Clinic Perspective

MRI of Autistic Brain Structure and Function

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Abstract

Autism is a complex development disorder defined by particular behaviors, with symptoms generally seen in three areas: deficient sociability, rigid behavior, and impaired communication skills. Early neuroimaging research focused on identifying anatomical differences between the brains of autistic versus non-autistic individuals. More recent work has emphasized the identification of functional brain areas involved in specific cognitive and social behaviors. Over the past decade, magnetic resonance imaging (MRI) has played a key role in quantifying characteristics of brain structures that possibly play roles in autism. MRI has proven extremely successful in providing functional information about brain activation and the functional connectivity of different brain regions, information that may help shed light on the neurophysiological complexities of autism etiology. *[N A J Med Sci. 2009;2(2):44-47.]*

Introduction

Autism is a widespread development disorder affecting about one percent of children in the U.S., and affecting four times more boys than girls.[1] Autism is a complex disorder that varies greatly among individuals, but speech delays, behaviors differing from the norm, and difficulties with social interactions are prevalent symptoms. The severity of autism's impact on cognitive functioning varies widely, with individual cognitive abilities ranging from profoundly delayed to gifted. Although its etiology is largely unknown, a family history of autism in a parent or sibling is a known risk factor. Autism symptoms typically appear by age three, and they generally persist throughout life, presenting lifelong challenges to the affected individual.

Symptoms of autism are typically seen in three areas: deficient sociability, rigid behavior, and impaired communication skills. Because autistic behaviors tend to appear in identifiable symptom groups, early neuroimaging research focused on identifying anatomical differences between the brains of autistic versus non-autistic individuals. These efforts yielded a vast amount of information about the structures of many brain regions, including the limbic system, cerebellum, cerebral cortex. More recent work has emphasized the identification of *functional* brain areas involved in specific cognitive and social behaviors.

Over the past decade, magnetic resonance imaging (MRI) has played a key role in quantifying the size, volume, hemispheric asymmetry, and signal intensity of various anatomical brain structures that possibly play roles in the etiology of autism. Moreover, MRI has provided functional information about brain activation and the functional connectivity of different brain regions. Recent functional MRI (fMRI) studies have shown specific brain regions that are activated in response to cognitive, motor, or auditory stimuli, and diffusion tensor imaging (DTI) has revealed abnormalities in the cortical networks of the brains of individuals with autism. Below, we review some of the more recent findings from structural MRI, fMRI, and DTI studies on autism.

Structural Magnetic Resonance Imaging

Structural MRI has revealed important information on the anatomical underpinnings for autism. A recent MRI study of 77 children with non-syndromic ("classic") autism found that 48% of subjects had abnormalities in their brains.[2] One common finding in MRI studies of brain structure is that autistic children tend to have larger brains[3]—about 5–10% larger—than normal children. Work also shows that people with autism have greater cerebellar and caudate nucleus volumes, but a smaller corpus callosum volume.[4,5] Because children with autism have difficulties with communication and dealing appropriately with social situations, and they show repetitive behavior, several researchers suggest that regional brain connectivity may play an important role in the pathophysiology of autism. This makes the autistic brain a natural target for connectivity research.[6] In addition, research indicates that the frontal lobes, the amygdala, and the cerebellum are abnormal in autistic individuals. The amygdala is a component of the limbic system that is important in regulating affective social responses, including

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fear; thus, it is particularly interesting that the amygdala is abnormal in individuals with autism. Although a large body of research has been conducted on patients with autism, there are large variations from patient-to-patient, and no clear pathology has been found that explains the disease.[7]

Mosconi et al.[8] studied children aged 2–4 with autism, and found an enlarged amygdala in autistic children compared to controls at age 2 and age 4. Because amygdala volume has been linked to the process of joint attention, the authors suggest that the amygdala may be responsible for a core deficit in autism. Webb et al[9] found that autistic children had reduced total cerebellar vermis volumes compared to controls. Since the cerebellar volume measurements did not correlate with the severity of symptoms or with IQ scores, it is unclear if there is any relationship between cerebellar structure and autistic symptoms. Freitag et al.[5] found that total brain volume, gray matter volume, and white matter volume were all greater in young adult and adolescent autistic patients than controls, but that the corpus callosum volume was lower than in controls. The authors also found that the posterior region of the corpus callosum was thinner in patients with autism than in controls. Toal et al.[10] found that adult autistic subjects had less gray matter in their temporal lobes and in their cerebellum, but more gray matter in their striatal regions, than controls. A smaller volume of gray matter in frontal and occipital lobes was also found in autistic subjects that had psychosis, and the volume of gray matter was found to be smaller in the right insular cortex and the bilateral cerebellum extending into the fusiform and lingual gyri.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI), which measures brain activity in response to specific tasks or stimuli, has been used to increase our understanding of autistic brain function. Recently, studies on autism have focused on functional brain connectivity—the extent to which different parts of the brain are correctly connected to one another. In general, they report reduced interregional coordination, or under-connectivity within the brain. The extent of under-connectivity in many brain areas has been studied using various cognitive tasks, and has been associated with numerous cognitive and behavioral deficits seen in autism.

