Structural and functional magnetic resonance imaging of autism

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Abstract

Magnetic resonance imaging (MRI) of brain structures and function is uniquely suited to characterize the range of neuroanatomical and physiological changes that characterize the autism phenotype as it develops over time. In this review, we examine the scientific literature in MRI as applied to autism and related areas, over approximately the last decade, discussing findings which have emerged, methodological stumbling blocks which have been identified, and potential future directions. Structural MRI studies have recently begun to elucidate the neurodevelopmental underpinnings and brain–behavior relationships in autism while fMRI studies, building on the wealth of data in normal individuals, are beginning to characterize the underlying neuropsychological deficits of the disorder. Together, these two methods combine to contribute to a better understanding of the neural basis and brain phenotype of this disorder.

Keywords: Magnetic resonance imaging; Autism; Neuropsychology

1. Introduction

Autism is a complex, severe and pervasive neurodevelopmental disorder associated with considerable impairment. Defined by the presence of social deficits, abnormalities in communication, stereotyped, repetitive behaviors, and a characteristic course (DSM-IV, American Psychiatric Association (APA, 1994)), the prevalence of autism is estimated to be approximately 1–2 per 1000 individuals (Fombonne, 1999). Even within those meeting DSM-IV criteria for autism there exists a wide range of clinical presentation. This variability may range from affected individuals with little interest in interacting with others, to those who have interest but show difficulties with the more subtle to and fro of complex social interactions. Similarly, stereotyped behaviors may range from simple motor stereotypes and a preference for routine, to complex, elaborate rituals and substantial upset with any change in routine or environment. Language deficits, while marked in some autistic individuals who have no useful speech, can be mild and limited to the presence of pragmatic language deficits in higher functioning autistic individuals. The majority of autistic individuals are considered to have Intellectual Quotients (IQs) in the mentally retarded range, however IQs may vary from the severe–profound range to markedly above average. While a range of neuropsychological theories has been put forth to help explain the underlying psychological mechanisms in autism, none fully explain the array of presenting symptoms or are abnormal in all affected individuals.

Based on the high concordance rate for monozygotic twins and a recurrence risk that is substantially greater than the population rate, there is now considerable evidence to support the importance of hereditary factors in autism (Bailey et al., 1995). Like most behavioral syndromes, autism is likely to be etiologically heterogeneous. In addition to the variability in the phenotype, support for this comes from the fact that approximately 10% of autistic individuals have an associated medical condition that is thought to play an etiologic role in the disease process. Thus, individuals with single gene disorders such as tuberous sclerosis, Fragile X syndrome and Smith–Lemli–Opitz syndrome (Baker et al., 1998; Martin et al., 2001; Bailey et al., 2001) have relatively high rates of autism compared to both the rate in the general population and the rate in individuals with mental retardation. In individuals without an obvious associated medical condition (i.e. idiopathic autism) the underlying mechanism is more likely the result of multiple, interacting genes or oligogenic inheritance (Risch et al., 1999; Pickles et al., 1995).

While over the last 15 years the phenotypic and etiologic complexities have contributed to numerous non-replicated reports, important and consistent findings in the MRI literature are now beginning to emerge which elucidate the neurodevelopmental underpinnings and brain behavior relationships in this disorder. Characterization of the structural and functional brain phenotypes in autism, as observed

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through structural and fMRI may lead, in turn, to a clarification of the genetic basis of this condition by providing insights into the brain phenotypes. MRI is a technology that is particularly well suited to study autism with its developmental nature and changing picture of symptoms over time. The fact that MRI is non-invasive, does not require radiation, can be performed multiple times, and can be employed to scan large samples of individuals makes it an appropriate tool to study this complex neurodevelopmental disorder, where large samples will be required to take into account heterogeneity and longitudinal studies will be necessary to characterize the brain development over time.

2. Structural imaging studies

Early structural studies of autism had a number of methodological shortcomings that made it difficult to interpret the significance of their results. Included among these problems were small sample sizes, lack of standardized diagnostic criteria or assessment protocols, inclusion of heterogeneous populations of subjects (i.e. with associated medical conditions), failure to take into account a number of confounding factors (e.g. gender, IQ, overall brain size), and the technological limitations of the available MRI hardware and image processing software. Most of the initial work in structural studies of autism consisted of either case reports or small samples of individuals with autism. This study design was unable to account for the broad range of phenotypic and etiologic variability that exists within autism, diminishing the potential for replication. Compounding this limitation was the individual variability known to exist in normal brain development over time and across gender, which was often not taken into account in these early studies. The variability associated with the vast differences in cognitive ability in autism was also not well considered. For example, 75% of individuals with autism also have mental retardation and many early studies made comparisons between autistic individuals and normal, non-mentally retarded controls, when IQ has been shown to contribute to the size of some brain structures on MRI (Piven et al., 1992). Additionally, these early studies often included autistic individuals who had associated medical and neurological conditions (e.g. tuberous sclerosis), increasing the heterogeneity already inherent in the disorder. Studies were further constrained by the early MR technology that was limited by the use of thicker slices and lower T field strength (“power” of magnetic field) that produced poor quality images compared to current data collected on 1.5 T scanners (and even more recently 3 T) with three-dimensional image acquisitions (e.g. the spoiled grass sequence). The brain imaging analysis programs available for these early MRI studies were also less sophisticated than current image processing programs, where images can be displayed simultaneously in three orthogonal planes for improved anatomical segmentation, larger scale studies are more feasible and reliable using automated methods of tissue segmentation, and advanced approaches like shape analysis allow for potentially more informative analysis of brain structures. Finally, advances in systematic assessments and diagnosis of subjects (e.g. Autism Diagnostic Interview and Autism Diagnostic Observation Schedule) have contributed substantially to the potential reproducibility of current studies by better characterizing the autistic individuals involved.

2.1. Studies of brain size

The earliest report suggesting that individuals with autism had evidence of brain enlargement, as indicated by increased head size, appeared in Kanner’s original 1943 paper that described eleven children with autism (Kanner, 1943). In that report, Kanner noted the relative absence of substantial dysmorphology, except for the presence of “large heads” in five of the children he described. Additional indirect evidence for increased brain size in autism came from systematic studies looking at the prevalence of dysmorphic features in autism (Stein and Rapoport, 1975; Walker, 1977), where increased head circumference was noted anecdotally. Similarly, Piven et al. (1992) inadvertently reported enlarged mid-sagittal brain area in a study of the cerebellar vermis in autism. Brain size in that study was measured as a covariate for cerebellar morphology, except where increased head size in autism (Bailey et al., 1993) was reported. Increased brain weight) in autism (Bailey et al., 1993) was also noted to be significantly enlarged. Subsequently, this same group of investigators employed a semi-automated technique to divide the brain into cortical lobes based on the method of Talairach and Tournoux (1988) in a larger, overlapping sample of 35 autistic individuals (age range 12–29 years) and 36 controls (age range 13–28 years). The total brain volume in the autistic individuals was found to be significantly larger than male controls, however, the sample of autistic females was too small to make any definitive comments. Analyses using the Talairach coordinate system suggested significant enlargements in the temporal, parietal, and occipital lobes in the autistic subjects compared to controls, whereas no differences were detected in the frontal lobe. These findings suggested that the pattern of brain enlargement was regional and not global. Postmortem studies support findings of megalencephaly (increased brain weight) in autism (Bailey et al., 1993). Further documentation of increased head size associated with autism come from head circumference studies (Bailey et al., 1995; Launhardt et al., 1997; Stevenson et al., 1997) showing that approximately 20% of autistic individuals have head circumferences above the 98th percentile (i.e. macrocephaly). In a retrospective chart review study of autistic individuals...
with macrocephaly, Lainhart et al. (1997) found evidence suggesting that while enlarged head size is often present at birth, macrocephaly is not present until the first few years of life. Other studies have found results consistent with this finding (Stevenson et al., 1997; Courchesne et al., 2001). Thus, the timing of the enlargement, which clearly encompasses the early postnatal period, is most consistent with an underlying mechanism that involves a decrease in the normal course of elimination of neuronal processes during early development (e.g. a decrease in the rate of dendritic pruning) (Huttenlocher, 1990).

