Childhood Autism: An Appeal for an Integrative and Psychobiological Approach

Robert D. Oades and Christian Eggers*

The difficulty that a person with autism has in establishing relationships, maintaining them (communicating and responding appropriately) is a common experience of those close to them. That impaired perceptual and cognitive processing can underlie this difficulty and the interactions of people with autism with the material environment has been established in the laboratory. The consequences at a psychological level of analysis may converge in the inadequacy of second-order representations of the world. An attenuation of such endogenous monitoring processes could also indirectly account for features of withdrawal and the stereotypies often observed. At another level of analysis there are delays in neurotransmission in the CNS and a lack of flexibility of physiological response shown by evoked potential recordings. Tomographic studies of blood flow and metabolism illustrate a lack of correlation between information processing centres in the brain that may sometimes arise from diffuse gray matter atrophy. A "stop-go" form of modulation of central processing is mediated by anomalous ascending serotonergic and dopaminergic function (transmitters with inhibitory and switching functions). On these bases it is no wonder that representations are not formed and inappropriate and repetitive behaviors follow, although the link remains somewhat speculative. Both levels of analysis are useful for an explanation. As behavioral and pharmacotherapy, though helpful, are severely limited in their efficacy, more effort is required to synthesize the different levels of analysis into a psycho-biological approach to remedial programs and new forms of therapy.

Introduction

Some 25 symptoms are well-known from syndromes of childhood autism covering sensory, attentional, cognitive, emotional, language and motor areas of function. For Leo Kanner (1943), who defined the core syndrome as we know it today, the problem expressed itself primarily in terms of social indifference and repetitive motor patterns. In the seventies, Lorna Wing (Wing & Gould, 1979) emphasized the aloneness, abnormal communication and the lack of pretend-play in children with autism. Uta Frith (1989) extended these observations and proposed that the significance of all these symptoms for the child finds its expression in the difficulty to develop a "Theory of Mind".

The relevance of this concept developed out of the appreciation that poor social functioning in children with autism is related to their verbal IQ abilities. In itself this is not surprising: but that as such a relationship is not so apparent in children with other developmental language problems it obtains significance (Rutter et al., 1991 in Bailey, 1993). Leslie (Baron-Cohen et al., 1985; Leslie, 1987) has proposed the idea that the intervening variable mediating this relationship is a "theory of mind" and that a comprehension of the mental states of others by children with autism is impaired as they have difficulty in establishing abstract representations of the way people may feel or even the way problems may be solved (Bailey, 1993; Prior et al., 1990).

On the basis of their undoubted impaired or "fragmented" perceptual abilities, Uta Frith suggested that by the age of 4 years children with autism (but not those with Down's syndrome, for example) have difficulty in developing a "theory of mind"; that is to say they have difficulty with

* Clinic for Child and Adolescent Psychiatry (RLHK), Pf 103 043, 45030 Essen, Germany

the cognitive development of second order representations of the world (e. g., pretend a banana is a telephone or having seen a pencil in a tube to imagine what another child might think is in the tube – to suspend one's own knowledge or belief in favour of another possibility or another's point of view: what has become known as the "Sally-Ann" experiment). This impairment of the ability to attribute beliefs or feelings to others that do not relate to the *actual* state of affairs perceived by the child with autism has been reinforced by experiments showing the difficulty these children have in lying about a situation (Sodian & Frith, 1992) but not in identifying what a photograph shows at a time after he or she has seen that the situation has changed (Leekam & Perner, 1991).

Much of what we see as autism, not least the problem of communication, is then a consequence of these perceptual and cognitive difficulties. As plausible as this reads for those who have tried to interact with children and adolescents with autism, it must be said that some have not been able to generalise these finding to other populations (Prior et al., 1990) and others have emphasized the perceptual or attentional side of the person's difficulty. Thus Kasari and colleagues (1993) found that their 3–4y old children with autism had problems, compared to a retarded group, in focussing attention on and initiating play with toys unless so led by the caregivers. Of course, one might argue that this was a consequence of their need for rapport which itself depends on communication and abilities to develop second order representations. This circular argument tends to obscure discussion over the primacy of the locus of impairment. But it should be noted that these particular children were rather young to be expected to have developed a "theory of mind".

The cognitive impairment of young people with autism may develop dependently or independently of a perceptual or attentional difficulty. Because the "theory of mind" description is based on a relative rather than a clear cut deficit (i. e., where are the borders of the concept of attribution?) there is a danger of oversimplification in applying it to laboratory test or explanatory hypothesis. This view has stimulating possibilities for therapeutic strategies but we should not lose sight of what makes up the phenomenon of childhood autism. Firstly there are other features of autism that Frith's explanation does not easily accomodate and secondly if cognitive therapy in a strict sense proves limited then we must learn how else we

may influence cerebral function (and which function). Thus one must ask what other research strategies in the neurosciences are showing?

Prevalence and the Question of Definition

Childhood autism almost always manifests itself in the first three years of life and and the core syndrome classically shows a male to female sex ratio of about 3–4 to 1. This ratio would be lower if the relatively high number of severely retarded girls were not excluded (Wing, 1993), if early onset epilepsy (which has a less marked male/female ratio) was not used as a criterion for exclusion and perhaps if a broader spectrum of autistic behaviour was used in diagnosis (Gillberg, 1993).

