Genetic and Neurodevelopmental Influences in Autistic Disorder

Rob Nicolson, MD, FRCPC[1], Peter Szatmari, MD, FRCPC[2]

Objective: In the past, autism was considered to be largely psychogenic. However, research in the last 2 decades indicates that autism is largely caused by genetic factors that lead to abnormal brain development. This article reviews research into the genetic and neurodevelopmental factors underlying autism.

Methods: We review the findings from genetic and brain-imaging studies of autism over the past 15 years and synthesize these findings as a guide for future research.

Results: Genome scans and association studies have suggested potential genomic regions and genes, respectively, that may be involved in the etiology of autism, and there have been some replications of these results. Similarly, the findings that brain volume is exaggerated in autism and corpus callosum size is reduced have also been independently replicated. Unfortunately, studies of other subcortical structures remain inconclusive or contradictory.

Conclusions: Overwhelming evidence now supports a neurobiological basis for autism. However, further refinements will be needed to guide future studies, particularly to identify the most informative phenotypes to investigate. Additionally, studies examining the role of genetic factors in the brain abnormalities underlying autism will likely lead to further findings that will enhance our understanding of autism's causes.
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Information on author affiliations appears at the end of the article.

Clinical Implications

- The diagnostic work-up of children with autism should include a detailed family history and a consideration of single-gene disorders associated with autism.
- Infant siblings of children with autism are at risk of developing the disorder, and their development should be monitored carefully.
- Evidence that the abnormal neurodevelopment underlying autism occurs during the first few years of life continues to accumulate. Among other things, future longitudinal studies will focus on the timing and course of this aberrant brain development.

Limitations

- No susceptibility genes have been identified, and the value of predictive or diagnostic genetic testing remains unclear at this point.
- Children with autism and typically developing children show small differences, with much overlap, in total and regional brain volumes. Therefore, brain-imaging studies are not indicated for routine clinical evaluation of children with autism unless there is evidence of other neurologic abnormalities, such as seizures.

Key Words: *autism, genetics, phenotype expression, neurodevelopment, magnetic resonance imaging*

Autistic disorder is a severe developmental disorder characterized by social deficits, impaired communication, and restricted and repetitive patterns of behaviour. Although once thought to be rare, recent research suggests that it may affect as many as 1 in 300 children (1,2).

While autism was once viewed as an almost entirely psychogenic disorder, compelling evidence now suggests that it is a disorder of abnormal brain development, the basis of which is largely genetic. As such, studies of autism's genetic and neurobiological nature have increased dramatically in the last 2 decades.

No current treatments are specifically designed for people with autism. Moreover, interventions are aimed at reducing the interfering symptoms associated with autism. This has led some to question the need for etiological research, arguing that it is perhaps better to focus exclusively on testing various interventions that might improve functioning or reduce symptoms. It seems likely, however, that specific and uniformly effective treatment will not be realized without a clear understanding of the disorder's underlying neurological and genetic causes. Hopefully, interventions aimed at the brain-level biochemical and structural changes leading to autism will result in long-lasting and significant improvement. In addition, greater understanding of the developmental processes involved in autism may make it possible to identify children at risk at a much younger age and to initiate treatment earlier, in the hope of reducing the often-severe disabilities associated with the disorder (see 3).

In this article, we review the current research on the genetics of autism and on the brain abnormalities underlying the disorder and discuss possible future avenues of research into the aberrant biological processes involved.

The Search for Susceptibility Genes in Autism

After many years of research and after many false starts, it is now clear that autism has a genetic basis (4). The risk to siblings of children with autism is around 3% to 6%—about 50 to 100 times greater than the risk to the general population. It is also true that the risk extends to other forms of pervasive developmental disorder (PDD), such as atypical autism and Asperger syndrome (AS), and to PDD-like traits that fall short of impairment. These data only provide evidence that the disorder runs in families; twin studies must be conducted to determine whether the basis of that familial aggregation is environmental or genetic. There are now 4 twin studies (4–8) comparing the rate of autism in monozygous (MZ) and dyzygous (DZ) twins when 1 member of the twin pair has autism. All studies have shown that the concordance rate for autism is much higher in MZ than in DZ twins, a finding that can only be explained by the presence of important genetic factors. From these studies, heritability estimates (that is, the extent to which clinical variance is accounted for by genetic factors) can be calculated; they appear to be greater than 90%. This makes autism the most heritable psychiatric disorder, even more so than schizophrenia and bipolar disorder (9). The only environmental factors possibly associated with autism include thalidomide use, certain viral infections in utero, and maternal anticonvulsants, yet these account for only a tiny fraction of cases (10–12). The strength of these genetic effects suggests that it should be possible to find autism genes, although studies modelling the mode of transmission indicate that as few as 3 or perhaps more than 10 interacting genes may be involved (13,14). Both association studies and genome scans have been employed to find these susceptibility genes.

