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EDITORIAL

The biology of autism[1]

Autism is a behavioural syndrome characterized by qualitative impairments in reciprocal social interaction and communication; the presence of restricted, repetitive and stereotyped patterns of behaviour, interests and activities; and, abnormal development before 36 months of age (ICD 10) (WHO, 1991). The children described by Kanner (1943) were said to be of normal intelligence, and for many years the syndrome was thought to be psychogenic. However, the finding that three-quarters of sufferers are mentally handicapped and a quarter develop epilepsy (Lockyer & Rutter, 1969; Rutter, 1970), suggested that the syndrome had a biological basis. Steady progress has been made in clarifying the role of aetiological factors and specifying the psychological deficits, whereas identification of the underlying neurobiological abnormalities has been less successful.

AETIOLOGY

There are two contrasting views regarding the aetiology of autism: one proposes that diverse organic aetiologies produce the syndrome of autism (Coleman & Gillberg, 1985); the other, while recognizing the existence of occasional cases associated with medical disorders, proposes that autism is more usually a specific genetic disease (Folstein & Rutter, 1988). There is now substantial evidence supporting the latter view. First, the recurrence risk for autism following the birth of an autistic child is 3% (Smalley *et al.* 1988); a rate 60 to 100 times the population base rate. Secondly, three epidemiological same-sex twin studies have reported high concordance rates for autism among identical twins, ranging from 36 to 91%, compared to zero concordance among non-identical pairs (Folstein & Rutter, 1977; Le Couteur *et al.* 1989; Steffenberg *et al.* 1989). Thirdly, the data from the combined British twin samples suggest that a range of cognitive and social abnormalities that are conceptually related to, and may include, autism is inherited: 92% of identical pairs were concordant for a braoder phenotype of cognitive and/or social abnormalities compared to 10% of non-identical pairs (Le Couteur *et al.* 1989). Fourthly, these cognitive and social abnormalities are significantly more common among the siblings of autistic singletons than among the siblings of probands with Down's syndrome (Bolton *et al.* 1991), indicating that the broader phenotype is not a consequence of twinning. Finally, the rate of mental handicap is not elevated among these siblings suggesting that the genetic factors are highly specific in their action, rather than pervasively influencing brain function.

By contrast, there is little evidence suggesting that a substantial proportion of cases are the result of diverse organic aetiologies, or that autism is associated with the common causes of brain damage. So, the Scandinavian twin study (Steffenberg *et al.* 1989) found an organic aetiology (fragile X) in only two of the 22 sets, while recognized medical disorders (such as fragile X or hypsarhythmia) of possible aetiological importance were found in only some 10% of the assessed British pairs (Bailey *et al.* 1991). Of course the findings from epidemiological twin studies may be unrepresentative of the aetiological factors affecting singletons: twins suffer more obstetric complications than singletons, and these might cause autism. However, the twin findings do not support this hypothesis. First, in none of the three studies did obstetric or neonatal hazards account for concordance in the vast majority of identical pairs. Secondly, although among discordant pairs any hazards usually affected the autistic twin, in the combined British sample virtually all of these individuals had a greater number of minor congenital anomalies than their non-autistic co-twin (Bailey *et al.* 1991). Because such anomalies are thought to arise early in gestation, it appears that obstetric hazards do not act

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randomly, but rather affect foetuses with evidence of prior developmental abnormality. The findings from the twin studies confirm data gathered from singletons: autism is not reported to be associated with severe obstetric hazards which may cause brain damage, such as extreme prematurity or very low birth weight; post mortem studies find virtually no evidence of obstetric injury; and autism is rarely associated with the common causes of mental handicap such as trisomy 21 or cerebral palsy (Wing & Gould, 1979).