The number of cases reported in 10,000 of the population ranges from 2–5 (Germany, Steinhausen et al., 1986; France, Aussilloux et al., 1989; USA, Ritvo et al., 1989; England, Wing, 1979; Sweden, Gillberg, 1984) to 10–16 (Canada, Bryson et al., 1988; Japan, Sugiyama & Abe, 1989; and for "pervasive development disorders" USA., Burd et al. 1987: review in Wing, 1993). These figures become more tangible, particularly in the health care context, if viewed in terms of the population: thus in Germany with a population of about 64 million there are estimated to be 12,000 cases (*Der Spiegel*, p. 118, Nr 35, 9/1993).

The variability indicates that we must ask what illness it is we are discussing (cf., discussions in Ritvo & Freeman, 1978; Burd & Kerbeshian, 1988). Epidemiological studies employing core syndrome criteria (e. g., after Kanner or Rutter) yield prevalence rates per 10,000 of under 10, those using other and DSM criteria more frequently find rates of 10–20 (Wing, 1993) and those expressly extending the diagnosis to spectrum and Asperger syndrome obtain figures close to 50 (Gillberg, 1993).

In Table 1 one can see that modern diagnostic schemes separate syndromes with a clear organic basis from others that may be phenomenologically or biologically separate, but aetiological factors, crucial in other areas of psychiatric diagnosis, here obfuscate the aims of defining unique illness forms. With this Table it is our intention to encourage caution in the interpretation of social, behavioural and neurobiological studies and to raise the ques-

Table 1. Sub-groups of "Autistic" syndromes, (examples).

Possible etiologically separate groups	Diagnostic groups	Organic associations	Inborn metabolic errors
Genetic vulnerability (1)	Infantile Autism	Cerebral Lipidosis	Phenyl-ketonuria
Food allergy (non-specific)	Atypical Autism	Tuberous Sclerosis	Purine-Autism
Perinatal insult (2)	Rett Syndrome	Cerebral Paresis	Histidin-emia
Postnatal physical abuse	Asperger Syndrome	Rubella Embryopathy	Lactate Acidosis
Social isolation	Pervasive Develop-mental Disorder (4)	Fragile X Syndrome	Hypocal cemia
Epilepsy (3)		Food allergy (specific)	

None of the above

Diagnostic categories refers to the major clinical groupings described by the 10th revision of the International Classification of Diseases (1991) excluding dominant features of disintegration and retardation.
(1) Rutter (1991) found 50% concordance for autism in monozygotic and 3% for dizygotic twins: (2) prevalence 45– 60% (but see Piven et al., 1993 where modified Gillberg-Optimality-Scale measures proved less significant after parity adjustment): 3. prevalence 30%: Gillberg (1993, table (3) lists 34 medical disorders possibly associated with autism including other gross chromosomal disorders: (for further details see Eggers et al., 1994): (4) the overlap of PDD-non-specific diagnosis with autism remains controversial (Happé & Frith, 1991).

tion of whether it is sensible to include or exclude cases with known comorbidity (e.g., tuberous sclerosis, infantile spasms; Gillberg et al., 1987; Riikonen & Amnell, 1981) or aetiology (brain damage, torture, Steffenburg, 1991, author's experience). Wing's recent epidemiological review (1993) found that the prevalence of some sort of neurological condition in children with autism ranged from 27 to 80% across studies (see also Eggers et al., 1994 p. 521).

Our own view is that while neurobehavioural studies may be justified in studying the spectrum of autistic behaviour, efforts should be made to clarify the origins in their sample (e.g., "neurocutaneous", "embryopathic"). Genetic and epidemiological work can only become more difficult to interpret if the borders between the subgroups are not made explicit.

Arguably the most difficult feature to disentangle from autistic phenomena is mental retardation. One in two people with autism has an IQ over 50 and one in four an IQ of over 70. While no one disagrees that retardation and autism are separate phenomena, in practice it is often difficult to distinguish their separate contributions in psychobiological studies of childhood autism. Thus on the one hand only a minority of studies have used a comparison group consisting of another developmental disorder or of mentally handicapped patients. On the other hand diagnostic schools still differ on the definition of the index group (e. g., nonspecific pervasive developmental disorder vs childhood schizophrenia; Green et al., 1992). One must always bear in mind the potential heterogeneity of the samples in psychobiological studies.

CNS – Neuropsychology

Michael Rutter (1983) emphasized that children with autism are not usually impaired in perceptual skills and visuo-spatial abilities; Gillberg and colleagues confirmed a relative sparing of motor and visuospatial performance compared to verbal and reasoning abilities in a study of 70 children and adolescents with autism (Sandberg et al., 1993). But they are usually deficient in making, or more particularly in maintaining cross-modal associations (Martineau et al., 1992). It is precisely this ability that Norman Geschwind (1965) emphasized was crucial to the acquisition of speech in development and we have already noted the relationship of verbal IQ to communication and social function. However even if children with autism are dysphasic in understanding they are not necessarily so in articulation. Those that do have retarded or absent speech are likely to show neurological impairment and are likely to show left cerebral hemisphere deficits (Yates, 1984) and the absence of left hemisphere dominance for speech-related evoked potentials (Dawson et al., 1989; see following sections).

In fact a deficit in selection and encoding of meaningful stimuli, as described by Hermelin and O'Connor (1970) and already implied in the previous section, is supported by more recent evoked potential studies (see below). But it should be borne in mind that the overselective aspect of attention, the tendency to respond to very limited parts of the environment, is also a feature of retarded children in general (Prior, 1979). Recent

Table 2. Examples of information-processing associated with autism seen in childhood autism and schizophrenia that are "similar but different".