More recently, Courchesne et al. (2001) studied brain volume in a cross-sectional examination of 60 autistic males (ranging in age from 2 to 16) and 52 normal controls. The individuals with autism were divided into two age groups: 2–4 and 5–16 years. Brain measurements of the 2–4-year-old group showed significant brain volume enlargement when compared to normal controls. This finding supports the head circumference findings above, indicating increased brain growth early in development. These results are also consistent with those from Sparks et al. (in press) showing brain volume enlargement in 3–4-year olds with autism. In contrast, brain volumes at the older age range (5–16 years) in the Courchesne study were smaller in autistic individuals than in the comparison group. The authors proposed that the findings indicate that the brain volume overgrowth is limited to the early childhood period. Given the findings by Piven et al. (1992, 1996) of enlargement in two independent adolescent/adult samples, further work on defining age effects on brain volume in autism is warranted.

Segmentation of the brain volumes into gray and white tissue in the Courchesne et al. (2001) study revealed that the 2–4-year-old autistic subjects also had increased gray and white tissue volumes in the cerebrum that were not present in the older autistic subjects (5–16-year old). Their data suggested that cortical white matter volume increased linearly with age, a finding similar to that of Giedd et al. (2001), but that the rate of increase was smaller in the autistic group than in normal controls. Also similar to the findings by Giedd et al. (2001), cortical gray tissue volumes were found to peak in early childhood for autistic and control subjects, although the autistic group had a decrease in gray tissue volume between 2 and 9 years while the normal controls continued to show an increase. By middle childhood, gray tissue volumes began to decrease for both groups, with the autism cases showing smaller gray tissue volumes than the normal controls.

Overall, the imaging studies of Piven et al. (1992, 1996), Courchesne et al. (2001) and Sparks et al. (in press) provide converging evidence for brain volume enlargement in autism and are consistent with postmortem and head circumference studies (see Table 1). The timing and nature of this enlargement, however, are less clear as the studies by Courchesne et al. (2001) and Sparks et al. (in press) suggest that the brain volume enlargement may be limited to early childhood whereas the findings by Piven et al. (1992, 1996), in two independent samples, show evidence of enlargement in adolescents and adults. Clearly, longitudinal studies will be necessary to clarify the timing of this phenomenon in autism and whether particular subgroups can be identified by early or later brain enlargement. In studies of normal developmental patterns, Giedd et al. (2001) has demonstrated that volumetric growth curves differ from cross sectional studies versus longitudinal studies, supporting the critical input of longitudinal designs in studying developmental disorders.

2.2. Cerebellum

In 1988, a MRI study appeared in the New England Journal of Medicine noting that the neocerebellar vermis (lobules VI and VII) showed a specific decrease in size (both absolute and relative to lobules I-V) in autism (Courchesne et al., 1988). This finding was not inconsistent with data from postmortem studies suggesting that the cerebellum played a role in autism (i.e. reduction in the number of Purkinje cells), however abnormalities in the cerebellum have been reported primarily in the cerebellar cortex and not vermis (Ritvo et al., 1986; Bauman and Kemper, 1985). The report by Courchesne et al. (1988) led to numerous attempts at replication (reviewed in Table 1). However, to date no independent, peer-reviewed research report has found support for the finding of hypoplasia of the neocerebellar vermis on MRI in autism, after taking the effects of cognitive ability into account (Piven et al., 1992, 1997; Holttum et al., 1992; Kleiman et al., 1992; Levitt et al., 1999; Hardan et al., 2001; Manes et al., 1999). Studies following the initial report by Courchesne suggested that IQ has a significant effect on the size of the cerebellar vermis (Piven et al., 1992, 1997). Other reports suggest, however, that while there is no evidence of selective hypoplasia of the neocerebellar vermis in autism, there is evidence of an overall increase in cerebellar volume that seems proportionate to the increase in total brain volume in autistic individuals (Piven et al., 1997; Sparks et al., in press). Of interest, several MRI studies of Fragile X individuals, a disorder with phenomenological overlap with autism, show evidence of hypoplasia of the neocerebellar vermis (Reiss et al., 1988).

2.3. Amygdala

The medial temporal lobe, and in particular the amygdala (AMY), has been implicated in autism because of its role in social behavior and cognition in human and animal lesion studies (Adolphs, 2001; Bachevalier, 1991). Recently Sparks et al. (in press) compared young children (3–4-year old) with “autistic spectrum disorders” (ASDs), which included autistic disorder and pervasive developmental disorder, not otherwise specified (PDD-NOS), to typically developing children and children with developmental delay. The children with autism displayed larger AMY volumes in the comparisons between groups. Subsequent analysis demonstrated that a subset of 31 children with autistic
### Table 1
Overview of main findings in autism on structural MRI in case-control studies

