A Review on the Cognitive Neuroscience of Autism

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Abstract.

With increased recognition in the media, heightened prevalence, and advances in research technologies, investigation into the causes of autism has broadened in recent years. Studies at the molecular, structural, and behavioral levels have resulted in significant findings, linking autism to qualitative differences in neurological function and an alteration of early development. Familial aggregation of autism demonstrate a strong genetic factor, although genetics can not completely account for its pathogenesis. Studies show autism having one of the most complex pathologies among neurodevelopmental disorders. Future studies applying sophisticated methodologies in new areas may shed light on current mysteries surrounding the disorder.

Introduction.

Autism is a pervasive neurodevelopmental disorder, primarily encompassing difficulties in the social, language, and communicative domains. Diagnosis is usually made within the first 2-3 years of life, from behavior such as lack of eye contact, joint attention, imitative behavior, and nonresponsiveness to speech. Other identifiable features are similar to that of related conditions, such as repetitive behavior and inattention seen in obsessive compulsive disorder and attention deficit disorder, respectively. Common secondary mood disorders including anxiety and depression are also seen.

Recognition of autism by the general public as well as clinicians and researchers has increased in recent years. In addition to media attention, this has been largely due to increased prevalence, with reported rates as high as 60/10,000[67]. Considered by some to be an epidemic, increased rates have been largely attributed to both heightened awareness of the condition as well as modifications to diagnostic criteria to define autism as a spectrum disorder, with a wide range of individual functioning[147]. On one end of the spectrum, individuals with low functioning autism (LFA) often are afflicted with severe behavioral difficulties, mental retardation and seizures, and require dependent care into adulthood. On the other end, individuals with high functioning autism (HFA) and its variants such as Asperger's syndrome (AS) have more subtle difficulties and sometimes can function independently. The majority of individuals diagnosed with autism are male, causing some to attribute the skewed ratio to genetic factors, or on the other hand, to a more subtle autistic profile in females[7].

Since its recognition by Leo Kanner in 1943[68], etiological research of autism has resulted in a wide range of theories. Early theories such as Bettelheim's[19] notion of "refrigerator mothers", have long since been dismissed, with modern theories categorizing autism as a neurodevelopmental disorder. Although there is a high concordance of identical twins with autism, finding the specific genetics markers of autism still remains a difficult task, with multiple candidate genes[96]. Current cognitive theories focus on functions primarily mediated by the frontal lobes, including theory of mind, weak central coherence, and executive dysfunction as primary areas of deficit. Biologically grounded theories implicate abnormalities in structures such as the cerebellum, amygdala, hippocampus, and the basal ganglia. Researchers have also found gross developmental abnormalities, such as increased total brain volume (TBV) and abnormal connectivity of white matter tracts. Many developmental disorders have patterned dysmorphologies, such as in the facial features of Willliam's and Down's Syndromes. However, in autism, dysmorphologies outside the neural substrate have been found to be subtle or

nonexistent, with limited findings in features like reversed second to fourth digit ratio[80, 85] and posterior ear rotation[118].

Cognitive Theories.

Theory of Mind.

One of more common social-cognitive theories of autism is based on Theory of Mind (ToM), the 'mentalizing' ability needed to infer that others have their own beliefs and desires in order to understand their behavior. Used as a basic measure of social intelligence, ToM is usually acquired by 3-4 years of age[146], and is generally correlated with language ability in both normally developing children[18] and autistic populations[132].

Behavioral studies have shown that individuals with autism, depending of level of functioning and age[132], often have delayed development of[11], or a qualitatively dissimilar[11, 126] ToM. In a PET study of adults, differences in regions of activation have been shown in a story based ToM paradigm, with task-related activation in medial prefrontal cortex in normal controls[48], and in a more ventral frontal region in subjects with Asperger's Syndrome[54]. These results suggest a qualitative rather than quantitative difference in the neural response to mental state tasks. The neural differences may be due to the atypical development of ToM in the autistic adults, where related social abilities are often learned at an intellectual level late in development rather than at an intuitive level in the early stages of childhood, thus causing regional differences in the cortical responses to ToM tasks.

An important ability needed to develop ToM is to infer another's emotions from facial expression. In addition to the abovementioned story based ToM paradigms, studies have also been conducted illustrating difficulty in inferring emotions in the eyes among adult autistic subjects[13, 72]. In similar tasks of emotional inference, fMRI evidence enhances this distinction, showing decreased activation of the amygdala and increased activation in the superior temporal gyrus[14], areas classically implicated in emotional perception and language comprehension. Since the subjects in these studies were instructed to look at images of eyes, a dysfunction at the sensory level of lack of eye contact can not account for the autistic subjects' performance. However, a lack of eye contact is a common feature of autism, in adults and children alike, and further confirmed in eye tracking studies, showing decreased attention on the eyes and increased attention on the mouth[73] or surrounding environment[139]. It is quite likely that a lack of attention on socially relevant stimuli during early childhood hinders proper social development, and consequently affects higher level social abilities such as ToM.