Attention with detail:	
miss repeated pattern,	
find shapes;	1) U. Frith, 1989
impaired Gestalt perception;	2) Schwartz-Place & Gilmore, 1980
Cross-modal integration impairment:	
slow RT auditory-visual change;	1) Bryson, 1970
slow RT visual-auditory change;	2) Sutton et al., 1961
Impaired signal-detection:	
criterion decrease (beta);	1) Oades et al., 1990
sensitivity decrease (d-prime);	2) Cegalis & Deptula, 1981
Perception of facial expression:	
recognize, not appreciate;	1) Hertzig et al., 1989
impaired recognition/ appreciation;	2) Gruesser, 1991
Recall impairment emphasizes:	
short term/episodic impairment;	1) Boucher, 1981
long term/semantic impairment;	2) Tamlyn et al., 1992
"Theory of Mind":	
chronic impairment;	1) Frith, U. 1989
impairment after 20 y development (attempts to repair communication);	2) Frith, C. 1992

1) for children with autism, 2) for schizophrenics: RT = reaction time: All the features listed have at one time or another been related to different aspects of temporal lobe function.

studies on attentional switching mechanisms (particularly from Eric Courchesne and colleagues) show a marked similarity between the deficits in voluntarily disengaging and accurately reengaging attention in patients with parietal or cerebellar damage and those with autism (see tomographic results below, Akshoomoff & Courchesne, 1992; Courchesne et al., 1992; also dopamine function in initiating and switching activity, neurotransmitter section below, Oades, 1985).

Such reports on the problems of subjects with autism with voluntarily initiating and switching between information-processing channels and planned behavior could underlie slowed learning, repetitive responses and contribute to impaired development of language and a "theory of mind". But we should remember that what may underlie the symptom may or may not be the same for the syndrome. It is striking how superficially similar,

yet in detail different, are the impairments in information processing found in children and schizophrenic adults with autistic symptoms (Table 2). Twenty years ago Michael Rutter (1972) argued persuasively for the term childhood autism rather than childhood schizophrenia to describe the Kanner syndrome (see also discussion in Eggers, 1978): it still remains a matter for debate to what extent the symptoms of childhood autism and psycho-motor poverty in schizophrenia have an underlying commonality.

Over the last 10–15 years there has been increased renewed interest in interpreting psychological impairments as soft signs of CNS regional dysfunction. Particularly popular are explorations of parallels between frontal lobe function and syndromes as disparate as schizophrenia (Straube & Oades, 1992, p. 611), attention-deficit-disorder (Oades, 1989, p. 355) and autism (Prior & Hoffmann, 1990). While such attributions appear premature with respect to attention-deficit-disorder (Loge et al., 1990), the similarities have been acclaimed for both of the other two syndromes, for example, with respect to performance on the Wisconsin card-sorting test, Rey-Osterrieth figures and Tower of Hanoi (in autism, Prior & Hoffmann, 1990; Bailey, 1993, Bishop, 1993). Apart from the absence of diagnostic specificity, the problems for accepting and applying these results are numerous: 1) the parallel to frontal brain damage should be more qualified than is widely assumed (Corcoran & Upton, 1993 and references therein on temporal lobe function); 2) the much cited parallel for autism (Damasio & Maurer, 1978) was based on circumstantial evidence and referred to extensive areas of the frontal lobes (neocortex), parahippocampal areas (allo/archicortex) and their interactions with the basal ganglia; 3) our own experience of perseverative card-sorting performance in children is one of very variable performance and that of Prior and Hoffmann was similar with some subjects with autism who were incorrigibly persistent and others who showed no perseverative responses; 4) While Prior and Hoffman found that subjects with autism had problems on the Rey-Osterreith figures Rumsey and Hamburger (1990) did not find this impairment; 5) Ozonoff et al. (1991 a) also found that those with milder Asperger symptoms were as impaired as those with a Kanner-type syndrome.

On the positive side we should recognize 1) that some of these studies have distinguished the responses of subjects with autism from those of dys-

Table 3. Event-related potentials (ERPs) elicited by novel or target stimuli and subtraction waves.

component and latency	(ms)	purported function	amplitude change in autism	examples of studies
P1	45–80	transmission into cortex	smaller normal	Garreau et al., 1985 Novick et al., 1980
N1	80–150	channel allocation	smaller larger normal	Garreau et al., 1985 Courchesne et al., 1985 Oades et al., 1988 Novick et al., 1980
P2	120–240	inhibition of processing	smaller normal	Novick et al., 1980 Garreau et al., 1985 Lincoln et al., 1993
P3 b	300–550	update stimulus significance	smaller larger	Cieselski et al., 1990 Niwa et al., 1983 Martineau et al., 1984
MMN	200–250	sensory mismatch – novelty (within features)	normal	Kemner, 1992
PN	200–300	saliency mismatch (between features)	smaller	Cieselski et al., 1990 Oades et al., 1988
Nd	200–300	stimulus–task relevance	normal trend smaller	Oades et al., 1988 Oades & Zerbin, 1991

Derivation of subtraction waves: MMN = ERP difference between 2 non-target stimuli; PN = ERP difference between target and a different non-target stimulus; Nd = ERP difference between target stimulus and the same stimulus previously presented as a non-target.

lexic comparison groups (Rumsey and Hamburger, 1990; Ozonoff et al., 1991 a); 2) that hypothesis–driven studies of executive function (and implicitly the "theory of mind"), such as the Tower of Hanoi, were found to correctly classify 80% of subjects with autism and comparison cases (Ozonoff et al., 1991 b); 3) that regional cerebral blood flow studies of normal adults performing a similar "Tower" task find particular activation of the left mesial frontal cortex including parts of the cingulate gyrus (Andreasen et al., 1992; cf. also dorsolateral prefrontal activation during card-sorting, Weinberger et al., 1986).

