Neuroimaging in developmental disorders

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Purpose of review

This review considers the role of neuroimaging in developmental disorders by highlighting recent studies in two distinct, but overlapping, developmental disorders: autism and fragile X syndrome.

Recent findings

After a decade of conflicting results in neuroimaging studies of autism, recent studies have provided some convergent data. One well-replicated finding is that autistic subjects have larger brains. Further, this enlargement, present as early as 3 years of age, appears to represent accelerated growth in infancy and may be followed by slowed growth in late childhood. Other findings are discussed but considered preliminary in the absence of converging evidence or replication studies. Recent work in fragile X syndrome suggests aberrant fronto-striatal and fronto-parietal networks and relates these abnormalities 'forward' to behavior and 'backward' to decreased protein expression.

Summary

As the field of neuroimaging has matured, it has revealed its promise as a safe, reliable, in-vivo tool in the study of developmental disorders. By insisting on larger, more homogeneous patient groups and longitudinal rather than cross-sectional studies, the field is poised to fulfill its ultimate role of linking defects in molecular biology to aberrant behavior.

Keywords

autism, fragile X syndrome, brain volume, MRI

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Abbreviations

CA	cornu ammonis
FMRP	fragile X mental retardation protein
fraX	fragile X syndrome
MRI	magnetic resonance imaging
PDD-NOS	pervasive developmental disorder not otherwise specified

1350-7540

Introduction

With seminal papers in functional and structural magnetic resonance imaging (MRI) dating back less than 15 years, neuroimaging remains a relatively novel discipline. Appropriately, therefore, it has been met with a healthy degree of skepticism in the broader field of neuroscience. Improved understanding of the strengths and limitations of neuroimaging techniques, combined with a higher standard for peer-review publication, has resulted in findings that are more readily replicated and, therefore, more credible. As the field has matured, neuroimaging has made substantial contributions to our understanding of normal adult brain function. More recently, investigators have also gained insight into neural network modulation during the course of normal development [1]. The purpose of this review will be to consider the current (and potential) roles of neuroimaging in the study of abnormal neural development. To do so, I will review recent neuroimaging studies in two distinct, but overlapping, developmental disorders: autism and fragile X syndrome (fraX).

Autism

Autism, a prevalent developmental disorder of uncertain etiology, is characterized by impaired communication skills; stereotyped, repetitive behaviors; and poor social interaction. It is presumed to have at least a partial genetic component [2]. Given the paucity of post-mortem studies and the lack of an animal model, neuroimaging is potentially well-suited to help advance our understanding of the neuropathological substrate of autism. Until quite recently, however, the literature had been plagued by limited replication of findings as well as outright contradictory findings. For an extensive review of earlier imaging studies in autism and a discussion of the inherent pitfalls related to neuroimaging in this disorder, the reader is referred to the excellent article by Cody *et al.* [3]. The focus here will be on studies from the last 2 years.

Megalencephaly

If there is a single, consistent finding that crosses clinico-pathologic and neuroimaging boundaries, it is that autistic subjects have larger brains than matched controls. A more controversial and important question pertains to the timing of brain growth. Several recent, well-designed, structural MRI studies have provided converging evidence that brain growth in autism is accelerated early in development and appears to fall off by late childhood or adolescence. In a cross-sectional study, Courchesne and colleagues [4••] compared brain

volumes between a group of 60 autistic boys aged 2–16 years and a group of 52 age-matched, typically-developing boys. Thirty autistic boys and 12 controls were imaged between the ages of 2 and 4 years. In this subgroup, brain volumes were significantly increased in the autistic cohort. There were no significant differences in brain volume between diagnostic groups in the older children aged 5 to 16 years. Subsequently, two studies performed on independent samples have also reported increased brain volumes in younger autistic subjects. Sparks *et al.* [5•] studied brain volumes in a group of 45 children, aged 3 to 4 years, with autistic spectrum disorders; 29 subjects had autistic disorder and 16 had pervasive developmental disorder not otherwise specified (PDD-NOS). These were compared with brain volumes in two other age-matched groups: typically-developing controls and controls with delayed development. They found that brain volume was increased in the autistic spectrum group compared with either of the control groups. In a second cross-sectional study, Aylward and colleagues [6••] examined brain volumes in a predominantly male group of autistic subjects aged 8–46 years and compared them with a group of 83 healthy, age-matched controls. As in the study by Courchesne *et al.*, brain volumes were only increased in the youngest cohort of autistic subjects (aged 8–12 years in this case).