Candidate Gene Strategy

Association studies typically focus on candidate genes for which there is functional evidence of etiologic involvement. For example, it has been known for many years that peripheral serotonin (5-HT) levels are raised in children with autism and in their first-degree relatives (15). As a result, genes involved in 5-HT metabolism are prime candidates for investigation. In recent years, many candidate genes, including those in the 5-HT system, have been found to be associated with autism (for a review, see 9; see also 16–19). However, attempts to replicate positive findings have been unsuccessful (15,20,21). Perhaps the most promising region identified by association methods is on chromosome 15, where frequent chromosome duplications have been documented in children with autism. Recent reports suggest that the *UBE3A* gene or a subset of GABA genes in that region (22,23) may be involved, although even in this region, it has proven difficult to replicate positive results.

Genome-Wide Scans

Researchers have conducted several genome-wide linkage scans in autism, using an affected-relative design; that is, a design sampling families with at least 2 affected relatives (most commonly, siblings). More dense pedigrees are generally not available, owing to the tendency of parents to stop having children after the birth of an affected child (24) and the reduced fecundity of people with autism. Genome scans assess the extent to which a disease is "linked" with a set of anonymous DNA markers. By "linked," geneticists mean that both marker and disease are transmitted together in a pedigree. Since we know the chromosomal position of the marker, we can assume that, if linkage exists, the disease gene will reside in the same chromosomal region.

As shown in Table 1, the autism genome scans (14,25–33) vary with respect to sample size, number of markers, map density, diagnostic instruments, method of diagnosis, and phenotypes analyzed. Of these elements, variation in the number of sib pairs (range 17 to 152) and in the diagnostic strategy

Table 1 Summary of genome scans in autism

Research group	Year	Affected sib pairs (*n*)	Markers (*n*)	Distance	Phenotype	Instrument	Method	Chr region	Highest LOD score
IMGSAC (25)[a]	1998	87	354	10	Autism	ADI	ASPEX	7q	MLS 2.53
					PDD	ADOS		16p	MLS 1.51
								4p	MLS 1.55
CLSA (26)	1999	75	416	9	Autism	ADI	Genehunter	13q	MMLS/het 2.3
						ADOS	HLOD	13q	MMLS/het 3.0
								7q	MMLS 2.2
Philippe (27)	1999	51	264	14	Autism	ADI	Mapmaker/Sib	6q	MMLS 2.23
Risch (14)	1999	147	519	10	Autism	ADI	ASPEX	1p	MMLS 2.15
						ADOS			
Auranen (28)	2000	17	390	10	PDD	—	Sib pair	3p	MLS 2.39
Buxbaum (29)[b]	2001	95 total	382	10	Autism and other	ADI	HLOD	2q	HLOD 1.96
		49 narrow			Autism and PSD		NPL	2q	NPL 2.39
								2q	HLOD 2.99
								2q	NPL 3.32
Liu (31)[b]	2001	188 total	335	13	Autism and autism	ADI	Mapmaker/Sib	5q	MMLS 2.55
		75 narrow			Autism and other			Xqter	X-MLS 2.56
								19p	MMLS 2.53
								Xqter	X-MLS 2.67
								16p	MMLS 1.93
								19q	MMLS 1.70
								5q	MMLS 1.63
IMGSAC (30)[a]	2001	152 total	392	10	Case 1-autism	ADI	ASPEX	2q	MMLS 3.74
		127 strict			Case 2a-autism/PDD IQ > 35	ADOS		7q	MMLS 3.20
					Case 2b-autism/PDD any	VABS		16p	MMLS 2.93
						IQ		17q	MMLS 2.34
								2q	MMLS 4.80
Shao (33)	2002	99	352	10	Autism	ADI	HLOD	3p	MLS 1.51
						ADOS	MLS	7q	MLS 1.66
								Xq	MLS 2.54
Alarcon (32)[c]	2002	152	335	10	Any ASD	ADI	NP-QTL Mapmaker/Sib	7q	NPL-Z 2.98

[a]83 from 1998 report; [b]82 of 95 overlap from Buxbaum; [c]same sample as Liu.