We conclude that while further studies bear the promise of defining an aspect of autistic dysfunction in regional CNS terms, autistic symptoms point to wider ranging anomalous CNS activity; e.g., orbitofrontal and temporo-limbic involvement in affect and cognition (see Table 2) and brainstem and neocerebellum involvement in the coordination of neural systems (cf. neuroanatomy sections). Surely more emphasis should be laid on these latter types of anomaly when we consider that autistic symptoms appear at three years of age or earlier but the results of frontal brain damage are seldom evident before puberty. Further it would be of great interest in view of the foregoing discussion both of neuropsychological signs and Frith's hypothesis to measure the pre- and post-pubertal performance of subjects in laboratory tests in subgroups where there is

a chance that symptoms and communication ability will/will not improve (e. g., Rett syndrome, fragile X, Asperger syndrome, Gillberg, 1993; Eggers et al., 1994).

CNS – Electrophysiology

EEG abnormalities are not consistent in nature and may be found in over 40% of subjects with autism. A smaller subgroup of patients is prone to seizure activity and spasms. Where EEG abnormalities are present, they are often bilateral with a tendency to be more marked on the left side. Normal asymmetries may be absent and where language abilities are poor, relatively more activity may appear on the right rather than the left side (Small, 1975; James & Barry, 1980; Ornitz, 1985; Garreau et al., 1985; Cantor et al., 1986; Dawson et al., 1989).

Electrodermal responses to neutral stimuli show there are responding and non-responding groups of subjects with autism, but that the response is often large with respect to other mentally retarded children. The response usually augments with intensity and is slow to habituate (Stevens & Gruzelier, 1984; Barry & James, 1988). Van Engeland's group in Utrecht reports that if stimulus presentation is changed then response may be attenuated, fixation time for visual stimuli may increase or, if a simple task is introduced, even
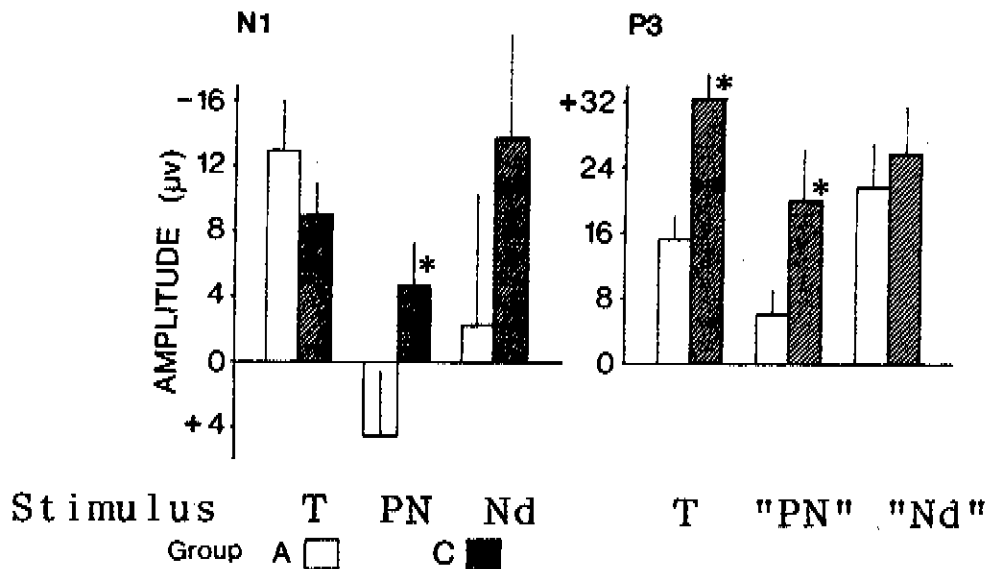
Figure 1. Amplitudes of the N1 and P3 event-related potentials elicited elicited in a 3-tone oddball discrimination after the target tone (T) and in the subtraction waveforms called "processing negativity" (PN) and "negative difference" (Nd): PN = ERP waveform elicited by the target stimulus minus that elicited by the rare non-target; Nd = ERP waveform elicited by the target stimulus minus that elicited by the same stimulus in an earlier non-task presentation. White bars represent the means for 7 children with autism, and the shaded bars means for 9 age-matched controls. * = significantly larger components in normal children (after Oades et al., 1990).

non-responders may start to respond (van Engeland et al., 1991).

In young patients with autism there is evidence of elementary perceptual abnormalities according to measures of brain stem evoked potentials, where some 20% have been found to show moderate to severe decrements of auditory and visual acuity (Steffenburg, 1991). Component latencies are often increased even with respect to other retarded subjects (Tanguay et al., 1982), although in older subjects the problem is less evident (Grillon et al., 1989). The delay may be marked in those showing strongly impaired language development (McClelland et al., 1992) or social withdrawal and poor attentional function (Fein et al., 1981).

Evoked potential studies (e. g., by Eric Courchesne and colleagues in San Diego, Gilbert Lelord's group at Tours, one of us in Australia and reports from Japan) find considerable variability of response. Event-related potential amplitudes (e. g., N1, P3, PN, Nd see Fig. 1) are often reduced but the components affected may vary (Table 3).