Taken together, these three studies suggest that there is an increase in brain growth that occurs relatively early in development but that the rate of brain growth becomes slower than normal some time between late-childhood and early adolescence. As these authors point out, however, longitudinal studies are needed to confirm or refute the hypotheses generated from cross-sectional studies.

Limbic system

The prominent social dysfunction of autism has prompted investigations of limbic system abnormalities in this disorder. Previous studies have yielded conflicting results [3] and more recent work has yet to resolve the issue. One study examined sub-regions of the medial temporal lobe in autism and reported a decreased cross-sectional area of the area dentata (dentate gyrus plus cornu ammonis field (CA) 4) in autistic subjects compared with healthy controls [7•]. However, the cross-sectional area of the subiculum and CA1-CA3 did not differ between groups. While the authors make compelling arguments for why such sub-regional differences may exist in the hippocampus, these findings will be difficult to replicate given the high resolution needed to perform accurate sub-regional analyses. Sparks *et al.* [5•] explored amygdala and hippocampal volumes in their group of children with autistic spectrum disorder and found that these two regions were increased in raw volume when compared with the two control groups, but that the differences between the autistic group and the typically-developing controls were no longer significant when regional volumes were corrected for total brain volume. Attesting to the importance of a homogenous sample, however, when the subjects with PDD-NOS were removed from the autistic group, the 'pure' autism group had increased corrected amygdala volumes, compared with either control group. Functional imaging studies have the potential to probe social dysfunction in autism, but few have been undertaken. In a small study of six autistic participants and eight healthy controls, Pierce and colleagues [8•] used a region-of-interest analysis to show decreased amygdala activation to facial processing in the autistic subjects.

Higher cortical regions

Language networks, like limbic system networks, are presumed to be prominently abnormal in autism. Two groups recently compared autistic subjects with healthy controls and found abnormalities in the planum temporale. Their results, however, are somewhat conflicting. Rojas *et al.* [9] compared 15 adults with autism with 15 age-matched controls and found that autistic subjects had a smaller left planum temporale than controls, after correcting for hemisphere volumes. It should be noted here that among the autistic subjects six were purely right-handed, eight were mixed right-handed, and one was left-handed. This skew in handedness was well-matched in the control group but raises questions about hemisphere dominance for language in these two groups. The authors also showed there to be little asymmetry in the autistic subjects' planum temporale, whereas in the control subjects, the left planum temporale was about 50% larger than the right. In contrast, Herbert *et al.* [10••], comparing 16 right-handed autistic boys with 15 healthy controls (13 right-handed, one mixed, one left-handed), reported that the planum temporale in autistic boys was 25% larger on the left side than on the right side. Controls had only a 5% leftward asymmetry. More strikingly, this group found a reversed asymmetry in the inferior lateral frontal lobe (overlapping with Broca's area). Specifically, control boys had a 17% leftward asymmetry in this frontal region whereas autistic boys had a 27% rightward asymmetry.

The fusiform gyrus is one of the most reliably activated brain regions in functional MRI studies, and typically shows increased activity during facial processing [11]. Because facial processing is a critical component of social interaction, Pierce *et al.* [8•] reasoned that a functional MRI study might reveal differential activation between autistic subjects and healthy controls as they processed faces. The authors reported fairly typical activation, that included the fusiform gyrus, in the healthy controls. As a group, the autistic subjects performed the task at an

equivalent level to the controls, but showed little to no fusiform activation. Fusiform dysfunction in autism is further supported by the Herbert *et al.* [10••] study in which autistic boys had significantly greater leftward asymmetry (20%) of the fusiform gyrus than did control boys (6%).

Fragile X syndrome

The limited replicability of findings in autism may be due in large part to it being a heterogeneous disorder. In this regard, the results of neuroimaging studies in fraX provide an instructive contrast. FraX, caused by an expanded trinucleotide repeat in the fraX gene, is the most common, heritable cause of developmental disability [12]. While males are most severely affected, a high proportion of females with the mutation have cognitive and behavioral abnormalities. Furthermore, autistic features are a relatively common finding in children with fraX. As such, this genetically homogeneous population has the potential to elucidate the neuroanatomical substrates of the heterogeneous population that makes up autism [13]. For an extensive review of the earlier fraX neuoimaging literature, with a focus on replicated findings, the reader is referred to the excellent review by Kates *et al.* [14]. The focus here will be on studies from the last 2 years.