Executive Dysfunction.

'Executive functions' is generally used as an umbrella term referring to high level functions including working memory, planning, initiation, cognitive flexibility, and inhibition.
The frontal lobes are implicated to process these functions, with evidence from patients with acquired frontal lobe damage. Executive function difficulties occur in autism as well as in other conditions such as obsessive compulsive disorder, schizophrenia, Tourette's syndrome, and attention deficit disorder.

Executive dysfunction in autism is evident in common perseverative behaviors such as a strong preference for sameness, elaborate rituals, and repetitive motor mannerisms. The Wisconsin Card Sorting Test is a commonly employed cognitive flexibility task where the subject must sort given cards according to a periodically changing set of rules. Autistic subjects have shown increased numbers of perseverative errors on this task[79, 104, 128]. A typical measure of planning is the Tower of Hanoi/Tower of London task, where subjects must move discs from a set sequence onto different pegs in as few moves as possible. Again, impaired performance has been seen in children with autism[65, 104]. In working memory tasks, there have been mixed results[17, 52, 105], possibly attributable to the difficulty in dissociating working memory from other

executive functions. One study however, found that performance was inversely related to task difficulty, suggesting working memory deficits are a result of the demands in organizing and integrating information[94]. Neuroimaging evidence also provides evidence for executive dysfunction from findings showing frontal cortical anomalies[55, 78].

Although anecdotal and clinical evidence both suggest executive dysfunction to accurately explain the cognitive phenotype of autism, problems arise as it is a non-unitary phenomenon. There are a large number of processes covered by the term and no general consensus as to which of the executive functions are affected in autism. However, given the evidence thus far, more studies that can dissociate the effects of different executive functions may clarify the debate.

Weak Central Coherence.

Another cognitive theory is the notion of weak central coherence (WCC), a term referring to a decreased ability in global processing, and an enhanced ability in processing local detail. This pattern of ability is reflected in the clinical presentation of autism as well as in studies showing autistic individuals to have superior performance on perceptual tasks requiring attention to detail, such as in block design[127], and visual search[103].

Although this theory's primary source of experimental evidence stems from visuo-spatial tasks, like with ToM, social difficulties may result from early inattention to socially relevant stimuli. However, a combination of inattention as well the inability to properly integrate social stimuli into a meaningful context may better explain social behavior. Since autistic individuals have been shown to not be completely inattentive to social stimuli such as gaze[75], yet show qualitative differences in functional neuroimaging studies of face processing[102, 108], it is likely that WCC is a higher level dysfunction affecting both social and non-social features of autism. In applying WCC to the autistic profile, specific areas of talent and special interests can be attributed to an intense and narrow focus, sometimes leading to attentional difficulties or on the other hand to a high level of competence in a task or hobby. An article by Happé[53] explores similar ideas further in characterizing autism as a cognitive style, rather than a deficit, with an overall increased attention to detail.

In the only functional study of central coherence[115], autistic subjects showed greater activation in ventral occipito-temporal areas and decreased activation in prefrontal cortical areas, suggesting increased processing at the sensory level, and decreased processing of the executive functions mediated by prefrontal cortex needed for holistic integration of sensory stimuli. Although the evidence suggests WCC can account for a variety of features in autism, additional studies are still needed to investigate its neural correlates.

Extreme Male Brain Theory.

First informally noted by Hans Asperger in his original paper[6], a theory proposed by Baron-Cohen[12] is the notion that autism may be an extreme manifestation of a sexually distinct cognitive profile more often seen in males. Although there is notable controversy of this theory from its highlighting gender stereotypes, there is considerable supportive behavioral evidence. Examples include increased performance favoring females in ToM tasks, levels of eye contact, language development, pragmatic communication, and several other tasks mainly based on social and communicative measures. Biological support includes increased testosterone levels in 6-10 year old autistic children[136] and the sexual dimorphism of decreased 2nd to 4th digit ratio in males[86], also decreased in autism[85], and found to be correlated with fetal testosterone levels[80].

Neuroanatomy.

Total Brain Volume.

One of the most consistent structural findings in autism is the high incidence of macrocephaly. Although macrocephaly can occur for several reasons including benign subarachnoid space enlargement, hydrocephalus, or subdural hematoma, such pathologies do not disproportionately contribute to macrocephaly in autism, but rather an increase in total brain volume (TBV).