The normal amplitude difference seen, particularly for the P3 component, between target and standard or between novel and repeated stimuli is much reduced. However Chantal Kemner (1992) from Utrecht found normal mismatch negativity

(MMN) measures of automatic attention processing. (MMN results from the subtraction of potentials to different non-targets). Thus the reduced amplitude difference between stimuli, as observed by eye (above) or in other subtraction waves that include target responses (e. g., PN, Table 3) would seem to be related to an aspect of controlled processing that includes the situational or task relevance of stimuli.

Courchesne's group (Lincoln et al., 1993) have recently illustrated this in a two-tone oddball paradigm that required separate button presses to each tone after completing a passive listening session. Healthy children and those with autism were equally fast and accurate and performed better than children with receptive developmental language disorder. Although the P3b amplitude in young subjects with autism was smaller, the interesting point is that it was sensitive to the difference between "response-required" and "response-not-required" conditions but not to the difference in stimulus probability, as usually recorded in other subjects. This demonstrates context-(in)sensitivity, but within limits.

Surprisingly, as autism is often viewed in terms of delayed maturation, latencies of these components are often (but not always) reduced. Inter-

pretation is hampered by the small numbers of subjects studied and the difficulty to choose appropriate controls and to match for maturation effects (e.g., component latencies), but clearly the controlled or conscious handling of salient and of relevant information is inappropriate.

CNS – Neurotransmitters

For more than 30 years laboratories find blood and urine levels of serotonin to be about a third higher than normal in at least one in three patients with autism (Schain and Freedman, 1961; Launay et al., 1988; Yuwiler et al., 1992; urine not blood in Herault et al., 1993). In view of the absence of change in the levels of serotonin metabolites or in serotonergic response to pharmacological challenge it is assumed that this monaminergic system is hyporesponsive (Cohen et al., 1977; Anderson et al., 1988; McBride et al., 1989). In support of this, the latter authors reported decreased 5HT-2 binding, – a finding reminiscent of obsessive compulsive disorder where similar decreased binding appears to be associated with increased serotonin outflow (Erzegovesi et al., 1992; Oades et al., 1994).

Levels of the dopamine metabolite are often higher in CSF or urine samples (Garnier et al., 1986; Garreau et al., 1988; Gillberg & Svennerholm, 1987). While it is not surprising that these levels are increased after treatment with the partial neuroleptic fenfluramine (Barthelemy et al., 1989), it is curious that the subjects with high HVA were those that responded best to treatment (Oades et al., 1990). Not surprisingly these were relatively high functioning cases. In contrast those with severe symptoms apparently excrete low levels of dopamine (Herault et al., 1993). However one cannot make inferences on amine metabolism from levels of the parent amine. Such measures can at best have diagnostic utility, which in the opinion of the french group is not the case for autism.

As has been shown even in CSF samples by Gillberg in Sweden, individuals may show marked increases of dopamine relative to noradrenaline metabolism but only minor changes of the serotonin metabolite (Gillberg et al., 1987). Changes in activity of various metabolic enzymes such as monoamine oxidase, dopamine-B-hydroxlase, acetyl cholinesterase have not been found (Deutsch et al., 1987; Launay et al., 1988). Evidently increases of

dopamine activity in young patients with autism are less compensated by serotonin or noradrenaline activity than in other groups of children, as remarked on by Cohen and Shaywitz (1982).

Evidence for altered opioid metabolism remains indirect and largely unsubstantiated. The rationale for such a disturbance in autism has been repeatedly and plausibly argued for over 15 years (Panksepp, 1979; Sandyk & Gilman 1986; Panksepp & Sahley, 1987) but the identification of peptides whose metabolism is altered in autism has remained stubbornly elusive (Reichelt et al., 1986; Le Couteur et al., 1988) and the positive effects of treatment of postulated increased opioid activity with antagonists are slight (see last section).

A grave problem for the evaluation of these results is that similar changes of the parameters discussed are reported for a proportion of mentally retarded children. Nonetheless severely ill children (e.g., also with Rett syndrome, Pelligra et al., 1992) show decreased catecholamine activity and better functioning children with autism have higher levels of dopamine metabolism. One framework for conceiving these results is mentioned in our summary, – a "stop-go" form of neural communication. This phrase refers to the inhibitory role of serotonin in the volume control of information processing and the initiation of a switch between competing information channels attributed to dopamine (Oades, 1985; 1994). Could this partly underlie the internal restlessness (Unruhe) that some young adult subjects with autism describe (e.g., *Der Spiegel*, Nr 35, 9/ 1993)?

CNS – Tomography and Regional Brain Function

CT examinations show that diffuse atrophy and larger ventricle size appear in 1 of 3–6 people with autism (Campbell et al., 1982; Balottin et al., 1989). MRI images reveal that individuals may show damage in the frontal or temporal lobes and that more than a third of subjects may show parietal abnormalities (Hashimoto et al., 1989; Gaffney et al., 1989). While some (e.g., Hashimoto et al.) have made the experience that the atrophy tends to be left sided in general, others claim that the right side is implicated where language development is particularly poor (e.g., Balottin et al.). A recent volumetric study on 11

patients with Rett syndrome describes a general reduction of brain size and decreased grey matter (c.30%) with respect to age-matched controls and a further relative reduction in the basal ganglia and brainstem (Reiss et al., 1993).