In a large study of children and adolescents with fraX, Eliez *et al.* [15•] examined structural MRI abnormalities in 37 fraX children (27 girls and 10 boys), compared with a group of 51 healthy controls. A particularly interesting difference, as pertains to autism, was that the caudate nucleus was significantly larger in the fraX group. Furthermore, there appeared to be a gene-dosage effect in that fraX boys (hemizygous) had a more pronounced increase in caudate size compared with control boys than did fraX girls (heterozygous) compared with control girls. The caudate nucleus and fronto-striatal network appear to play critical roles in the abnormal behaviors of obsessive-compulsive disorder [16] which overlap with stereotyped behaviors in autism. Using diffusion tensor imaging, a novel MRI technique that evaluates white matter tract integrity, this same group showed abnormal white matter tracts in the fronto-striatal pathways of female fraX patients [17].

Moving one step beyond gene–dosage effects, investigators showed correlation between neuroimaging measures and the amount of the fragile X mental retardation protein (FMRP) – expressed in females. In a functional MRI study of arithmetic processing, Rivera and colleagues [18••] showed reduced left angular (parietal) activation in female fraX patients compared with controls. Within the fraX group, activation in this same region increased as a function of increasing levels of FMRP, suggesting a protein–dosage effect. A similar relationship between FMRP expression and functional MRI activation was noted in a study by Kwon *et al.* [19••]. During a working memory task, fraX females showed decreased activation of the parietal lobes bilaterally when compared with healthy controls. Here again, the amount of FMRP expressed in female fraX patients was positively correlated with parietal activation.

Conclusion

Neuroimaging holds considerable promise as a safe, reliable, in-vivo research tool in developmental disorders. Converging evidence in autism suggests accelerated cerebral growth early in childhood followed by relatively slowed growth in late childhood/early adolescence. It will be critical to see if these hypotheses, derived from cross-sectional studies, are supported by ongoing longitudinal studies. Recent studies of fraX have yielded convergent evidence of aberrant fronto-parietal and fronto-striatal networks. Further, these studies highlight the link between abnormal FMRP levels, brain activation, and behavior. Despite these promising advances, a great deal of work remains before neuroimaging can fulfill its ultimate role of focusing basic science research on specific neuropathologic targets. In the study of heterogeneous syndromes such as autism, it is particularly important to restrict studies to as large and homogeneous a sample as possible. Given the inherent insensitivity of neuroimaging techniques, the deck is stacked against investigators who combine autistic subjects with PDD-NOS subjects. Using homogeneous genetic disorders to study sporadic syndromes may be a more reliable means of linking molecular biology to anatomy to behavior. This approach has the potential to enhance our understanding of several diseases including schizophrenia (with studies of velo-cardio-facial syndrome [20]), Alzheimer disease (with studies of Down syndrome [21••]), and autism (with studies of fraX).

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Kwon H, Reiss AL, Menon V. Neural basis of protracted developmental changes in visuo-spatial working memory. Proc Natl Acad Sci U S A 2002; 99:13336–13341.

2 Korvatska E, Van de Water J, Anders TF, Gershwin ME. Genetic and immunologic considerations in autism. Neurobiol Dis 2002; 9:107–125.

3 Cody H, Pelphrey K, Piven J. Structural and functional magnetic resonance imaging of autism. Int J Dev Neurosci 2002; 20:421–438.

4 Courchesne E, Karns CM, Davis HR, *et al.* Unusual brain growth patterns in •• early life in patients with autistic disorder: an MRI study. Neurology 2001; 57:245–254.
The large sample size in this study allowed the authors to perform a sub-group analysis which drove the main finding of increased brain volume in young autistic children but not in older autistic children. An additional strength is that the young children were scanned at 2–4 years of age but reevaluated at an age of 5 years to ensure accuracy in the diagnosis of autism.

5 Sparks BF, Friedman SD, Shaw DW, *et al.* Brain structural abnormalities in • young children with autism spectrum disorder. Neurology 2002; 59:184–192.
Here again the large sample size and young age of the subjects makes this a particularly valuable study. One drawback is that the autistic sample combines autistic disorder and PDD-NOS.

6 Aylward EH, Minshew NJ, Field K, *et al.* Effects of age on brain volume and •• head circumference in autism. Neurology 2002; 59:175–183.
This was a large study with 67 autistic children and 83 controls. The autistic group was homogeneous in that PDD-NOS children were not included. It supports the early growth hypothesis from Ref. [4••] because only the youngest autism sub-group had increased brain volumes, but all sub-groups had increased head circumferences.

