Autism is diagnosed when a child or adult has abnormalities in a "triad" of behavioural domains: social development, communication, and repetitive behaviour/obsessive interests. Autism can occur at any point on the IQ continuum, and IQ is a strong predictor of outcome. Autism is also invariably accompanied by language delay (no single words before 2 years old). Asperger syndrome (AS) is a subgroup 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 with an IQ in the average range or above. In this editorial, the main cognitive theories of autism are summarised. These are then followed by a summary of the key neurobiological findings.

AUTISM: COGNITIVE ASPECTS

The mind blindness theory of autism proposes that in autism spectrum conditions there are deficits in the normal process of empathy, relative to mental age. These deficits can occur by degrees. The term "empathising" encompasses a range of other terms: "theory of mind", "mind reading", "empathy", and taking the "intentional stance". Empathy involves two major elements: (1) the ability to attribute mental states to oneself and others, as a natural way to make sense of the world; and (2) having an emotional reaction that is appropriate to the other person’s mental state (such as sympathy).

Since the first test of mind blindness in children with autism, there have been more than 30 experimental tests. The vast majority of these have revealed profound impairments in the development of their empathising ability. These are reviewed elsewhere. Some children and adults with AS only show their empathising deficits on age appropriate adult tests. This deficit in their empathising is thought to underlie the difficulties such children have in social and communicative development, and in the imagination of others’ minds. We can think of these symptoms as the triad of deficits (see fig 1).

Systemising is the drive to analyse systems, in order to understand and predict the behaviour of 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). 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 relations. The empathising-systemising (E-S) theory holds that alongside the empathising deficits in autism (see above), systemising is either intact or superior. Studies suggest systemising in autism is at least in line with mental age, or superior. Systemising may relate to a different set of features which we can think of as the triad of strengths (see fig 2).

People with autism spectrum conditions show unusually strong repetitive behaviour, a strong desire for routines, and a “need for sameness”. One cognitive account of this aspect of the syndrome is the executive dysfunction theory. This assumes that autism involves a fronto lobe pathology leading to persevering or inability to shift attention. There is some evidence for such executive deficits. But the fact that it is possible for people with AS to exist who have no demonstrable executive dysfunction while still having deficits in empathising and talents in systematising, suggests that executive dysfunction is unlikely to be a core feature of autism spectrum conditions.

The executive account has also traditionally ignored the content of “repetitive behaviour”. The E-S theory in 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 faucets) 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 test to cluster in the domain of systems. Weak central coherence (CC) 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) and the block design subtest. It has also been shown in terms of an autistic deficit in integrating fragments of objects and integrating sentences within a paragraph. 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.

Systemising requires 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, so 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. In contrast, the CC theory predicts that they should fail to understand whole (global) systems or the relation between parts of a system. This has not yet been tested.

AUTISM: NEUROBIOLOGICAL ASPECTS

Neuropathology
Anatomical abnormalities have been identified in many brain areas in autism. These include the cerebellum, the brain stem, parietal lobes, hippocampus, and the amygdala. Epilepsy also occurs commonly, at least in classic autism. In terms of neuropathology, the number of Purkinje cells in the cerebellar cortex is abnormally low. This has been postulated to lead to disinhibition of the cerebellar deep nuclei and consequent overexcitement of the thalamus and cerebral cortex. Abnormalities in the
density of packing of neurons in the hippocampus, amygdala, and other parts of the limbic system have also been reported. An abnormally low degree of dendritic branching was also found in a Golgi analysis of the hippocampus of two autistic brains, though it remains to be seen if such an abnormality is confirmed in a larger sample. A separate report suggests a reduction in the size of cortical minicolumns and an increase in cell dispersion within these minicolumns. These might indicate an increase in the number of and connectivity between minicolumns.

Neurophysiology
Hyper arousal in response to sensory input, and decreased ability to select between competing sensory inputs, has been reported. Functional neuroimaging suggests increased activity in sensory areas of the brain normally associated with stimulus driven processing, and decreased activity in areas normally associated with higher cognitive processing. Thus, on the EFT, people with autism show unusually high activation in ventral occipital areas and abnormally low activation in prefrontal and parietal areas. In one study they also failed to show normal activity in the fusiform “face area”, instead showing abnormally high activity in the peristriate cortex and inferior temporal gyrus. The visual N2 to novel stimuli is abnormally delayed in autistic individuals. The P3 in response to auditory stimuli is abnormally generalised to occipital sites in visual cortex.

Regarding EEG results, the P1 evoked potential is either abnormally heightened in response to auditory stimuli that are the target of attention, or abnormally generalised to stimuli that are outside the target of attention. Both hemispheres show abnormal activation—indiscriminately—during shifts of attention into either hemifield. Regarding attention research, a deficit has been found in rapid shifting of attention between modalities and between spatial locations and between object features.

Figure 1 The triad of impairments in autism

Figure 2 The triad of strengths in autism

Morphometry
Magnetic resonance imaging (MRI) morphometry shows volume deficits in the cerebellum, and posterior corpus callosum. Regarding the cerebellar abnormalities, a subgroup shows increased cerebellar volume. A volume deficit has also been reported in the parietal lobe. Neuropsychology suggests this is associated with a narrowed spatial focus of attention.