<table>
<thead>
<tr>
<th>Region</th>
<th>Study</th>
<th>Subjects</th>
<th>M age in years</th>
<th>Cognitive ability</th>
<th>Main finding(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBV</td>
<td>Piven et al. (1992)</td>
<td>15 AUT</td>
<td>27.7</td>
<td>PIQ = 92.5</td>
<td>MSA ↑ in AUT</td>
<td>Adjusted for MSA, A, IQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>30.3</td>
<td>PIQ = 99.9</td>
<td></td>
<td>Adjusted for MSA, A, SES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>28.8</td>
<td>PIQ = 130.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Piven et al. (1996)</td>
<td>35 AUT</td>
<td>18.0</td>
<td>PIQ 90.0</td>
<td>↑ TBV in AUT</td>
<td>Adjusted for H, IQ, G</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36 CON</td>
<td>20.2</td>
<td>PIQ 102.1</td>
<td></td>
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<tr>
<td></td>
<td>Courchesne et al. (2001)</td>
<td>60 AUT</td>
<td>-</td>
<td>PIQ 36-122</td>
<td>↑ TBV in 2-4, ↓ TBV in 5-16</td>
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<td></td>
<td></td>
<td>30</td>
<td>2-4</td>
<td>↓ Cerebellum GM/WM in 2-4</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>30</td>
<td>2-16</td>
<td>↓ Cerebellum WM in 2-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>52 CON</td>
<td>5-16</td>
<td>PIQ 90-140</td>
<td>GMWM NS in 5-16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sparks et al. (in press)</td>
<td>45 ASD</td>
<td>3.2-4.6</td>
<td>AE = 25.9</td>
<td>↑ TBV in ASD</td>
<td>Adjusted for TBV, G, A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 DO</td>
<td>3.1-4.9</td>
<td>AE = 25.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 CON</td>
<td>3.1-4.7</td>
<td>Average AE</td>
<td></td>
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<tr>
<td></td>
<td>Piven et al. (1996)</td>
<td>15 AUT</td>
<td>27.7</td>
<td>PIQ = 92.5</td>
<td>↑ Temporal, parietal, and occipital in AUT</td>
<td>Adjusted for MSA, A, IQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>30.3</td>
<td>PIQ = 99.9</td>
<td></td>
<td>Adjusted for MSA, A, SES</td>
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<td></td>
<td></td>
<td>15 CON</td>
<td>28.8</td>
<td>PIQ = 130.0</td>
<td></td>
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<tr>
<td>Brainstem</td>
<td>Elia et al. (2000)</td>
<td>22 AUT</td>
<td>10.92</td>
<td>MR</td>
<td>NS MSA of pons, midbrain</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>11 CON</td>
<td>10.86</td>
<td>Normal</td>
<td></td>
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<tr>
<td></td>
<td>Gaffney et al. (1988)</td>
<td>13 AUT</td>
<td>11.3</td>
<td>IQ = 84.9</td>
<td>↓ MSA of brainstem, medulla, and pons</td>
<td>Adjusted for G</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 CON</td>
<td>12.0</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hashimoto et al. (1988)</td>
<td>18 AUT</td>
<td>3.8</td>
<td>DO = 65.5</td>
<td>↓ Brainstem/pons in AUT</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>11 CON</td>
<td>2.8</td>
<td>DO = 67.2</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>18 CON</td>
<td>7.1</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hashimoto et al. (1992a)</td>
<td>29 AUT</td>
<td>4.3</td>
<td>10 DO ≥ 80</td>
<td>↓ MSA of brainstem/pons especially in</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19 DO ≤ 80</td>
<td>DO ≤ 80 group</td>
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<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>4.6</td>
<td>NA</td>
<td></td>
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<tr>
<td></td>
<td>Hashimoto et al. (1992b)</td>
<td>12 AUT</td>
<td>6.6</td>
<td>DO = 88</td>
<td>↓ MSA of brainstem, medulla in AUT and DO ≤</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>7.1</td>
<td>DO = 88</td>
<td>80 pons ↓ in CON DO ≤ 80</td>
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<tr>
<td></td>
<td></td>
<td>14 CON</td>
<td>7.4</td>
<td>NA</td>
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<tr>
<td></td>
<td>Hashimoto et al. (1993)</td>
<td>12 AUT</td>
<td>6.1</td>
<td>DO = 92.2</td>
<td>↓ Midbrain, medulla in AUT, NS in pons</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 CON</td>
<td>5.9</td>
<td>DO = 105.9</td>
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<tr>
<td></td>
<td>Piven et al. (1992)</td>
<td>15 AUT</td>
<td>27.7</td>
<td>PIQ = 92.5</td>
<td>NS pons, IV ventricle</td>
<td>Adjusted for MSA, A, IQ</td>
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<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>30.3</td>
<td>PIQ = 98.9</td>
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<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>28.8</td>
<td>PIQ = 130.0</td>
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<tr>
<td>Study</td>
<td>Group 1 (N)</td>
<td>Group 2 (N)</td>
<td>ROI</td>
<td>Measure</td>
<td>Result</td>
<td>Notes</td>
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<tr>
<td><strong>Cerebellum</strong></td>
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<tr>
<td>Courchesne et al. (1988)</td>
<td>18 AUT</td>
<td>21.9</td>
<td>PIO</td>
<td>88</td>
<td>↓ MSA</td>
<td>of vermis in lobes VI, VII</td>
</tr>
<tr>
<td>9 CON</td>
<td>24.8</td>
<td>–</td>
<td>MR</td>
<td>Normal</td>
<td>NS MSA of cerebellum</td>
<td></td>
</tr>
<tr>
<td>Elia et al. (2000)</td>
<td>22 AUT</td>
<td>10.92</td>
<td>MR</td>
<td>Normal</td>
<td>NS MSA of cerebellum</td>
<td></td>
</tr>
<tr>
<td>11 CON</td>
<td>10.86</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Hardan et al. (2001)</td>
<td>22 AUT</td>
<td>22.4</td>
<td>PIO</td>
<td>97.5</td>
<td>↑ Total volume of cerebellum in AUT, NS vermis</td>
<td></td>
</tr>
<tr>
<td>22 CON</td>
<td>22.4</td>
<td>PIO = 99.6</td>
<td></td>
<td></td>
<td>Adjusted for TBV</td>
<td></td>
</tr>
<tr>
<td>Holtum et al. (1992)</td>
<td>18 AUT</td>
<td>20.2</td>
<td>PIO</td>
<td>92.1</td>
<td>NS in MSA of vermis and lobules</td>
<td></td>
</tr>
<tr>
<td>18 CON</td>
<td>20.2</td>
<td>PIO = 94.5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Klitman et al. (1992)</td>
<td>13 AUT</td>
<td>7.4</td>
<td>–</td>
<td>Normal</td>
<td>NS in MSA of lobes I-V, VI-VII</td>
<td></td>
</tr>
<tr>
<td>28 CON</td>
<td>6</td>
<td>–</td>
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<tr>
<td>Manes et al. (1999)</td>
<td>27 AUT</td>
<td>14.3</td>
<td>MA</td>
<td>4.5</td>
<td>NS MSA</td>
<td></td>
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<tr>
<td>17 MR</td>
<td>11.8</td>
<td>MA = 4.5</td>
<td></td>
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<tr>
<td>Piven et al. (1992)</td>
<td>15 AUT</td>
<td>27.7</td>
<td>PIO</td>
<td>92.5</td>
<td>NS MSA of cerebellar vermis in AUTO</td>
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<tr>
<td>15 CON</td>
<td>30.3</td>
<td>PIO = 99.9</td>
<td></td>
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<tr>
<td>15 CON</td>
<td>28.8</td>
<td>PIO = 130.0</td>
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<tr>
<td>Piven et al. (1997)</td>
<td>35 AUT</td>
<td>18.0</td>
<td>PIO</td>
<td>91.0</td>
<td>NS in area of lobes I-V, VI-VII</td>
<td></td>
</tr>
<tr>
<td>36 CON</td>
<td>20.2</td>
<td>PIO = 102</td>
<td></td>
<td></td>
<td>Adjusted for PIIQ, G, TBV</td>
<td></td>
</tr>
<tr>
<td>Sparks et al. (in press)</td>
<td>45 ASD</td>
<td>3.2–4.6</td>
<td>AE</td>
<td>25.9</td>
<td>NS for ASD, DD was ↓ compared to ASD and CON</td>
<td></td>
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<tr>
<td>12 DD</td>
<td>3.1–4.9</td>
<td>AE = 25.5</td>
<td></td>
<td></td>
<td>Adjusted for TBV, G, A</td>
<td></td>
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<tr>
<td>23 CON</td>
<td>3.1–4.7</td>
<td>Average AE</td>
<td></td>
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<tr>
<td><strong>Basal ganglia</strong></td>
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<tr>
<td>Sears et al. (1999)</td>
<td>35 AUT</td>
<td>20.2</td>
<td>PIO</td>
<td>91.0</td>
<td>↑ CN volume, NS globus pallidus, putamen</td>
<td></td>
</tr>
<tr>
<td>36 CON</td>
<td>102.5</td>
<td></td>
<td></td>
<td></td>
<td>Adjusted for TBV, G, IQ</td>
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<tr>
<td>Re-analyzed Piven et al., 1992</td>
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<td></td>
<td></td>
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<tr>
<td>Egas et al. (1995)</td>
<td>51 AUT</td>
<td>15</td>
<td></td>
<td></td>
<td>↑ CN volume</td>
<td></td>
</tr>
<tr>
<td>51 CON</td>
<td>Age matched</td>
<td>16 with IQ &lt; 70</td>
<td>MSA of CC ↓ in AUT</td>
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<td>Elia et al. (2000)</td>
<td>22 AUT</td>
<td>10.92</td>
<td>MR</td>
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<td>MSA of CC</td>
<td></td>
</tr>
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<td>11 CON</td>
<td>10.86</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Hardan et al. (2000)</td>
<td>16 AUT</td>
<td>22.4</td>
<td>FSIQ</td>
<td>100.4</td>
<td>Gena and somum ↓ in AUT</td>
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<td>19 CON</td>
<td>22.4</td>
<td>FSIQ = 100.5</td>
<td></td>
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<td>Adjusted for TBV, RCV, WMV</td>
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<td>Manes et al. (1999)</td>
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<td>14.3</td>
<td>MA</td>
<td>4.6</td>
<td>MSA of CC ↓ in AUT</td>
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</tr>
<tr>
<td>17 MR</td>
<td>11.8</td>
<td>MA = 4.5</td>
<td></td>
<td></td>
<td>Adjusted for A, MA, H, IC</td>
<td></td>
</tr>
<tr>
<td>Piven et al. (1997)</td>
<td>35 AUT</td>
<td>18</td>
<td>NVIQ</td>
<td>91</td>
<td>Body and posterior CC ↓ in AUT</td>
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</tr>
<tr>
<td>36 CON</td>
<td>20</td>
<td>NVIQ = 102</td>
<td></td>
<td></td>
<td>Adjusted for TBV, G, IQ</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>Study</td>
<td>Subjects</td>
<td>M age in years $^a$</td>
<td>Cognitive ability $^a$</td>
<td>Main finding(s)</td>
<td>Comments</td>
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<td>Medial temporal lobe</td>
<td>Abell et al. (1999)</td>
<td>15 HFA</td>
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<td>Average matched</td>
<td>↑ AMY volume in AUT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 CON</td>
<td>25.4</td>
<td></td>
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<tr>
<td></td>
<td>Aybward et al. (1999a,b)</td>
<td>14 AUT</td>
<td>Adolescent and adult matched</td>
<td>Non-MR matched</td>
<td>↓ Volume of HIPF and AMY in AUT</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>14 CON</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Hamnedar et al. (1997)</td>
<td>7 AUT</td>
<td>24.3</td>
<td>60–125</td>
<td>↓ Brodmann’s area</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 CON</td>
<td>26.4</td>
<td>88–136</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Hamnedar et al. (2000)</td>
<td>17 AUT</td>
<td>27.7</td>
<td>55–125</td>
<td>NS HIPF, AMY, or ACG volume differences</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 with ASD</td>
<td>17 CON</td>
<td>28.8</td>
<td>88–136</td>
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<td></td>
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<td></td>
<td>Howard et al. (2009)</td>
<td>10 HFA</td>
<td>15.8–40.3</td>
<td>Normal</td>
<td>NS HIPF volume, but marginally ↓ in AUT, ↑ AMY volume in AUT, NS for temporal lobe volume</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 CON</td>
<td>Matched</td>
<td>Matched</td>
<td></td>
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<tr>
<td></td>
<td>Plven et al. (1998)</td>
<td>35 AUT</td>
<td>12–29</td>
<td>91.1</td>
<td>NS HIPF volume differences</td>
<td>Adjusted for G, NVIQ, TBV</td>
</tr>
<tr>
<td></td>
<td>36 CON</td>
<td>13–28</td>
<td>102.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Satooh et al. (1995)</td>
<td>33 AUT</td>
<td>5.9–42.2</td>
<td>12 IQ &lt; 70</td>
<td>NS HIPF findings in cross-sectional area</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 CON</td>
<td>6.2–42.7</td>
<td>21 IQ &gt; 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Satooh et al. (2001)</td>
<td>45 AUT</td>
<td>11.2 (2–42)</td>
<td>56–85</td>
<td>↓ Volume of the dentata but not CAS (subiculum and CA1–CA3)</td>
<td>Adjusted for TBV</td>
</tr>
<tr>
<td></td>
<td>51 CON</td>
<td>11.4 (2–43)</td>
<td>90–150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sperks et al. (in press)</td>
<td>45 ASD</td>
<td>3.2–4.6</td>
<td>AE = 25.9</td>
<td>↑ AMY volume in AUT</td>
<td>Adjusted for A, G, NVIQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 DD</td>
<td>3.1–4.9</td>
<td>AE = 25.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 CON</td>
<td>3.1–4.7</td>
<td>Average AE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUT, participants with an autistic disorder; ASD, participants with autism spectrum disorder (AUT, PDD, PDD-NOS); DD, developmental delay; HFA, participants with high functioning autism; CON, control participants; MR, controls with mental retardation; NS, not significant; TBV, total brain volume; FVC, intracranial volume; WMV, white matter volume; GM, gray matter; WM, white matter; MSA, mid-sagittal area; CC, corpus callosum; CN, caudate nucleus; HIPF, hippocampus; AMY, amygdala; ACG, anterior cingulate gyrus; ↑, increased; ↓, decreased; IQ, intellectual quotient; PIQ, performance IQ; NVIQ, nonverbal IQ; DQ, developmental quotient; MA, mental age; AE, age equivalent; G, gender; A, age; H, height; HC, head circumference; SES, socioeconomic status.

