Review

Developments of Neuroimaging in Autism: Aims in approaching a Diagnostic Fingerprint

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This review focuses on developments and ongoing advances in neuroimaging research that help to characterize the structural and neuronal phenotype of autism. Autism is a disorder in which early diagnosis is paramount in order to intervene and initiate therapies early. While there are limitations to current diagnostic modalities, a variety of neuroimaging techniques are emerging as possible objective means in providing an early bio-marker for the diagnosis of autism in those at risk.
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INTRODUCTION

Autism spectrum disorders, as currently defined by the DSM-IV (Diagnostics and Statistics Manual of Mental Disorders 4th edition)[1] criteria are a group of neuro-developmental disorders that impact a child's social and communication skills with repetitive mannerisms, interests and often restricted adherence to routines. Advances in this heterogenous disorder has been challenging due to the inability to link the onset of the disorder to any one gene or environmental trigger. The CDC (Center for Disease Control) now estimates a 1 in 88 prevalence of autism spectrum disorders. It is unclear now how this number will be affected with the upcoming change in the diagnostic criteria in 2013 as outlined by the DSM V.

The single known best tool in altering the course of this disorder is early intervention and initiation of therapies. It follows that early diagnosis is imperative to improved long-term outcome. The total annual societal per capita cost of caring for and treating a person with autism in the US has been estimated to be about $3.2 million and approximately $35 billion for an entire birth cohort of people with autism. The total lifetime cost could range from $13 billion to $76 billion. Literature shows that people with autism spend twice as much as the typical American over their lifetimes and spend approximately 60% of those incremental direct medical costs after 21 years of age.[2] These costs will continue to rise with the increase in prevalence.

In 1987 Lovaas showed that the earlier the intervention, the greater the impact on cognitive and social functioning which has been confirmed in later studies and randomized control trials.[3,4,5] The positive effect of early intensive behavioral intervention as well as the difference in early presentation of autistic feature onset leads to the understanding of autism spectrum disorders as a group of disorders marked by plasticity and heterogeneity.[4,6] Atypical markers for autism such as impairments in visual tracking, eye contact, social interest, orienting to name, etc. are present at as early as 12 months of age.[4,7,8,9] However, clinical testing of early onset of autistic features are currently experimental in children less than 18 months of age.[8,10,11] In addition to decreased sensitivity and specificity of clinical tests in early infancy, there is also instability of the diagnosis in children younger than 30 months of age.[8] In the search for an objective diagnostic phenotype, potential advances in neuroimaging may in the future be utilized to aid in the earlier diagnosis of autism when concerning developmental indicators arise.

STRUCTURAL MRI

Structural MRI studies have contributed to the current understanding of the neuroanatomical phenotype of autism. Reports have indicated an onset of increased white and gray matter cortical volume in autistic subjects 2-4 years of age that may be tied to the onset of the core features of autism that occur around that age.[12,13,14] Volume differences have been seen with age related enlargement of the caudate nucleus[15] the amygdala[12,16] reduced size of the corpus callosum[17,18,19] with variable and inconsistent findings in volume size of the cerebellum, brainstem and hippocampus.[12,14,18,20,21]

FUNCTIONAL MRI

While the early increase in grey and white matter volume provides supporting evidence for abnormalities in connectivity pathways, it is functional neuroimaging that has added insight to the differences in connections between cortical regions that exist in autism.[22,23] Functional MRI (fMRI) provides information regarding the functional organization of cognitive changes and has shown changes in

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this organization in children with autism. FMRI techniques have been used to examine the neural bases of social cognition and facial processing. For example, differences in activation during theory of mind tasks including decreased activation of frontal cortical components, decreased amygdala and increased superior temporal gyrus activation are seen in individuals with autism. These differences suggest that dysfunction of the amygdala results in failure of emotional and mental state processing in autism and a reduction in frontal activation results in deficits of executive function.[24] Facial processing in individuals with autism is also effected as elucidated by fMRI studies. During facial recognition in typical subjects, activation has been seen in the right fusiform gyrus.[25,26] Schultz reproduced this finding in controls showing that levels of activity in the right fusiform gyrus were increased during facial recognition while there was increased activity observed in the inferior temporal gyri during object processing. In the study group with autism and Asperger's syndrome, there was significantly less right hemisphere fusiform gyrus activation and instead, more right inferior temporal gyrus activation in response to facial recognition.[27]

