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Brief Report: Neuroimaging in Autism: The State of the Science 1995[1]

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Since its advent just over 10 years ago, many researchers have used magnetic resonance imaging (MRI) to try to identify brain anomalies characteristic of the autistic spectrum disorders (ASD). This review address the following questions relative to ASD: *What structural anomalies of the brain have been identified by MRI? Why are these collective findings inconclusive? Where should neuroimaging research go from here?* It should be noted that the vast majority of MRI scans performed is ASD are clinically interpreted as "normal," without obvious structural abnormalities (Filipek, Kennedy, & Caviness, 1992).

WHAT STRUCTURAL ANOMALIES OF THE BRAIN IN ASD HAVE BEEN IDENTIFIED BY MRI?

The Cerebellar Vermis

Courchesne et al. (1994) and Courchesne, Yeung-Courchesne, Press, Hesselink, and Jernigan (1988) reported smaller (hypoplastic) cerebellar vermis lobules VI–VII in a total of 41 male and 9 female autistic (AD) patients, ages 2 to 40 years. However, using similar techniques, Filipek, Richelme, et al. (1992), Garber and Ritvo (1992), Hashimoto, Murakawa, Miyazaki, Tayama, and Kuroda (1992), Hashimoto, Tayama, Miyazaki, Mu-

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rakawa, and Kuroda (1993), Hashimoto, Tayama, Miyazaki, Murakawa, Shimakawa, et al. (1993), Holttum, Minshew, Sanders, and Phillips (1992), Kleinman, Neff, and Rosman (1992), and Piven et al. (1992) did not replicate these findings in a total of 111 male and 21 female AD subjects, ages 2 to 53 years. Courchesne et al. (1994) subsequently reported two subtypes of vermal abnormality in AD: hypoplastic and larger (hyperplastic), the combination of which within the other AD study cohorts apparently produced the reported "normal" areas. Courchesne, Townsend, and Saitoh (1994) then reanalyzed the results published in Courchesne et al. (1988, 1994), Kleinman et al. (1992), and Piven et al. (1992) (totaling 78 AD patients) and noted smaller vermal VI–VII areas in the collective cohort, 87% with vermal hypoplasia and 13% with hyperplasia. Most recently, Hashimoto et al. (1995) noted vermal lobules I–V, VI–VII, and VIII–X were all significantly smaller in 102 AD patients, ages 3 months to 20 years.

Cerebral Hemispheres

Gaffney, Kuperman, Tsai, Minchin, and Hassanein (1987) and Piven et al. (1992) reported that the cerebral hemispheres in AD were similar, and larger in midsagittal area, respectively, and Filipek, Richelme, et al. (1992), and Piven et al. (1995) reported larger total cerebral volume in AD. Filipek, Richelme, et al. (1992) noted that the larger hemispheric volumes (in 29 AD children, ages 6–11 years) were localized to the temporal and posterior parietal-occipital regions, and limited to only white matter (the connections between nerve cells) without differences in cerebral cortical volumes (the nerve cells themselves). In contrast, Courchesne, Press, and Yeung-Courchesne (1993) reported visual (qualitative) loss of tissue in the parietal lobe (atrophy) on single selected MRI slices in 33% of AD patients, ages 6–32 years.

Individual cerebral structures have been evaluated as well. Filipek, Richelme, et al. (1992) noted that the thalamic area and lenticulate (part of the basal ganglia) were larger in the AD children than in controls, with similar volumes noted of the ventricles, cerebral cortex, and caudate. These investigators also reported that the corpus callosum, which connects the two cerebral hemispheres, was similar in area, whereas Egaas, Courchesne, and Saitoh (1995) noted that it was smaller in AD. The limbic system, implicated in neuropathologic studies by Bauman and Kemper (1994), includes the hippocampus and amygdala, as well as other structures. Saitoh, Courchesne, Egaas, Lincol, and Schreibman (1995) found areas of the posterior hippocampus (including the subiculum and the dentate gyrus), and Filipek, Richelme, et al. (1992) noted volumes of the total hippocampus and amygdala to be similar in AD patients and controls.

WHY ARE THESE COLLECTIVE FINDINGS SO INCONCLUSIVE?

To answer this question, one must consider the following: the choice of autistic patient and control cohorts, the MRI scanning protocols, and image analysis methods used across these collective studies: *Who is studied? Who is the comparison group? How are they scanned? What is being measured and how is it measured?*

These collective ASD cohorts are heterogeneous with respect to age, gender, IQ, and neuropsychological and behavioral parameters. They were not uniformly matched to the collective controls on these variables. In addition, some studies used medical controls with "normal" MRI scans obtained for clinical reasons, including seizures, while others used normal control volunteers (Filipek, Kennedy, & Caviness, 1992; Filipek, 1995).

The collective studies represent vastly differing protocols for MRI scanning, with variable MRI slice thickness, orientation, and position. MRI slices can be obtained from 1–10 mm in thickness. The anatomy seen on any given two-dimensional (2D) slice represents the averaged anatomy through the thickness of that slice (e.g., volume averaging). Therefore, the anatomy on three contiguous 3-mm slices will be more accurate than on a single 9-mm slice. Some scanning methods produced variable interslice gaps, where the brain is not imaged, while others produced thin contiguous slices. The MRI slice orientation and position also contribute to neuroanatomic variability, and single selected slices may significantly differ across subjects (Filipek, Kennedy, & Caviness, 1992; Filipek, 1995).

The studies also represent a combination of qualitative and quantitative image analysis methods, without uniform anatomic definitions. It is not surprising, therefore, that the collective combination of measures of length, width, or area on a single selected slice, 3D volume interpolated through interslice gaps, and 3D volumes on thin contiguous slices, all performed with variable anatomic definitions, have produced heterogeneous results that often appear conflicting, but cannot be directly compared (Filipek, Kennedy, & Caviness, 1992; Filipek, 1995).

WHERE SHOULD NEUROIMAGING RESEARCH IN ASD GO FROM HERE?

Future studies require larger samples, should be limited to specific ages, have improved neuropsychological and behavioral profiles, and use normal controls who are matched to the autistic patients for age, gender, and IQ. Matched comparison groups with other developmental disorders should also

be considered in study designs. Comparable MRI scanning protocols across study sites, using contiguous thin MRI slices, quantitative instead of qualitative analyses, and comparable anatomic definitions will help to reduce the current highly variable results (Filipek, Kennedy, & Caviness, 1992; Filipek, 1995).

Despite these factors, current data justify the continued use of quantitative MRI in the study of ASD. Simultaneous structural and functional MRI studies are now possible, and recent methods for cortical parcellation (Rademacher, Galaburda, Kennedy, Filipek, & Caviness, 1992) will improve neuroanatomic localization and individualized anatomic templates for functional imaging studies. Sequential studies in ASD and normal children may further elucidate both normal and abnormal developmental trajectories in the brain. Such future methodological refinements may even eventually assist in identifying structural correlates of subtypes of ASD.

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