural level. In either case, behaviour would become reinforced into a pathological state. Neural network modellers have used the term "stable attractor" to delineate states of their networks with similar properties. Whether this conceptualisation is useful remains to be determined, but it seems clear that understanding what underlies the similarities and differences between FXS and autism may offer significant insight into the complexity of both disorders.

FMRP, of course, is not the only regulatory protein with a possible association with autism. The abnormalities in 15q11-q13 are of especial interest because of the association of a known gene in 15q11-q13 with two neurogenetic disorders, Prader-Willi syndrome (PWS) and Angelman syndrome (AS), and overlapping clinical features between AS and autism. The AS gene, *UBE3A,* is maternally expressed only in brain tissue and codes for a ubiquitin protein ligase, an enzyme that can regulate the levels of many intracellular proteins by labelling them for ubiquitin-mediated degradation. *UBE3A* abnormalities thus are capable of producing a wide range of fan-out effects.

The majority of patients with PWS or AS have a deletion of 15q11-q13, on the paternal chromosome in PWS and on the maternal chromosome in AS [127]. In contrast, a smaller fraction of PWS and AS patients have uniparental disomy for chromosome 15, with two paternal chromosomes causing AS and two maternal chromosomes causing PWS. In each case the balance between maternally and paternally derived genes is altered; however, in the case of deletion the aetiology is clearly genetic, whereas in the case of uniparental disomy it is epigenetic: in these disomic individuals there is no abnormality of the genomic sequence, yet the phenotype is indistinguishable from that caused by genetic deletion. Epigenetic disease of this sort may be more common than previously considered [26]. Similar phenomena may be operating in autism, with both genetic and epigenetic alterations contributing to autism susceptibility.

Despite the association of autism with maternal duplication of 15q11-q13, interstitial duplications in the homologous region on the paternal chromosome are associated with a relatively normal phenotype. These data strongly suggest that there is an imprinted, maternally expressed gene or genes within 15q11-q13, epigenetically-induced over-expression of which can contribute to autism. The best studied form of epigenetic modification is DNA methylation, and abnormalities of DNA methylation and/or its effects are implicated in

several genetic diseases whose clinical features overlap with those of autism, including FXS, PWS, AS, and Rett syndrome. The dynamic changes in DNA methylation that occur during early embryonic development and during germ cell development provide ample opportunity for germ-line or somatic errors in epigenetic processes, 'epimutations' [188]. If an abnormality of DNA methylation were proven in autism, an immediate therapeutic intervention could be explored using drugs or dietary manipulations known to alter DNA methylation, such as folate supplementation.

Success in modelling Angelman syndrome in *UBE3A* knockout mice suggests that murine 15q11-q13 manipulations may also hold promise for the development of an animal model of autism. Mice with maternal deficiency of *UBE3A* recapitulate the human AS phenotype with motor dysfunction, seizures, deficiency in contextual learning, and impairment in hippocampal long-term potentiation [128]. The role of 15q11-q13 in autism can be dissected by making mice with various locus-specific duplications [267] of the homologous PWS/AS domain. This approach may produce a valid mouse model for autism even before a specific autism-related gene within 15q11-q13 is conclusively identified.

3.3 γ-Aminobutyric Acid

The 15q11-q13 region also codes for several subunits of the $GABA_A$ receptor, an ionotropic receptor whose hyperpolarising effect is mediated by chloride. *GABRB3, GABRA5* and *GABRG3* (encoding the $GABA_A$ receptor's β_3, α_5, and γ_3 subunits, respectively) all are clustered within 15q11-q13, and there is evidence for association with autism of genes in this chromosomal region [38]. The increased incidence of epilepsy in patients with autism and 15q11-q13 duplications is consistent with the involvement of GABA. Hippocampal $GABA_A$ receptor binding in autism is abnormally low [31], as are platelet GABA levels [198]. GABAergic interneurons have a special role in establishing the computational architecture of cortical columns; double bouquet interneurons, for example, send axon bundles from layers 2 and 3 to synapse on pyramidal and spiny stellate cells in columnar arrangements [80, 170]. In addition, GABAergic neurons may be particularly vulnerable to developmental errors, since they arise from a different portion of the neural tube than the excitatory cells with which they integrate: GABAergic cells migrate into neocortex from the primordium of the basal ganglia [8].

GABAergic transmission in the mature brain plays primarily an inhibitory function. In the forebrain GABAergic neurons have a number of central roles. For instance, GABAergic projection neurons of the basal ganglia are an essential link in the extrapyramidal circuit. GABAergic projection neurons of the reticular nucleus regulate thalamic function. GABAergic local circuit neurons have essential roles in information processing in the cerebral cortex, hippocampus and olfactory bulb. Thus, reduced function of GABAergic neurons would affect most aspects of forebrain function. Primary sensory information would reach the cerebral cortex, but the intrinsic and basal ganglia circuits that process this information would be abnormal. Furthermore, several regions of the forebrain would be hyper-excitable.

These characteristics resemble our present understanding of features of the autistic mind, and reflect the fact that many people with autism have epilepsy and high levels of anxiety.

