

# The neurocognitive basis of autism

Uta Frith

**The cognitive study of the underlying mental abnormalities in autism has advanced rapidly, while the biological study of the underlying brain abnormalities and of putative genetic mechanisms is lagging somewhat behind. However, the linking of cognitive and biological studies has become a real possibility. Developmental cognitive neuroscience has transformed our understanding of this enigmatic disorder, which was once misguidedly thought to be caused by maternal rejection. The hypothesis of a specific theory of mind deficit was a crucial step in this process. It explains the puzzle of the characteristic social and communication impairments of autism and allows for the fact that they can coexist with good general abilities. This hypothesis has been widely accepted and a start has been made at pinpointing the brain basis of theory of mind. The non-social impairments of autism have now become a major focus for cognitive research. One theory proposes dysfunction in executive processes, in an attempt to explain repetitive behaviour and inflexibility. Another theory proposes weak information integration, in an attempt to explain narrow interests and special talents. Autism research has thus stimulated ideas on important mind-brain systems that may be dedicated to the development of social awareness, executive functions and integrative processing.**

**A**utism holds a peculiar fascination from which neuroscientists have not been immune. This fascination is reflected in the publication of three major field reviews in the last two years<sup>1–3</sup>. Why does a rare disorder excite such interest? And what are the advances in research that prompted the recent reviews?

Autism was first labelled by Kanner<sup>4</sup> and Asperger<sup>5</sup> in the forties and has had a firm place in psychiatric textbooks ever since. Many theories about the origin of autism have been put forward and these have gradually become focused on genes, brain and mind<sup>6</sup>. But in what way has the explanation of autism progressed? Both cognitive and biological studies have contributed to a better understanding. However, it is the promise of linking together the cognitive and biological aspects of autism in a principled way, that makes the field so particularly exciting.

#### A rare disorder?

Autism, defined as a psychiatric disorder of early onset with marked aloofness and obsessive desire for sameness, was found to occur in four out of every 10 000 births<sup>7</sup>. These inspired, if somewhat arbitrary, criteria have now been broadened on the basis of better knowledge of the nature and course of the disorder. Given these broader criteria, recent studies show that autism affects between 10 and 30 individuals in every 10 000, that is, 0.1–0.3%. Males predominate at a ratio of ~2.5:1, and this ratio increases with

higher levels of ability<sup>8</sup>. Whether or not this reflects an increase in the condition remains conjecture<sup>9</sup>. The population estimates do not include individuals with more subtle forms of impairment. A Scandinavian study suggests that the prevalence of this variant, now labelled Asperger syndrome, might be as high as 0.5–0.7% (Ref. 10).

#### Individual differences in the clinical picture

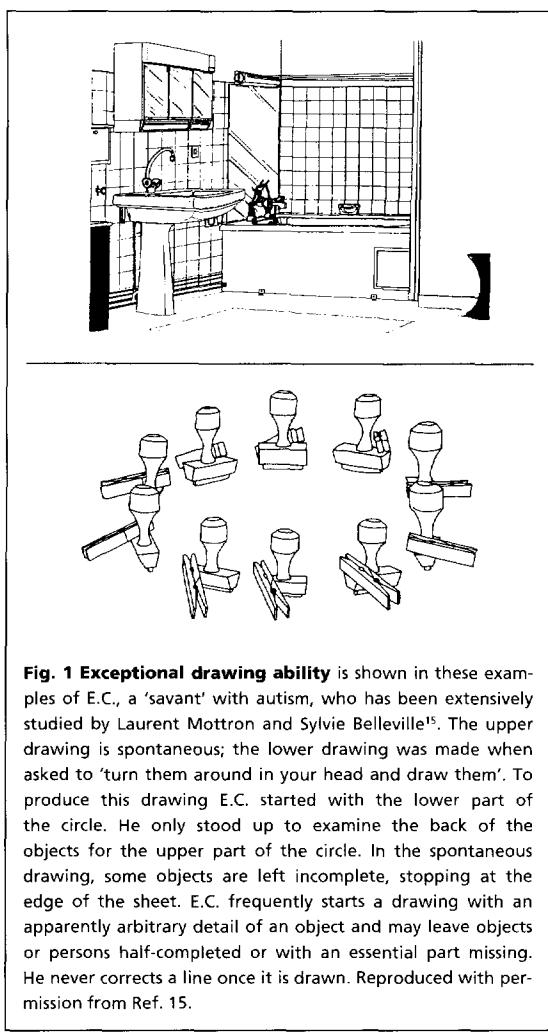
The chief diagnostic criteria for autism, as set out in ICD-10 (Ref. 11) and DSM-IV (Ref. 12), are abnormalities of social interaction, impairments in verbal and non-verbal communication and a restricted repertoire of interests and activities, all being present from early childhood. The diagnostic criteria for Asperger syndrome overlap, but stipulate that there should be no significant developmental delay in cognitive and language functions.

