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Autism: research into causes and intervention

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Summary

Autism spectrum conditions are neuro-developmental syndromes with strong heritability. Cognitive theories have had some success in explaining why the cluster of features should co-occur. Empathizing deficits have the potential to make sense of one triad of impairments (social difficulties, communication difficulties and imagining others' minds), and may have a brain basis in the amygdala and left medial frontal cortex. A strong systemizing drive may account for a distinct triad of strengths (good attention to detail, deep, narrow interests and islets of ability). The brain basis of systemizing is yet to be understood. Family genetics studies suggest that these same cognitive dimensions (reduced empathizing alongside a strong drive to systemize) may also characterize the 'broader phenotype' among first-degree relatives. Molecular genetic studies are underway and any candidate genes for autism will ultimately need to be tested in relation to the observed differences in the brain, cognition and behaviour. The ethics of genetic screening or gene therapy should be thought about well ahead of these becoming available, since there is by no means any consensus that these would be desirable given the wide range of phenotypic traits, not all of which are disabling. Future research will need to focus on evaluating the extent to which any form of intervention reduces the triad of impairments whilst supporting the triad of strengths.

Introduction

Autism is diagnosed when a child or adult has abnormalities in a 'triad' of behavioural domains: social development, communication, and repetitive behaviour/obsessive interests [1, 2]. Autism can occur at any point on the IQ continuum, and IQ is a strong predictor of outcome [3]. Autism is also invariably accompanied by language delay (no single words before 2 years old). Asperger Syndrome (AS) [4] is a sub-group on the autistic spectrum. People with AS share many of the same features as are seen in autism, but with no history of language delay and where IQ is in the average range or above. The main cognitive theories of autism are summarized next.

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Cognitive theories

A. THE MIND-BLINDNESS THEORY

The mind-blindness theory of autism [5] proposed that in autism spectrum conditions there are deficits in the normal process of empathizing, relative to mental age. These deficits can occur by degrees (relative to mental age). The term 'empathizing' encompasses a range of other terms: 'theory of mind', 'mind-reading', 'empathy' and taking the 'intentional stance' [6]. Empathizing involves two major elements: (a) the ability to attribute mental states to oneself and others, as a natural way to make sense of agents [7–9]; and (b) having an emotional reaction that is appropriate to the other person's mental state. In this sense, it goes beyond what is normally meant by the term 'theory of mind' [10] to include having some affective reaction (such as sympathy). (Sympathy is considered here as a special case of empathy, where the observer's affective response to another's affect is to want to alleviate suffering in some way [11].)

Since the first test of mind-blindness in children with autism [12], there have been more than 30 experimental tests. The vast majority of these have revealed profound impairments in the development of their empathizing ability. These are reviewed elsewhere [5, 13]. Some children and adults with AS only show their empathizing deficits on age-appropriate adult tests [14–16]. This deficit in their empathizing is thought to underlie the difficulties such children have in social and communicative development [17, 18], and in the imagination of others' minds [19, 20].

B. THE EMPATHIZING-SYSTEMIZING (E-S) THEORY

Systemizing is the drive to analyse and build systems, in order to understand and predict the behaviour of

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non-agentive (inanimate) events. Systems are all around us in our environment, and include: technical systems (such as machines and tools); natural systems (such as biological and geographical phenomena); abstract systems (such as mathematics or computer programs); and even social systems (such as profits and losses in a business, or a football league table). The way we make sense of any of these systems is in terms of underlying rules and regularities or, specifically, an analysis of input-operation-output relationships [21]. The E-S theory holds that alongside the empathizing deficits in autism, systemizing is either intact or superior [22]. The evidence for deficits in autism was reviewed earlier, but studies suggest systemizing in autism is at least in line with mental age, or superior [23–25].

C. EXECUTIVE FUNCTION THEORY

People with autism spectrum conditions show 'repetitive behaviour', a strong desire for routines and a 'need for sameness'. To date, the only cognitive account to attempt to explain this aspect of the syndrome is the executive dysfunction theory [26–28]. This paints an essentially negative view of this behaviour, assuming that it is a form of 'frontal lobe' perseveration or inability to shift attention. People with autism who have additional learning disabilities are more likely to show executive deficits [29]. But the fact that it is possible for people with AS to exist with no demonstrable executive dysfunction, whilst still having deficits in empathizing and talents in systemizing [30], suggests that executive dysfunction cannot be a core feature of autism spectrum conditions.

The executive account has also traditionally ignored the *content* of 'repetitive behaviour'. The empathizing-systemizing theory, by contrast, draws attention to the fact that much repetitive behaviour involves the child's 'obsessional' or strong interests with mechanical systems (such as light switches or water taps) or other systems that can be understood in terms of rules and regularities. Rather than these behaviours being a sign of executive dysfunction, these may reflect the child's intact or even superior interest in systems. One study suggests that autistic obsessions are not random with respect to content (which would be predicted by the content-free executive dysfunction theory), but that these tend to cluster in the domain of systems [31].

D. CENTRAL COHERENCE (CC) THEORY

The normal brain is held to show 'strong' central coherence (or Gestalt processing), i.e. a preference for global over local processing. 'Weak' central coherence [32, 33] refers to the individual's preference for local detail over global processing. This has been demonstrated in terms of an autistic superiority on the Embedded Figures Task (EFT) [34] and the Block Design sub-test of the Weschler IQ tests [35–37]. It has also been demonstrated in an autistic deficit in integrating fragments of objects and integrating sentences within a paragraph [38, 39]. The faster and more accurate performance on the EFT and Block Design Test have been interpreted as evidence of good segmentation skills and superior attention to detail. The latter has also been demonstrated on visual search tasks [40, 41].