Recent genetic studies in mice suggest molecular mechanisms that could underlie this pathological physiology [199]. Mice lacking the *GAD65* gene, encoding an enzyme that makes GABA, have defective cortical plasticity that can be corrected with a GABA agonist [107]. Mutations in the *Dlx1* and *Dlx2* genes disrupt development of most telencephalic GABAergic neurons [8, 153]. It is worth noting that the human locus that has the highest LOD score for autism susceptibility (D2S2188 on chromosome 2q) maps very close to both the *GAD65* and the *Dlx1* and *Dlx2* genes [118]. Furthermore, the autism susceptibility locus (D7S477) on chromosome 7q maps within about six megabases of the *Dlx5* and *Dlx6* genes. These genes are also implicated in regulating forebrain GABAergic development [218, 219, 148] [Cobos and Rubenstein, unpublished]. Also in this region is the gene for reelin, a protein expressed in cortical GABAergic neurons [3].

One of the $GABA_A$ receptor subunit genes in particular, *GABRB3*, is highly expressed during brain development in rats [142], and its deletion in mice disrupts GABA-related pharmacology and electrophysiology and produces behaviours reminiscent of autism [82]. In mice homozygous for a disruption of *GABRB3,* $GABA_A$ receptor binding in neonatal and adult brain is reduced by half, with most of this reduction occurring in cerebral cortex and thalamus [125]. GABA function is impaired in these knockout mice in dorsal root ganglia, hippocampus, and the thalamic reticular nucleus, with an 80% reduction in GABA-activated chloride current in homozygotes and a 25% reduction in heterozygotes [125]. As a result, *GABRB3* knockout mice have epileptiform EEG containing high-amplitude slow and sharp waves, and develop overt seizures as they mature [125, 82]. Behaviourally, *GABRB3* knockouts are hypersensitive to thermal and tactile stimuli [239]. They are hyperactive, exhibiting stereotyped circling [125, 82]. They lack motor coordination, often falling and failing to learn a rotating-rod task [82]. Their cycles of rest and activity are lengthened [82], and EEG spectral characteristics during slow-wave sleep are abnormal [263]. There are also cognitive deficits, as measured by abnormalities of passive-avoidance conditioning and contextual fear conditioning [82]. Mothers homozygous for the *GABRB3* knockout fail to engage in normal nurturing behaviour, even towards their wild-type pups [125]. These similarities to autism suggest either a direct involvement of *GABRB3* in autism, or some GABA pathology that shares physiological or developmental effects with the *GABRB3* knockout.

Collectively these observations suggest that reduced GABA signalling is a candidate mechanism that may contribute to the causation of autism. Perhaps the co-inheritance of a combination of hypomorphic alleles that all affect GABAergic tone is a basis for some forms of autism. Efforts should therefore focus on studying known genes in known autism susceptibility loci that affect development and/or function of the GABAergic system. In particular, the exons and known regulatory elements of the *Dlx1,2,5,6* and *GAD1* genes should be sequenced in autism patients and their family members. This analysis will identify SNPs and potential function-altering mutations. Furthermore, GABAergic agonists should

be considered as potential therapeutic agents for autism.

3.4 Acetylcholine

GABAergic dysfunction can be produced not only by direct alterations in GABA systems but also by changes in neuromodulation of GABAergic neurons. Several neuromodulators may be involved in such changes, potentially with synergistic effects. Abnormal developmental changes in the population of septal neurons in autism suggest a cholinergic abnormality: septal neurons are excessive in younger and reduced in older individuals with autism [25]. Acetylcholine affects performance during sustained attention [157], possibly by shifting the dynamics of cortical networks so that afferent influence predominates over intracortical inputs [135]. In mice, knockout of the α_4 nicotinic subunit produces reduced antinociception and increased anxiety [154, 171]; abnormal pain sensitivity and anxiety both are features of the autistic syndrome. In addition, nicotinic receptors are essential for normal early synaptic development [75, 231] and thus nicotinic dysfunction may produce abnormal neural microarchitecture.

The $\alpha_4\beta_2$ nicotinic acetylcholine receptor is decreased in autopsied brains of adults with autism [169, 145]. This deficit is most pronounced in the cerebral neocortex, where the $\alpha_4\beta_2$ receptor subtype has an important regulatory effect on GABAergic neurons [4]. The decrease is selective; the other principal nicotinic receptor subtype, α_7, is not involved. Although normal levels of choline acetyltransferase suggest that cholinergic input to the cerebral cortex and the cerebellum is intact, the level of BDNF in the basal forebrain has been observed to be three times higher than normal [145]. In addition to its role in GABAergic development outlined above, BDNF is involved in enhancing cholinergic transmission [112] and in promoting the survival of developing cholinergic neurons of the basal forebrain [248]. This BDNF abnormality at the major source of forebrain cholinergic projection may therefore be significant for cholinergic function.

As these neurochemical results come from adult brains, it remains to be seen whether nicotinic abnormality is present at early stages of autistic development. Cholinergic dysfunction may be an indirect contributor to autistic development via its influence on GABAergic neurons, a correlate of prior GABAergic dysfunction, or a direct contributor via its influence on synaptic development. *In vivo* studies at early ages, using PET and MR spectroscopy, will give further information on the role of acetylcholine in autism. Pharmacologic therapies targeting the cholinergic system may be of value; there has been one report of success using the acetylcholinesterase inhibitor donezipil to treat autistic symptoms of irritability and hyperactivity [103].