Although the role of specific genetic factors is clear, a number of outstanding issues remain. The mode of inheritance is uncertain, and may not be determined until the broader phenotype can be identified with sufficient sensitivity and specificity. Similarly, the factors producing variable expressivity are obscure, as there is little evidence of environmental influences. The possibility that there is more than one specific genetic form of the disorder may be addressed by examining either associated clinical features, specific cognitive deficits or biological measures.

PSYCHOLOGICAL ABNORMALITIES

If autism is predominantly a genetic disorder, then the associated mental handicap is unlikely to be caused by exogenous insults. Rather, the cognitive impairment is probably the result of the disease process. Further evidence for this view comes from the finding that particular types of cognitive activity are specifically impaired in autism: unlike IQ matched controls, autistic individuals score unevenly on subtests of the WISC or WAIS; performing poorly on subtests involving verbal abstraction or sequencing skills, and well on subtests involving visuo-spatial or rote memory skills (Lockyer & Rutter, 1970). Moreover, the social functioning of autistic individuals studied into adulthood is correlated with verbal IQ; no such relationship exists for verbal IQ matched individuals with specific language delay (Rutter *et al.* 1991). The psychometric and follow-up data suggest that the impaired cognitive functions are essential for normal language acquisition, and are also probably necessary for normal social functioning. A theoretical link between cognitive skills and social functioning has been hypothesized by Leslie (1987), who suggests that meta-representational deficits impair autistic individuals' comprehension of the mental states of others; that is to say they lack a 'Theory of Mind'. There is evidence that some autistic individuals perform poorly when tested about the beliefs and knowledge of other people (see for instance Baron-Cohen *et al.* 1985; Leslie & Frith, 1988). However, it is also clear that the cognitive deficits are not specific to dealing with social stimuli: high functioning autistic individuals perform more poorly than verbal-IQ matched controls on non-social tasks such as the Wisconsin card sort test or the Tower of Hanoi (Rumsey, 1985; Ozonoff *et al.* 1991). A relative inability to form abstract representations or ideas is probably one of the central cognitive features of the disorder. Without these influences upon behaviour, prepotent responses will tend to dominate to the exclusion of planned or novel activity. Deficits on tests of 'Theory of mind' and executive function may provide useful models for clarifying the nature of the general underlying cognitive deficits.

Are autistic socio-emotional and affective abnormalities entirely attributable to cognitive deficits? Hobson (1989) has argued that the lack of social relatedness arises from a deficit in an inborn capacity to recognize and respond to the expression of emotional states in other people. In general, autistic subjects perform nearly as well as verbal IQ matched controls on tests of emotional recognition; subjects who do perform more poorly are also impaired on tests of executive function (Ozonoff *et al.* 1991), indicating residual non-social cognitive differences between the groups. Because performance on emotion recognition tasks is so sensitive to cognitive influences it will be difficult to determine if there are pure emotional recognition abnormalities. A more profitable approach may be to investigate affective responsivity; clinically, even individuals who appear to understand a simple social or emotional event show a decreased affective response. It would be premature to exclude the possibility that the underlying neurobiological abnormality affects both relatively high-level cognitive processes and affective responses to stimuli.

NEUROBIOLOGY

Two particular factors seems to have contributed to the slow progress in identifying the neurobiological basis of autism. First, although the combination of high-level cognitive impairments, preserved cognitive abilities and affective abnormalities provides clues and constraints to possible neurobiological hypothesis, these findings have often been ignored. A consequence is that probably too much neurobiological research has focused on relatively low-level impairments, which may be secondary to higher cognitive abnormalities. Secondly, many studies have not included mentally handicapped controls, and so abnormalities that may be consequences of abnormal brain development or function are interpreted as causal.

In the field of neurochemistry considerable effort has been expended measuring monoamine metabolites (reviewed by Cook, 1990), although drug effects are minimal and generalized under or over activity of an entire ascending system would be unlikely to produce the characteristic behavioural and cognitive profile. Testing hypotheses of localized abnormalities will require more refined methodologies than have been used to date; such as post mortem neurochemistry or receptor binding studies using Positron Emission Tomography.