A comprehensive search of the NLM Medline database yielded seventeen MRI studies either specifically investigating brain volume or measuring volume for correction purposes in relative volumes of specific structures. Studies either measured TBV, which included the medulla and cerebellum, or cerebral volume, which excluded both structures as well as the ventricular system. Eight studies showed evidence of increased volume[9, 27, 32, 57, 64, 109, 110, 131], while nine studies had negative findings[10, 58, 61, 89, 90, 119, 120, 125, 138]. Of these nine, two approached a significant level of decreased volume[119, 120], and another approached a significant level of increase[61]. Due to the small number of females diagnosed with autism, gender effects were measured in two studies only, with conflicting results. Piven et al.[109] found increased TBV in males only, while Sparks et al.[131] showed increased cerebral volume in both sexes. However, these results reflect low statistical power, from relatively small samples (n=9, n=7). Studies measuring head circumference, with larger sample sizes, similarly have not reported consistent gender effects[36, 47, 76, 93]. Three studies included subjects under 5 years of age and all reported increases in cerebral volume[27, 32, 131]. Head circumference measures have shown consistent macrocephaly at a higher rate in autism in adults and children from 1 year[9, 31, 45, 47, 49, 76, 93, 148]. Neonatal measures have been less consistent, with studies showing reduced[31], normal[32, 88, 137], and increased[49] head circumference.

Although there is some level of variability, findings in TBV and head circumference suggest normal measures at birth followed by a pronounced acceleration in growth in early childhood beginning at 1-2 years. The age range of the most significant effects is consistent with the onset of autistic symptomatology, suggesting genetic and/or environmental factors may play a role in this critical period. The neuropathology of early overgrowth is as of yet unknown.
Abnormalities in the normal process of neuron growth and pruning may play a role, although there is little empirical evidence for this hypothesis. A cross-sectional study[32] has suggested an unusual growth trend in TBV throughout life, including early increases in both white and grey matter, localizing the cause of overgrowth at a structural level. Another possibility involves two neurotrophins, brain derived neurotrophic factor (BDNF) and neurotrophin-4 (NT-4), both known to be required for nerve growth in development[140], and found in increased concentrations in the bloodstream of newborns later diagnosed with autism[100] as well as children and adults[95].

Figure 1 - *Structural MRI studies of total brain volume in autism*

Study	N	Age Range	Mean Age ± SD	M:F Ratio	Matched controls	Results
Piven et al. (1995)	22	13-29	18.4 ± 4.5	22:0	age/sex/IQ	increased TBV, with or without ventricular cavities
Piven et al. (1996)	35	12-29	18.0 ± 4.5	26:9	age/sex/IQ	increased TBV in males only, increases in temporal, parietal, occipital lobes
Aylward et al. (1999)	14	11-37	20.5 ± 1.8	14:0	age/sex/IQ	no significant differences in TBV
Haznedar et al. (2000)	17	n/a	27.7 ± 11.3	15:2	age/sex/IQ	no significant differences in TBV
Howard et al. (2000)	10	15.8-40.3	28.8 ± 6.9	10:0	age/sex/IQ	larger cerebral hemisphere and lateral ventricle volume
Courchesne et al. (2001)	60	2.4-16.4	6.2 ± 3.5	60:0	age/sex	increased cerebral and cerebellar white and grey matter at 2-3 years of age, no difference in neonatal head circumference for 14 subjects
Hardan et al. (2001)	16	n/a	22.2 ± 10.1	16:0	age/sex/IQ	Increased cerebral volume, third ventricle

Townsend et al. (2001)	9	16-38	28.3 ± 7.8	9:0	age/sex	no differences in TBV, grey and white matter, but increased ventricular volume
Aylward et al. (2002)	67	8-46	18.8 ± 10.0	58:9	age/sex/IQ	increased TBV in subjects aged 8-12, after correction for height. Head circumference increased in all ages
Carper et al. (2002)	38	2.7-10.8	5.7± 2.2	38:0	age/sex	increased cerebral volume in 2-4 year olds only, in frontal and parietal white matter and frontal and temporal grey matter
McAlonan et al. (2002)	21	18-49	32 ± 10	19:2	age/sex	no differences in total grey and white matter, or ventricles, but fronto-striatal grey matter decreases and local white matter decreases in left hemi
Rojas et al. (2002)	15	19-47	29.9 ± 9.1	13:2	age/sex	no differences but trend for decreased TBV
Sparks et al. (2002)	45	3-4	3.9 ± 0.4	38:7	age/sex	increased cerebral and cerebellar volume
Herbert et al. (2003)*	17	7-11	n/a	17:0	age/sex	trend for larger TBV, white matter increase, and cerebral cortex decrease
McAlonan et al. (2004)	17	8-14	12 ± 1.8	16:1	age/sex/IQ	no differences in TBV, but decreased grey matter and increased ventricular volume
Rojas et al. (2004)	15	19-47	30.3 ± 9.1	13:2	age/sex	no differences but trend for decreased TBV
Schumann et al. (2004)*	71	n/a	13 ± 3	71:0	age/sex	no significant differences in cerebral volume

*Indicates age range of combined case and control groups; Schumann et al. (2004) employed HFA, LFA, and AS subgroups; Courchesne et al. (2001) and Carper et al. (2002) employed partial LFA subgroup; Howard et al. (2000) and McAlonan et al. (2002) employed partial AS subgroup

Corpus Callosum.