3.5 Serotonin

There has been a growing interest in the role of serotonin (5-hydoxytryptamine, 5-HT) in autism since the initial report of elevated levels of platelet 5-HT in individuals with autism

[204]. An increasing awareness of 5-HT's critical involvement in guiding neurodevelopment and in modulating sensory input and arousal has provided a convincing theoretical basis for 5-HT's role in the aetiology and pathophysiology of pervasive developmental disorders. Serotonin's especially rich innervation of limbic areas critical for emotional expression and social behaviour and the extended ontogeny and apparent plasticity of the central serotonergic system have provided additional support for its possible involvement.

As might be expected from its phylogenetically ancient role in neurodevelopment and neural transmission, and its extensive CNS projections, 5-HT has been shown to play a key role in a variety of behaviours and processes. Much of the early expression of 5-HT appears related to its role as a growth factor and regulator of neuronal development. Thus, in addition to functioning as a modulator of neural transmission, 5-HT appears to have critical effects on neurogenesis, morphogenesis, and synaptogenesis in the developing brain [260].

In adult animals, 5-HT plays important roles mediating diverse autism-relevant behaviours, including sleep, mood, arousal, aggression, impulsivity, and affiliation [151]. Reduced serotonergic function has been associated with worsened sleep, depressed mood, altered arousal, increased aggression, greater impulsivity, and reduced social behaviour. Genetic data have connected 5-HT-related genes to disorders defined by symptoms in these areas of behaviour (*e.g.* mood, social phobia, obsessive-compulsive, and anxiety disorders), and it is clear that the serotonergic system is intimately interconnected with GABAergic and glutamatergic neurons throughout the brain.

Empirical studies of 5-HT in autism include pharmacological treatment and challenge studies, biochemical/neurochemical studies of 5-HT and related species, and genetic studies of 5-HT-related genes. Drugs targeting the 5-HT transporter, including the 5-HT reuptake inhibitors fluoxetine, fluvoxamine, and clomipramine, are now widely used in autism [183]. The reuptake inhibitors appear to affect most aspects of autistic behaviour. Risperidone, another frequently used medication, also acts predominantly through a serotonergic target, the 5-HT_{2A} receptor.

Platelet hyperserotonaemia has been especially well studied and is generally considered the most robust and well-replicated biological finding in autism [7, 61, 6]. Most studies have reported group mean elevations of 25-50% in platelet serotonin in persons with autism. The mechanism of the alteration and its possible relationship to brain abnormalities remain unknown. The platelet does not appear to be exposed to greater amounts of 5-HT; attention has therefore focused on handling of 5-HT within the platelet. To date, no clear alteration in the platelet has been identified although there is some suggestion that uptake may be increased in some subjects with increased platelet levels.

Genes encoding a number of the components involved in 5-HT neural transmission have been examined as possible contributors to the potentially relevant behaviours and disorders mentioned. Research in autism has focused on the influence of 5-HT transporter gene (*SLC6A4*) variants on risk to autism. Although taken together the studies do not convincingly support a role for *SLC6A4* variants in determining overall risk to autism,

investigators are now examining allelic influences on the severity of specific aspects or domains of autistic behaviour [230]. There have been several reports of variants in the transporter promoter having modifying effects in neuropsychiatry, and a recent report of strong influence on vulnerability to stress [46]. Reports of effects of 5-HT-related alleles on therapeutic response to serotonergic antidepressants and atypical neuroleptics (in mood disorders and psychosis, respectively) also tend to link 5-HT and autism [243].

At present, the areas of neuroimaging and postmortem brain research seem to offer the greatest potential for elucidating the role of serotonin in autism. The recent availability of postmortem brain tissue has opened a wide window of opportunity. Reciprocal interchange between imaging, neuropsychological, and postmortem research should be especially useful and illuminating. Work on the mechanism of the platelet hyperserotonaemia may provide critically important information regarding possible central 5-HT dysfunction; the advantages of having identified a specific biochemical alteration in a delineated cell type might be best exploited by applying gene array or expression technology to this question.

3.6 Lipids

Another genetic condition that shares autistic symptoms is Smith-Lemli-Opitz syndrome (SLOS), an autosomal recessive, multiple malformation/mental retardation syndrome [213] with an estimated incidence among individuals of European ancestry of one in 40,000 to one in 60,000 births [150, 202, 39, 132], and a probable average carrier frequency of 1% [132]. Principal abnormalities include a characteristic facial appearance, microcephaly, hypotonia, postnatal growth retardation, 2-3 toe syndactyly, and hypogenitalism. In 1993, SLOS was shown to be caused by a defect of cholesterol biosynthesis at the level of the 7-dehydrocholesterol reductase [120, 226]. This defect impairs the conversion of 7-dehydrocholesterol (7-DHC) to cholesterol, causing an increased level of 7-DHC in blood and tissues, and, in most patients, decreased blood and tissue cholesterol levels. A major consequence of these biochemical abnormalities is the alteration of normal embryonic and foetal somatic development, causing postnatal abnormalities of growth, learning, language, and behaviour.