Children and young adults with autism appear to show cerebral metabolism and blood flow in the normal range. Tendencies towards increased glucose metabolism (Horwitz et al., 1987; De Volder et al., 1987) may merely reflect the anxiety of the subjects felt in the rather overbearing test situation but have been considered to support evidence of increased membrane breakdown products reported by the Pittsburgh group specializing in magnetic resonance spectroscopy measures (Minshew et al., 1993). Others have taken particular care to reduce the anxiety of their subjects and found no changes of glucose metabolism (Herold et al., 1988; Heh et al., 1989). The study in London of Herold et al. also examined labelled oxygen metabolism. Their six subjects showed a small non-significant decrease which has been taken to support the finding of a 30–40% decrease in cerebral blood flow in 4 young adults with autism (George et al., 1993). This decrease was particularly marked in frontal and right temporal regions. Unfortunately it is possible that anticonvulsant medication was in part responsible for the decreases reported. These reports were based on very few subjects who differed markedly in age and level of function and thus can at best be taken only as pointers for future investigation.

Gillberg et al. (1993) responded to this indicator and took SPECT images from 31 young patients with autism (4.5–22y), half of whom had conditions associated with epilepsy. Fourteen of their patients showed apparent decreases of blood flow of 10% or more in the left or right temporal lobe. We take this figure from their data as it is roughly comparable to SPECT studies of similar numbers of patients in studies of "nonautism" cases reporting borderline significance. Unfortunately the report does not provide a statistical analysis and instead makes use of the authors' SPECT experience with 300 other patients for comparison. The authors commented on an apparently greater left-sided decrease in severe cases and that frontal regions were frequently affected. But in the absence of a formal analysis of other regions of interest it is difficult to assess how unique or overt the reported decrease in the temporal lobe was. A previous SPECT study reported no differences with a similar number of patients (Zilbovicius et al., 1992).

The aforementioned studies did not for the most part attempt comparisons of lateralized activity. But Lelord's group did attempt this with ultrasonographic recordings of blood flow in the middle cerebral artery of eight 5–8y old children with autism vs normal controls (Bruneau et al., 1989; 1992). A non-significant decrease of flow on the left at rest became significantly lower under auditory but not visual stimulation. This supports similar observations on lateralization (above) particularly where language is impaired.

Buchsbaum's group at Irvine, California, also took account of a potential lateralization of measures of metabolism (Siegel et al., 1992). They found a reversed asymmetry (like Bruneau et al. above) in high functioning young adult subjects with autism. Rectal gyrus metabolism was higher on the left whereas in controls it was higher on the right. However considering the number of comparisons made and the variability of the measures we think it may be more pertinent to emphasize one of the conclusions of another american study centred on the National Institutes of Health (Horwitz et al., 1988). They reported that adults with autism (with a wide range of IQ) showed remarkably few regional activity correlations, particularly between various association cortices and the thalamus. This lack of cohesion is suggestive of an anatomical counterpart to the cognitive problems of integration described earlier.

Recent reports from Courchesne's group and cooperative work between Tours and Marseilles claim a degree of hyoplasia in the neocerebellar vermis of perhaps three out of four subjects with autism (e. g., Courchesne et al., 1988; Murakami et al., 1989). While the extent of the anomalies may be more severe in those with autism, qualitatively the picture is not dissimilar to that in other retarded subjects. Thus Piven and colleagues (1992) at the Johns Hopkins University found that significant differences from healthy subjects disappeared if age and IQ were controlled. This is supported by a similar study from Pittsburgh (Holtum et al., 1992). However while the former studies included T2 weighted images (designed to show up damaged matter) the latter reported only T1 images that are better for describing healthy tissue. Tomographic studies confirm the recurring problem of selecting appropriate controls and highlight the contribution of the complexity of the methods to the difficulty for replicating investigations. Nonetheless we should bear in mind that the neocerebellum has connections with both tem-

porolimbic and brainstem regions that could be important for integrative functions.

The emphasis in this section has been on relatively normal cerebral metabolism with low responsivity (blood flow). But from early pneumoencephalographic and tomographic studies (Hauser et al., 1975; Hier et al., 1979) to modern spectroscopic studies (Minshew et al., 1993) it has been clear that ventricle size is increased and that atrophy and degeneration is apparent in more than half the subjects studied.

Isolated histological studies, mostly from one laboratory, report abnormalities such as reduced neuronal and, in particular, dendritic development in the cerebellum, amygdalo-hippocampus and brainstem (Bauman & Kemper, 1985; Raymond et al., 1989; Plioplys et al., 1990; Arin et al., 1991; Bauman, 1991). Spectroscopy shows that the availability of membrane building blocks decreases as their metabolic products increase and that these measures correlate with the decline of function (Minshew et al., 1993). These authors cite recent work by the groups of Svennerholm and Gillberg (e. g., Ahlsen et al., 1993) which shows large increases of CSF levels of gangliosides and Glial Fibrillary Acidic Protein in children and adolescents with autism compared to other psychiatric groups. These measures could also refer to increased synaptic turnover and provide a relatively specific indicator of the type of atrophy.

Perhaps research strategies that would currently be helpful should ask if these measures of regression are progressive, if they relate to measures of autoimmune activity and whether neurotrophic properties of some peptides and amines can be beneficially harnessed at any stage.