Three-quarters of the individuals affected by autism suffer from mild to severe mental retardation. Measured IQ, at all levels, shows marked peaks and troughs on different subtests<sup>6,13</sup>. The presence of savant skills is as high as 10% in the autistic population, and conversely, almost all savants are diagnosed as suffering from autism<sup>14</sup>. The savant is defined as an individual with outstanding skill in one of a small range of areas of interest, including calendar calculation and high musical or artistic competence, while his other intellectual abilities can be at a very low level. Examples of drawings by a savant artist are shown in Fig. 1 (Ref. 15).



U. Frith is at the  
MRC Cognitive  
Development Unit,  
4 Taviton Street,  
London,  
UK WC1H 0BT  
and University  
College London, UK

tel: +44 171 387  
4692  
fax: +44 171 383  
0938  
e-mail: u.frith@cdu.  
ucl.ac.uk



The extent of individual variability in signs and symptoms, and intellectual abilities, has only recently become appreciated fully<sup>13</sup>. The interaction between specific disabilities and general compensatory processes might account for some of the variability, but has hardly been investigated. Thus, some individuals, notably those with more severe forms of mental retardation, never develop speech or other means of communication, while others acquire fluent language<sup>16</sup>. However, even well compensated individuals will show some difficulty with the to-and-fro of everyday chat. This will be noticeable in the prosody, style and content of speech. Obsessive and repetitive tendencies, as well as narrow interests, also vary and are prevalent in individuals of both low and high general ability. They often impose a heavy burden; long neglected, these features are now receiving renewed research interest<sup>13,17</sup>.

#### The developmental course

The clinical picture of autism differs between individuals and changes markedly over the course of development, with a tendency towards improved adaptation. Nevertheless, the underlying cognitive disorder (and by implication, brain abnormality) appears to remain throughout life. It is during early childhood that all the characteristic signs of autism are most strongly apparent, in particular, poverty of imaginative play and lack of social-emotional rapport with other children. A simple screening instrument applied at 18 months

of age has been remarkably successful at predicting autism. Identification of autism at this age is based on a failure to show ordinary pointing for the purpose of shared attention, an absence of gaze monitoring and an absence of pretend play<sup>18</sup>.

Autistic individuals with near normal or higher intellectual ability, while not exempt from behavioural problems, can show a high degree of improvement and adaptation, and this may make their diagnosis controversial. One particular challenge is to explain why the prospects of leading an independent normal life are poor, even in individuals whose overt impairments are subtle. These individuals still show problems with peer interaction and are extremely unlikely to have intimate friends. They also tend to have difficulties in planning their daily life and, perhaps as a secondary consequence of their condition, may suffer from high levels of anxiety or depression. An important question concerns the factors contributing to compensation and their costs to the individual. For instance, 'passing for normal' in social interactions may require continuous effort, perhaps because non-intuitive and non-automatic information processing strategies are required.

It is less difficult to explain the daily living problems of autistic individuals who also suffer from mental retardation. The most severe cases remain socially unaware, lack both verbal and non-verbal communication, and often have challenging behaviour problems, including self-injury. The management of these problems is largely based on behaviour modification techniques. Cognitive models have so far contributed little to this area. Since cooperation in psychological experiments is hard to gain from this subgroup, relevant research is rare.

