

Introduction: autism — the challenges ahead

Michael Rutter

*Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry,
De Crespigny Park, Denmark Hill, London SE5 8AF, UK*

There have been many important advances in research into the nature of autism and, as a result, our concepts of autism have undergone a radical change (Rutter 1999). At one time, the prevailing view was that autism was an unusually early variety of schizophrenia that had been caused, in large part, by so-called refrigerator parenting. It became clear that that was a wholly mistaken concept and that, instead, autism constitutes a neurodevelopmental disorder with a rather distinctive pattern of cognitive deficits, and that it is strongly genetically influenced.

Nevertheless, we are a long way from understanding the basic pathophysiology, and numerous puzzles and paradoxes remain. The aim of this symposium is to grapple with these issues, tackling the challenges from a range of different perspectives in the hope that a coming together of minds, and of different research strategies, may point the way ahead. My task is to set the scene by outlining some of these challenges in order to provoke us all to abandon the safety of our own research territory, and of the findings that are well established, in order to focus on the difficulties that are inherent in our favoured theories.

We need to begin with implications of the huge rise in diagnosed autism (Baird et al 2000, Chakrabarti & Fombonne 2001, Fombonne 1999). To a substantial extent, this rise is a consequence of a major broadening of the concept of autism together with better ascertainment. However, is that all? When like is compared with like, has there been a real rise in the rate of autism? If that should prove to be the case, what is the environmental factor that has brought this about (the rise is unlikely to have been genetically determined)? There have been claims that the rise is due to the use of the combined measles/mumps/rubella (MMR) vaccine but that does not seem very likely. The rise began before the introduction of MMR and it continued to rise, without any plateauing, after MMR was used with the vast majority of the population (Dales et al 2001, Farrington et al 2001, Taylor et al 1999). But, if that is not the cause, what is?

The prevailing consensus at the moment is that autism spectrum disorders constitute a continuum extending from mild autism to severe handicap. That could prove to be the case but, if so, why is it that individuals with the so-called broader phenotype do not have associated mental retardation and do not seem to have an increase in the rate of epilepsy, both being very characteristic correlates of autism (Rutter 2000)? The question has to be addressed if only because the limited genetic evidence from twin studies indicates that the broader phenotype seems to share the same genetic liability (Le Couteur et al 1996). Could there be some kind of two-hit mechanism? If so, what is it that provides impetus for the shift from the broader phenotype to major handicap?

Asperger syndrome appears to involve exactly the same qualitative deficits as those associated with autism, but, unlike autism, this has not been associated with any delay in early language development and abnormalities are usually not clearly manifest until after infancy. Of course, that is not to suggest that language development is necessarily fully normal (indeed there are good reasons to suppose that it is not) but the existence of the syndrome provides a challenge to those who have viewed the language deficits as basic. It also provides a challenge to those who have argued that autism is almost always manifest from at least the age of 18 months, if not considerably earlier (Osterling et al 2002). Of course, it may be that a careful analysis of the social and communicative behaviour of individuals with Asperger syndrome would show early abnormalities, but what is clear is that the abnormalities are usually not recognized by either parents or professionals until quite a lot later (Gilchrist et al 2001). If Asperger syndrome is synonymous with mild autism, what does this mean?

In most cases, autism involves no developmental regression or loss of skills. However, numerous studies have shown that in about a quarter of cases, there is a temporary loss of language skills usually in the second half of the second year (Kurita 1985, Rogers & DiLalla 1990). This is often accompanied by a change in social interaction and a loss of pretend play, but it is not usually accompanied by a loss of motor, or other, skills. So far, evidence suggests that there is nothing distinctive about autism that is accompanied by regression. Interestingly, regression seems to be as common in autism when it occurs in two or more members of the same family (Parr et al 2003), with the implication that regression is neither more nor less common when it is likely that there is a strong genetic liability. What, therefore, does the regression mean?