Cholesterol is necessary for the proper functioning of cells, and a defect in cholesterol synthesis impairs multiple systems in the body. Decreased cellular cholesterol levels may impair the development of cellular components and cellular function. Hedgehog proteins, which are partially responsible for embryonic patterning, require cholesterol for proper functioning. Individuals with SLOS have been found to have various CNS structural abnormalities including holoprosencephaly. Studies *in vitro* have shown that the activity of receptors for serotonin and other ligands is impaired in cholesterol-deficient environments. Low cholesterol levels impair the function of G-proteins, and thus the operation of metabotropic receptors. Low cholesterol production in individuals with SLOS may thus illuminate the decreased serotonergic functioning associated with autism.

Clinical data show that SLOS is associated with autism, and suggest that cholesterol supplementation ameliorates autistic behavioural symptoms. Of 17 subjects with SLOS for

whom the Autism Diagnostic Interview (ADI-R) [149] algorithm questions were administered, 9 (53%) met the ADI-R criteria for autism [225]. Of the 9 subjects who began cholesterol supplementation before the age of 5.0 years, 2 (22%) met the ADI-R algorithm criteria for autism at age 4.0 to 5.0 years. Of the remaining 8 subjects who began supplementation after the age of 5.0 years or had not yet started supplementation, 7 (88%) met the ADI-R algorithm criteria for autism.

Despite these behavioural similarities, the extent to which SLOS may share neurobiological mechanisms with non-SLOS autism remains unclear. Individuals with SLOS manifest some anatomical abnormalities [132] reminiscent of those often seen in autism: hypoplasia of the corpus callosum, and of the cerebellum and particularly the vermis. However, the developing macrocephaly in autism contrasts with a microcephaly in SLOS present from birth and persisting into later life. The comparison between SLOS and autism at the level of microanatomy remains an open question which could be usefully explored by quantitative neuropathological studies. Even in the absence of proven shared mechanisms of neuropathology, SLOS's comorbidity with autism does suggest several lipid-associated pathways that may be disrupted in non-SLOS autism and which may be examined for further clues. Abnormalities of the lipid membrane may affect membrane-associated proteins involved in neural or developmental signalling [37]. Individuals may also have dysfunctions of sterol or steroid metabolism, beginning *in utero* or later in life.

3.7 Immunological Signalling

In addition to genes related to specific neurotransmitter systems and to factors that directly regulate gene expression, recent studies have suggested that genes within the major histocompatibility complex (MHC, or HLA in humans), on chromosome 6p21.3, may encode predisposing factors in autism [253, 78, 252] (but see [197]). Genes in this region encode products that are required for self-nonself recognition by the adaptive immune system. In particular, an unusual number of people with autism may share all or part of the extended MHC haplotype B44-SC30-DR4 [253, 78, 252, 232]. Evidence also exists for a link between autism and a null allele of the C4B gene, in the class III MHC region, [254], and correspondingly low levels of C4b protein [249] which is essential in activation of the classical complement pathway. The previously mentioned possible involvement of the *UBE3A* gene also ties into MHC functioning, since the peptide fragments presented by MHC molecules can be produced by the proteolytic activity of ubiquitin ligase. Alterations in ubiquitin-related proteins or in other aspects of the peptide-generating machinery can therefore be expected to have profound effects on the intensity and specificity of MHC-dependent immune signalling. These and other genetic correlates between autism and immune-related genes could be causal, or alternatively may result from linkage disequilibrium with nearby autism-associated genes that are as yet unknown.

In support of an immune signalling aetiology, there are many reports of elevated incidence of immune disorders in the autistic population and in their first-degreee relatives (reviewed in [242, 138]). A subset of autism patients displays abnormal cell-mediated immunity and

abnormal T cell populations and functions [217, 251, 255, 265, 83], reduced NK cell activity [250], and lower Th1 and higher Th2-like cytokines [100]. In addition, autism patients often exhibit abnormal humoural immune and autoantibody responses [259, 211, 210, 58]. Genetic and symptomatic links between elevated serotonin levels and autism (see above) could also contribute to immune dysfunction in autism; besides being a neurotransmitter, serotonin is an immunomodulator [266]. Interestingly, immune dysfunction and strong genetic linkage to the MHC are seen in dyslexia, another neurodevelopmental disorder that is similarly far more prevalent in boys (*e.g.* [113, 40]). It appears that abnormal immune responses may be predisposing but not sufficient to cause autism, since non-autistic first-degree relatives often share these abnormalities [57]. Rather, an environmental insult such as an infection may interact with these genetically-based predisposing factors to cause autism.

The timing of any such environmental insult remains unclear, though the predictive relationship between autistic symptoms later in development and increased brain volume in the first 2 to 12 months [65] seems to suggest a perinatal or prenatal time frame. Some maternal viral infections are known to increase the risk for schizophrenia and autism (reviewed in [52]), and in mice, experimental maternal influenza infection produces profound anatomical, motor, and other behavioural defects reminiscent of autism spectrum disorders, including hyperanxiety in novel situations and early postnatal macrocephaly [86, 208]. These infectious links may be due to viral infection of the developing brain, or infection of the pregnant mother. Infection in turn could lead to changes in expression of cytokines [168] or neuronal class I MHC [116], or to production of autoantibodies [77]. While it is unknown if autism is correlated with a change in neuronal MHC expression, maternal neuronal autoantibodies have been associated with autism [77], and neuronal autoantibodies have also been detected in autistic individuals themselves [210, 58].