As the largest interhemispheric commissure, the corpus callosum (CC) is primarily responsible for relaying cortical and subcortical information between homologous regions in the cerebral hemispheres. It has been implicated in processes requiring bilateral sensory and motor integration, including bimanual motor coordination[149], visual attention shifting[62], and procedural learning[39].

Studies investigating CC anomalies in autism have employed structural MRI to find reductions in area on the midsagittal plane as well as in volumetric measures. Results include decreased size in the anterior[56, 84], middle[40, 84, 111], and posterior[84, 111, 121, 142] subregions of the CC. The majority of non-statistically significant results from these studies also showed a trend towards a decrease in area in all subregions. The only two studies yielding negative results employed MRI systems operating at 0.5 Tesla, potentially causing less accurate data from reduced signal to noise ratios. In four of the six studies yielding positive results, measurements corrected for total brain volume resulted in analogous findings, indicating a disproportionate decrease in callosal size independent of brain size. The findings of these studies are illustrated in Figure 2.

The combined results of statistically significant differences and nonsignificant trends show a consistent pattern of overall decrease in corpus callosum size, particularly in posterior regions. These findings are consistent with white matter based theories, postulating that autism may be a disorder of connectivity. This theory is empirically supported by various studies showing white matter abnormalities including a recent functional study[66] of language comprehension and another showing abnormal increased development of white matter in early childhood[32]. Another possibility may be the result of the biased male distribution in autism, evident in the male to female ratios shown in Figure 1. However, attributing the size differences to gender differences assumes a sexual dimorphism of the CC in favor of females, a highly debated topic with inconsistent findings. Researchers have posited other theories to explain the cause of a smaller CC, such as increased levels of ipsilateral connections[56] or abnormal neural migration[84].

Figure 2 - *Structural MRI studies investigating the corpus callosum in autism*

Study	N	Age Range	Mean Age ± SD	M:F Ratio	Matched controls	# of CC Subregions	Results
Gaffney et al. (1987)	13	5-22	11.3 ± 4.7	10:3	age/sex	n/a	no significant differences
Saitoh et al. (1995)	33	5.9-42.2	13.8 ± 9.1	30:3	age/sex	5	smaller posterior CC
Egaas et al. (1995)	51	3-42	15.5 ± 10.0	45:6	age/sex	5	overall smaller; middle and posterior regions smaller
Piven et al. (1997)*	35	12-29	18.0 ± 4.5	26:9	age/sex/IQ	3	middle and posterior regions smaller
Manes et al. (1999)*	27	n/a	14.3 ± 6.8	22:5	age/sex/IQ	7	2-6 smaller, rostrum, splenium trend to be smaller in autism
Hardan et al. (2000)*	22	12.2-51.8	22.4 ± 10.1	22:0	age/sex/IQ	7	anterior CC smaller
Elia et al. (2000)	22	4.7-16.6	10.9 ± 4.0	22:0	age/sex	n/a	no significant differences
Waiter et al. (2005)	15	12-20	15.2 ± 2.2	15:0	age/sex/IQ	n/a	smaller anterior splenium, isthmus

*No difference in relative volume after correction for brain size; Manes et al. (1999) and Elia et al. (2000) exclusively employed LFA subjects; Egaas et al. (1995) employed partial LFA subgroup; Saitoh et al. (1995) includes all subjects from Egaas et al. (1995); Waiter et al. (2005) results from volumetric analysis (all other studies on midsagittal area)

Cerebellum.

A variety of studies have indicated several abnormalities in the cerebellum, a structure classically implicated in the sequencing and integration of motor functions. However, the cerebellum has also been implicated in cognitive functions. Patients with cerebellar damage from a variety of causes including surgery, stroke, postinfectious cerebellitis, and cerebellar cortical atrophy have been found to display executive function, visuospatial, language, and affective deficits[50, 106, 124].

In autism, noted structural abnormalities in the cerebellum have been demonstrated at the microscopic and macroscopic level. At the microscopic level, post-mortem studies have revealed a reduction in size[43] and number[116] of Purkinje cells, abnormalities in nicotinic receptors[77] and reduced levels of Reelin[44] and Bcl-2[5, 44], proteins responsible for lamination and anti-apoptotic processes during development, respectively. At the macroscopic level, findings in the size of the cerebellar hemispheres suggest an abnormal growth trend, with early increased volume up to 2-4 years[32, 131] and decreased volume thereafter through adulthood[32]. Another study by Piven et al.[114] also showed increased volume but in an adult population. The focus of a large portion of existing literature includes the volumetric abnormalities of the cerebellar vermal lobules VI-VII. Among the findings of the first MRI studies of the cerebellum in autism were hypoplasia in lobules VI-VII[35, 97] and reduced cerebellar hemisphere size[97]. These findings were further corroborated by the findings of another group[29] as well as in future studies by the same group, using populations of increasing sample size[32, 33]. However, two other studies[71, 84] did not replicate these findings. Another investigation[113] used two control groups, and found reduced volume in lobules VI-VII but only when compared to non-IQ matched controls.