ADOS = Autism Diagnostic Observational Schedule, ADI = Autism Diagnostic Interview, ASD = autistic spectrum disorder; CHR = chromosone; CLSA = Collaborative Linkage Study of Autism; HLOD = heterogeneity of LOD score; LOD = logarithm of the odds; MLS = maximum LOD scores; MMLS = multipoint maximum LOD scores; NPL = nonparametric LOD score; NPL -Z = nonparametric LOD score-Z; NP-QTL = nonparametric quantitative trait locus; sib = sibling; VABS = Vineland Adaptive Behavior Scales; X-MLS = X-linked maximum LOD score

employed is most marked. The only consistent element across studies is the use of the Autism Diagnostic Interview (ADI) to identify affected individuals. The use of other phenotypic data is surprisingly limited. Despite this variability, it is encouraging to see that suggestive linkage signals (that is, logarithm of the odds [LOD] scores above 1.5) from different scans overlap particularly on chromosomes 7q, 16p, and 2q. It is difficult to interpret these results, however, because none of the linkage signals reach genome-wide statistical significance according to current criteria (34), and the use of overlapping samples and different markers makes it difficult to conclude that a finding has been truly replicated. What is important, though, is that the linkage signals from different groups are reasonably consistent. The problem is that the regions identified are too large, and the linkage signals too weak, to start sequencing genes in these regions to identify the pathogenic variants.

Bradford and others (35), Buxbaum and others (29), and now Shao and others (36) report that LOD scores on chromosome 2 and 7 and 13 increase when analysis is restricted to sibling pairs with language delay. Alarcon and others report a similar increased linkage signal on chromosome 7 if the quantitative trait "age at first phrases" is used (32). The higher linkage signals associated with these alternative phenotypes suggest that the genes on chromosome 2 and 7 may be involved in a subgroup of families with autism. This strategy of stratifying sib pairs to deal with possible genetic heterogeneity may be an important avenue for further research.

Chromosome 7q and Autism

Based on several lines of evidence, perhaps the most promising susceptibility region for autism is on chromosme 7. First, several genome scans have reported suggestive LOD scores between 7q31 and 7q35. Second, the region 7q31 to 7q35 also contains the recently cloned *FOXP2* gene responsible for a type of language disorder (37). Third, most children with autism have a serious language deficit (38). Fourth, 2 groups have reported that their LOD scores in this region increase if the phenotype is narrowed by requiring some measure of language delay in probands and relatives (32,35). Fifth, several pedigrees with an autistic proband have been reported with apparent deletions in this region (39). Sixth, a recent metaanalysis of linkage results concurs that a susceptibility gene may well exist on 7q (40). This enthusiasm must be balanced, however, by several reservations. First, the *FOXP2* gene has been ruled out as a major susceptibility gene in autism and in specific language impairment (41). Second, characterization of genes that were found to be interrupted directly by the chromosomal translocation breakpoints in children with autism have not revealed mutations that segregate in a familial manner in other children having autism (42,43). Third, the signals on chromosome 7 are separated by large distances, suggesting that there are perhaps several genes in the region or that the most appropriate phenotype has not yet been determined. It seems that narrowing the region on chromosme 7 is not simply a matter of sample size or density of markers: even the study with the largest sample size and the most markers (30) could not resolve this issue. We may have reached an impasse in refining the signals on chromosme 7 (and by implication elsewhere), unless we reduce the genetic complexity of autism by defining more specific phenotypes within and between families.

There are 2 types of genetic complexity that will obscure linkage signals. First, there may be interfamily heterogeneity so that susceptibility genes on chromosome 7 and elsewhere may be risk factors for only a subgroup of families. Stratification of sibling pairs on clinical variables is an important strategy that can be used to deal with this type of heterogeneity (44,45). Second, there may be intrafamily heterogeneity in which sibling pairs may not share genes for all components of the phenotype (44). In this scenario, autism may be caused by many genes, each of small effect, in interaction, and each gene (or set of genes) may be a risk factor for a specific component of the autism phenotype. It may be easier to find genes associated with these so-called "endophenotypes" than to find genes associated with autism.

Decomposing the Autism Phenotype into Endophenotypes

To find out which genes are associated with which endophenotypes, it may be necessary to disentangle the autism phenotype. Several different variables have been investigated to see whether they reflect familial components of the autism phenotype. These variables have included serum 5-HT levels, head circumference, and language impairments; all have been found to be different both in children with autism and in their first-degree relatives, compared with control groups (47–49). These dimensions, however, are somewhat peripheral to the core autism phenotype, and so their relevance to the genetics of autism is unclear.

Focusing on the core features of autism may be more helpful. In a recently completed factor analysis, we found that symptoms from the 3 ADI domains (that is, reciprocal social interaction, communication, and repetitive activities) and measures of IQ and adaptive behaviour load on 2 discrete factors, which we call autistic symptoms and level of functioning (50). Level of functioning is usually measured with IQ (51) or the Vineland Adaptive Behavior Scales (VABS) (52) and refers, in general, to the extent to which typical adaptive behaviours needed for daily functioning are reached at appropriate developmental benchmarks. It appears that sex (53) and birth order (54) affect IQ but not autistic symptoms, further supporting the distinction between these 2 factors.