Together, reports of genetic linkage to the MHC and immune comorbidity point to the potential for an autoimmune aetiology for some cases of autism. It is worth noting that viral or bacterial infections are suspected in the induction of many autoimmune diseases, perhaps due to molecular mimicry or to sequelae of persistent subclinical infection [138]. Alternatively, it may be that the paired neurological and immunological symptoms of some autism patients reflect the impact of abnormal neuronal function on the immune system, with which it is known to have extensive crosstalk (reviewed in [1]). A third possibility is that immune and neurological symptoms are parallel manifestations of a single form of genetic or metabolic disorder.

This last possibility is interesting in light of the recent discovery that class I MHC, in addition to its well-characterised role in immune function, is expressed in neurons and is critical for normal brain development and function [62, 116]. This novel finding suggests that defects in MHC function could give rise, in parallel, to both immunological and neurodevelopmental dysfunctions (reviewed in [34]). Although originally not thought to be expressed by normal, uninjured neurons, class I MHC was identified in an unbiased screen for genes involved in activity-dependent refinement of developing visual projections [62]. Here, as in many other regions of the developing brain, initial projections are large and imprecise, and patterned

neuronal activity arising in the periphery is necessary for the removal of inappropriate connections and stabilisation of appropriate ones. This process is critical to achieving mature patterns of connectivity, and in mammals occurs in early postnatal life. Strikingly, class I MHC mRNA is regulated by the spontaneous activity that drives refinement of the developing visual system [62], and is expressed by neurons precisely at the times and places of widespread activity-dependent structural and functional plasticity, both during development and in the adult [62, 116]. This positive association between MHC signalling and synaptic development is reinforced by the negative effects of MHC knockouts. Mice deficient for class I MHC signalling retain the immature pattern of visual connections, presumably due to a failure of activity-dependent refinement [116]. In addition, hippocampal synapses in these mice are not weakened in response to patterned activity, and instead are inappropriately strengthened. Both of these defects are also found in mice lacking CD3ζ, a component of many known receptors for class I MHC [116]. These changes in plasticity are not a nonspecific effect of immune compromise, since neural plasticity is normal in even more severely immunocompromised (RAG1$^{-/-}$) mutant mice [116]. Thus class I MHC is required, either developmentally or acutely, for activity-dependent synaptic weakening and removal of inappropriate connections, changes that are crucial for normal brain maturation and function [116, 34]. The idea that shared molecular mechanisms may underlie both neuronal plasticity and cellular immunity is further supported by the fact that much of the MHC signal transduction machinery found in the immune system is also expressed in neurons (reviewed in [34]).

In the context of the hypothesis of abnormal connectivity in autistic brain development, the implications of such a failure of synaptic weakening and synaptic specificity are straightforward. The combination of early brain overgrowth, immunological abnormalities, and genetic linkage to the MHC is consistent with the possibility that a defect in MHC signalling is causal for a subset of people with autism. Defects in MHC signalling lead to abnormal activity-dependent refinement and plasticity in the developing visual system, the adult hippocampus, and perhaps elsewhere in the brain. Abnormal information processing later in life could stem from the excessive connectivity laid down during development as well as persistent abnormal potentiation of synaptic strength. The patterns of expression of various MHC genes are diverse, varying with neuron type, brain region, and age [116]. This chemical diversity provides a route whereby a general abnormality in MHC signalling may interact with normal development to produce specific patterns of abnormality.

To date, the connections between autism and immune genes and dysfunction have been interpreted as support for an autoimmune or infectious aetiology. It may be that class I MHC expression by populations of neurons at a given time in development confers selective vulnerability to autoimmune attack, particularly if T cells are entering the brain in large numbers, as they do during some infections. It would therefore be of interest to determine if neurons affected early in autism, such as cerebellar Purkinje cells and granule cells, express high levels of MHC around the time of onset. In addition, it would be of great value to know if MHC is expressed in abnormal patterns or levels in the developing autistic brain, although such experiments await the further refinement and validation of animal models of autism.

The studies linking immune genes and immunological functions to autism are fragmentary and a topic of heated debate. Methodological differences, small sample sizes, and a lack of appropriate control groups, as well as likely heterogeneity in aetiology and pathology, all hamper interpretation of conflicting studies. Causal heterogeneity in particular will likely frustrate attempts to determine genetic, functional, and anatomical correlates until other, perhaps biochemical, diagnostic criteria are developed to classify causal subtypes of autism. To that end, the hypothesis that MHC signalling is involved in the aetiology of a subset of cases of autism suggests candidate markers and neural substrates that may identify one such population. The current data appear to link altered immune function to abnormal neuron development through shared molecular mechanisms, and offer testable hypotheses regarding the possible relationship to autism. Understanding the role of immune molecules in brain maturation and function may ultimately lead to unexpected new strategies for the screening, treatment, and prevention of autism and other neurodevelopmental disorders.