Though these results yield an inconsistent pattern, when methodological factors such as the control population, sample size, and the subjects' level of functioning are taken into account, a more consistent trend develops. One significant variable is the distribution of individual case subject data. An analysis of four separate studies by Courchesne et al.[34] illustrated a bimodal distribution of both hypo- and hyperplasia of lobules VI-VII, possibly accounting for negative results in other studies as a result of positively skewed mean measurements. Another significant variable is the use of IQ matched controls, where studies using IQ-matched clinical and normal controls, did not find significant reductions in area[84, 113, 114]. Additionally, in one of these

studies[113] and in another of total cerebellar volume[131], within-group analysis of the case group did not yield IQ based size differences. These findings suggest a selective vermal hypoplasia based on level of cognitive functioning not specific to autism. Further studies utilizing more comparable methodologies may clarify whether or not the pathology of vermal hypoplasia is qualitatively unique in autism, or similar to that in other developmental disorders. Several studies also computed relative volumes correcting for brain size in the form of TBV, cerebral volume or midsagittal area. These findings are summarized in Figure 3.

Motor problems in autism often exhibit themselves in the form of delayed development of fine and gross motor skills, gait difficulties, or clumsiness, symptoms less severe than in classical cases of cerebellar lesions with basic motor difficulties. As a result of the studies implicating cognitive functions of the cerebellum, the abovementioned structural findings lend more credence towards a strong link between cerebellar abnormalities and the behavioral profile in autism. As far as the cause of these findings, various possibilities exist, including purely genetic contributions, teratogenic factors, or to external factors such as atrophy from long-term paucity of social stimuli in early development[29].

Figure 3 - *Structural MRI studies investigating the cerebellum in autism*

Study	N	Age Range	Mean Age ± SD	M:F Ratio	Matched controls	Results
Gaffney et al. (1987)	13	5-22	11.3 ± 4.7	10:3	age/sex	no significant differences, with trend for smaller cerebellar hemispheres
Courchesne et al. (1988)	18	6-30	20.9	16:2	age/sex	smaller VI-VII; smaller cerebellar hemispheres
Murakami et al. (1989)**	10	14-39	26	8:2	age/sex	smaller VI-VII; smaller cerebellar hemispheres
Kleiman et al. (1992)	13	2-17	7.4	10:3	age	no significant differences in lobules I-V,VI-VII
Piven et al. (1992)*	15	8-53	27.7 ± 10.7	15:0	age/sex/IQ	smaller VI-VII relative only to non-IQ matched controls, no changes in volumes relative to midsagittal brain area
Garber et al. (1992)	12	18-38	27.2 ± 5.3	9:3	age/sex	no differences in cerebellar volume or in vermal lobules
Courchesne et al. (1994)**	50	2-40	16.5	41:9	age/sex	smaller lobules VI-VII, with bimodal distribution and small subgroup of lobule VI-VII hyperplasia
Piven et al. (1997)	35	12-29	18.4 ± 4.5	26:9	age/sex/IQ	no significant differences in lobules VI-VII, larger absolute total cerebellar volume but no difference when adjusted for TBV
Ciesielski et al. (1997)	9	10-23	16.8	5:4	age/sex	smaller lobules I-V and VI-VII
Abell et al. (1999)	15	n/a	28.8 ± 6.6	12:3	age/sex/IQ	increased grey matter bilaterally in anterior cerebellar lobes and vermal lobule VIII
Manes et al. (1999)	27	n/a	14.3 ± 6.8	22:5	age/sex/IQ	no significant differences in relative volume of lobules I-V,V-VII,VIII-X
Courchesne et al. (2001)**	60	2.4-16.4	6.2 ± 3.5	60:0	age/sex	smaller VI-VII
Sparks et al. (2002)	45	3-4	3.9 ± 0.4	38:7	age/sex	increased cerebellar volume, no differences relative to cerebral volume
McAlonan et al. (2004)	17	8-14	12 ± 1.8	16:1	age/sex/IQ	decreased cerebellar white matter, bilaterally

*No difference in relative volume after correction for brain size; **Partially includes subjects from prior studies; Manes et al. (1999) exclusively employed LFA subjects; Kleiman et al. (1992) and Courchesne et al. (1988) employed partial LFA subgroup;

Amygdala.

From the early findings of Kluver-Bucy syndrome in monkeys[24] to current behavioral studies in human patients, the amygdala has been implicated primarily in fear perception of facial expressions[21], as well as in the recognition of other emotions such as sadness[3] and "social" emotions[2] like guilt, arrogance, admiration, and flirtatiousness. Similar findings have been illustrated in the auditory modality, in vocal intonations of fear and anger[2] and in a complex ToM task[133]. In addition to fear perception, the amygdala has also been implicated in related processes including eye gaze[69], affective memory[25], olfactory learning[23], and social judgment[4].