The post mortem studies are remarkable for the lack of gross pathology detected; subtle alterations in cell packing (Bauman, 1991) and morphology (Raymond *et al.* 1989) in the hippocampus and related limbic structures, and abnormalities in the cerebellum have been recently reported in mentally handicapped autistic individuals (Williams *et al.* 1980; Ritvo *et al.* 1986; Bauman M, 1991). Pathology in the medial temporal structures is a superficially attractive contender for a localized lesion, but at present it is difficult to reconcile abnormalities confined to the limbic system with the clinical picture of relatively well preserved memory for facts versus impaired abstraction, and the pattern of scores on IQ tests. The limbic and cerebellar abnormalities may be secondary to abnormal innervation from other areas, or coexist with as yet unrecognized pathology. However, because mentally handicapped controls were not included in the post mortem studies, it is possible that some of the findings are non-specific consequences of brain abnormality.

The neuroimaging studies are equally remarkable for the wide variety of macroscopic abnormalities that have been reported; for instance, dilatation of the various ventricles (Hauser *et al.* 1975; Campbell *et al.* 1982; Bauman *et al.* 1985; Jacobson *et al.* 1988), basal ganglia abnormalities (Jacobson *et al.* 1988; Gaffney *et al.* 1989) and diverse cortical malformations (Piven *et al.* 1990). Methodological issues aside, the more significant difficulty is that the majority of reported abnormalities cannot account for the cognitive data; their heterogeneity and non-specificity suggest that they are probably consequences rather than causes of autism. A recent very specific claim is that abnormalities of the cerebellum may be responsible for autism (Courchesne *et al.* 1988). It is difficult to reconcile this notion with current neurobiological concepts: the cerebellum is not implicated in the higher cognitive processes that are impaired in autism, nor does cerebellar damage lead to repetitive or stereotyped behaviours. However, a more circuitious explanation for cerebellar involvement has also been suggested: it is hypothesized that abnormal output from the cerebellum intermittently interferes with attentional processes, resulting in autism (Courchesne, 1987). Although there is evidence that autistic individuals have attentional abnormalities (Ciesielski *et al.* 1990), at present it is not clear how these could produce their characteristic behaviours and particular cognitive strengths and weaknesses. The converse interpretation of attentional abnormalities is that attentional mechanisms are controlled by cognitive hypothesis about the environment, and it is these cognitive processes that are primarily impaired in autism.

Another neurobiological approach is to study the systems that theoretically seem likely to underlie the high level cognitive and affective functions that are impaired in autism. Over a decade ago Damasio & Maurer (1978) drew attention to the similar behaviours of autistic individuals and patients with acquired lesions of the frontal lobes. Despite the obvious differences between acquired and developmental abnormalities, the hypothesis of frontal lobe involvement is particularly

attractive because the similarities between the two groups extend across cognitive and affective domains. However, to date this hypothesis has generated little research. The structural imaging studies have not measured frontal areas or volumes; functional imaging using frontal activation paradigms has not yet been reported; and there is at present only tentative neurophysiological evidence for possible frontal involvement (Courchesne *et al.* 1985; Horwitz *et al.* 1988). Frontal postmortem findings have been subtle (Williams *et al.* 1980), suggesting that any possible pathology is likely to be related to the connectivity of frontal cells; or to be functional in nature.

Because the recent psychological studies of autistic individuals find impairments on tasks thought to be frontally mediated, this region is likely to be increasingly investigated. Two important aims of such research should be to determine if particular areas or connections of the frontal lobes are critically important, and to establish the psychological commonalities and differences between autistic developmental deficits and those acquired in adulthood following frontal damage. The principal benchmark against which to judge any neurobiological findings must be their power to explain the robust psychological data on autism. If this requirement can be satsified, then it will be possible to determine if neurobiologically based measures can help to identify relatives with the braoder phenotype.

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