4 Animal Models

Although several primate models of autism have been developed [106, 152], research on neurodevelopmental abnormalities and treatments for autism has had to cope with a dearth of non-primate animal models [63, 193]. Targeting relatively simple behaviours in rodent models has proven useful in the development of pharmacological targets in other neuropsychiatric diseases such as schizophrenia and affective disorders [97, 147]. Establishing the face, predictive, and construct validity of an animal model of autism may prove extremely useful in advancing understanding of autism's neuropathology and in screening potential therapies. Approaches to animal models of neuropsychiatric disease involve modelling the aetiology or pathophysiology of the disease (*e.g.* producing mice with cerebellar pathology) or modelling particular behavioural attributes (*e.g.* studying animals with abnormal social interactions or deficient sensorimotor gating).

If people with autism are hyper-responsive to sensory stimuli, then existing methods of examining sensory responsiveness may be useful in defining endophenotypes and developing animal models of autism. One approach to measuring sensory processing arises in the context of sensorimotor gating. Prepulse inhibition (PPI) of the startle response is a cross-species measure of the normal decrement in startle when a barely detectable prestimulus immediately precedes (30-500ms) a startling stimulus [123, 98, 79]. PPI appears to reflect the activation of a ubiquitous centrally mediated behavioural 'gating' process, and has been widely applied in studies of information processing and cognition in animals and humans. In particular, the inhibitory processes activated by the weak 'prepulse' and the resulting decrement in startle amplitude have been used as an operational measure of sensorimotor gating. Studying PPI has enabled a focus on well-defined measures of information processing having substantial homology among different species and, in the case of schizophrenia, significant predictive validity for treatments [221]. As reviewed elsewhere, schizophrenia-like deficits in PPI have been mimicked in animals using both pharmacological [96] and anatomical manipulations

[222].

Deficits in PPI have been observed in schizophrenia [35], obsessive-compulsive disorder [220], Huntington's disease [223], nocturnal enuresis and Attention Deficit Disorder [164], and Tourette syndrome [47]. Although an earlier study of autism showed no abnormality in PPI [165], a more recent examination, parametrised in terms of prestimulus amplitude and prestimulus-to-stimulus interval, revealed a selective impairment in the inhibition of startle response at high prestimulus amplitude and longer interstimulus intervals [155]. While normal subjects showed the typical pattern of increased prepulse inhibition at higher prestimulus intensities (12 dB versus 4 dB) and longer interstimulus intervals (120ms versus 30ms), people with Asperger syndrome did not. This failure to make use of extra processing time to rapidly modify response bias is reminiscent of results on slowed shifting of attention in autism (*e.g.* [236]), and the absence of an effect of prepulse amplitude suggests abnormal sensory responsiveness – a possibility supported by skin conductance findings of abnormally high tonic arousal [216] and abnormally high phasic response to stimuli [241] in autism. Similar findings of high arousal [30] and high responsiveness [156] in FXS support the idea that these abnormal sensory phenomena may be markers of abnormal neural development. More comprehensive studies assessing startle plasticity in adults and children with autism are warranted, and are currently underway (William Perry, personal communication).

Sensorimotor gating abnormalities similar to those in human neuropsychiatric conditions have been produced in rats by a variety of neurodevelopmental manipulations. Models include alterations of the intrauterine environment (*e.g.* viral insult, neurotoxin exposure, prenatal maternal stress), birth complications [240], postnatal maternal and/or social deprivation [85, 258], and neonatal ventral hippocampal lesions [146]. The developmental model most extensively studied for its effects on PPI has been post-weaning social isolation, a manipulation that induces profound abnormalities in behaviour, drug responses, and neurochemistry [185]. Neurodevelopmental animal models like those developed for schizophrenia are now being brought to bear on autism. Some of these autism models are based on prenatal exposure to teratogens such as Borna disease virus [182] or valproic acid [119]. Others derive from findings of abnormal cerebellar anatomy in people with autism, and include both mutant animals with specific cerebellar malformations [49, 139] and animals with surgical lesions of the midline cerebellum [32]. Several such cerebellar models have begun to find application in the study of sensorimotor gating and other behaviours relevant to autism: deficits in PPI have been observed in heterozygous reeler mice [238] and in mice homozygous for the cerebellar deficient folia (cdf) mutation [167].

A further model is based on the hypothesis of low signal-to-noise as a basis of autistic brain development: if this is the case, developmental errors similar to those in autism ought to be able to be induced by manipulating signal-to-noise directly, independently of any neurochemical antecedents. A straightforward way of implementing such a direct manipulation is to supply the developing brain with consistently noisy sensory inputs. In rats reared in continuous 70dB acoustic noise, neurons in primary auditory cortex retain into adulthood the immature pattern of broad, high-frequency tuning curves and imprecise

tonotopy typical of the earliest stage of auditory development [51]. This physiological finding of broad tuning in the auditory system seems very much akin to the psychophysical finding of abnormal bandwidth of auditory filters in people with high-functioning autism [180]. In addition to retarding the emergence of normal activity-dependent patterns of neural tuning, developmental exposure to noise prolongs the critical period during which any input, regardless of behavioural context, is significant for activity-dependent plasticity [51]. A delay of this transition from unconditional plasticity to context-dependent plasticity may underlie the ease with which people with autism learn arbitrary associations, and the difficulty with which they incorporate behavioural context into such learning. Furthermore, a delayed and abnormal closing of this critical period may be the trigger for the onset of autistic regression during the second or third year of life.