To date, findings on amygdala structure in autism have been mixed, with studies indicating reduced[10, 108, 120] and increased[1, 64, 125, 131] volumes, as well as nonsignificant[61] differences. Aylward et. al[10] reported decreased amygdala size, in absolute volume and relative volume after adjusting for TBV, suggesting a disproportionate decrease. In the second study, Pierce et al.[108] also reported similar findings, with reduced bilateral amygdala volume. The third study by Rojas et al.[120] found reduced left amygdala volumes in autistic adults. However, the latter two studies employed a small sample size (n=7), and found no significant differences after correction for TBV, respectively. In the remaining studies, of those which adjusted for TBV, no statistically significant changes in results were found.

In light of these results, there is a strong trend for amygdala size to be increased, rather than decreased in autism. However, as in all structural findings, several methodological variables must be taken into account. As autism is a developmental disorder, one of the most significant variables is age. Schumann et al.[125] found increased right amygdala volume in all case subgroups of LFA, HFA, and AS. Statistical analyses on separate age groups revealed the most significant differences of bilateral amygdala enlargement in the youngest age group of 7.5-12.5. Herbert et al.[61] conducted a similar study using an almost identical age group of 7-11, and found a trend for smaller amygdala volumes. However, this study measured the volumes of the amygdala and hippocampus as a single complex, possibly biasing results as hippocampal volume in autism is another area with mixed findings. Sparks et al.[131] used a limited age group of 3-4 year old children and similarly to Schumann et al. found increased bilateral amygdala volumes. These studies suggest that amygdala enlargement may be a direct function of development, similar to atypical growth patterns of grey matter and TBV in autism. Further cross-sectional or longitudinal studies on the amygdala may shed further light on current findings.

Many of the social and affective behaviors in autism are similar to the symptoms of amygdala damage. However, Siebert et al. investigated individuals with bilateral damage from Urbach-Wiethe disease found no significant differences in subjects' ratings of basic emotions from facial expressions[129]. Furthermore, this study employed a sample size (n=10) larger than most using bilateral amygdala damage patients. The authors suggest that compensatory strategies of the adult subjects may have enabled them to properly recognize basic facial expressions, a theory compatible with amygdala function in autism, as the social tendencies in most autistic individuals may not facilitate similar compensatory measures. Another question of the amygdala in autism is the cause of increased volume. One post-mortem study has reported increased cell packing density in the amygdala[15], but these results reflect a single case study and may be difficult to replicate due to the scarcity of post-mortem samples. Another possible explanation is the influence of anxiety, a commonly reported mood disorder in autism. Increased volumes have been reported in pediatric populations with anxiety disorders[37, 81], suggesting that amygdala enlargement may be the result of use-dependent changes from excessive anxiety. Alternatively, genetic factors may cause amygdala enlargement which in turn result in abnormal functioning and consequent emotional and behavioral symptoms.

Figure 4 - *Structural MRI studies investigating the amygdala in autism*

Study	N	Age Range	Mean Age ± SD	M:F Ratio	Matched controls	Results
Abell et al. (1999)	15	n/a	28.8 ± 6.6	12:3	age/sex/IQ	larger L. amygdala/periamygdaloid cortex
Aylward et al. (1999)*	14	11-37	20.5 ± 1.8	14:0	age/sex/IQ	smaller bilateral amygdala
Haznedar et al. (2000)*	17	n/a	27.7 ± 11.3	15:2	age/sex/IQ	no significant differences in volume
Howard et al. (2000)	10	15.8-40.3	28.8 ± 6.9	10:0	age/sex/IQ	larger bilateral amygdala
Pierce et al. (2001)	6	21-41	29.5 ± 8.0	7:0	age/sex	smaller bilateral amygdala
Sparks et al. (2002)	45	3-4	3.9 ± 0.4	38:7	age/sex	larger bilateral amygdala
Herbert et al. (2003)**	17	7-11	n/a	17:0	age/sex	trend for smaller hippocampus-amygdala complex
Schumann et al. (2004)**	71	7.5-18.5	13.0 ± 3.0	71:0	age/sex	larger absolute R. amygdala, relative R. amygdala in LFA, most significant effect bilaterally in ages 7.5-12.5 for HFA/LFA
Rojas et al. (2004)	15	19-47	30.3 ± 9.1	13:2	age/sex	smaller absolute L. amygdala, no differences bilaterally for relative volume

*No difference in relative volume after correction for brain size; **Indicates age range of combined case and control groups; Schumann et al. (2004) employed HFA, LFA, and AS subgroups ; Howard et al. (2000) employed partial AS subgroup

Hippocampus.