$^a$ Means reported unless otherwise indicated.
disorder had AMY volumes that were significantly larger than the 14 children with PDD-NOS, suggesting that increased volume of the AMY may be related to the severity of symptoms present in autism. AMY volume has been examined in other, smaller samples (ranging from 7 to 17 autistic subjects) as noted in Table 1, with inconsistent results. Some studies show increased volume (Howard et al., 2000), some decreased volume (Aylward et al., 1999a,b; Pierce et al., 2001), and others reveal no significant group differences (Haznedar et al., 2000). Of interest, Abell et al. (1999) examined the amygdaloid complex in 15 high-functioning autistic (HFA) adults using a voxel-based whole brain analysis (statistical parametric mapping), after noting that 11 HFA subjects failed a second-order false belief task (indicating a deficit in social cognition that goes beyond the defining behavioral features of autism, perhaps identifying a subset of autistic individuals). The autistic subjects had decreased gray tissue volume in the anterior amygdaloid complex (right paracingulate sulcus, left inferior frontal gyrus) but increased gray volumes in the posterior portions (AMY, peri-AMY, middle temporal gyrus (MTG), inferior temporal gyrus (ITG)). Similarly, Howard et al. (2000) employed neuropsychological measures to further define the social cognitive deficits in a small sample of autistic individuals. Howard et al. (2000) reported an increase in total AMY volume in 10 HFA individuals shown to have deficits in eye gaze, recognition of facial affect and memory for faces. Unfortunately, neither of these studies examined the correlations between AMY volumes and these selected tests of social cognition. Overall, the weight of the evidence suggests an increase in AMY volume probably exists in autism. The variability of the findings may be attributed to the diagnostic variability between studies, the range of ages studied, and/or the different procedures for segmenting the AMY, a brain structure with a complex shape.

2.4. Hippocampus

To date, no consistent hippocampal findings in individuals with autism have been reported (Saitoh et al., 1995; Piven et al., 1997; Aylward et al., 1999a,b; Howard et al., 2000; Haznedar et al., 2000; Sparks et al., in press, and Saitoh et al., 2001). In the first systematic study of the hippocampus, Saitoh et al. (1995) examined a cross-sectional area of the hippocampus and found no significant size differences in autistic individuals versus normal controls. Piven et al. (1997) found no differences studying the volume of the hippocampus. Subsequent studies on samples ranging from 10 to 14 autistic subjects reported both decreased volume (Aylward et al., 1999a) and no significant differences in volume (Haznedar et al., 2000; and Howard et al., 2000). The influence of cognitive ability may be important in future studies, as Aylward et al. (1999b) reported evidence for an IQ effect on AMY volume in Down’s syndrome. Most recently, Sparks et al. (in press) examined 45 individuals with autistic spectrum disorders (which included DSM-IV diagnoses of autistic disorder and PDD-NOS) and found they had increased volume of the hippocampus when compared to a non-autistic, developmentally-delayed sample, but not to a typically-developing comparison group. Saitoh et al. (2001) recently examined subcomponents of the hippocampus and noted a decrease in the dentate gyrus and in area CA4, but not the CAS (defined as the subiculum + CA1–CA3) in the autistic group with reference to a normal comparison group, after adjusting for TBV.

2.5. Cingulate gyrus

The anterior cingulate gyrus (ACG), which is believed to be involved in information processing and response to emotional cues has been found to be abnormal on MRI PET and postmortem studies. This region, along with other medial temporal lobe structures, has been implicated by neuropathological findings in autism showing small, densely packed cells (Bauman and Kemper, 1985). Haznedar et al. (2000) has reported that individuals with autism displayed both decreased volume and diminished activation in this brain region in a study that co-registered PET and structural MRI data to localize the metabolic findings.

In summary, while the findings from structural MRI studies seem to suggest increased volume in the AMY, given the variability of reports to date, it is not possible to make firm conclusions regarding hippocampal volume on MRI in autism.

2.6. Basal ganglia

The basal ganglia include the caudate nucleus, putamen, and globus pallidus, and have received relatively little attention in imaging studies of autism. The basal ganglia have been implicated obsessive–compulsive disorder and Tourette’s syndrome (Rosenberg and Keshavan, 1998; Peterson et al., 1993), disorders that overlap phenomenologically with the ritualistic, repetitive behaviors seen in autism. Sears et al. (1999) examined the volume of the caudate, putamen, and globus pallidus two independent samples of autistic individuals and controls, comparable in age, gender, and nonverbal IQ. Volume of the caudate nucleus, but not globus pallidus or putamen, was increased in individuals with autism. Modest, but significant, correlations (r = 0.5) were noted between caudate size and stereotyped repetitive behaviors, but not social or communication deficits as assessed on the Autism Diagnostic Interview. Finer grained analyses, however, revealed more robust correlations (r = 0.5) between caudate volume and compulsions and rituals, difficulties with minor change in environment and routine, and complex motor behaviors. Complex repetitive motor behaviors were positively correlated with caudate enlargement, while compulsions/rituals and difficulties with minor change in environment and routine were negatively correlated. In an analysis of a second independent sample of 15 autistic individuals and 30 controls, reported in this same
paper, enlargement of the caudate nucleus was again noted. A correlation between ritualistic-repetitive behaviors and increased volume of the caudate nucleus has also been found in Fragile X (Reiss et al., 1995).