Noonan et al.[11] used fMRI with a source-recognition task to study whole brain connectivity with the following three cerebral cortices: left middle frontal, left superior parietal, and left middle occipital. They found that fMRI patterns in these areas were largely similar in high-functioning autistic subjects compared to controls, but that they were more extensive in the autistic subjects. The authors suggest that autistic subjects have deficits in task-specific network connections.

Using multiple statistical analytic methods, Solomon et al.[12] showed that, compared to controls, adolescent patients with autism showed less functional connectivity and network integration between the frontal, parietal, and occipital brain regions. Reduced fronto-parietal connectivity in autistic subjects was associated with symptoms normally associated with ADHD. Monk and colleagues[13] used fMRI to study the intrinsic connectivity within the default network comprised of the hippocampus, para-hippocampal region, and frontal lobe in patients with autism. Compared to the control group, autistic subjects showed the following: (1) less connectivity between the posterior cingulate cortex and superior frontal gyrus and (2) more connectivity between the posterior cingulate cortex and both the right temporal lobe and right parahippocampal gyrus. Weaker connectivity between the posterior cingulate cortex and the superior frontal gyrus in autistic subjects was correlated with poorer social functioning, and stronger connectivity between the posterior cingulate cortex and right parahippocampal gyrus was correlated with behaviors that were more restricted and repetitive. The autistics subjects generally showed weaker intrinsic connectivity in the default network, which was related to specific behavioral and cognitive symptoms.

fMRI has detected differences in neural functioning between autistic and control individuals even when no behavioral differences were seen. Tesink[14] measured neural functioning with fMRI and compared these data with the integration subjects could perform with information from spoken voices. They presented autistic and control individuals with two types of spoken sentences: in one sentence type, sentences had meanings that were congruent with inferences provided by voice about the age, gender, or background of the person speaking (speaker congruent); in the other sentence type, sentences had meanings that were incongruent with voice-provided information (speaker-incongruent). Behavioral data from the autistic and control groups were indistinguishable, however the autistic subjects had increased activation of the right inferior frontal gyrus of the frontal lobe when given speaker-incongruent sentences compared to speaker-congruent sentences. The right inferior frontal gyrus, which is known as Brodmann area 47, is involved with processing verbal information.

Motor deficits are common in patients with autism. The neural underpinnings of these motor deficits are unclear. Understanding the cause of these early appearing deficits in autistic children may provide insight into the neuropathologies associated with abnormal behaviors that are part of the development of higher-order social and communications skills. Mostofsky et al.[15] found that high-functioning autistic children showed greater activation in the supplementary motor area (SMA) than controls, whereas controls showed greater activation in the cerebellum. In addition, children with autism showed lower connectivity in the primary motor pathway. The authors suggest that the decreased activation of the cerebellum in the subjects with autism may reflect difficulties with shifting motor execution, and that the decreased connectivity may be associated with compromised circuitry for automating patterned motor behavior. These results add insight to our understanding of the deficits found in the development of motor skills in

autistic children, which might also be associated with deficits in their social and communication skills.

Dysfunction of the amygdala may also play an important role in autism-related impaired social skills. Kleinhans et al.[16] used fMRI to monitor changes in activation of the amygdala and the fusiform gyrus in response to facial stimuli in adult subjects with autism compared to controls. The autistic subjects showed less habituation than the controls did. Among individuals with autism, lower levels of habituation were related to greater social impairment. The authors suggest that activation of the amygdala in response to socially relevant stimuli may contribute to social impairment in subjects with autism.