Over the years, evidence has accumulated that the clinical picture of autism in early childhood is seen in several atypical circumstances. Thus, for example, it was described in children with congenital rubella, the follow-up indicating that, although the children tended to remain severely handicapped, the autistic features lessened (Chess 1977). Autistic-like syndromes have also been described in congenitally blind children (Hobson et al 1999), and in children who have

suffered severe institutional deprivation (Rutter et al 1999). Careful analysis suggested that the picture is in some respects slightly atypical and, at least in the case of the institution-reared children, the autistic features tend to diminish as the children grow older. What do these findings tell us about the nature of autism or the cause of the syndrome? Some may be tempted just to dismiss the descriptions as representing phenocopies but there is still the need to account for the emergence of the picture strongly resembling autism.

There is then the further question of the overlap with semantic-pragmatic language disorders (Bishop 2000). It is clear that the two cannot be regarded as entirely synonymous because by no means all children with semantic-pragmatic language disorder show the features of autism (Bishop & Norbury 2002). The follow-up of the sample of boys with severe developmental disorder of receptive language, first seen in early childhood has brought out two further findings that need taking into account. First, although the children with language disorder did not appear at all autistic when young, at least half of them showed substantial social impairment early and mid-adult life (Howlin et al 2000). Second, the adults who had shown this severe developmental disorder of receptive language, were found to have impairments in 'theory of mind' skills at follow-up (Clegg 2002). It is not known, of course, whether the impaired 'theory of mind' skills had been present in early childhood but it seems likely that they must have been. If so, why were they not showing autistic features when young?

One further epidemiological finding requires highlighting. Autism is very much more common in males than females. The ratio is usually given as about 3 or 4:1, but evidence from recent epidemiological studies suggest that the male preponderance is very much greater in the case of autism that is not accompanied by severe mental retardation (Baird et al 2000). As we shall hear, hypotheses have been put forward to account for this sex ratio in autism. However, it is not self evident that the explanation will be found in a feature that is specific to autism. It is noteworthy that a similar marked male preponderance is found in most neurodevelopmental disorders such as dyslexia, attention deficit disorder with hyperactivity, and developmental language disorders (Rutter et al 2003). Is this just coincidence or is there some common factor that is responsible for the male preponderance across this range of disorders? They are all associated with cognitive deficits of one kind or another that are evident in the preschool period. This is quite different from what is seen with female preponderant psychopathological disorders such as depression or eating disorders, which typically have an onset in adolescence and are not accompanied by any marked cognitive deficits. Does this provide a clue as to a causal explanation? Do we need to consider epigenetic mechanisms and, if so, what might they be? Is it likely that prenatal differences in sex hormone pattern have been influential?

Another well established clinical finding concerns the tendency for autism to be associated with increased head size (Lord & Bailey 2002). Probably, this arises after birth and possibly, too, is associated with an increased head size in other members of the family. If the emergence of increased head size after birth is confirmed, what does this imply with respect to the neural processes that are responsible?

As the pioneering studies of Hermelin and O'Connor (1970) demonstrated, it has long been evident that autism is associated with an unusual pattern of cognitive deficits. During the 1980s and 1990s, attention particularly focused on what came to be called 'theory of mind' deficits—meaning an impairment in mentalizing skills that enabled children to use context to assess what another person was likely to be thinking. However, impairments in executive planning, the use of central coherence, and in facial processing have also been found (Hobson 1993, Lord & Bailey 2002, Medical Research Council 2001). It may certainly be accepted that deficits in social cognition constitute an intrinsic part of autism. Nevertheless, questions remain. What are the interconnections, if any, among these various deficits? If theory of mind skills are so crucial, why is autism manifest such a long time before theory of mind skills can be clearly demonstrated? Of course, the answer could lie in cognitive precursors of theory of mind but, if so, what is the explanatory power of theory of mind as such? Even infants are highly social, and so should the explanation be sought in some aspect of social relationships, rather than cognition, as Hobson has suggested? How might these highly specific cognitive deficits account for the language delay and mental retardation that are so commonly associated with autism (Rutter & Bailey 1993)? What accounts for the savant skills or special cognitive talents that occur in a substantial minority of individuals with autism (Hermelin 2001)? Conversely, if these are closely associated with the specific cognitive deficits, why are such talents not found in most individuals with autism? How might the cognitive deficits account for the repetitive stereotyped behaviours that are so characteristic of autism? I have spent quite some time outlining the epidemiological and clinical background because these are the findings that require explanation.