Characteristics of Familial Phenotypes

The second crucial issue is whether both these phenotypes are familial. It turns out that measures of level of functioning are more familial than are autistic symptoms; the variance within a sibship on this variable is less than the variance between sibships (55)—something not generally seen for autistic symptoms (or much less so, see references 56 and 57). For example, in our data for affected siblings with autism, the intraclass correlation on communication scores from the VABS is 0.50 ($P < 0.001$); on IQ, it is 0.42 ($P = 0.01$), compared with 0.20 (P = ns) for autistic symptoms from the ADI (55). While other groups have reported similar findings (49–52), one study (56) also reports that repetitive, stereotyped behaviours are familial. Taken together, these data suggest that perhaps high- and low-functioning PDD may arise from separate familial, presumably genetic, mechanisms. In other words, interfamily heterogeneity is a real possibility in autism.

An analysis of family history data provides further evidence of this possibility. We have reported that the risk to relatives of the broader autism phenotype (BAP)—that is, PDD-like traits that fall below threshold for a diagnosis—is greater if the PDD proband is higher-functioning rather than lower-functioning (60, although see 61 and 62 for conflicting results). Our studies show that, in the lower-functioning group, a family history of the BAP is only marginally higher than prevalence rates in nonbiological relatives. The lower-functioning group may thus comprise the tail end of children with high-functioning autism and children with nonspecific mental

retardation syndromes, in whom the autism is secondary to the retardation (not to the susceptibility genes that cause autism and the BAP in the higher-functioning group). This suggestion is supported by years of research showing that probands with autism and an IQ below 50 differ from high-functioning probands: they include a higher proportion of female subjects; a greater concentration of minor physical anomalies; and more CT scan abnormalities, microcephaly, chromosome abnormalities, and epilepsy (see reference 63 for a systematic review). Moreover, children with known chromosomal abnormalities and medical disorders such as tuberous sclerosis and phenylketonuria are concentrated in this lower-functioning group (64). Including the lower-functioning sib pairs may thus bias linkage signals associated with the susceptibility genes for autism and the BAP.

In addition to interfamily heterogeneity, it is also important to consider intrafamily heterogeneity. This latter type of heterogeneity would explain the large differences occasionally seen in IQ and language ability among autistic twins and nontwin siblings. Decomposing a categorical phenotype into simpler quantitative dimensions was a key to identifying regions with significant LOD scores in several disorders (65–70). There is only a single example of this in autism, using age-of-phrase speech as the dimension (32). In this study, the authors were able to demonstrate a stronger linkage signal. Similar analyses will soon be conducted with other dimensions, such as repetitive behaviours and nonverbal IQ.

A Model for the Genetics of Autism

Based on these findings, it is possible to develop a genetic model for autism (although admittedly not all results from the different studies are consistent). The model is similar to the sequential multiple-hit model used to explain the development of cancers and other complex genetic disorders. In autism, we have proposed that the first risk factors are the susceptibility genes associated with the BAP, or more precisely, the genes for impairment in reciprocal social interaction (perhaps measured by the VABS socialization scores; 71). These susceptibility genes (which are common and of low penetrance, however) will initiate or place one at risk for a PDD trajectory. Other susceptibility genes (the second set of risk factors) will influence the shape of those trajectories and transform the BAP phenotype into AS, high-functioning autism, or atypical autism. Good evidence for the 2-hit model comes from the twin studies showing that, although MZ twin concordance for autism is around 60%, concordance for the BAP is almost 90% (72). Since these PDD subtypes differ largely on the degree of language impairment (showing little or no impairment in AS and most impairment in autism), some of the genes in the second set may account for variation in language ability among sibling pairs with PDD and will interact with genes in the first set. Other susceptibility and modifier genes may influence nonverbal IQ. In essence, we propose that the genes for the BAP, for nonverbal IQ, and for language impairment in autism are independent and that these 3 genetic mechanisms interact to cause the complex phenotype called high-functioning autism, AS, or atypical autism. The "dose" of genetic effects associated with each mechanism determines the type of PDD a child has, or more precisely, the specific developmental trajectory a child will follow. Low-functioning autism will comprise the tail end of high-functioning autism, as-yet-undiscovered familial mental retardation, and brain damage syndromes that resemble low-functioning autism. This model emphasizes the combined effects of inter- and intrafamily heterogeneity as a basis for the multivariate phenotype known as PDD. Studies proposing to find genes will have to take this complexity into account.

Clinical Implications of Genetic Studies

For now, there are perhaps 2 clinical lessons to be learned from these genetic studies. First, a family history of autism should alert clinicians to look for structural or metabolic disorders underlying autism in a child. Although these structural disorders will only account for around 10% of the cases of autism, a family history of autism or mental retardation indicates the need for a systematic review of diagnostic possibilities. Other markers of central nervous system (CNS) disorder that may underlie autism include epilepsy, prolonged vomiting, growth disturbance, congenital anomalies, and regression in development (73). Second, the infant siblings of children with autism should be followed closely from birth to track the possible development of autism symptoms. There is some evidence that the risk of autism to siblings of children born after the proband with autism may be as high as 9% (74). A larger percentage may have early signs of the broader autism phenotype. Following these children early and enrolling them in early-intervention programs may not only alleviate parental anxiety but may also prevent mild developmental delays.