Life span studies of autism covering middle and old age are as yet lacking. Similarities between low-functioning autistic individuals in middle age with negative symptom schizophrenics have been pointed out. This observation may yield clues to dysfunction at the neural level, even if onset and course of the disorders are different<sup>19</sup>.

#### The autistic spectrum

Three primary features: characteristic impairments in socialization, communication and imagination were identified as highly correlated in a geographically defined population study<sup>20</sup> of autism. They have been shown to emerge early and persist in development even though their precise manifestation changes (Fig. 2). For example, aloofness may give way to social pestering. The triad of impairments appears to be a common denominator throughout a spectrum of autistic disorders.

#### The broader phenotype

Twin studies too have resulted in the recognition of a broader autistic phenotype that confirms and extends the notion of the autistic spectrum. The strong heritability of autism is beyond doubt. Given a narrow definition of autism, if one member of a pair of monozygotic twins has the disorder, then in over a third of cases the other twin also has it. In contrast, such concordance is hardly ever found in dizygotic twin pairs. When a wider definition of autism is used, allowing for more subtle impairments, then the concordance rate doubles, with 72% for monozygotic vs 10% for dizygotic

pairs<sup>21</sup>. Clearly, the clinically based category of autism currently used is rather strict compared to the phenotypically derived category. This suggests that there may be hidden cases. There could be as yet unknown factors that protect some individuals from being affected by the clinically significant disorder, despite a genetic predisposition.

#### Asperger syndrome

One of the most important changes in autism research and practice in the last five years has been the growing recognition of a subgroup of individuals with high verbal ability and the potential for good social adaptation. Asperger syndrome is still a controversial concept and has uncertain boundaries with other clinical categories, such as high-functioning autism, atypical autism and schizoid personality<sup>22,23</sup>. Typically, the diagnosis of Asperger syndrome is made in later childhood, or even adulthood, even though abnormalities have been present from early in life. Sometimes, a late diagnosis is made where the initial diagnosis was classical autism, and where language and social communication has improved beyond expectation. Sometimes, a late diagnosis is made where the initial assumption was 'eccentricity', tolerated within the family, but not outside. The Asperger variant of autism is often called 'mild'. This obscures the fact that Asperger syndrome sufferers have distinct handicaps in social and non-social spheres of everyday life, ranging from mild to severe. Thus, an individual who is also very able intellectually, can become a respected academic whose communication problems, obsessive tendencies and restricted interests may be overlooked; however, a less fortunate and less able individual may be shunned by society and be a danger to himself and others.

#### Biological studies

Behavioural genetic data suggest a small but significant recurrence rate in families and favour a multiplicative, multi-locus model of inheritance, perhaps involving only a small number of genes<sup>2</sup>. However, no precise findings are as yet available. Other disorders of known biological origin, such as fragile-X syndrome, phenylketonuria and tuberous sclerosis, can lead to the clinical picture of autism, but this is usually linked to severe mental retardation<sup>24</sup>.

Neurological and neuropsychological signs, such as epilepsy, motor abnormalities and abnormal profiles on psychological tests have always been noted. Recent studies have highlighted the resemblance of the profiles to those of patients with frontal lobe and right hemisphere lesions<sup>25-27</sup>. Post-mortem brain studies have revealed a number of abnormalities in cell structure in the hippocampus, amygdala and cerebellum. The findings suggest a curtailment of neuronal development at, or before, 30 weeks of gestation<sup>28</sup>. *In vivo* brain imaging studies have also shown a number of abnormal patterns in brain structure and function in these and additional regions. None of these studies are, however, specific or consistent enough to build up a coherent theoretical picture of the origin and nature of the brain abnormality.