Overall, these findings suggest that the caudate may play a role in the stereotyped repetitive behaviors seen in autism and are consistent with findings in other phenomenologically related disorders (e.g. Fragile X, obsessive-compulsive disorder and Tourette’s syndrome). These results provide evidence for specific brain-behavior relationships with the autism syndrome showing a specific relationship between ritualistic, repetitive behaviors (but not social or communication deficits) and caudate volume. Teasing apart such brain behavior relationships will be critical in dissecting the heterogeneity of the autistic syndrome and will help increase our chances of finding more homogeneous subgroups and subsystems with this complex disorder. In addition, these findings may have implications for other areas of exploration in autism. The caudate has connections to the pre-frontal cortex (e.g. ventral and dorsolateral) and is known to play an inhibitory role in behavior (Stuss et al., 2001; Cummings, 1993). The correlational data from Sears et al. (1999) suggests the possibility of two different frontal-striatal mechanisms, one pathway involved in motor stereotypes and another for compulsions and ritualistic behavior. These findings suggest that the exploration of frontal-striatal connections, perhaps using diffusion tensor imaging to measure the integrity of the white matter connections between these regions (Lim et al., 1999), is warranted to explore the relationship of these pathways to stereotyped behaviors as they relate to autism.

2.7. Corpus callosum

The corpus callosum (CC) is the major axonal pathway linking the two hemispheres and, as such, abnormalities in the CC, in addition to being potential markers for brain abnormalities, are hypothesized to index disruption in connectivity. In reality, the proportion of cortical fibers which cross at the CC is actually quite small (approximately 2–3%) and whether or not abnormalities of connectivity can be inferred when morphological differences are detected in the CC is highly speculative (LaMantia and Rakic, 1990; Abbotiz et al., 1992). Nevertheless, although various segments of the CC have been implicated in MRI studies of autism, there is consistency across studies in the finding that the CC is generally reduced in size in autistic individuals. Egaas et al. (1995) found that the area of the caudal third of the CC was significantly reduced in a sample of 51 subjects with autism compared to 19 healthy male controls, matched on age and SES, and after adjusting for brain volume. These findings of a reduction in the size of the CC are of interest in that, given the evidence for increased brain volume, enlargement of the CC might be expected. The discrepant findings of enlarged brain volume and reduced CC size may offer an index of overall disconnectivity in autism, or provide clues to particular cortical layers that may be implicated in the increased brain size as only selected layers (e.g. cortical layer III) contribute axons that cross at the CC (Lassonde, 1986; Innocenti, 1986).

2.8. Brainstem

Early theories of autism implicated the brain stem as playing a critical role in mediating attention, hyperactivity, reactivity, and integrating sensory information. More recently, Rodier et al. (1996) reported that the brainstem was decreased in size in an autopsy of the brain of one autistic individual, and this reduction was located primarily in the region developed from the third rhombomere (i.e. the region between the Vth and VIIth cranial nerves). Gaffney et al. (1988) obtained mid-saggital measurements of the brainstem, medulla oblongata, and pons on MRI. The cases with autism had significantly smaller total brainstem areas and pons measurements. The pons was found to be smaller in width in a sample of 18 children with autism (M age = 3.8 years) compared to medical controls and a comparison group with mental retardation in a series of studies (Hashimoto et al., 1988; Hashimoto et al., 1992a; Hashimoto et al., 1992b). However, the Hashimoto group found a significant reduction in the mid-saggital areas of the midbrain and medulla oblongata, but not pons, in their autistic sample (Hashimoto et al., 1993). IQ was not consistently taken into consideration.
account in these studies, many of which compared autistic
individuals with mental retardation to non-autistic individu-
als with normal IQs (Table 1). Others have failed to replicate
this finding in mid-sagittal measurements of the pons and
midbrain (Elia et al., 2000). Piven et al. (1992) performed
mid-sagittal measurements of the pons and found the autis-
tic individuals had evidence of reduced size of the pons.
However, these results were no longer present after taking
into account total mid-sagittal brain area (i.e. overall brain
size), age, and IQ. Overall, there does not appear to be strong
evidence for size differences in brainstem on MRI in autism.

2.9. Summary of structural imaging findings

Until very recently, the findings from MRI studies of brain
structure in autism could perhaps best be characterized by
a disappointing series of non-replicated findings. This lack
of replication may be attributed to a failure to consistently
account for important design and analysis issues, such as
having adequate power in the face of the etiologic hetero-
geneticity and overall complexity of autism or failure to ex-
clude potential confounding factors such as IQ, gender and
brain volume. However, a recent convergence of studies re-
porting increased brain volume in autism provides reason for
renewed enthusiasm about the promise of structural imaging
studies in this disorder. Clearly, characterization of the nature
of this brain volume abnormality will be of great importance
in providing a basis for defining the structural brain pheno-
types in autism. Areas for clarification include the timing of
the size differences, gender differences, gray and/or white
matter changes, and the relationship to other sub-structures
and connections. The finding of brain enlargement also
indicates the importance of taking into account changes in
brain size over time for studies of the volume of individual
structures, tissue volumes, as well the need for longitudinal
studies to fully clarify the true nature of this phenomenon.

Characterization of brain phenotypes in autism on MRI
may provide evidence for specific brain–behavior correla-
tions, such as that suggested in the studies of caudate vol-
ume and stereotyped repetitive behavior, as well as provide
cues to underlying brain mechanisms that might cause these
phenotypes. Furthermore, the pattern of brain size changes
over time may be considered with reference to emerging
information on brain morphology in genetically engineered
animal models, linking patterns in animals (with knockouts
of genes known to play a role in brain development) and
affected human subjects. Several such gene candidates af-
fected brain development have recently been suggested as
susceptible genes in autism (Wassink et al., 2001; Persico
et al., 2003).

Future structural imaging studies will benefit greatly from
new technologies for data acquisition, new approaches to im-
age analysis and new methods for image processing. The 3 T
magnet offers substantial gains in detail of neuroanatomical
images. New approaches to indexing connectivity through
diffusion tensor imaging studies of water diffusion through
myelin tracts in the brain (i.e. diffusion anisotropy) will pro-
vide new information about white matter connections and
the integrity of communication pathways. This approach
is suitable for use in very young children under sedation,
allowing the characterization of the early development of
white matter tracts. Recent reports in the study of normal
pediatric brain development have underscored the critical
need for longitudinal studies of normal and abnormal brain
development (Giedd et al., 2001). Emerging work in the
field of fetal brain development, combining the technologies
of ultrasound and MRI (e.g. linking ventricular enlargement
to neurodevelopmental disorders, Gilmore et al., 2001)
underscores the importance of multi-modal neuroimaging
studies in pediatric samples. Furthermore, advanced meth-
ods of image processing are now making automated tissue
segmentation possible. This efficient and reliable approach
will facilitate large scale imaging studies that can take into
account the heterogeneity of behavioral syndromes such as
autism. New image processing methods that allow for high
speed dimensional warping and shape analysis provide dra-
matically more information about the morphological char-
acteristics of brain structures than was previously available
from volume measurements alone (Csernansky et al., 1998).
Finally, methods are being perfected that enable behavioral
training and desensitization of the pediatric age group (both
normal and developmentally disabled individuals) so that
they may effectively participate in MRI studies at younger
ages without the need for sedation. This will allow the
addition of more pediatric samples that would provide the
ability to look at early development and longitudinal data.

3. Functional imaging studies

By providing information about brain activity in response
to specific cognitive tasks, functional MRI (fMRI) differs
markedly from structural MRI, which provides informa-
tion only about brain structure. Consequently, fMRI can be
employed to study the neurofunctional organization of cog-
nitive processes, and can be used to document changes in
the organization of these processes in neurodevelopmental
disorders such as autism. Notably, fMRI is a non-invasive
in vivo neuroimaging method that does not involve ionizing
radiation, but rather employs an endogenous contrast prop-
erty of the brain, blood oxygen level dependent contrast
(BOLD), to provide information about localized changes
in blood flow—an indirect measure of underlying neural
activity. Because fMRI does not involve ionizing radiation,
it is preeminently suited for longitudinal studies of autistic
and typically developing children and adults. Furthermore,
the spatial and temporal resolution of fMRI is generally
quite good, with spatial resolution of approximately 3 mm
and temporal resolution of approximately 1 s.