As a region particularly susceptible to epileptic seizures as well as degeneration in Alzheimer's and necrosis from hypoxia, the hippocampus is a well studied structure most implicated in declarative memory consolidation. It has been shown to have structural effects, most consistently with volume reductions, in conditions such as schizophrenia[99, 107], unipolar[141] and bipolar depression[20].

The combined findings of ten structural MRI studies yield no consistent pattern, with a near equal distribution of increased, decreased, and non-significant differences in hippocampal volumes. The first five studies from 1995-2000 showed few robust effects[10, 58, 64, 112, 121], indicating no structural abnormalities in the autistic hippocampus. Of the next two studies, Saitoh et al.[122] reported a smaller area dentata in the autistic group, with the most significant effect in subjects aged 2-4 (n=11), while Sparks et al.[131] discovered a larger bilateral hippocampus in a near identical age group of 3-4 years (n=45). While the results are highly conflicting, considerable methodological differences exist in these two studies, including unit of measure (mean cross-sectional area vs. volume), level of functioning of the case population, and inclusion of subregion analyses. Two other studies also revealed increased hippocampal volumes in child and adult populations[120, 125] and another showed decreased volumes[61], although this study measured the amygdala and hippocampus as single complex. A summary of these studies is shown in Figure 5. All results are of volumetric measurements except for Saitoh et al. (1995) and (2001), which measured cross-sectional area.

It is difficult to elucidate on the range of findings as they can be interpreted as either structural abnormalities with explicable pathologies or insignificant variations within a normal distribution. If there are indeed abnormalities, there can be several possible explanations. Similar to the amygdala and other limbic structures, limited findings in increased cell packing density[16] has been reported in the hippocampus, contributing to potential decreases in volume as well as increases as a result of incomplete apoptosis. Declarative memory in autism is relatively intact, often with enhanced rote memory ability, supportive of use-dependent increases in volume. Also, enlarged hippocampus volumes have been associated with

enhanced spatial memory in humans[83] and animals[30]. Similarly, enhanced ability in visuo-spatial tasks has been shown in autism[26, 127], further supporting hippocampal enlargement. On the other hand, theories also exist to support decreases in hippocampus volumes. For example, Saitoh et al.[122] suggest cytoarchitectonic differences in autism, where a granule cell abnormality in the dentate gyrus could reduce CA4 area by reducing the amount of mossy fibers traversing it. Although further studies are need for stronger substantiation, the neuropsychological profile of autism more accurately fits the functional changes likely to be associated with an increase, rather than a decrease in hippocampus size. Correlational analyses between individual subjects' neuropsychological test scores of declarative memory and hippocampal volumes and may clarify current findings.

Figure 5 - *Structural MRI studies investigating the hippocampus in autism*

Study	N	Age Range	Mean Age ± SD	M:F Ratio	Matched controls	Results
Saitoh et al. (1995)	33	5.9-42.2	13.8 ± 9.1	30:3	age/sex	no significant differences (1.4% difference in cross-sectional area between groups)
Piven et al. (1998)*	35	12-29	18 ± 4.5	26:9	age/sex/IQ	no significant differences or second-order effects
Aylward et al. (1999)	14	11-37	20.5 ± 1.8	14:0	age/sex/IQ	no differences in absolute volume, decreased volume relative to TBV
Haznedar et al. (2000)*	17	n/a	27.7 ± 11.3	15:2	age/sex/IQ	no significant differences in hippocampal volume
Howard et al. (2000)	10	15.8-40.3	28.8 ± 6.9	10:0	age/sex/IQ	marginally smaller hippocampus, parahippocampal gyrus volumes
Saitoh et al. (2001)	59	2-42	11.2 ± 9.2	52:7	age/sex	smaller dentate gyrus, CA4 in all age groups, with most significant differences in ages 2-4
Sparks et al. (2002)	45	3-4	3.9 ± 0.4	38:7	age/sex	larger bilateral hippocampus
Herbert et al. (2003)**	17	7-11	n/a	17:0	age/sex	no differences but trend for smaller amygdala-hippocampus complex
Schumann et al. (2004)**	71	7.5-18.5	13 ± 3	71:0	age/sex	absolute and relative R. hippocampus larger in HFA/LFA groups, L. in HFA with trend in LFA
Rojas et al. (2004)	15	19-47	30.3 ± 9.1	13:2	age/sex	bilateral increase in absolute volumes, larger L. and trend for R. increase in relative volumes

*No difference in relative volume after correction for brain size; **Indicates age range of combined case and control groups; Schumann et al. (2004) employed HFA, LFA, and AS subgroups; Saitoh et al. (1995) and Saitoh et al. (2001) employed partial LFA subgroup

Mirror Neurons.