Executive functioning tasks have shown less robust activation in brain regions in autistic individuals compared to controls. In one study by Ring et al. that performed fMRI during an embedded figure task showed activation of areas of the mesial temporal gyrus and inferior temporal gyrus, the supramarginal gyrus and precuneus, the inferior frontal gyrus and the middle occipital gryus in both the study and control groups. The control group however demonstrated greater activation in the right dorsolateral prefrontal cortex and bilateral parietal cortex than the autistic study group. The authors therefore postulated that subjects with autism rely on visuospatial feature analysis rather than working memory, while controls rely more on working memory when performing the embedded figure task.[28] In a planning and execution motor task by Muller analysis found activation in the contralateral perirolandic cortex, basal ganglia and thalamus, bilateral supplementary motor area and ipsilateral cerebellum for both control and autism groups. Activation was less pronounced however in the autistic study group. These brain imaging studies have shown that people with autism show less activation in regions related to higher level cognition and more activation in the regions associated with lower level cognition when compared to controls.[29]

Table 1. Summary of Task-based fMRI techniques in autism.

Author	Published time	Study Size	Children Adolescents or Adults	Task Category	Encephalic Region	Increased or Decreased Activation
Baron Cohen et al.	1999	N=18	Adults	Theory of Mind	Left inferior frontal gyrus Left Amygdala ---------- Bilateral Superior temporal Gyrus	Decreased --------- Increased
Schultz et al.	2000	N=28	Adults	Facial Processing	Right Fusiform Gyrus ---------- Inferior Temporal Gyrus	Decreased --------- Increased
Ring et al.	1999	N=18	Adults	Executive Functioning	Bilateral Parietal Cortex Right Dorsolateral prefrontal cortex ---------- Right occipital cortex Right Inferior Temporal Gyrus	Decreased --------- Increased
Muller et al.	2001	N=16	Adults	Planning Motor Tasks	Contralateral Perirolandic Cortex, Basal Ganglia, Thalamus, Bilateral Supplementary Motor Area and Ipsilateral Cerebellum	Decreased
Just et al.	2004	N=34	Adults	Language Sentence Comprehension	Left Inferior Frontal Gyrus ---------- Left Superior Temporal Gyrus	Decreased --------- Increased
Koshino et al.	2005	N=27	Adults	Working Memory Tasks	Left dorsolateral prefrontal Cortex Left inferior frontal gyrus Left posterior precentral sulcus ---------- Right inferior parietal lobe Left inferior Temporal, Left temporal, Right temporal, Left inferior Extrastriate	Decreased --------- Increased

Functional MRI in a study by Just et al. during language and sentence comprehension tasks further supported the growing view that autism was a disorder of functional connectivity with decreased synchronization in specific cortical areas compared to controls. The authors conclude that there is a disruption in the coordination or integration of cortical circuitry making particular tasks such as social interaction, which requires high demands on information integration, deficient in individuals with autism.[23] Again, patterns found in fMRI studies have supported that subjects with autism prefer visually based processing styles with more activation in the posterior brain regions while there is less activation in the anterior cortical regions during memory and language tasks.[30] There appears to be greater processing of information in the right hemisphere compared to the left indicating use of nonverbal strategies in information processing in the autistic population.[30] Task Based functional MRI techniques (**Table 1**), while valuable, require active participation by the subject and are less suited for studies in infants and toddlers.[14]

Resting fMRI studies have demonstrated differences in the default neuronal circuitry when the brain is at rest. The fMRI studies in autism previously described were performed in the context of a cognitive social or non-social task. However, when the brain is not engaged in any task, the brain is still active. The regions involved in the default network include the posterior cingulate cortex, retrosplenial, lateral parietal/angular gyrus, medial prefrontal cortex, superior frontal gyrus, regions of the temporal lobe and the parahippocampal gyrus.[31] It is unclear what the exact function of this activation is, however it is speculated that it may be involved in the homeostasis of excitatory and inhibitory neuronal function.

