

## The Neural Basis of Autism: A Review

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### Abstract

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition for which there is no known cause or cure. Autism is a highly variable disorder, the most prominent difficulties of which include aberrant behavior, poor social skills and disrupted communication skills. Evidence suggests that the prevalence of ASD is steadily rising and this has led to widespread speculation and research concerning the causes of the disorder. Following about 50 years of intensive study, researchers now believe that autism is a complex disorder whose core aspects have distinct causes that often co-occur. Some of these distinct neurological causes are the focus of this review. We focus on findings that suggest that children with ASD have larger overall brain volumes and differences in brain growth trajectory. By adulthood those with ASD have anatomical and functional abnormalities in prefrontal cortex, basal ganglia, temporal lobe, and the limbic system. Impairments in these areas, as well as under-connectivity between and within these brain regions, can lead to range of interrelated deficits in interpersonal interaction such as problems remembering and identifying people, the inability to perceive social cues, and misunderstanding nonverbal communicative cues such as gestures, facial expressions, and emotional prosody. A mechanistic understanding of the underlying neurology of ASD is a prerequisite before new therapeutic tools can drive functionally atypical brains in corrective directions. Recent studies investigating the neural response to treatment in autism are briefly reviewed. These highlight the need to study the neural basis of and response to treatment in ASD.

### Introduction

Much of the phenomenology of autism can be described in terms of a triad of impairments in social, communication and behavioural domains. Such impairments can result in stereotyped movements, an insistence of sameness, delayed speech including echolalia, and aberrant behaviour. There is a failure to develop normal social interactions and relationships with others. Autism is usually noticed by caregivers in the first or second year of life by distinguishable differences in language ability, repetitive behaviour and/or preoccupation with objects [1]. A diagnosis of autism typically follows shortly after. While therapy such as Applied Behaviour Analysis (ABA) has been shown to be an effective tool in helping individuals with autism manage their difficulties [2], autism is a lifelong condition for which there is no cure [3].

Although currently there is no cure, researchers are now beginning to understand the neural mechanisms of ASD and how they relate to treatment of the disorder. Some promising new areas of therapeutics are also showing the remarkable plasticity of the brain in response to intervention. The aim of this review is to provide a brief overview of the current theories as to the neurological causes of autism. Understanding the neural underpinnings of ASD is critical before we can elucidate the mechanisms of ASD treatment.

### Historical Overview

Leo Kanner [4] first described autism after observing a group of patients with similar impairments. The patients who he had seen in his clinic all exhibited: an inability to relate to people; failure to develop speech; abnormal responses to environmental objects and events, an obsessive desire for sameness; and excellent memory. Kanner labeled

this condition 'early infantile autism'. One year on, Hans Asperger [5] described a group of children using similar terminology. In addition to these characteristics, however, he also noted that the children had developed normal language but the content of their speech was slightly abnormal, tending to be pedantic. The symptoms characteristic of this higher functioning group became known as Asperger's syndrome.

There have been recent changes to the new Diagnostic and Statistical Manual of Mental Disorders (DSM V; APA 2013) [3]. According to the new clinical manual, 'Asperger's syndrome' no longer exists as a label to describe high-functioning autism. Instead, all individuals with autism are considered to lie on part of a spectrum, with very low functioning children on one end (who will be mute with general cognitive impairments) and high functioning children on the other end (who will have normal or higher IQ and difficulties with social interaction). All children with autism or Asperger's are now considered under the umbrella term Autism Spectrum Disorders (ASDs). Here we use the term autism interchangeably with ASD to refer to all individuals on the spectrum.

The prevalence of ASD is estimated to be 60 in 10,000 (0.6%), with a male:female ratio of 4:1 [6]. The prevalence of autism has been steadily rising [7-10], leading to widespread speculation concerning the factors that may be responsible.

### The Brain Basis of Autism

There is a vast body of evidence demonstrating that the autistic brain is functionally and structurally different from the neurotypical brain, particularly in brain areas subserving inhibitory control, communication, and emotions. Impairments in these areas lead to range of interrelated deficits in interpersonal interaction such as problems remembering and identifying people, the inability to

perceive social cues, and misunderstanding nonverbal cues such as gestures, facial expressions, and speech prosody.

### Greater total brain volume

Magnetic Resonance Imaging (MRI) data reveals that by age two to four years, 90% of autistic children have a significantly larger average brain volume than neurotypical controls [11-13]. This is particularly the case in the dorsolateral frontal cortex [14,15].

Not surprisingly, increased brain volume corresponds with accelerated head growth (i.e., greater head circumference), at least in young children with autism [16]. Indeed, enlarged head circumference about 2 standard deviations above the general population mean is one of the most replicated clinical findings in autism [17]. However, a recent Norwegian population study suggests that it is the variability of the head circumference, and not the average, which is greater in boys with autism relative to neurotypical children [18].