#### The theory of mind deficit hypothesis

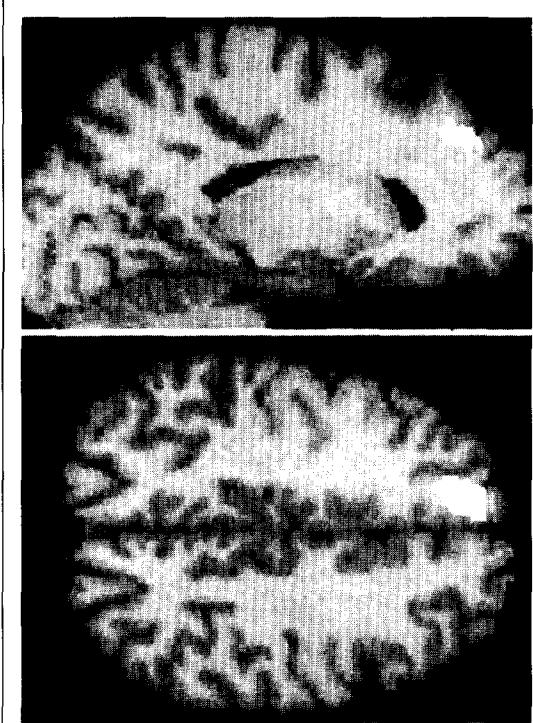
Cognitive explanations of the core features of autism provide a vital interface between brain and behaviour. The proposal



**Fig. 2 Photograph of a young autistic child.** Children with autism are often fascinated by unusual objects. While the social and communication impairments of autism have received a great deal of research interest, the non-social features are now beginning to be understood as well. This photograph is reproduced by kind permission of Sue's family.

of a specific neurologically based problem in understanding minds was a significant step in this endeavour<sup>29</sup>. The hypothesis that autistic children lack the intuitive understanding that people have mental states, was originally tested with the Sally-Ann false-belief paradigm<sup>30</sup>. This hypothesis has been confirmed in a number of studies, and the idea of a theory of mind deficit in autism has been widely accepted<sup>31</sup>. Individuals with autism fail to appreciate the role of mental states in the explanation and prediction of everyday behaviour. Hence they lack a full understanding of deception, and of those emotions which depend on monitoring other people's attitudes, such as pride.

Individuals with Asperger syndrome stand out from other autism sufferers because they appear to possess an understanding of mental states, although they achieve success on theory of mind tasks at a much later age than normal and, to do this, they require higher levels of verbal knowledge than normally developing children<sup>32</sup>. This could be because they show extremely delayed development of the prerequisite neurocognitive mechanism or because they have been able to work out an alternative non-intuitive theory of mind. The relationship between better mental state understanding and better verbal ability in Asperger syndrome is consistent with the suggestion that language acquisition itself is facilitated by the ability to attribute intention to other speakers<sup>16</sup>. A recent PET scan study of story comprehension, revealed that an area in the left medial prefrontal cortex, shown in Fig. 3, was active when normal volunteers had to infer the mental states of the story characters<sup>33</sup>. This



**Fig. 3 A PET scan study** by Fletcher *et al.*<sup>33</sup> revealed that when normal volunteers read a story which critically involves 'theory of mind', the highlighted area in the left medial prefrontal cortex (Brodmann area 8/9) is activated.

remarkably circumscribed area was not active in individuals with Asperger syndrome when studied under the same conditions<sup>34</sup>. Further studies are needed to elaborate these results; however, it is striking that another study using a different mental state inference task also found increased activation in this area<sup>35</sup>, as did a previous study on story comprehension<sup>36</sup>. Such findings may provide an exciting lead to the brain-mind basis of self-awareness.

#### The executive dysfunction hypothesis

A specific deficit in theory of mind is unable to account for the whole of the clinical picture of autism. This is particularly true for those features of autism that are encompassed by an obsessive desire for sameness. These features are being successfully tackled by a theory which proposes a deficit in executive functions. These functions include planning, working memory, impulse control, shifting set and the initiation and monitoring of action<sup>37</sup>. All are thought to depend on systems which involve prefrontal activity in the brain and are typically impaired in a range of disorders that are likely to involve defects in the frontal lobe, including attention deficit disorder, obsessive compulsive disorder<sup>38</sup>, Tourette syndrome, phenylketonuria and schizophrenia. Poor performance on many executive function tasks has been documented in autism<sup>17,38</sup>; for instance, individuals with autism and Asperger syndrome often fail to inhibit overlearned responses when these are no longer appropriate. Poor performance on these tasks is directly related to stereotyped and rigid behaviour in everyday life as shown in highly repetitive thought and action. Problems are also observed in the initiation and monitoring of action. The

underlying brain abnormality is likely to involve a distributed system with strong neural connections between basal ganglia, striatum and prefrontal cortex, such as the dopamine system<sup>40</sup>. This would fit in with the tentative brain imaging results on theory of mind which highlighted the medial prefrontal cortex. However, the relationship between deficits in executive functions and theory of mind has yet to be investigated across frontal lobe disorders.