7 Saitoh O, Karns CM, Courchesne E. Development of the hippocampal • formation from 2 to 42 years: MRI evidence of smaller area dentata in autism. Brain 2001; 124 (Pt 7):1317–1324.
This is the same group as in Ref. [4••], so the confirmatory reevaluation of young subjects at age 5 years was done here as well. Subdividing the hippocampus, however, is difficult to do reliably and stretches the limits of structural MRI resolution.

8 Pierce K, Muller RA, Ambrose J, *et al.* Face processing occurs outside the • fusiform 'face area' in autism: evidence from functional MRI. Brain 2001; 124 (Pt 10):2059–2073.
This study tested autistic subjects in a fundamental aspect of social interaction (facial processing). It revealed abnormalities in the autistic group in two regions known to be critical to social interaction: the amygdala and the fusiform gyrus.

9 Rojas DC, Bawn SD, Benkers TL, *et al.* Smaller left hemisphere planum temporale in adults with autistic disorder. Neurosci Lett 2002; 328:237–240.

10 Herbert MR, Harris GJ, Adrien KT, *et al.* Abnormal asymmetry in language •• association cortex in autism. Ann Neurol 2002; 52:588–596.
The authors studied a homogeneous population (autistic boys) with a metric (symmetry index) that makes correcting for total brain volume unnecessary. The findings in language regions and in the fusiform cortex converge nicely with neuropsychological deficits in autism.

11 Gauthier I, Tarr MJ, Moylan J, *et al.* The fusiform ''face area'' is part of a network that processes faces at the individual level. J Cogn Neurosci 2000; 12:495–504.

12 Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. Am J Med Genet 1996; 64:196–197.

13 Feinstein C, Reiss AL. Autism: the point of view from fragile X studies. J Autism Dev Disord 1998; 28:393–405.

14 Kates WR, Folley BS, Lanham DC, *et al.* Cerebral growth in Fragile X syndrome: review and comparison with Down syndrome. Microsc Res Tech 2002; 57:159–167.

15 Eliez S, Blasey CM, Freund LS, *et al.* Brain anatomy, gender and IQ in • children and adolescents with fragile X syndrome. Brain 2001; 124 (Pt 8):1610–1618.
This study is notable for its large sample size and rigorous methods. The increased caudate volumes in fraX children are intriguing in light of the overlap between autistic symptoms and symptoms in obsessive-compulsive disorder (see Ref. [16]).

16 Giedd JN, Rapoport JL, Garvey MA, *et al.* MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. Am J Psychiatry 2000; 157:281–283.

17 Barnea-Goraly N, Eliez S, Hedeus M, *et al.* White matter tract alterations in fragile X syndrome: preliminary evidence from diffusion tensor imaging. Neuropsychiatric Genetics; (in press).

18 Rivera SM, Menon V, White CD, *et al.* Functional brain activation during •• arithmetic processing in females with fragile X Syndrome is related to FMR1 protein expression. Hum Brain Mapp 2002; 16:206–218.
This article is important in pointing out the relationship between levels of FMRP expression and functional MRI activation. It demonstrates some internal validity in that (roughly) the same parietal region that differed in activation between groups showed increased activation with increased protein expression within the fraX group.

19 Kwon H, Menon V, Eliez S, *et al.* Functional neuroanatomy of visuospatial •• working memory in fragile X syndrome: relation to behavioral and molecular measures. Am J Psychiatry 2001; 158:1040–1051.
This paper also demonstrates that parietal (and frontal) brain activation is related to fraX protein expression. Activity in these regions also tended to correlate with behavioral performance, but there was no correlation between fraX protein expression and behavioral performance.

20 Eliez S, Schmitt JE, White CD, *et al.* A quantitative MRI study of posterior fossa development in velocardiofacial syndrome. Biol Psychiatry 2001; 49:540–546.

21 Krasuski JS, Alexander GE, Horwitz B, *et al.* Relation of medial temporal lobe •• volumes to age and memory function in nondemented adults with Down's syndrome: implications for the prodromal phase of Alzheimer's disease. Am J Psychiatry 2002; 159:74–81.
This article provides an excellent example of how studying a homogeneous genetic disorder (Down syndrome) can shed light on a predominantly sporadic disorder (Alzheimer disease).