Pharmacotherapy

Some new drugs show encouraging results in open trials, but largely due to the pioneering work of Magda Campbell (U.S.A.) neuroleptics still remain the agents of choice. More than half of those treated show some response, with decreases of symptoms by a third being reported. Prescription must be guided by careful appraisal of the symptoms in the individual to be treated (reviews: Eggers, 1984; Campbell et al., 1987; Moll & Schmidt, 1991; Gadow, 1992).

In the 1970s hopes were raised that a form of vitamin therapy was effective (Rimland et al., 1978). Others have found a limited degree of behavioural improvement associated with increased excretion of dopamine metabolites (Martineau et al., 1985). It has been suggested that a facilitation of dopaminergic metabolism underlies the cases where this treatment helps (Guilarte et al., 1987).

Fenfluramine is an indirect serotonergic stimulant with dopamine antagonist properties and can be as effective as conventional neuroleptics (see Table 4), but a real improvement is seen in only 10% of subjects (Ekman et al., 1989; Stern et al., 1990). It is intriguing, as one of us has reported, that dopamine metabolism increased with improvement and was associated with normalized scalp-recorded Nd (difference negativity after a given stimulus with/without meaning). But the P3 component in the difference wave, reflecting stimulus-meaning, did not improve.

Unrealistic hopes for fenfluramine treatment were raised by early reports of an increased IQ (e. g., Ritvo et al., 1983). It is unfortunate that subsequent negative reports concentrated on intellectual and IQ measures in very small groups (e. g., n = 5) of low-functioning subjects (some with a "mean IQ of 31") tested over a short time (e. g., Coggins et al., 1988; Sherman et al., 1989).

Other serotonergic agents have fairly numerous side-effects and rather modest therapeutic effects on subjects with autism and the mentally retarded alike. However a recent double blind comparison of clomipramine, desipramine and placebo at NIMH shows an encouraging effect of the serotonin uptake inhibitor (Gordon et al., 1993). Various symptom improvements were judged on average to exceed 20% and more for locomotor activity. Except for activity, desipramine seemed contraindicated. This report follows more than two decades of positive experience in treating obsessive compulsive disorder with clomipramine, where the degree of improvement for responders is about twice that reported for those with autism.

The recent report from Magda Campbell and colleagues in New York (Campbell et al., 1993) has dampened hopes that the opioid antagonist naltrexone might prove a helpful tool. They used a parallel study design double-blindly assigning 23 children with autism to the drug- and 18 to placebo-treatments (ages 2.9 to 7.8 y). They excluded subjects with histories of genetic metabolic problems, thyroid dysfunction or a history of seizures. Doses of 0.5 to 1.0 mg/kg/d produced a modest

Table 4. Pharmacotherapy

Agent	Pharmacological Action	Therapeutic Response
Haloperidol	DA antagonist	improved retention-learning and language-based therapy; reduced behavioral withdrawal, tantrums, stereotypy, activity, lability, abnormal object relations; side effects rare (e. g., weight gain, dyskinesia)
Pimozide	DA antagonist	as with haloperidol but more appropriate for non-hyperactive subjects
Trifluoperazine Molindone, Fluphenazine, Thiothixene	DA antagonists	mild symptom reduction
Chlorpromazine	DA antagonist	poor response, excess sedation
Amphetamine L-DOPA Methylphenidate	DA (indirect) agonists	reduce hyperactivity, exacerbation of other symptoms (e. g. stereotypies)
Propranolol	B-NA antagonist	reduces aggression
Desipramine	NA uptake block	poor, decreases activity but can induce uncharacteristic aggression
Imipramine	NA and 5HT uptake block	poor, can stimulate, tranquillize, disorganize
Methysergide	5HT antagonist (non-selective)	mixed, mild symptom reduction and worsening
dl-Fenfluramine	l-enantiomer indirect 5HT agonist and DA antagonist	better response in better functioning subjects: more appropriate stimulus-responsiveness, attention, less restless, reduce stereotypies, more speech, improved mood and social interaction
Fluoxetine	5HT uptake block	mild symptom reduction, decreases perseveration and stereotypies; but increased activity/agitation, reduced sleep and appetite
Buspirone	5HT-1 a agonist	mild symptom reduction
Clomipramine	5HT uptake block	can reduce anger, rituals, activity and self-injury; adverse effects can include insomnia, appetite, sedation; rarely tachycardia, unsuitable for seizure-prone
Carbamazepine	Stabilize GABA transmission, (inhibit NA reuptake)	reduces aggression, useful if epileptic activity present, but danger of paradoxical increased impulsivity and aggression — *valproic acid* suggested as agent of choice
Naltrexone	mu opioid receptor antagonist	very mild symptom reduction (e. g., decreases hyperactivity, improves social behavior and speech, but some sedation or aggression/irritability likely as side-effect)
ACTH 4-9 /ORG 2766	Steroidogenic activity absent; component of opioid precursor peptide	improved social interactions, contact and behavioral patterning
Vitamin B6 and Magnesium (Pyridoxine)	Cofactors for enzymes in monoamine, opioid and (e. g., DA) metabolism	mild symptom reduction (incl. irritability, oversensitivity, enuresis), improved physiological measures, but not stereotypies nor agitation; symptom rebound on treatment withdrawal
Lithium	Indirect effects on NA and 5HT metabolism	reduces aggression/auto-aggression, mood-lability
Cannabis (THC)	Modulate monoamine, opioid and prostaglandin activity	reduced autistic behavior

DA = dopamine, NA = noradrenaline, 5HT = serotonin
selected refs. see text for reviews and Buitelaar et al., 1992; Cook et al., 1992; Deutsch and Campbell, 1986; Ernst et al., 1992; Campbell et al., 1990; Gillberg, 1991 (where epilepsy is associated with autism) and Campbell et al., 1993 (opioid).