Little is known about whether macrocephaly contributes to other known coexisting features of autism such as epilepsy or headache. It has, however, been shown to be related to excessive cerebrospinal fluid. In a recent prospective study of infants at risk for autism spectrum disorder, MRI scans were conducted at three time points (8-11, 14-17, 20-26 months of age; [19]). Infants later identified with autism showed significantly greater extra-axial fluid (i.e., excessive cerebrospinal fluid in the subarachnoid space, particularly over the frontal lobes) at all testing periods. There was also a positive correlation between extra-axial fluid amount and severity of symptomatology.

Autopsy data also reveals an excess of neurons in the prefrontal cortex among young children with autism. Young children with autism also exhibit more cortical (18%) and cerebellar (39%) white matter than controls [11,12]. The over-production of brain cells and axons eventually slows down as the autistic child develops [20,21].

Although the over-production of neurons is a normal feature of brain development, typical development involves the subsequent pruning of excess neurons and synapses. The progressive elimination of synapses is one of the general principles of brain plasticity. It ultimately improves neural circuit functioning and coincides with increasing cognitive and motor skills in the typically developing child. In the case of autism, however, the normal pruning of excess neurons and their connections appears to be faulty, leading to abnormal white matter connectivity by adolescence and young adulthood [20].

Together, the particular neural defects that cause early brain overgrowth may underlie the neural basis of autism. Although it is unclear what causes this gray and white matter overgrowth, one result appears to be fewer and/or abnormal connections between areas of the brain involved in inhibitory control and face recognition, namely the frontal cortex, temporal cortex, and amygdala.

### Inhibitory control and brain connectivity

Individuals with autism often show impaired executive functioning, including inflexibility and social reciprocity deficits. At the neural level these characteristics have been associated with problems in the frontal cortex and with the circuits leading to and from the frontal lobe.

Executive functions include planning, working memory, attention, problem solving, verbal reasoning, mental flexibility, task switching, and monitoring of actions, and inhibitory control.

Inhibitory control allows individuals to withhold dominant responses or ignore distracting stimuli in order to give an appropriate response. In real-world situations inhibitory control is important as it stops us from performing a potentially inappropriate action when given the urge (e.g., an extreme emotional outburst). Withholding inappropriate urges is a necessary criterion for performing socially appropriate behaviour.

Inhibitory control deficits and repetitive behavior are part of the core features of autism. The communication and integration of specific brain networks are vital in order for the successful execution of motor and executive functions. Inhibitory control, in particular, requires synchronization of neuronal networks mostly in the frontal lobe (anterior cingulate gyrus, middle cingulate gyrus) and posterior areas of the brain such as the striatum, basal ganglia, and the insula (which is folded deep within the **lateral sulcus**, separating the **temporal lobe** from the **frontal lobes**).

Research using a variety of techniques has shown that the connectivity of posterior regions to prefrontal cortex is atypical in people with ASD. For example, diffusion tensor imaging (DTI), which measures white matter connectivity, indicates that those with autism show abnormal anatomy of fronto-striatal white matter tracts [22]. Functional MRI imaging (fMRI), able to measure functional connectivity between brain areas during task performance, corroborate the structural findings. The inhibition circuitry is under-activated and less synchronised in individuals with autism compared to neurotypical controls [23]. Resting state functional MRI or electroencephalography (EEG) recording can measure cortical synchronisation in the absence of task performance. Abnormal resting state cortical connectivity between frontal and posterior regions has similarly been found in individuals with autism [24,25].

Interestingly, the fronto-striatal pathway is also impaired in individuals with attention deficit hyperactivity disorder (ADHD) [26] and executive functioning deficits are among the core features of ADHD. As there are high rates of comorbidity between autism and ADHD [27], we now need to know how this pathway functions in individuals with just one or both conditions Vissers, et al. [28]. Previously, the **DSM diagnostic manual** did not allow the co-diagnosis of ASD and **ADHD**. The **DSM-5** removed this prohibition of comorbidity. Thus, individuals with autism spectrum disorder may also have a diagnosis of ADHD. A better understanding of the etiology of autism and its associated conditions will help with earlier diagnosis and treatment strategies.

### Face processing and brain connectivity

Though there is great variability in symptom severity and intellectual functioning in ASD, all individuals with autism have social difficulties involving eye contact, reciprocal interactions, and responding to emotional cues. This section describes research that suggests that these social difficulties may be the result of the nature of face processing in autism. The brain areas involved in our ability to attend to and process information from faces (fusiform face area and amygdala) may be impaired in people with autism.

Children with ASD perform worse on face processing tasks including face discrimination and face recognition. In very young children, the ability to use facial information (e.g., engaging in joint attention) is considered a critical early marker of ASD [27]. Individuals with ASD also process faces using abnormal strategies. They pay less

attention to core features of the face like the eyes and nose relative to typically developing adults [29,30].