#### The weak central coherence hypothesis

A cognitive theory which proposes weak information integration/central coherence<sup>6,13,41</sup> addresses the islets of ability and exceptional talents which are present in a significant proportion of individuals with autism and Asperger syndrome. The theory links these assets to the striking phenomenon of restricted interest. The attention of the autistic individual is often captured by fragments or surface features of objects and sensations that are usually of little interest to normal people. In one particular case, the special interest was the colour of the doors of juvenile magistrates courts – not those of adult courts<sup>22</sup>! Performance peaks in tests such as 'block designs' and 'embedded figures', as well as outstanding feats of rote memory or detailed drawing of objects<sup>15</sup>, appear to demonstrate a preference for segmental over holistic information processing. Evidence that people with autism process information in an unusually piecemeal fashion, at both the behavioural and physiological level, was provided by the brain imaging study of Happé *et al.*<sup>34</sup> Here the autistic participants showed less difference in performance, as well as in brain activity, for processing meaningful stories versus meaningless text (jumbled sentences) compared with normal controls. This is consistent with the findings of a study where they failed to integrate information so as to derive contextually relevant meaning. For instance, when reading aloud: 'the dog was on a long lead', they pronounced the word lead as 'led'<sup>42</sup>. A study in the visual domain that may relate to lack of integration showed that individuals with autism are less susceptible to certain visual illusions: this may be because they are less affected by the context surrounding the lines to be judged<sup>43</sup>.

The relationships between central coherence, executive functions and theory of mind are as yet unclear. The brain basis of central coherence is an open question. One particularly intriguing suggestion follows from the finding that the brain is organized to sense the synchronicity of cells firing in different locations<sup>44</sup>. This capacity is thought to provide the necessary cues for the binding of information. Thus, at the level of brain physiology, impairment in the sensing of synchronicity could lead to lack of coherence in perceptual processing. At the cognitive level this might be reflected as a lack of coherent perceptual experience.

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## Outstanding questions

- The unravelling of the biological causes of autism is eagerly awaited. Such work should clarify diagnosis through direct biological markers. It might lead also to new approaches to the treatment and/or prevention of autism. Important bridges between neurobiology and cognitive processes, such as those underpinning 'theory of mind' and executive functions, are currently being built by a number of different investigators. In this sense, the study of autism serves a much wider aim than that of understanding the basis of the disorder.
- The question of individual variability and compensation is notoriously difficult. It will be fascinating to compare high functioning autism, Asperger syndrome and normal eccentricity. Are there sharp dividing lines? Are there also marked individual differences in the normal population in the critical abilities underlying the social and non-social impairments in autism? The systematic study of the most severely impaired individuals is overdue. It will be important to investigate how well autistic and non-autistic individuals can be distinguished on specific cognitive tests at moderate and severe levels of mental retardation. The study of the course of the disorder over time should eventually lead to the identification of useful predictors of the quality of social adaptation and communication.
- The juxtaposition of impaired and intact abilities in autism appears to support a modular model of the mind where specific deficits can be confined to particular modules. The neurological system underlying theory of mind is close to being identified in functional brain imaging studies. A similar approach should also elucidate the non-social features of autism. However, the effects of poor executive functions, weak central coherence and general mental retardation are pervasive rather than modular. How do specific mental components and general cognitive systems interact?
- Autism research has stimulated philosophical debate on self-consciousness, since it provides an example of the failure to reflect on mental states. The further experimental study of this topic should intensify with the development of ideas on subcomponents and precursors of theory of mind in other species. These ideas, in turn, might stimulate neuropathological, neurochemical and neurogenetic research on the development of conscious experience. This provides a thrilling prospect for a long-term research programme of far reaching importance.

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