Results of resting fMRI studies in adults with autism have been variable. Underconnectivity was found between anterior and posterior regions along with medial structures including the anterior cingulate and posterior cingulate cortices in a study by Cherkassky et al. involving 57 adults with high functioning autism compared with age and IQ matched controls.[32] In a more recent study in adults with ASD (autism spectrum disorder), it was found that compared to controls, the ASD group showed weaker connectivity between the posterior cingulate cortex and superior frontal gyrus and a stronger connectivity between the posterior cingulate and the right temporal lobe as well as right parahippocampal gyrus. Interestingly, in this study the poorer the social functioning, the weaker the connectivity between the posterior cingulate cortex and the right superior frontal gyrus. Repetitive and restricted behaviors correlated with stronger connectivity between the posterior cingulate cortex and the right parahippocampal gyrus.[33] In examining adolescents with ASD, Weng et al. found decreased connectivity between the posterior cingulate cortex and the superior frontal gyri, the temporal lobes and the parahippocampal gyri. This weaker connectivity also correlated to social impairment. The repetitive behaviors, in contrast to findings in adults with autism correlated with weaker functional connectivity between the posterior cingulate cortex, the prefrontal gyri, the temporal lobes and the parahippocampal gyri. They attributed this difference to a dramatic change in the relationship between the default network and the repetitive behaviors.[31]

In further investigating the striatum during the resting state in school-aged children with Autism, Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified, it was found that there was excessive as well as aberrant functional connectivity in striatal-cortical circuitry compared to typically developing controls.[34] In toddlers with autism during natural sleep, resting fMRI has shown significantly weaker inter-hemispheric correlations in the inferior frontal gyrus and superior temporal gyrus regions compared to typically developing and language delayed controls; again, specifically areas which are known to be associated with language production and comprehension. It appears that synchronization and functional connectivity are disrupted early in autism development as supported by fMRI studies.[35]

PET AND SPECT

Functional neuroimaging such as positron emission tomography (PET), and single photon emission computed tomography (SPECT) give insight to cortical activation during rest or during a performance task. Studies involving both SPECT and PET scans have detected bitemporal hypoperfusion in the superior temporal gyrus in autistic subjects.[22] During functional activation studies, in both PET and SPECT scans, there is more activation of the right hemisphere than the left during verbal auditory stimulation again supporting the idea of the use of aberrant neural circuitry in the processing of verbal information in autistic individuals.[22,29]

MEG

Recently, MEG (magnetoencephalography), which has typically been used in identifying epileptogenic foci in epilepsy, has been introduced in studying possible neural markers for autism. Similar to an EEG (electroencephalogram) MEG measures neural electrical activity; however, it uses MRI technique to measure the magnetic fields produced by the electrical activity. Using MEG to measure auditory evoked responses, studies have shown delayed latency of M100 in response to a tone stimulus in subjects with autism.[36,37,38] This finding appears to be specific to autism and not just a feature of language delay and impairment.[39]

DTI

Another neuroimaging technique, diffusion tensor imaging (DTI), has also given insight into the connectivity of neural pathways in autism. Specifically, white matter provides the physical foundation for corticocortical and cortico-subcortical connectivity. DTI is a visualization of white matter tract integrity in vivo. Areas of white matter disruption have been shown in autism with significantly reduced fractional anisotropy (FA), a measure of structural integrity. In a study by Barnea-Goraly et al. reduced FA values were seen adjacent to regions of the brain which are activated during social and emotional processes such as facial recognition including the fusiform gyrus, the superior

temporal sulcus, anterior cingulate, amygdala and ventromedial prefrontal cortex. Also, disrupted white matter integrity was seen in regions required for theory of mind tasks such as the ventromedial prefrontal cortex, anterior cingulate, temporoparietal junction and its connection to the extrastriate region, the superior temporal sulcus and amygdala. In addition, decreased FA was found in the corpus callosum, which is postulated to impair executive functioning, and sensorimotor processing.[40] Further, these structural differences are seen over time when compared with age matched controls. Reduced FA has been seen in areas crucial in interhemispheric connectivity including the posterior midbody/isthmus of corpus callosum, left and right anterior corona radiata near the genu of the corpus callosum, right anterior corona radiata/forceps minor and right retrolenticular portion of the internal capsule over an age range of 10-35 years where FA, although increasing over time does not reach that of controls.[41] This confirms there is an abnormal neuronal developmental trajectory in autism.