Inevitably animal models will play an important role in future research on the causes and cures for autism. Creative translational brain-behaviour designs will be needed, wherein tests demonstrating specific brain-behaviour relationships in children with autism are formatted for animal model studies. For instance, a recent human study showed that when allowed to explore freely an open area containing novel objects, children with autism spent less time exploring the novel information than normal children, and that the more abnormal the exploration behaviour, the smaller the cerebellar vermis [173]. Such a study design can be easily formatted for testing animal models of candidate genetic or non-genetic causes of autism, and in fact several candidate models already exist. The GS guinea pig, a mutant with malformation of cerebellar vermal lobules VI and VII, shows decreased exploratory behaviour [49], as do Purkinje cell degeneration mutant mice [140]. Specific loss of Purkinje cells in cerebellar vermal lobules VI and VII in L1CAM knockout mice is associated with decreased exploration and stereotyped circling in a novel environment [131, 90]. Rats with cerebellar lesions show deficits in long-term habituation of the acoustic startle response [144] and increased spontaneous motor activity and perseverative behaviour [32]. As the definition of human behavioural endophenotypes in autism proceeds, measurable, homologous behaviours can be quantified in animal models. Prepulse inhibition and other forms of startle modulation (*e.g.* fear potentiated startle) may be useful in constructing such animal behavioural homologues.

5 Research Imperatives

5.1 Phenotypes within and beyond the Diagnosis

To those who treat patients with autism spectrum disorders, or who work with them as researchers or caregivers, it can often seem as if there are as many kinds of autism as there are people with autism. Since the diagnosis of autism rests on broad and entirely behavioural criteria, studies whose inclusion criteria follow the diagnostic criteria are liable to recruit subject groups that are heterogeneous in terms of ultimate causes. Reducing this heterogeneity demands a more detailed taxonomy, extending not only within the diagnosis but also outside it. The accepted wisdom has been to restrict studies to only the most

severe cases – for example those patients who satisfy both ADI-R and ADOS criteria and whose clinical diagnoses exclude Asperger syndrome and PDD-NOS. Although this strategy certainly reduces heterogeneity, it puts blinders on efforts to identify behavioural endophenotypes. In contrast, broadening studies beyond the strict diagnosis of autism holds a great deal of promise for identifying which components of the autistic syndrome are genetically transmitted, and how these components interact. The early results of such work reveal familial patterns of repetitive behaviours, impaired nonverbal communication, and impaired or delayed development of phrase speech, but not social interaction or verbal communication [209].

Autism may well occur when several root factors combine to produce a core dysfunction – a dysfunction which we have suggested may involve neural signal-to-noise – to a degree that brings on a grand change in developmental course and produces autism's many symptoms. Information on the abnormal events surrounding this critical developmental event becomes much more valuable when it can be contrasted with information on what happens when the event is avoided. Such a contrast can be obtained by studying siblings and other family members of patients with autism, people who presumably share some of the genetic susceptibility factors but in whom those factors have not become magnified into the full syndrome of autism. A wealth of behavioural data suggests that such factors are operative in first-degree relatives and do produce subclinical abnormalities. Siblings of autistic children show a cognitive profile reminiscent of that of autism itself, with superior spatial and verbal span, poor set-shifting, poor planning, and poor verbal fluency [115]. Parents of autistic children perform in the superior range on the Embedded Figures Test [20], visual search tasks [163], and other tasks that require processing of parts and details [102], but are below normal performance at inferring mental state from facial expression [20], a task that demands configural and integrative processing. In addition, parents share difficulties in pragmatic language tasks [87], impairments in some tasks that tap executive function [114], and autistic personality characteristics such as rigidity, aloofness, and anxiety [179, 178]. Many first-degree relatives show a disparity between performance IQ and verbal IQ, with the performance score being lower [89, 177, 87] due to impairment on Picture Arrangement and Picture Completion, both of which demand attention to global, contextual information. These subtle characteristics of the broader autism phenotype are visible in the cognitive skills that relatives tend to develop: occupations in engineering, which demands meticulous attention to detail, are over-represented in the fathers and grandfathers of people with autism [23] and, conversely, the incidence of autism is increased in the families of engineers, mathematicians, and physicists [19]. Siblings are at greater risk than the general population for a wide array of cognitive and affective disorders [176, 10], and there is some epidaemiological evidence relating autism to familial history of affective disorder [81].