Let me turn now to the genetic findings. The findings suggest that genetic factors account for over 90% of the population variance in the underlying liability (Folstein & Rosen-Sheidley 2001, Rutter 2000). In view of the new evidence indicating that the prevalence of autism is considerably higher than used to be believed, there must be some caution about the precise heritability, because it will be affected to some extent by the assumptions made about the general population base rate. Nevertheless, even if the true rate of autism is as high as 0.6%, the rate in siblings would still be at least 10 times that. The marked fall off rate between monozygotic and dizygotic pairs, together with the fall off in the broader phenotype from first degree to second degree relatives, suggests that it

is likely that some three to 12 genes are involved in the susceptibility to autism, and that there is a synergistic interaction among the susceptibility genes (Pickles et al 1995). But, what are the effects of each of these genes? Do they provide a vulnerability to autism as such or, rather, do they involve susceptibilities for individual components of autism (Bradford et al 2001, Folstein et al 1999)? If they do operate on different components, why is not the rate of each component very much higher than the rate of the syndrome as a whole?

Of course, there are no epidemiological studies that provide precise estimates of each component but such evidence as there is provides no indication that the rates are high. Also, one might expect that individual members of families with a proband showing autism might have only single elements, because they are likely to have only a few of the susceptibility genes. Findings suggest that, although that is sometimes the case, familial loading is mainly for a combined pattern that is similar to autism in quality, although much milder in degree. The history of medical genetics indicates that it must be expected that autism will prove to be genetically heterogeneous. To some extent, we know that it is heterogeneous because of the associations with tuberous sclerosis and with the fragile X anomaly (Lord & Bailey 2002, Medical Research Council 2001). Nevertheless, it is not yet quite clear why either of these conditions predisposes to autism.

If autism is genetically heterogeneous, we have to ask whether the heterogeneity is indexed by clinical variability. Of course, it need not be. The findings on concordant monozygotic pairs show that there is huge clinical variability in the manifestations of autism and of the associated cognitive impairment, even when one may assume that the genetic liability is the same (Le Couteur et al 1996). It is also known that even single gene conditions such as Rett syndrome or tuberous sclerosis show surprisingly wide clinical expression (Sharbazian & Zogbi 2001). What is not known, however, is what causes such variable expression. When variable expression is not properly understood even with single gene disorders, elucidation is likely to prove even more challenging with a multifactorial disorder such as autism.

In sorting out genetic heterogeneity, there must be consideration of the possibility of either multiple mutations of the same gene, as found in Rett syndrome or multiple different genes, as is the case with tuberous sclerosis. As already noted, although the heritability of autism is very high, it does appear to be a multifactorial disorder in which environmental factors also play a role in the overall susceptibility. What are those environmental susceptibility factors? Of course, these may not necessarily involve specific environmental hazards. Thus, they could reflect developmental perturbations of one kind or another (Rutter 2002). The increase in the rate of minor congenital anomalies is perhaps consistent with this suggestion. Recently, it has been argued that the rate of twinning in autism is much increased (Greenberg et al 2001) but it seems likely

that this is an artefact of ascertainment. No substantial increase in twinning was found in the British twin studies of autism (Bailey et al 1995). Nevertheless, the possibility that developmental perturbations might play a role in aetiology is worth further exploration.