While abnormal white matter integrity in the autism population has been demonstrated in the literature, the application of tract-based spatial statistics has given further understanding of the aberrant long range neural connections. In a study by Shukla, reduced fractional anisotropy and increased mean diffusivity were seen in the corpus callosum, anterior and posterior limbs of the internal capsule, inferior longitudinal fasciulus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, cingulum, anterior thalamic radiation and corticospinal tract in the autism group compared with controls.[42] In the further aim for determining the presence of a specific autistic neural phenotype, Jou et al. suggest there are several long-range fiber tracts that are affected in autism; specifically the inferior fronto-occipital fasciculus and superior longitudinal fasciculus are most severely affected.[43] The inferior fronto-occipital fasciculus has been known to connect directly to the fusiform gyrus as well as give connections between the frontal, temporal, parietal and occipital lobes. Disruption of this connection results in impairments in the ability to properly identify and recognize facial emotions.[44] The superior longitudinal fasciculus connects areas of the temporo-parietal cortex to areas of the frontal lobe and functions to regulate motor behavior, aid in working memory and auditory information processing. It is specifically these long-range fiber tracts that are used in social information processing and language and communication skills that are impaired in autism.[43]

The above has illustrated the aberrant development of white matter and connectivity in the autistic population through neuroimaging and describes the abnormal developmental trajectory that corresponds with autistic symptoms. However are there any indicators prior to onset of symptoms when it is so crucial to diagnose early? More recently a prospective study that performed DTI sequences on high-risk siblings of individuals with autism at 6, 12 and 24 months showed statistically significant higher fractional anisotropy at 6 months of age in those who developed autism followed by a more attenuated developmental trajectory resulting in a lower fractional anisotropy by 24 months compared to those high risk individuals that did not go on to develop autism.[45] Fiber tractography indicated while lower at 6 months, the rate of change in FA from 6 to 24 months was significantly greater in the ASD-negative group in the corpus callosum, bilateral fornix, association tracts including the inferior longitudinal fasciulus and uncinate as well as projection tracts such as the left anterior thalamic radiation and internal capsule compared to the ASD positive group. This blunted developmental trajectory in white matter integrity is suggested to begin prior to the onset of clinical features in the autistic population. While it is the abnormal trajectory demonstrated over time, which is more difficult to illustrate in a single study, it may be a potential area of monitoring in high-risk siblings. This study implicates that the aberrant development of neural connectivity as seen by DTI can precede the manifestations of autistic symptoms in the first year of life.

Table 2. Neuroimaging Techniques used in Autism.

Structural MRI	Increased white and gray matter cortical volume, enlarged caudate nucleus, amygdala, decreased size of corpus callosum
Functional MRI	Decreased synchronization, Bias towards lower level perceptual functioning, more visually based processing
PET	Bitemporal hypoperfusion, increased activation of right hemisphere during verbal auditory stimulation
SPECT	Left hemispheric dysfunction
MEG	Abnormal auditory cortex maturation, delayed latency of M100 in response to a tone stimulus
DTI	Aberrant neural connectivity, decreased white matter tract integrity, significant reduction in fiber tract fractional anisotropy and increased mean diffusivity

CONCLUSION

The promising developments and advances in newer neuroimaging techniques (**Table 2**) reinforce the conception of autism as a disorder of neural connectivity that is pervasive among multiple networks and not localized to any one specific brain region. The heterogeneity of this disorder makes diagnosis a challenge. Attempts to give objective diagnostic determinations are limited by the age at which these tests are valid. This is particularly problematic when early diagnosis is crucial to improved developmental outcome. Current neuroimaging studies shed light on

evidence of potential critical time periods of abnormal white matter pathway development, which may give insight to the pathogenesis of autism prior to the onset of symptoms. Further goals to depict the onset of neural abnormalities may also help in illuminating the mechanisms underlying them as well as give optimal opportunity for intervention.

CONFLICT OF INTEREST

None.

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