If the cognitive profile in siblings is, as it seems, reflective of that in autism, then the same may be true at the levels of neuroanatomy, neurophysiology, and neurochemistry. Studies of first-degree relatives at these levels of analysis can expose primary factors closer to the roots of autistic brain development, unobscured by so many of the secondary developmental sequelae that may overshadow or mask such factors in autism probands. In particular, there

is a wealth of electrophysiological and morphometric findings in autism whose value would be greatly augmented if the same experiments and measures were applied in autism relatives, and the results compared. Do relatives manifest to any degree the anatomically over-generalised activation found in autism probands during attentional tasks? Is focused spatial attention associated with abnormally modulated mid-latency visual evoked potentials as it is in autism probands? Are there any changes in the amplitude or latency of frontal negativities, or in the late positive component? Do relatives show any abnormality in cerebellar volume, or in cross-sectional area of the corpus callosum? What about head circumference and early overgrowth of the frontal lobes? Many of these comparative questions can be answered quite easily, and should be addressed. Where differences exist, they may be subtle, and large groups of subjects may be required in order to achieve sufficient statistical power. As autism susceptibility genes begin to be identified, these non-autistic relatives will be of the utmost value in defining the behavioural and physiological phenotypes with which single susceptibility factors are associated.

The potential for large-scale secondary dysfunctions to mask more primary abnormalities has implications for studies within autism probands, too. A great deal of research attention has been devoted to autism's most apparent and most debilitating symptoms, those that make up the diagnostic triad of impaired social interaction, impaired communication, and restricted and repetitive interests and behaviours. Even physiological studies have addressed complex social capacities such as theory-of-mind [22] and emotion perception [76]. Observations at all levels of behavioural and physiological complexity are useful in reverse-engineering autistic development. However, in concentrating exclusively on the most diagnostic features of autism, such work may be overlooking cognitive and perceptual features at low levels of processing that are closer to autism's core dysfunction. There is a great need for further exploration of the neurophysiology associated with low-level perceptual abnormalities. It is quite remarkable and difficult to fathom that we currently have more functional imaging data about how the autistic brain processes a face or a theory of mind than we do about the way it processes, say, location, colour, orientation, or spatial frequency; at what level of processing do the perceptual and cognitive abnormalities begin? It is also important to recognise that absence of behavioural performance or functional activation does not necessarily imply incapacity of the corresponding brain subsystems. Rather, an apparent lack may be due to failure to engage an intact capacity. The proper stimuli or experimental paradigm can bring out such hidden abilities.

The finding of early brain overgrowth illustrates the importance of looking for primary abnormalities at the youngest possible ages, before all of the secondary changes have occurred. Although autism currently cannot be decisively diagnosed until the age of 5 years, its sibling recurrence risk of 4.5% opens the possibility of conducting the study in advance of the diagnosis. After the collection of data from all at-risk siblings, observations of siblings who do not meet full criteria at age 5 can be excluded from the autism sample. These observations of siblings who turn out not to have autism are not wasted, since, as noted previously, the sibling group is an informative contrast both to the autism group and to unrelated control subjects.

In addition to these more traditional, cognitively based elements of behaviour, attention must be paid to even lower-level aspects of the phenotype. Parent reports are rife with anecdotal observations of low-level dysfunctions. Motor abnormalities, in particular, may be one of autism's earliest signs, appearing within the first year of life [17]. Abnormal gait is common in autism [245, 101], and motor clumsiness seems particularly prominent in Asperger syndrome [214]. Other oft-reported abnormalities (*e.g.* gastrointestinal problems, blink rate, pupillary dilation), and the unproven interventions that have been designed around some of them, may yet contain a kernel of truth and should be subjected to controlled study.

5.2 A Synthetic Approach

Most experimental observations of autism yield correlations rather than definite causal relationships, and these correlations often exist in a vacuum: it is possible to implicate a chromosomal locus without knowing what genes it contains, a gene without knowing the function of its protein product, a protein without knowing its physiologic effect, and so forth. Connecting the many stages from genetics and biochemistry to brain structure and function and behaviour demands studies that bridge these levels of analysis.

Postmortem studies and *in vivo* MRS studies aimed at elucidating the neuronal and molecular bases of early brain growth abnormalities in cerebellar and cerebral white matter and cerebral grey matter are needed. Studies can and should be designed to demonstrate explicitly relationships between such postmortem microscopic findings and *in vivo* MRI-based macroscopic effects. Also, detailed knowledge of brain growth defects may help guide the effort to create more developmentally realistic animal models of the disorder. Techniques such as MRI morphometry and event-related potentials make it possible to associate specific sites of brain abnormality with specific types of neurobehavioural deficits. Event-related potentials and other brain-behaviour correlation studies have elucidated relationships between anatomical sites of abnormality and deficits in visual selective attention, shifting attention, motor activation, motor learning, visuospatial exploration, and orienting attention. An important hypothesis for future research is that the age of onset, rate, and duration of aberrant brain growth are related to the severity and age of onset of autistic behaviours.

Like the individuals whom it seeks to understand, the field of autism research often falls victim to a sort of weak central coherence. Its challenge is to unify a complex set of local observations and details into coherent explanations of the autistic syndrome. Isolation of specific endophenotypes and examination of contributing genes will aid in uncovering the neurobiological roots of autism's core dysfunctions, while targeting low-level processes and examining early stages of development will highlight the steps through which those core dysfunctions unfold into autism's complex behavioural syndrome.

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