Social deficits, ritualistic–repetitive behaviors, and
language impairments, are prominent features of autism.
These behaviors are thought to reflect neuropsychological
deficits in social cognition (e.g. processing emotional and social cues reflected in facial expressions, failures in understanding the intentions of others on the basis of nonverbal cues) and executive function (e.g. generating flexible task-appropriate actions while inhibiting task-inappropriate ones, stereotyped-repetitive behaviors, deficits in central coherence) Consequently, two principal cognitive frameworks—abnormal processing of social information and a deficit in executive function—have been proposed as theories to explain the neuropsychological basis of these behavioral impairments. Functional neuroimaging studies, aimed at characterizing the activity of the neural substrates underlying the core behavioral and neuropsychological components of autism, offer an important strategy for addressing the heterogeneity in and complexity of autism by identifying biologically meaningful phenotypes that map on to characteristic behavioral and psychological. Furthermore, with fMRI, researchers can address key developmental questions, including how brain and behavioral development interact over ontogeny. Longitudinal studies that combine fMRI with well-designed behavioral assessments of development will be particularly valuable in this regard.

In this section, recent fMRI studies of neuropsychological processes in autism spectrum disorders are reviewed (see Table 2 for capsule summaries of these studies). This section focuses on pivotal studies that have used fMRI to examine brain activity in response to specific cognitive tasks. Functional neuroimaging studies of social cognition and executive functioning in autism are explored, as are the few functional neuroimaging studies of language in autism. The intent is to provide an overview of the still relatively small body of literature that has developed (and continues to grow) around the study of key neuropsychological processes in autistic disorders via functional neuroimaging methods, and to provide suggestions for potential avenues of research.

### 3.1. fMRI studies of social cognition in autism

Although autism affects multiple domains, evidence suggests that it disproportionately affects social cognition. For example, autistic individuals can be selectively impaired on tasks that require processing of social information (e.g. making inferences about other people’s mental states), yet relatively unimpaired on tasks measuring other perceptual and cognitive abilities (e.g. Baron-Cohen, 1995; Ring et al., 1999). These social impairments might result from a “theory-of-mind” (ToM) deficit (i.e. autistic individuals lack an intuitive understanding of the mental states of others including their false beliefs, intentions, desires and feelings and are unable to predicting others’ behavior from this.

<table>
<thead>
<tr>
<th>Citation</th>
<th>AD</th>
<th>HFA</th>
<th>AS</th>
<th>TYPS</th>
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<th>Task(s)</th>
<th>Core finding(s)</th>
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<td>Muller et al. (1999)</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>PET</td>
<td>Listening to tones or sentences or repeating sentences or generating sentences</td>
<td>Reversal of typical left hemisphere dominance for language during sentence listening and aberrant activity in ACG during tone listening</td>
</tr>
<tr>
<td>Muller et al. (1998)</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>PET</td>
<td>Secondary analysis of Muller et al. (1999)</td>
<td>↓ In left PFC, thalamus, and right dentate nucleus during receptive and expressive language tasks; reversal of left hemisphere bias in PFC for tone listening</td>
</tr>
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<td>Baron-Cohen et al. (1999)</td>
<td>6</td>
<td>?</td>
<td>?</td>
<td>12</td>
<td>fMRI</td>
<td>Inferring mental states form pictures of eyes</td>
<td>↑ In frontal-temporal regions instead of in the AMY during mentalistic inferences</td>
</tr>
<tr>
<td>Happe et al. (1996)</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>PET</td>
<td>Attribution of mental states to story passages</td>
<td>Atypical ↑ seen in adjacent and more ventral region of medial PFC (BA 9/10) as compared to medial PFC (BA 8/9) in TYPs during mentalistic attributions</td>
</tr>
<tr>
<td>Schulte et al. (2000)</td>
<td>14</td>
<td>8</td>
<td>28</td>
<td>18</td>
<td>fMRI</td>
<td>Face picture discrimination</td>
<td>↓ In FG, aberrant ↑ in ITG during face processing</td>
</tr>
<tr>
<td>Critchley et al. (2000a,b)</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>fMRI</td>
<td>Implicit and explicit processing of emotional expressions from face pictures</td>
<td>↓ In FG across tasks; ↑ in left STG and left PVC, ↓ in left AMY and left CB during implicit processing</td>
</tr>
<tr>
<td>Pierce et al. (2001)</td>
<td>7</td>
<td>?</td>
<td>0</td>
<td>8</td>
<td>fMRI</td>
<td>Perception of face pictures</td>
<td>↓ In FG and left AMY, idiosyncratic ↑ in aberrant regions (e.g. frontal cortex, visual cortex, CB)</td>
</tr>
<tr>
<td>Ring et al. (1999)</td>
<td>6</td>
<td>?</td>
<td>?</td>
<td>12</td>
<td>fMRI</td>
<td>Embedded figures test</td>
<td>↓ In right DLPFC and bilateral parietal cortex; aberrant ↑ in right ventral occipitotemporal cortex</td>
</tr>
<tr>
<td>Muller et al. (2001)</td>
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<td>fMRI</td>
<td>Visually prompted</td>
<td>Abnormal variability in peak HDRs amid ↓ in SMA finger movements and contralateral putaminal cortex</td>
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Abbreviations: AD, participants with an autistic disorder (autism or Asperger’s syndrome); HFA, high functioning autistic participants; AS, individuals with Asperger’s syndrome; TYPS, typically developing control participants; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; ↑, increased activity as compared to controls; ↓, decreased activity as compared to controls; ACG, anterior cingulate gyrus; PFC, prefrontal cortex; AMY, amygdala; FG, fusiform gyrus; ITG, inferior temporal gyrus; STG, superior temporal gyrus; PVC, peristriate visual cortex; CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area.
yond the ToM conceptual framework. For example, Adolphs search demonstrates deficits in social cognition that fall be-

In a study of individuals with autism and Asperger’s syndrome, Baron-Cohen et al. (1999) used fMRI to measure autism. In a study of individuals with autism and Asperger’s syndrome reliably showed deficits on this task (Baron-Cohen et al., 1997). In this fMRI study, the participants viewed photogra-

Researchers have started to use fMRI to examine the po-
tential neuroanatomical basis of social cognitive deficits in autism. In a study of individuals with autism and Asperger’s syndrome, Baron-Cohen et al. (1999) used fMRI to measure brain activity during a task requiring participants to infer the mental state of another individual from the expression of that individual’s eyes. The autistic disorders group consisted of six (four male, two female) high-functioning adults with autism or Asperger’s syndrome. The control group consisted of 12 typically developing adult participants (six males, six females). Participants were right-handed and comparable on IQ and age. Average ages of the two groups were 26.3 and 25.5 years for the autism and control group, respectively. The focal task was an adaptation of an advanced ToM task developed by Baron-Cohen et al. (1997), originally for use outside of the MRI scanning environment. In behavioral studies, higher-functioning adults with autism and Asperger’s syndrome reliably showed deficits on this task (Baron-Cohen et al., 1997). In this fMRI study, the participants viewed pho-

Behavioral studies have consistently confirmed the pres-
ence of face processing deficits in autistic disorders (e.g. Brauerman et al., 1989; Langdell, 1978; Ozonoff et al., 1990; Tantam et al., 1989; Carps et al., 1992; Celani et al., 1999; Hobson, 1986a, 1986b; Hobson et al., 1988; Hobson and Lee, 1989; Loveland et al., 1997; Ozonoff et al., 1990). These behavioral findings are strongly corroborated by re-

In this line of research in autism. Future work will benefit from the recent burgeoning of interest among neuroscientists in studying social cognition via functional neuroimaging tech-
niques (for reviews, see Adolphs, 1999, Allison et al., 2000).

Furthermore, forthcoming work should examine the neural basis of both the global aspects of social cognition (e.g. ToM abilities) and the component processes that support social cognition (e.g. joint attention and the perception of eye gaze direction).

3.1.1. Using fMRI to examine the neural bases of social cognition in autism

Researchers have started to use fMRI to examine the po-
tential neuroanatomical basis of social cognitive deficits in autism. In a study of individuals with autism and Asperger’s syndrome, Baron-Cohen et al. (1997) originally for use outside of the MRI scanning environment. In behavioral studies, higher-functioning adults with autism and Asperger’s syndrome reliably showed deficits on this task (Baron-Cohen et al., 1997). In this fMRI study, the participants viewed photographs of eyes and judged their gender (male/female) or mental state (e.g. concerned/unconcerned), indicating these judgments with a button press.