Longitudinal morphometry
Using either MRI volumetric analysis, or measures of head circumference, the autistic brain appears to involve transient postnatal macrocephaly. The brainstem, hippocampus, amygdala, and other parts of the limbic system, and so plausibly plays a role in nurturing behaviour and have epileptiform EEG. At least four loci on the X (STG). Together, she called these the “social brain”. Abnormalities in autism have been found in the amygdala, the orbito and the medial frontal cortex.

Regarding the amygdala, there are four lines of evidence for an amygdala deficit in autism. Firstly, a neuroanatomical study of autism at postmortem found microscopic pathology (in the form of increased cell density) in the amygdala, in the presence of normal amygdala volume. Secondly, patients with autism tend to show a similar pattern of deficits to those seen in patients with amygdala lesions. Thirdly, a recent structural MRI study of autism reported reduced amygdala volume. Finally, in a recent functional magnetic resonance imaging (fMRI) study, adults with high functioning autism (HFA) or Asperger syndrome (AS) showed significantly less amygdala activation during a mentalising task (Reading the Mind in the Eyes task) compared with normal.

Reduced activity has also been found in the left medial frontal cortex, during an empathising (theory of mind) task, and also in the orbitofrontal cortex.

GENETICS OF AUTISM SPECTRUM CONDITIONS
Ultimately, the cognitive and neural abnormalities in autism spectrum conditions are likely to be caused by genetic factors. The sibling risk rate for autism is approximately 4.5%, or a tenfold increase over general population rates. In an epidemiological study of same sex autistic twins, it was found that 60% of monozygotic (MZ) pairs were concordant for autism versus no dizygotic (DZ) pairs. When they considered a broader phenotype (of related cognitive or social abnormalities), 92% of MZ pairs were concordant versus 10% of DZ pairs. The high concordance in MZ twins indicated a high degree of genetic influence, and the risk to a co-MZ twin can be estimated at over 200 times the general population rate.

Molecular genetic studies are beginning to narrow down candidate regions. There is still little consensus, but two regions have been identified in several (but not all) studies. These are 15q11-13, near the GABABR1 receptor subunit gene (GABBR1) and a second one on 17q11.2, near the serotonin transporter gene (SLC6A4). The latter is of interest because of reports of increased serotonin (5HT) levels of platelets in autism [204]. Serotonin innervates the limbic system, and so plausibly plays a role in emotion recognition and empathy. Mothers homozygous for GABBR1 knockout fail to engage in normal nurturing behaviour and have epileptiform EEG. At least four loci on the X
chromosome have also been implicated in autism, and are of interest for their power to explain the sex ratio in autism (markedly biased towards males). These are the neurulin genes (NLGN3, NLGN4), FMR1 (which causes fragile X syndrome), and MECP2. Several reviews of the genetics of autism literature are available, but this is a fast changing field.

As of yet, specific genes for autism have not yet been identified, despite the encouraging possibility of candidate regions on chromosomes. The future of research in this field will be not only to isolate the relevant genes but also to understand the function of these genes, and ultimately the relation between these different causal levels in autism. It is hoped that during this research endeavour there will also be evaluations of the most promising treatments.

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the non-motor manifestations of essential tremor may be important

L J Findley

The non-motor manifestations of essential tremor may be important
EDITORIAL COMMENTARY

Motoric neurorehabilitation

Optimising multi-task performance: opportunities for motoric neurorehabilitation

M A Hirsch

The stops walking while talking test; a dual task for motoric neurorehabilitation—further complexities of the test?

In their study, Hyndman and Ashburn administered the stops walking while talking test (SWWT) to predict the occurrence of falls (see p 994, this issue). Optimising multi-task cognitive and motor performance and targeting individuals who may benefit from therapeutic interventions to improve gait and reduce falls after stroke are important goals of neurorehabilitation. Dual task paradigms, such as walking while talking, can substantially alter motor and cognitive performance in younger and older adults with and without pathology. The authors’ results are particularly interesting in the light of the possibilities of dual task therapies to prevent falls in persons with brain dysfunction. For example, one study showed that treatment with electromagnet fields improves dual task performance. Much time is spent during rehabilitation to improve a patient’s functional gait parameters and few therapies are evidence-based. Evidence-based techniques in motoric neurorehabilitation of gait following stroke often include treadmill training with partial body weight support (TTPBWS). Dramatic improvements in gait can be observed during a single TTPBWS session where patients practice

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up to several thousand gait cycles on a motorised treadmill, while their bodyweight is partially supported by a parachute harness. This is thought to maximise motor practice time because the treadmill “forces” patients to ambulate in a safe environment with minimal fear of falling. Future studies should address the complementary nature of SWWT during TTPBWS, by assessing the precise effect of a cognitive task on gait in older adults. Rather than asking simple questions and measuring if patients respond by stopping or not stopping, future studies should examine elements of speech itself, such as speech rate, grammatical complexity, sentence length and structure, and their effects on gait patterns. Gait velocity should be controlled and this can be done with a treadmill. Then we may begin to ask if gait (and speech) patterns differ between stopper and non-stoppers. Optimally, the effects on gait should be studied in greater detail using three dimensional computerised gait analysis systems. Lower extremity leg strength and activity level should also be assessed. Most importantly, does dual task therapy transfer to functional gains in a real world environment? Answers to these questions may give further insights into the wondrous potential of the brain to recover from injury.


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