Robert Schultz was one of the first to discover through fMRI that, at the basic neural level, a face is just another object for people with autism. His typical methodology was to ask people with autism and neurotypical controls to press a button to indicate whether pairs of faces or pairs of objects (e.g., cups, chairs) were the same or different. The findings revealed that neurotypical individuals primarily use the fusiform gyrus (known as the fusiform face area) when processing faces and the inferior temporal gyrus to process the objects. In contrast, participants with autism used the inferior temporal gyrus for both the chairs and the faces [31-33].

In addition to neglecting the fusiform face area when responding to faces, individuals with autism have impaired connectivity between the right fusiform gyrus and the amygdala. The amygdala itself also is abnormally large in autistic children [34]. The amygdala measures just an inch long, resides deep inside the brain and is shaped like an almond. It plays a significant role in facial expression and emotion processing [35,36] and, if the amygdala is damaged, there is difficulty recognizing strong emotions such as fear [37]. In neurotypical individuals, the amygdala is significantly more activated when a fearful face is perceived as opposed to a neutral face [38].

Kleinmans, et al [39] found that the degree of social impairment in those with autism was associated with decreased connectivity between the amygdala and the fusiform face area. Social impairment was measured with the Autism Diagnostic Interview-Revised (ADI-R) social score. This negative correlation between amygdala- fusiform face area connectivity and the ADI-R score [39] suggests that abnormalities in the connections between the emotional centre of the brain and the face processing area plays an important role in the social skills difficulties in autism.

### Neural response to ASD treatment

Given that the long-term wellbeing of communities is increasingly determined by the social behaviour of individuals, it is now clear that social difficulty is a key source of disability. Though neuroimaging studies have demonstrated both anatomical and functional differences in the so-called social areas of the brain in individuals with autism when compared to controls, research on the neural basis for response to intervention in those with autism is in its infancy. Two such studies have recently investigated the neural response to treatment in ASD [40,41]. These studies reflect a broader trend to seek objective measures, or biomarkers, to help evaluate the effects of ASD treatment.

Dawson et al.[41]used EEG to measure the brain activity of ASD children (ages 4-6 years) while they viewed images of unfamiliar faces and toys on a screen. Fifteen of the participants with ASD had completed a two-year program of Early Start Denver Model (ESDM; 20 hours / week), 14 with ASD had received other community-based behavioural therapies, and there were 17 typically developing controls. The investigators used an EEG-based biomarker that indicates treatment response (the evoked potential N170 reflects the brain's early response as it recognizes that a face is a face). Both intervention groups showed typical N170 responses following treatment, but those who received ESDM had other EEG indicators that were more comparable to the control children.

Gordon et al. [41] measured fMRI changes in 17 children with ASD following intranasal administration of oxytocin. The scanning

activities included judgments of socially meaningful pictures (Eyes) and nonsocially meaningful pictures (Vehicles). The therapy increased activity in the striatum, nucleus accumbens, left posterior superior temporal sulcus, and left premotor cortex, during social judgments and decreased activity during nonsocial judgments. The activations during processing of socially relevant stimuli was the same as controls. The authors suggest that oxytocin may enhance social functioning in children with ASD.

In both studies, children with ASD processed social information more similarly to typically developing children after therapy (behavioural in the first, oxytocin in the second). This suggests that the extent of neuralplasticity is such that their brains were able to move toward "normalizing" the processing of social information.

### Summary and Conclusions

Autism is a heritable and lifelong neurodevelopmental disorder with increasing prevalence. The most robust neurological finding to account for autism is greater brain volume. The early brain overgrowth and related dysfunction is most strongly evident in the prefrontal cortex. Other sites of regional gray and white matter overgrowth include the temporal cortex and amygdala.

Many of the characteristic features of ASD can be described in terms of specific cognitive deficits, which together conspire to make it hard to communicate effectively and to develop and maintain social relationships. Abnormal inhibitory control (of motor and general cognitive skills) and atypical face processing are thought to underlie such features. These, in turn, can be partially explained by atypical connectivity between the frontal lobe and striatum (including basal ganglia), and between the temporal cortex and amygdala. Other regions implicated in social processing include fusiform gyrus, medial prefrontal cortex, and insula.

Results of the two recent studies that have examined the neural mechanisms underlying treatment response are promising. Following behavioural or hormone treatment, the brains of children with ASD seem to "normalize," responding more similarly to those of typically developing children. In both cases, it will be interesting to see if the biomarkers remain normalized in long-term follow-up studies and whether the social gains persist outside the laboratory. The research in this area is indeed its early stages, and we look forward to further effort examining the neural basis of treatment response in ASD.

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