Brain Imaging in Autism

As noted previously, autism was once thought to be caused by psychogenic factors. However, as appreciation developed of the high rates of mental retardation and epilepsy occurring with the disorder, the involvement of neurologic factors became widely accepted (75). While original neurologic consideration of the disorder attributed it to an unusual consequence of brain damage, later family and twin studies indicated that autism is an expression of a specific disease process that, acting through genetic factors, results in abnormal brain development and the autism syndrome.

Although many brain regions have been implicated in the pathogenesis of autism, the aberrant neurodevelopment underlying the disorder remains unknown, in part because many early studies have not been replicated. The frequent nonreplication of earlier reports may in turn be related to methodological shortcomings, particularly in subject selection (76). Many initial studies of brain structure in autism were plagued by small sample sizes, a lack of standardized diagnostic criteria and assessment instruments, the inclusion of very heterogeneous subjects (for example, those with associated medical conditions and subjects with and without mental retardation), and a failure to account for potentially significant confounding factors (for example, age, IQ, and sex). In the last 15 years, however, several important and consistently replicated findings have appeared from magnetic resonance imaging (MRI) studies; these have provided important insights into the neurobiological basis for autism. Methodological advancements, particularly the careful characterization of subjects (aided by the introduction of validated diagnostic instruments such as the ADI and the Autism Diagnostic Observation Schedule [ADOS]) and improvements in the technology used to acquire and analyze MRI scans, have contributed significantly to the recent increased understanding of neurodevelopmental abnormalities in autism. The more recent introduction of functional MRI (fMRI) has yielded further insight into the abnormalities of neuronal circuits implicated in autism.

Brain Size in Autism

In his seminal paper describing autism, Kanner noted that 5 of his original 11 patients appeared to have relatively large heads (77). Since then, studies from several paradigms have demonstrated the presence of enlarged brain size in autism sufferers. Several studies have reported increased head circumference, and estimates suggest that up to 20% of patients with autism may have head circumferences above the 97th percentile (78,79). Additionally, the few published postmortem studies suggest that some patients with autism may have brains with an increased mass, relative to control subjects (75,78,80).

Over the past 10 years, MRI studies of autism have consistently found elevated brain volume. Following their earlier unexpected report of increased mid-saggital brain area (81), Piven and colleagues noted increased brain volume in 22 male subjects with autism, compared with 20 male subjects without the disorder (82). In a follow-up study with an overlapping sample, Piven and colleagues again reported exaggerated brain volume in patients with autism, with a regional subanalysis indicating that the volumetric elevation was most pronounced in posterior brain regions and that frontal regions did not differ between the groups (83). Several other research teams have also reported increased brain volume in autism (84–87). The finding of elevated brain volume appears to be unique to autism, as most neurodevelopmental disorders and most mental retardation syndromes are associated with a reduced brain volume.

While it appears relatively clear that autism is associated with enlarged brain volume, the timing and persistence of this exaggeration remains unclear. This increase seems to occur early in postnatal life (85,88), and 2 studies have reported increased brain size in preschoolers with autism (85,87). However, Courchesne and others (85) also noted that, while young patients (ages 2 to 4 years) had elevated brain volume, with the elevation being greatest in frontal regions, older patients (ages 5 to 16 years) had smaller brain volumes. This observation led the authors to speculate that, in autism, the period of brain overgrowth is restricted to early childhood and is followed by a period of abnormally slowed growth. This suggestion is not inconsistent with the finding that autism patients under age 12 years have an elevated brain mass but that adults with the disorder have a slightly reduced brain mass (80). While the use of cross-sectional data to make inferences about longitudinal development is fraught with limitations (89), the results of another volumetric MRI study seem to support Courchesne's hypothesis. A relatively large study compared the brain volumes of 67 children and adults with autism with those of 83 comparison subjects (90). While patients of all age groups had a greater head circumference, the increase in brain volume was limited to those under age 12 years; patients over age 12 years did not differ from the comparison group. The elevated head circumference in the older patients, however, suggests that these patients likely had exaggerated brain volume when they were younger.

Thus, the relative consistency in the finding of exaggerated brain volume in patients with autism supports the hypothesis that the disorder is associated with accelerated brain growth early in development. However, the discrepancy in the persistence of these findings remains unresolved, with several studies reporting elevated brain volumes in adults (82,83,86) and others noting that this elevation is restricted to childhood (85,90). It is likely that only longitudinal brain-imaging studies, in which the same subjects are scanned repeatedly as they develop, will resolve these disparate findings. Additionally, future research will need to examine the brain regions contributing to this exaggerated brain volume (for example, to determine whether increased gray matter or white matter, or both, contributes to elevated brain volume).