First discovered through single unit recording in area F5 of macaque premotor cortex[117], "mirror neurons" is the term given to a group of neurons shown to respond both when an individual sees or performs an action. In later human studies, corresponding areas in left inferior frontal cortex were found to display similar behavior. A later study by Buccino et al.[22] clarified on the function of these neurons, showing that response is dependent on species relevance. Results showed that biting motions observed in non-humans by a human consistently activated left inferior frontal and inferior parietal areas, while lip-smacking motions of a monkey produced less activation and barking motions from a dog did not produce any frontal activity. Another study by Saygin et al.[123] demonstrated similar frontal activity in response to the perception of point-light biological motion.

As mirror neurons respond to both the perception and production of matching actions, there is a strong implication of their role in processes shown to be impaired in autism, such as imitation, empathy, ToM. There is also a strong association with language, not only through the importance of imitation in language development, but also due to the activity of mirror neurons

in Broca's area. In addition, multiple abnormalities have been shown in left inferior frontal cortex, including hypoperfusion in language tasks[66] and reversed asymmetry in volume[38, 59, 60]. As of yet, there have been few functional studies specifically investigating mirror neurons in autism. Avikainen et al.[8] compared motor cortex activity through MEG and did not find any differences between the AS case group and controls. However, another MEG study by Nishitani et al.[101] found a statistically significant delay and decreased amplitude in the activation of left inferior frontal areas. Due to the small number of functional mirror neuron studies in autism, as well as the small sample sizes (n=5 and n=8, respectively) of the aforementioned studies, further research is needed to confirm possible mirror neuron dysfunction.

Alternative Theories.

One of the more well known alternative theories is the possibility of autism caused by the MMR vaccine. Empirical evidence originates from a study by Wakefield et al.[144] illustrating frequent co-occurrence of gastrointestinal disease and autism in children (n=12). Parental reports also associated the onset of autistic behavior with MMR vaccination in 8 children. The authors theorized that the results may represent a unique form of autism characterized by gastrointestinal symptoms and in select groups with specific risk factors such as concurrent infection at the time of immunization or following antibiotic use, a history of atopy, exposure to multiple vaccines concurrently, or a family history of autoimmune disease[143]. Additional evidence includes primarily anecdotal reports, from parents noticing the onset of autism closely following immunization. Epidemiological evidence consistently does not support any correlation between the administration of the MMR vaccine and the incidence of autism[28, 46, 70, 135], suggesting that anecdotal evidence may often be due to the concordance in the age of MMR vaccination and onset of autistic symptomatology.

Another related theory is autism induced by neurotoxic levels of mercury, or from the presence of ethylmercury in the vaccine preservative thimerosal. Associational evidence for this theory exists in well-documented regional reports of prenatal methylmercury exposure resulting in developmental disorders and neuropsychological effects often similar to those in autism[42, 51]. However, some studies have not shown significant adverse effects from methylmercury exposure[87, 91, 98]. One animal study has shown differential neurotoxic effects between ethylmercury and methylmercury[82], suggesting ethylmercury may be less toxic due to increased protective potency of the blood brain barrier as well as a shorter half life. In addition to the results of MMR vaccine epidemiological studies, although thimerosal has been largely removed from vaccines in the United States since 1999, increases in autism prevalence has remain unchanged. Although fixed belief in vaccine induced autism remains among various public groups, the combined evidence does not suggest that autism is induced by vaccines or mercury exposure.

In 1998, a study by Horvath et al.[63] reported behavioral improvements in three preschool children after intravenous administration of secretin, a gastrointestinal polypeptide produced in the duodenum and secreted in response to increased acidity. Animal studies suggest a role for secretin in autism, showing its distribution in the developing central nervous system of mouse embryos[130] as well as immunoreactivity in several brain areas in rats including the cerebellum, amygdala, motor and sensory cortices[74, 145]. Following publicaiton of this study, secretin administration as a treatment option for autism was popularized after widespread media attention on television shows such as Dateline and Good Morning America. However, several comprehensive reviews of case reports and clinical trials have not concluded significant positive effects from secretin administration[41, 92, 134].

Conclusion.

Although one of the most heterogeneous developmental disorders, findings in the past decade have greatly increased our understanding of the etiology of autism. Cognitive theories attempting as well as structural findings have linked likely frontal lobe abnormalities to the social and cognitive profiles of autism. Since the acquisition of MRI technology, studies have shed new light on the localization of structural abnormalities and the associated cognitive functions. Many of the most robust and consistent findings also occur in younger populations ages 2-5, emphasizing the role of genetic and/or environmental factors in the onset of autism as well as the already emphasized importance of early behavioral intervention. Various alternative theories also exist, often suggesting environmental or non-neurological causes of autism. Although some of these theories lack considerable empirical evidence, further studies may be needed to solidify their potential efficacy. Future studies may elucidate existing data by taking advantage of new and infrequently used data acquisition technologies such as TMS. Alternative frameworks for experiment design may also help, focusing on studying both the strengths and weaknesses of autism, to better understand the disorder and in turn, effectively improve the well being of those affected by autism.

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