Neuropathological studies have been consistent in showing abnormalities but the findings are inconsistent on just what these are (Bailey et al 1996, Lord & Bailey 2002, Medical Research Council 2001). Some reports have emphasized abnormalities in the cerebellum; some have drawn attention to abnormalities in the cerebral cortex and some have focused on neurochemical features. How does this picture fit together? To what extent are the findings a consequence of the fact that most of the brains examined have come from individuals who are severely retarded as well as autistic and most of whom have had epilepsy? How do the human findings fit in with what has been shown with animal models? Are the neuropathological findings informative about the area of the brain that is affected in autism or, rather, do the findings reflect variations in the time point at which development went awry? How do the neuropathological findings fit in with the brain localization findings that have derived from functional imaging studies? In what way, if any, are the findings helpful in understanding why the epilepsy associated with autism so frequently has an onset in late adolescence and at early adult life, rather than the more common onset in early childhood? Are the neuropathological findings informative about the origins of the increased head size in autism? Do they help with respect to the phenomenon of regression?

It has long been known that blood serotonin levels tend to be raised in autism (Cook & Leventhal 1996). However, levels are similarly raised in many other neuropsychiatric disorders and, at least so far, this finding has not helped in understanding the basis of autism. It is clear that reduction of serotonin levels by drugs has not helped. There is a mixed bag of other positive findings in the field of neurochemistry but few have been replicated and they do not seem to add up to any coherent story (Bailey et al 1996, Medical Research Council 2001). On the other hand, it has to be said that the quality of this field of research has not been as high as one might have wished. Is there a potential for doing more and, if there is, what are the strategies that ought to be employed? Similar queries arise with respect to the immune system. Although the claims in relation to MMR do not seem to be well based, there are some pointers indicating that it is too early to rule out the possibility of some form of immune disorder as the basis for at least some cases of autism. Is this possibility a research priority and, if it is, how should it be pursued?

In the field of psychiatry as a whole there are reasonably good pointers that neurotransmitter abnormalities are likely to play some role in disorders as diverse as schizophrenia, depression, and attention deficit disorder with hyperactivity. With each of these conditions, too, there are drugs that have been shown to have quite marked beneficial effects in many, although not all, individuals with the

conditions in question. Attention has been drawn to neuropeptide abnormalities in autism, but these seem not to differentiate autism from mental retardation (Nelson et al 2001). Given the expectation that autism is likely to prove to be some kind of systems disorder, it is surprising that there is so little evidence of either neurotransmitter abnormalities or major benefits from pharmacological interventions. Has research been looking in the wrong place, or are there lessons to be drawn from the largely negative findings? Where do we go from here?

Finally, I need to turn to the benefits associated with psychological interventions. There is no doubt that developmentally modulated, behavioural interventions can bring worthwhile short-term and long-term benefits in autism (Howlin & Rutter 1987). But, how much do they achieve? There have been recent strong claims that early intervention can make a difference (National Research Council 2001) but what is the evidence that this is so? Why are the benefits of intervention specifically focusing on psychological deficits, such as 'theory of mind' that are supposed to underlie autism, so disappointing (Hadwin et al 1996, Ozonoff & Miller 1995)? If the early interventions do make such a major difference, what are the implications for our understanding of the neural basis of autism? What is the evidence that early interventions can alter the neural substrate?

I am hugely impressed by the immense amount that has been achieved through systematic, thoughtful, innovative research into autism. Views have been transformed as a result of that research. That constitutes a considerable achievement. I am equally impressed, however, by the major questions that remain and by the puzzles involved in putting together diverse research findings. I hope that, by the end of this symposium, we will at least have narrowed down this list of questions. Also, I am hopeful that where the questions cannot as yet be properly answered, we will have identified at least the outlines of the research programme that will be needed in order to provide the answers. Those are the challenges that I am counting on all of you to meet over the next few days.

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