Recent work suggests that the pattern of abnormal brain growth in autism may be due to abnormal brain-growth factors. Nelson and colleagues examined neonatal blood spots taken from children later diagnosed with autism and from a comparison group (91). They found that patients had significantly increased levels of vasoactive intestinal peptide, calcitonin gene-related peptide, brain-derived neurotrophic

factor, and neurotrophin 4/5. These factors are involved in neural proliferation, migration, differentiation, and growth; it is possible that abnormal elevations in their concentration may lead to aberrant patterns of development through excessive sparing of neurons (that is, a reduced pattern of normal neuronal death). Importantly, Perry and others also reported a threefold increase in the level of brain-derived growth factor in the forebrain of autism patients studied postmortem (92). These findings are intriguing and suggest a possible mechanism for the enhanced period of brain growth in autism. Future studies are necessary to replicate these results and to examine further the relation between these findings and abnormal brain growth patterns in autism sufferers.

Corpus Callosum

The corpus callosum is the largest commissure in the brain. It permits communication between the 2 cerebral hemispheres. Given the overall increased brain volume in autism, one might also expect increased corpus callosum size. Surprisingly, however, most studies of the corpus callosum in autism, and all studies within the past 10 years, have reported reductions in the area of the corpus callosum. Although different studies have noted various segments of the corpus callosum to be abnormal, they consistently find a reduced callosal size (93–96). Most studies have reported a reduced posterior corpus callosum, although one found that the reduction was limited to the anterior portion (96).

As the largest commissure in the brain, the corpus callosum has, through evolution, permitted far greater lateralization of cerebral function than is seen in other organisms, as well as increased cortical capacity through reduced redundancy (97). Higher-level cognitive functions, such as language and linguistic processes and the ability to represent the action of others, depend upon hemispheric specialization; integrating these functions therefore depends upon intact callosal pathways and functioning (97).

Given the the corpus callosum's importance in the lateralization of cerebral functions, its reduced size in autism patients, particularly in the context of an enlarged brain, suggests the possibility of aberrant lateralization of brain functioning in the disorder. Many studies have provided clinical evidence of abnormal motor and language lateralization in autism patients, including increased left- and mixed-handedness and an unusual pattern of cerebral dominance for language (reviewed in reference 98). More recently, anatomic MRI studies have suggested a reduction in the normal level of asymmetry in brain regions involved in language (99,100), while studies using single photon emission computed tomography (SPECT) have reported a reduction in the normal asymmetry seen in frontal blood flow (101). Further, a positron emission tomography (PET) study of boys with autism found an unusual pattern of 5-HT synthesis asymmetry in the frontal cortex, thalamus, and dentate nucleus (102).

The possibility that abnormalities of cerebral asymmetry and the corpus callosum may be involved in autism warrants further investigation, particularly when one considers the importance of cerebral asymmetry in functions, such as language, that are impaired in autism. Studies with other clinical groups, such as children with language disorders, will help to determine the specificity of these findings to autism.

Cerebellum

Clinical studies of autism patients and increased recognition of the cerebellum's role in functions such as affect regulation (103) have generated many hypotheses regarding the cerebellum's potentially significant role in autism. The first MRI study to examine the cerebellum's structure found a reduction in the area of the neocerebellar vermis (lobules VI and VII; 104). This result is consistent with postmortem studies noting reduced Purkinje cells in autism, although Purkinje-cell abnormalities have been reported more often in the cerebellar hemispheres than in the vermis. However, since the initial report of vermal hypoplasia, MRI studies (reviewed in reference 74) have typically found that increased total cerebellar volume is proportional to cerebral volume. Abnormal patterns of cerebellar development have also been described, with Carper and Courchesne reporting that autism patients showed an inverse relation in the size of the cerebellar vermis and the frontal lobes, whereas a comparison group of children showed no relation (105). Courchesne and others also noted significantly increased volume in cerebellar white matter of young children with autism, relative to control subjects (85). However, their cross-sectional data suggested subsequent slowed growth of cerebellar white matter. Interestingly, this group also found that the volume of cerebellar gray matter in young children with autism did not differ from the volume in control subjects but that older patients had reduced cerebellar gray matter volume, again suggesting a slowed period of growth. Longitudinal studies of the cerebellum, undertaken in conjunction with an examination of changes in cerebral volume, will be crucial to clarifying the nature of aberrant cerebellum development.

In addition to using structural MRI to examine the cerebellum, recent work has used fMRI to explore its function in autism. A recent study of 8 autism patients and 8 control subjects reported that, relative to control subjects, the patients had increased cerebellar activation during a motor task (specifically, pushing a button at a comfortable rate) and less cerebellar activation during an attentional task (specifically, pushing a button in response to a target) (106). The results of this study suggest that abnormalities of cerebellar development in

autism may have different implications for motor and attentional functioning.