Systemizing requires as a first stage excellent attention to detail, identifying parameters that may then be tested for their role in the behaviour of the system under examination. So, both the E-S theory and the CC theory predict excellent attention to detail. However, the E-S and CC theories also make opposite predictions when it comes to an individual with autism being able to understand a whole system. The E-S theory predicts that a person with autism, faced with a new system to learn, will show a stronger drive to learn the system, compared with someone without autism, as long as there are underlying rules and regularities that can be discovered. Moreover, they will readily grasp that a change of one parameter in one part of the system may have distant effects on another part of the system. By contrast, the CC theory predicts that they should fail to understand whole (global) systems or the relationships between parts of a system. This has not yet been tested.

Autism and the brain

A neural basis of empathy or social intelligence was first proposed by Brothers [42]. She suggested from animal lesion studies [43], single-cell recording studies [44] and neurological studies that social intelligence was a function of three regions: the amygdala, the orbitofrontal cortex (OFC), and the superior temporal sulcus and gyrus (STG). Together, she called these the 'social brain'. In this next section, I focus particularly on the role of the amygdala in social intelligence [45].

THE AMYGDALA

There are two important lines of evidence implicating the amygdala in primate social behaviour. Extensive reviews exist elsewhere [43]. Here we summarize two main lines of evidence.

(a) Lesions of the primate amygdala affect social behaviour

Amygdala-lesioned monkeys become socially isolated. They fail to initiate social interactions and to respond appropriately to social gestures [43, 46].

(b) Neuro-imaging studies in humans

The human amygdala is activated in humans when decoding signals of social importance, such as gaze, expression-recognition (especially of fearful faces) and body movements) [47–52].

There are four lines of evidence for an amygdala deficit in autism [53].

(i) Post-mortem evidence

A neuro-anatomical study of adults with autism at post-mortem found microscopic pathology (in the form of increased cell density) in the amygdala, in the presence of normal amygdala volume [54, 55].

(ii) Similarities between autism and patients following amygdalotomy

Patients with amygdala lesions show impairments in social judgement [56, 57] that have been likened to 'acquired autism' [58]. The age of onset of deficits in acquired vs. idiopathic cases is likely to mean that the two syndromes also differ in many ways, too. Similarly, patients with autism tend to show a similar pattern of deficits to those seen in patients with amygdala lesions [59].

(iii) Structural neuro-imaging

A recent structural magnetic resonance imaging study of autism reported reduced amygdala volume [60]. This is not the only structural abnormality in the brain (see below), but the amygdala abnormality has some potential relevance to the social symptoms observed. It is not yet known why this difference occurs.

(iv) Functional neuro-imaging

Using single photon emission computed tomography (SPECT), patients with autism spectrum conditions show significant reductions in temporal lobe blood flow. This is not simply an effect of temporal lobe epilepsy [61]. In a recent functional magnetic resonance imaging (fMRI) study, adults with High Functioning Autism (HFA) or AS showed significantly less amygdala activation during a mentalizing task (Reading the Mind in the Eyes task), compared with normal [47].

OTHER BRAIN AREAS THAT MIGHT BE ABNORMAL IN AUTISM

Whilst the above section highlights the likely role an amygdala abnormality might play in autism, it is likely that this is not the only abnormal neural region. For example, the case has been made for anomalous functioning in the cerebellum [62], hippocampal formation [63], left medial frontal cortex [64], and fronto-limbic connections [65] in autism. Reduced neuron size and increased cell-packing density has also been found in the limbic system, specifically the hippocampus, subiculum, entorhinal cortex, amygdala, mammillary bodies, anterior cingulate and septum in autism [54, 66–69]. A full review of neuro-imaging of autism may be found elsewhere [70].

Genetics

Ultimately, the behavioural, cognitive, affective and neural abnormalities in autism spectrum conditions are likely to be due to genetic factors. For example, in an epidemiological study of same-sex autistic twins, studying 27 pairs of MZ twins and 20 DZ twins, it was found that 60% of MZ pairs were concordant for autism vs. 0% of DZ pairs [71]. When this study considered a broader phenotype (of related cognitive or social abnormalities), 92% of MZ pairs were concordant vs. 10% of DZ pairs. The high concordance in MZ twins indicates a high degree of genetic influence. Molecular genetic studies are beginning to narrow down candidate regions on certain chromosomes. The International Molecular Genetic Study of Autism Consortium (IMGSAC) [72] conducted a two-stage genome search for susceptibility loci in autism in 87 affected sib pairs plus 12 non-sib affected relative-pairs from a total of 99 families. Regions on six chromosomes were identified that generated a multi-point maximum lod score of greater than 1. A region on chromosome 7q was the most significant, with a maximum lod score of 3.55 near markers D7S530 and D7S684 in the subset of 56 UK affected sib-pair families, and a maximum lod score of 2.53 in all 87 affected sib-pair families.

There may also be a relationship between autism and specific language impairment (SLI) because genetic studies in each disorder point to a locus on chromosome 7q31 [73]. The IMGSAC's later study [74] analysed 125 sib pairs meeting stringent inclusion criteria and found a multi-point maximum lod score of 2.15 at marker D7S477, whereas analysis of all 153 sib pairs generated a multi-point maximum lod score of 3.37. Linkage disequilibrium mapping identified two regions of

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