Diffusion Tensor Imaging

Deficits in social communication and relationships are common characteristics of autism. Based on the premise that autism is a disorder of cortical networks instead of discrete cortical regions, research has suggested that abnormal connections may contribute to the social impairment seen in autism.[17] Cortical under-connectivity may result in deficits in the integration of various cognitive processes. Thus, the cognitive deficits seen in autistic individuals might involve an inability to successfully synthesize multiple cognitive inputs.[17] Information about the physical structure of cortical networks can be gathered by a type of MRI called diffusion tensor imaging (DTI). DTI measures the diffusion of water molecules in the brain to provide information about the structure of white matter, based on the amount of water diffusion restriction (given by the apparent diffusion coefficient, ADC) and the direction of water diffusion (given by the fractional anisotropy, FA). DTI is a very sensitive means of assessing white matter maturation. Abnormalities in myelination, axonal number, axon diameter, and axon orientation all cause changes in FA and ADC values.[17,18]

Ke and colleagues[19] used a combination of DTI and T1-weighted MRI to study white matter abnormalities in children with high-functioning autism. White matter densities were measured to be lower in autistic individuals than in controls in the right medial frontal gyrus, left precuneate nucleus, left supramarginal gyrus, and right anterior cingulate gyrus. The authors also found lower white-matter density in the right frontal precentral gyrus, left precuneate nucleus, and left cingulate gyrus in autistic subjects. Fractional anisotropy is an index of the extent to which structures are aligned. Fractional anisotropy in the frontal and left temporal lobes was observed to be lower in autistic subjects than in controls.

Thakkar et al.[20] studied the structure and function of the anterior cingulated cortex during response monitoring to see if they were associated with the repetitive behaviors that are characteristic in autism. Anterior cingulated cortex activation was measured in response to correct and erroneous eye movements in response to a stimulus. The authors also looked at the integrity of the white matter microstructure in the anterior cingulated cortex using DTI to measure the fractional anisotropy. Autistic subjects showed a reduced FA and increased activation on correct trials, and reduced FA and diminished activation with repetitive behavior. The authors suggest that repetitive behaviors often seen in autism may be in part related to abnormalities in the structure and function of the anterior cingulated cortex.

Sundaram and colleagues[17] found that relative to controls, young autistic children had higher ADC values in the frontal lobe, and higher ADC values in both short- and long-range association fibers. They also found that young autistic children had lower FA in short-range fibers but not in long-range fibers. The numbers of fibers in the frontal lobe were similar in both groups. Long-range, frontal-lobe association fibers were longer in the autistic subjects. The authors suggest that the abnormal FA and ADC values found in the frontal lobe of young autistic children might be caused by disorganization in the white matter. Lee et al.[21] found that regions of the temporal lobe are abnormal in patients with autism. They performed DTI measurements of white matter in the superior temporal gyrus (STG) and temporal stem (TS) in autistic and control subjects. In the brain regions studied in subjects with autism, fractional anisotropy was significantly lower, mean diffusivity was significantly higher, and mean radial diffusivity was significantly higher.

Summary

In conclusion, MRI is a powerful tool for the evaluation of brain structure and function in autistic individuals. The advantages MRI offers to the study of autism include the following: (1) it is non-invasive; (2) it involves no ionizing radiation; (3) it can safely be used for repeated measurements over time in an individual; (4) it provides structural measurements with high spatial resolution; and (5) it can provide *functional* measurements of neurophysiological processes with high spatial and *temporal* resolution. MRI can provide details about the functional neurophysiology of people with autism; it can also be used to evaluate the efficacy of, and to stage the progress of behavioral, educational, dietary, and biomedical treatments for autism. Great gaps remain in our understanding of how neuroanatomy, neurophysiology, and genetics interact to contribute to the behaviors associated with autism. For example, why are the brains of autistic children larger than normal, and what significance does this have for cognitive functioning and behavior? Recent work has found that monoamine oxidase A (MAOA) can influence the size of the cerebral cortex, as measured by MRI.[22] MAOA is an enzyme that breaks down important neurotransmitters in the brain, including serotonin, dopamine, epinephrine, and norepinephrine. Changes in neurotransmitter levels are involved with autism. For example, autistic individuals generally have elevated serotonin levels, and changes in serotinin levels, as influenced by abnormal MAOA levels, may contribute to the increased size of the cerebral cortex seen in autistic children.[22] This increased brain growth, in turn, may interfere with the normal modeling of brain networks, leading to cognitive abnormalities and resulting behavioral issues. This is an example of how a causal cascade connecting genes, enzymes, neurotransmitters,

neuroanatomy, cognitive functioning, and behavior can contribute to the disease. Discoveries such as these will continue to rely on the high structural and functional resolution provided by MR imaging, in combination with genetic, neurotransmitter, developmental, and behavioral data. Such discoveries will lead to the development and testing of new treatment strategies. The application of MRI to the study and treatment of autism holds great promise to expand as a technological tool in the study of this widespread disease.

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