Medial Temporal Lobe Structures

Postmortem and animal studies have motivated study of the medial temporal lobe, as have the role of its structures, particularly the amygdala, in social behaviour and cognition (107,108). Some (80) but not all (78) histopathological studies of autism have demonstrated unusually small and densely packed neurons in the hippocampus and amygdala. Bachevelier also found that monkeys with neonatal lesions of medial temporal lobe structures had significant patterns of memory loss and socioemotional impairments, suggesting that early functional abnormalities of these structures may be involved in the pathogenesis of autism (109).

Unfortunately, structural MRI studies of the hippocampus and amygdala in autism patients have yielded inconsistent results. Different studies have reported that the volume of the amygdala is increased, decreased, or no different in autism patients, relative to control subjects (76). Most recently, Sparks and colleagues found that, while their sample of patients aged 3 and 4 years with autism and PDD not otherwise specified had enlarged amygdala volume proportional to their overall increased brain size, the subjects with strictly defined autism had increased amygdala volume in excess of the increased brain volume, suggesting that amygdala volume might be related to severity in their sample (87).

Studies of the hippocampus have been similarly inconsistent, with different studies finding increases, decreases, or no difference in hippocampal volume in autism patients (76). In a more detailed examination of the hippocampus, Saitoh examined its subcomponents and found a reduction in the size of the area dentata (even after controlling for total brain volume) but no difference in the other regions examined (110).

While structural studies of medial temporal lobe structures have been marked by inconstistent and contradictory results, functional studies using fMRI have consistently found abnormalities in activation of the amygdala and the fusiform gyrus (which contains the "fusiform face area," so called because of its involvement in facial processing). Based upon autism's hypothesized deficit in "theory of mind"—the intuitive understanding of the mental states of others—fMRI studies of the disorder have used various paradigms examining social cognition and the processing of facial expression. In each, patients showed limited or no activation of the amygdala and the related fusiform gyrus, compared with robust activation in control subjects (111–114). In 2 of these studies (112,114), the authors reported that patients appeared to use brain regions not typically associated with facial processing, suggesting that they were performing the tasks but were using alternate and idiosyncratic regions to do so, including regions more typically used for object perception. In contrast to the disappointingly inconsistent results of structural studies of temporal lobe structures, fMRI studies using different paradigms have repeatedly demonstrated that patients with autism do not use brain regions typically involved in social cognition in the same way that comparison subjects do.

Postmortem Studies in Autism

To date, there have been few neuropathological studies of postmortem brains of autism patients. The 2 most comprehensive studies have demonstrated abnormal brain size, although a discrepancy exists about the timing of this increase, as it does in the literature on brain imaging (78,80). Bailey and colleagues reported that their single child patient, as well as 3 of their 5 adult patients, had megalencephaly (78). Kemper and Bauman noted that the brains of 8 of their 11 subjects under age 12 years showed increased mass, while only 2 of their 8 subjects over age 12 years showed increased mass (80).

Both groups found abnormalities of the cerebellum, most notably a reduced number of Purkinje cells, which are the projection cells of the cerebellar cortex that project to the deep cerebellar nuclei. Kemper and Bauman also reported age-related changes in the neurons of the deep cerebellar nuclei, with younger patients having abnormally large neurons and older patients having abnormally small neurons in these nuclei (80). These latter authors suggested that their findings, in conjunction with others, indicate that the cerebellar abnormalities occurred at or prior to 30 weeks' gestation. These findings also accord with suggested abnormalities of the cerebellum in brain-imaging studies (see above), although the finding of a reduced Purkinje cell number in the context of an overall elevation of cerebellar volume remains to be explained.

Kemper and Bauman also reported that neurons in parts of the limbic system, particularly in the hippocampus and amygdala, were unusually small and densely packed (80); they interpreted these findings as evidence of curtailed maturation. However, Bailey and colleagues did not find any statistically significant increase in neuronal density in the hippocampus of their subjects, although 2 subjects did appear to have a relatively high density of neurons in the hippocampus (78). These authors concluded that they could find no evidence of a highly localized pathology underlying autism and suggested instead that a combination of diverse but related neurodevelopmental abnormalities lead to the autism syndrome.

Summary: Studies of Brain Structure and Function in Autism

Brain-imaging studies and neuropathological studies are beginning to indicate the regions involved in the abnormal neurodevelopment underlying autism. While there remain many uncertainties, it appears that there is almost certainly

elevated brain volume in autism, at least in early childhood, and that the pattern of brain development is atypical in children with autism. Future studies will need to consider the developmental nature of these findings, and longitudinal studies will be necessary to delineate the course of brain development in autism. Such longitudinal studies may aid in understanding the pattern of brain development in subcortical structures in autism patients and may help to explain the inconsistency in findings thus far.