Members of the autistic disorders group (on average) performed less well on both tasks than did the control group members, but the individuals with autistic disorders were relatively more impaired on the task that required mentalistic inferences. Relative to the gender recognition task, the ToM task elicited greater activation of frontal–temporal cortical regions and subcortical regions, including the left AMY, the STG bilaterally, left hippocampal gyrus and bilateral insulae, and left striatum, in the control participants. The autistic group activated frontal components less extensively than did the controls, did not activate the AMY, and showed enhanced activation in the STG. Activation in the frontal–temporal regions, and not the AMY, was observed when participants with autistic disorders were required to make mentalistic inferences. As the authors discussed, the results suggest that AMY dysfunction may underlie failures of emotional and mental state processing in autism and that reduced frontal activation may underlie a deficit in executive function.

3.1.2. fMRI studies of face processing in autism

Nonetheless, this study provides a foundation for a critical line of research in autism. Future work will benefit from the recent burgeoning of interest among neuroscientists in studying social cognition via functional neuroimaging tech-
niques (for reviews, see Adolphs, 1999, Allison et al., 2000).

Furthermore, forthcoming work should examine the neural basis of both the global aspects of social cognition (e.g. ToM abilities) and the component processes that support social cognition (e.g. joint attention and the perception of eye gaze direction).
A consistent pattern of activation emerged in the two control groups. Significant levels of activity were observed in the (predominantly right) fusiform gyrus (FG) during face perception, whereas activity was observed in the inferior temporal gyrus (ITG) during object processing. Notably, this pattern of activation is consistent with a large body of neuroimaging findings that, using a variety of imaging techniques, has demonstrated reliable activity in (primarily right lateral) FG in response to faces (e.g. Kanwisher et al., 1997; McCarthy et al., 1997). In contrast, a very different pattern of activity was observed among the participants with autism and Asperger’s syndrome. In this group, significantly less right hemisphere FG and significantly more right ITG activity was observed in the participants with autism and Asperger’s syndrome (n = 7) or autism (n = 2) and in a control sample of typically-developing adult males (n = 9). The groups were comparable in terms of age and IQ. The average ages of the groups were 37 and 27 years for the autistic disorders and control groups, respectively. All control participants were right-handed. Handedness information was not provided for volunteers in the autistic disorders group. Participants completed two tasks during as many scanning sessions. In both tasks, photographs of faces were shown with face gender mixed equally and expressions consisting of angry, happy, or neutral emotional displays. In a blocked design, stimulus presentations were divided into alternating 30 s “on/off” conditions. During “on” periods, participants viewed pictures exhibiting happy or angry emotional expressions. During “off” periods, participants viewed photographs posing neutral expressions. On one testing occasion, participants attended to and judged the emotional expression of each face stimulus, and indicated their judgment by pressing one of two buttons. During the other experimental session, participants attended to and judged the gender of each face, and indicated their judgment by pressing one of two buttons. The first task entailed explicit processing of emotional expressions, the authors reason, whereas the second task, because participants were attending to another characteristic of the face stimuli (i.e. gender), involved implicit processing of emotional expressions.

The authors remarked that this study was prompted, in part, by self-reports of high-functioning autistic individuals using explicit mechanisms to guide social behavior and judgments concerning emotional expressions (e.g. checking to see if the corners of the mouth are upturned, indicating happiness) even as they demonstrated deficits in social behavior. Moreover, in a previous study, Critchley et al. (2000b) reported that temporal lobe regions in typically developing volunteers were active in response to the explicit processing task, whereas limbic/paralimbic regions were active during the implicit task. Hence, in the present study, the authors predicted significant group differences in the patterns of activation uniquely associated with explicit versus implicit processing. They further reasoned that the autistic disorders group would show less activity than controls in areas previously linked with implicit processing of facial expressions.

In the control group, the results confirmed the previous pattern of findings (Critchley et al., 2000b). Moreover, as in the findings of Schultz et al. (2000), the participants with autism spectrum disorders showed significantly less activity in the FG across experimental tasks. They also had greater activity, as compared to controls and across the two experimental tasks, in the left superior temporal gyrus (STG) and left peristriate visual cortex. Consistent with the authors’ predictions, the autistic disorders group differed from the control group in the activity of cerebellar, mesolimbic, and temporal lobe regions when processing facial expressions, and this difference varied as a function of processing demands. Specifically, individuals with autistic disorders did not show activation in the FG (bilaterally) when explicitly appraising emotions, or the left AMY and left cerebellum when implicitly processing emotional facial expressions. Commenting on their findings, Critchley et al. (2000a) concluded that they appeared to indicate abnormalities among individuals with autistic disorders in the functional organization of explicit and implicit processing of emotional facial expressions. They further suggested that their findings might indicate dysfunction in pathways between limbic and paralimbic regions, the cerebellum and the extrastriate visual cortices.

Pierce and Courchesne (2000) conducted a third functional neuroimaging study of face processing in autistic disorders using fMRI. Their sample consisted of seven high-functioning autistic males and eight typically developing male controls. The two groups were matched for sex, age, and handedness. Two of the autistic participants were left-handed and the remaining four were right-handed. Mean ages of the two groups were 29.5 years versus 28.3 years for the autistic and control groups, respectively. Participants performed alternating face and shape perception tasks, pressing a button in response to female faces and circles, respectively. Data analyses involved both native space and spatial normalization analytic procedures. Native space procedures focused on a priori selected regions of interest (ROIs) including the FG, ITG, MTG, and the AMY.

Anatomical analyses of the four ROIs revealed significantly reduced AMY volumes (~15%) bilaterally and marginally reduced FG volumes (~8%) bilaterally in the autism group as compared to the control group. Group differences in anatomical volumes were not observed in the
ately needed developmental studies to examine the ways in which aberrant neural regions become specialized for face processing in autism. As noted by Pierce and Courchesne (2003), there is a need for studies that will investigate possible experiential or neurodevelopmental explanations for why there is decreased activation of the FG during face processing in autism spectrum disorders. Additionally, much work remains to be done to link individual differences in aberrant functional activation and localization during cognitive processing with potential individual differences in the magnitude of developmentally based structural defects. This class of question can only be answered through longitudinal structural and functional studies of information processing in children with autism spectrum disorders.

Functional neuroimaging studies of face processing in autistic disorders have been exceptionally successful in part because of an extensive understanding of the typical neural organization of the face processing system, which has been developed through prolific basic research within the fields of cognitive and comparative neuroscience. Given this area of success, it might useful to think about other emerging paradigms that could be borrowed from basic cognitive neuroscience research and applied to further our understanding of face processing in autistic disorders. One possibility concerns what neuroscientists have referred to as the “the distributed face processing system” (Haxby et al., 2000; McCarthy, 1999). That is, the FG is not the only region involved in face processing. Several models of the organization of the human face processing system distinguish between cortical regions involved in processing invariant aspects of faces that carry information about identity and those involved in processing variable aspects that facilitate social communication (e.g. Haxby et al., 2000; McCarthy et al., 1999; Puce et al., 1998). Future research could be profitably devoted to examining the neurofunctional organization of those regions responsible for processing the fluctuating aspects of faces (e.g. eye and mouth movements) that are particularly relevant to social interaction.

3.2. fMRI studies of executive functions in autism

Frith, Happe, and others have explored a putative cognitive style in autism, demonstrated in both assets and deficits across experimental tasks (for a review see Happe, 1999). They suggest that people with autism show a processing bias in favor of featural or piecemeal information at the expense of configural or holistic information. For example, people with autism often excel at the Wechsler block design subtest, and the embedded figures test (EFT), tasks that require breaking the gestalt of a whole figure whole into its component parts (Shah and Frith, 1983, 1993). However, the detail-focused processing style leads to poor performance on other tasks where configural processing is necessary— for example, in determining the appropriate meaning and pronunciation of homographs in written text (Happe, 1997). Most functional neuroimaging studies of autistic disorders have focused on examining the neural bases of...
prominent deficits. In contrast, Ring et al. (1999) employed fMRI to study BOLD activity in the brains of autistic and typically developing individuals during completion of a kind of visuospatial processing task on which high-functioning autistic individuals often perform quite well—the EFT. This study was designed to examine the neural basis of the proposed weak central coherence cognitive style. Their sample included six subjects with autism or Asperger’s syndrome (four males: M age = 26 years) and twelve typically developing controls (six males: M age = 25.5 years). The groups were matched on age, handedness (all were right-handed), IQ, socioeconomic status, and educational level. The experimental task involved an adaptation of the standard EFT (Witkin, 1962). Participants pressed a button when they found a simple figure (the target) within a more complex figure. The study involved a blocked periodic design with repeated contrasts between a baseline condition and an activation condition. During the baseline condition, subjects performed a simple fixation task. They performed the adapted EFT during the activation condition.