Future studies should also be designed to exploit phenotypic differences among patients, as has been done in genetic studies. For example, nonverbal patients and those with speech could be compared on measures of brain anatomy to determine the effects of anatomical differences on language development. Additionally, studies contrasting patients with autism and those without the disorder, but who may have some symptoms in common (for example, language disorders or attention-deficit hyperactivity disorder) will permit researchers to determine the specificity of the anatomical abnormalities seen in autism. To date, there has been a disappointing lack of relation between clinical severity and anatomic structure, with only 1 study noting such a relation (specifically, patients with larger caudates had higher levels of ritualistic behaviour and stereotypies; 117). In part, this likely reflects the lack of valid and reliable measures of symptom severity in autism. This deficiency also limits the ability of longitudinal studies to examine the effects of different patterns of brain development on symptom development. With the advent of more sophisticated technology and research methodology, brain-imaging studies are likely, in the coming years, to significantly increase our understanding of autism's neurobiological basis.

Discussion and Future Directions

It is now apparent that autism has a strong biological basis, with evidence continuing to accumulate for an underlying genetic cause that results in abnormal brain development. Future genetic and brain-imaging studies will undoubtedly contribute to a greater understanding of the disorder's etiology and pathophysiology. However, despite tremendous and remarkable progress in these areas, surprisingly little consideration has been given to the manner in which genetics and neurodevelopment are related in autism. As Jones and Murray so lucidly pointed out, genes code for proteins, not psychiatric symptoms (116). As such, it seems likely that the cause of autism is a genetic defect in the control of neurodevelopment—a defect that results in a set of structural and, ultimately, functional changes predisposing an individual to autism. Given this, studies incorporating genetics and brain structure and function in autism may be of greatest value. For example, including measures of cerebral structure (for example, enlarged brain volume and reduced corpus callosum area) as an intermediate phenotype in linkage studies or in association studies may provide significant information beyond that obtained using only a behavioural definition of autism.

Hariri and colleagues recently demonstrated the potential strength of combining brain imaging and genetics (117). Healthy adults underwent an fMRI study using a paradigm designed to elicit amygdala activation and were genotyped at their 5-HT transporter gene. Subjects with 1 or 2 copies of the short allele of the 5-HT transporter promoter polymorphism (which has been associated with reduced 5-HT expression and function and, clinically, with increased anxiety behaviours) had greater amygdala activation in response to fearful stimuli than did subjects who were homozygous for the long allele. The authors concluded that these results demonstrated genetically driven differences in brain function.

It seems certain that the coming years will yield many exciting and important clues to autism's etiology and pathogenesis. The combination of continually evolving methodological and technological advances will, hopefully, bring us closer to the goal of better and earlier intervention in autism.

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[1]Assistant Professor, Department of Psychiatry, University of Western Ontario, London, Ontario.
[2]Professor, Department of Psychiatry and Behavioural Neuroscience, McMaster University, Hamilton, Ontario.
Address for correspondence: Dr R Nicolson, 800 Commissioners Road East #6110, London, ON N6C-2V5
e-mail: Rnicolso@uwo.ca

Résumé : Influences génétiques et neurodéveloppementales sur le trouble autistique

Objectif : Par le passé, on considérait que l'autisme était largement psychogène. Toutefois, la recherche des 20 dernières années indique que l'autisme est en grande partie causé par des facteurs génétiques qui entraînent un développement anormal du cerveau. Cet article se penche sur la recherche des facteurs génétiques et neurodéveloppementaux qui sous-tendent l'autisme.

Méthodes : Nous examinons les conclusions d'études génétiques et d'imagerie cérébrale sur l'autisme menées durant les 15 dernières années et présentons une synthèse de ces résultats à titre de guide de futures études.

Résultats : L'imagerie du génome et les études d'associations ont indiqué un potentiel de régions génomiques et de gènes qui, respectivement, peuvent participer à l'étiologie de l'autisme, et il y a eu certaines reproductions de ces résultats. De même, il existe maintenant une reproduction indépendante du résultat selon lequel le volume du cerveau est exagéré dans l'autisme, tandis que la taille réduite du corps calleux a aussi été reproduite indépendamment. Malheureusement, les études des autres structures sous-corticales demeurent non concluantes ou contradictoires.

Conclusions : Des preuves accablantes appuient désormais le fondement neurobiologique de l'autisme. Toutefois, il faudra peaufiner les futures études, particulièrement pour déterminer les phénotypes les plus instructifs à étudier. En outre, les études qui examinent le rôle des facteurs génétiques dans les anomalies du cerveau sous-jacentes à l'autisme mèneront vraisemblablement à d'autres conclusions qui éclaireront notre compréhension des causes de l'autisme.