The two groups did not differ significantly in terms of performance accuracy, nor were there sex differences in performance. Analyses of the fMRI data indicated some overlapping activation in cerebral regions between the two groups. These areas included the MTG and ITG, the supramarginal gyrus and precuneus, the inferior frontal gyrus, and the middle occipital gyrus (MOG). The control group demonstrated greater activation than did the autistic disorders group in right dorsolateral prefrontal cortex (DLPFC) and bilateral parietal cortex. Relative to their overall activation (which was lower than that of controls) the autistic group showed a more powerful response in the right ventral occipitotemporal region than did controls.

Building upon the knowledge that prefrontal regions have been implicated in spatial relations, visual search, and working memory for objects and the associations between regions in ventral occipitotemporal cortex, object perception, visual imagery, and separation of figure from background, the authors suggest that the findings from this study support their hypothesis that the two groups of participants would employ different brain region and that differences in the patterns of these regional activations would support distinct models of cerebral processing underlying EFT performance. They further discuss these findings as supporting the weak central coherence model of autism (Frith, 1989; Happe and Frith, 1996).

Most fMRI studies of autism have focused on complex cognitive functions (e.g. language or ToM) that represent the amalgamation of many simpler functions. In contrast, Muller et al. (2001) investigated patterns of brain activation in seven higher-functioning autistic males and seven typically developing male controls during performance of a very simple visually paced finger movement task that might reflect aspects of executive functioning (i.e. planning and execution of a prompted action sequence). Activity during this task was compared to a control condition that involved identical visual stimulation in the absence of motor responses. The two groups were matched on mean age (autism = 28.4 years versus control = 28.5 years) and handedness. Five of the autistic participants were right-handed, two were left-handed, and one was ambidextrous. This experiment involved a blocked design. Participants watched a diagram of a hand on a screen and a dot flashed on the index finger of the hand every 640 ms. In one condition, participants simply watched the hand and the dot. In the other condition, the participants pressed a button with their index finger each time the dot appeared on the screen.

Analyses of the behavioral responses indicated that responses were temporally more irregular in the autism group than in the control group, though not significantly, and levels of accuracy were equivalent between the two groups. Analyses of the group level data showed activation in contralateral peritrolandic cortex, basal ganglia and thalamus, bilateral supplementary motor area, and ipsilateral cerebellum for both groups. However, activations were less pronounced in the autism group. Direct group comparisons demonstrated greater activation in peritrolandic and supplementary motor areas in the control group and greater activation (or reduced deactivation) in posterior and prefrontal cortices in the autism group. Intrainsider analyses further showed that strongest activations were consistently located along the contralateral central sulcus in control subjects but occurred in locations different from individual to individual in the autism group.

The authors suggested that their findings indicate abnormal individual variability of functional maps and less distinct regional activation/deactivation patterns in autism. The observations may be related to known motor impairments in autism and are compatible with the general hypothesis of disturbances of functional differentiation in the autistic cerebrum. The authors raise the possibility that higher order impairments in autism are secondary to problems that are more elemental such as the one tested in this study.

3.3. Studies of language processes in autism

To date fMRI studies of language processes in autism have not emerged. Consequently, two PET studies are discussed here to highlight the potential for further valuable work in this area. Muller et al. (1999) conducted an O-15 PET study to examine the neurofunctional organization of audition and language (receptive and expressive processes) in five higher-functioning autistic adults (four males: M age = 26.6 years) and five typically developing adult control participants (four males: M age = 27.6 years), matched on age, gender, and handedness, but not IQ. The experiment consisted of five conditions: resting, listening to a sequence of simple tones, listening to simple sentences, repeating simple sentences, and generating sentences from a stimulus sentence and word prompt. Results indicated a significant reversal of the more typical left hemisphere language domi-
nance among the autistic participants during the listening to sentences condition. In contrast, greater left hemisphere activity was observed in the autism group during the sentence generation task, with activations observed in left inferior frontal regions. Significant reductions in bilateral STG and cerebellar rCBF in the autistic participants as compared to the controls were observed. The authors concluded that their results provide partial support for atypical (reduced or reversed) hemispheric dominance in the autistic group. They further discussed their findings in the context of potential ontogenetic delays in brain development leading to reduced left hemisphere dominance in language and enhanced right hemisphere dominance occurring due language delays. In addition to the finding of atypical hemispheric organization, anomalous activations of the ACG were observed in the autism group while they passively listened to sequences of simple tones. The researchers suggested that this finding might relate to the symptoms of hyperarousal and/or auditory hypersensitivity that have been observed in autistic disorders.

Muller et al. (1998) analyzed the rCBF data from the five autistic participants reported in Muller et al. (1999) to focus more precisely on regions previously identified as showing serotonergic abnormalities in PET studies (the prefrontal cortex (PFC), the thalamus, and the dentate nucleus) (e.g. Chugani et al., 1997), and to examine whether functional defects in these previously unexamined areas might have an impact on language. Among autistic participants, there was reduced activation in the left prefrontal cortex, the left thalamus, and the right dentate nucleus during receptive and expressive language tasks (i.e. listening to sentences and generating sentences). Furthermore, the typical left hemisphere bias in PFC for the auditory condition (i.e. listening to sequenced tones) was reversed in the autism group. These findings corroborate the previous finding of atypical hemispheric lateralization and, as the authors discussed, the results are compatible with atypical functional specialization of regions in the dentato-thalamo-cortical pathway.

To date, the two studies by Muller et al. (1998, 1999) are the only published (to our knowledge) functional neuroimaging studies of language in autistic disorders. Conclusions from these two investigations remain preliminary due to the relatively low spatial resolution of PET and small number of participants. Nonetheless, the results suggest a potentially profitable avenue for future research. Future studies of language in autism via functional neuroimaging methods will benefit from recent advances in basic research concerning neurofunctional organization of language (for a review, see Binder and Price, 2001). In this regard, basic research aimed at dissecting the various processes that make up language is of considerable interest (e.g. pragmatic versus semantic aspects of language). If paradigms developed to disaggregate specific language processes in typically developing volunteers are applied to studies of individuals with autism and Asperger’s syndrome, the results will likely help us to characterize biologically meaningful sub-phenotypes that might underlie the heterogeneity of language functioning in autistic disorders.

4. Concluding comments

In this review, we have attempted to provide a critical overview of the past decade of neuroimaging research in the field of autism. We focused primarily on the main structural MRI findings and fMRI findings that have produced the currently held hypotheses about the neuropathology and neurobiology underlying this complex disorder. The most compelling structural findings reveal that the brains of autistic individuals are increased in size compared to their normally developing peers. This brain enlargement appears to be localized to regions rather than global in nature. Conclusive findings related to specific structures do not yet exist, but studies of subregions and structures remains an important area of interest. There are findings that the CC is reduced in size, although investigations have yet to pinpoint if a particular subregion is involved, and that the caudate nucleus is enlarged. Most evidence indicates that there are no significant differences in cerebellar size or brainstem structures when total brain size and/or IQ are taken into account. Future research, perhaps structural studies combined with fMRI, will help place focus on the temporal lobe abnormalities, in the hippocampus and AMY, that are hypothesized to be involved in autism. Finally, recent cross-sectional work has highlighted the importance of looking at change over time, as development appears to be a critical factor in the findings of brain tissue volume differences.

Whereas functional neuroimaging holds promise for elucidating the neural basis of autism spectrum disorders, its application to their study is still in its infancy. Many of the functional studies reviewed here should be viewed as exploratory, given the small and frequently heterogeneous samples, wide age ranges, and limited normative data. The studies have begun to suggest alterations in brain organization for language and cognition. These studies should prove useful in delineating the neural basis of abnormalities in sensory, perceptual, attentional, emotional, and cognitive processing if designed and conducted within a solid theoretical framework. Such studies will need to address specific hypotheses in well-defined subsamples and use multiple control groups (e.g. age- and gender-matched typically developing controls, developmentally disabled controls matched for language function and general intelligence). This improved methodology will strengthen the studies and will help establish the specificity of findings. Studies should be well integrated with developmental psychology as well as structural MRI work to better characterize the deficits as they exist at various developmental ages and as they relate to various structural differences.
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