168

reduction of hyperactivity where present but had no effect on the core symptoms, rated blindly on several scales. Half the subjects showed side effects such as irritability aggressive features or tantrums.

From this brief discussion of some mildly useful drugs, we believe some support may be deduced for saying that dysfunction of dopamine and serotonin systems achieves clinical significance. For opioid systems the evidence if encouraging, is yet to prove convincing. But approaches to the treatment of non-opioid peptidergic systems or those using excitatory amino acids are still in their infancy and largely untried in patients with autism. Nevertheless Table 4 is indicative of a number of strategies that have been attempted. We should again emphasize that for those not accustomed to considering pharmacotherapy of particularly problematic cases that they must refer to the primary literature and relevant texts.

Conclusion

Precisely because children with autism have perceptual and cognitive difficulties, reduced monoaminergic transmission and show impaired brainstem and cerebellar, temporal and frontal lobe function (particularly on the left side), research strategies must try to integrate these. It is not difficult to imagine potential multilevel approaches: it is pleasing that we have been able to refer to some.

Precisely because the impairment of children with autism manifests itself at so many levels, treatment concepts must attempt to integrate these. Just as the individual's needs must be assessed before introducing art or music therapy, behavioral or speech therapy, computer games or sensorimotor practice sessions, so should s/he be appraised psychobiologically for the most useful mixtures of medical support.

If it is within our grasp, then it should be tried, — to help these children appreciate their world, develop a theory of mind, to respond to care and comfort.

Acknowledgment

Résumé

L'incapacité des sujets autistes d'établir des relations avec l'autre, ca veut dire, de communiquer d'une manière adéquate, est un problème majeur pour l'entourage. Le fait, que le comportement relationel anormal est partiellement causé par l'empêchement des fonctions perceptives et cognitives, a été approuvé par des recherches expérimentales. Sur le plan psychologique il y résulte par conséquence l'incapacité d'établir une réprésentation adéquate du monde intérieur et extérieur dans le sense des "représentations d'ordre secondaire". Une autre vue s'appuye sur des faits neurobiologiques: des troubles des fonctions neurotransmetteurs qui, sur le plan neurophysiologique, indiquent une assomilation d'excitation perturbée (cela ce montre par des potentiels évoqués sensoriels transformés). Les recherches tomographiques montrent une interaction troublée entre des différentes régions nerveuses-central, qui sont responsables pour les processus d'information. Il y a des indications pour une interaction inhibée entre des fonctions serotonergiques et dopaminergiques, qui ont pour conséquence une balance troublée entre des fonctions inhibitives et actives. Il en résulte l'incapacité des enfants autistes, d'établir des réprésentations symboliques adéquates de leur entourage et d'établir des relations normales. Pour le développement et l'évaluation des stratégies de recherche et de thérapie au future, il est important de mettre en relation les plans différents psychologiques, neurophysiologiques, biochimiques, neuroanatomiques et d'arriver à une vue globale psychobiologique.

Zusammenfassung

Die Unfähigkeit autistischer Patienten, Beziehungen zum Anderen herzustellen und aufrechtzuerhalten, d.h.adäquat mit ihm zu kommunizieren, stellt für nahe und entfernte Bezugspersonen ein erhebliches Problem dar. Daß das abnorme Beziehungsverhalten durch abnorme perzeptive und kognitive Funktionen mitbedingt ist, ist inzwischen durch experimentelle Untersuchungen belegt. Auf der psychologischen Ebene resultiert dadurch eine beeinträchtigte Fähigkeit zur Etablierung adäquater Vorstellungs- und Verweisungszusammenhänge im Sinne beeinträchtigter "second order representations". Eine andere Betrachtungsebene ist die neurobiologische: Störungen der Neurotransmitter-

funktionen, die auf neurophysiologischen Ebene einhergehen mit Hinweisen für eine gestörte Reizverarbeitung (ablesbar in veränderten ERP). Tomographische Untersuchungen weisen auf eine gestörte Interaktion zwischen verschiedenen zentral-nervösen Strukturen, die für die Informationsverarbeitung zuständig sind. Es gibt Hinweise für eine gestörte Interaktion zwischen serotonergen und dopa minergen Funktionen mit der Folge einer gestörten Balance zwischen reaktionshemmenden und -fördernden Mechanismen. Möglicherweise könnte damit die Schwierigkeit autistischer Kinder zusammenhängen, adäquate symbolische Repräsentationen der Umwelt aufzubauen und normale kommunikative Bezüge zu ihr herzustellen. Es ist wichtig für die Entwicklung und Evaluation zukünftiger Forschungs- und Behandlungstherapien, die verschiedenen Betrachtungsebenen (psychologisch, neurophysiologisch, biochemisch, neuroanatomisch) miteinander in Beziehung zu setzen, und dadurch zu einer ganzheitlichen, psycho-biologischen Betrachtungsweise zu gelangen.

References

Ahlsen, G., Rosengren, L., Belfrage, M., Palm, A., Haglid, K., Hamberger, A. & Gillberg, C. (1993). Glial fibrillary acidic protein in the cerebrospinal fluid of children with autism and other neuropsychiatric disorders. *Biological Psychiatry, 33,* 734–743.

Akshoomoff, N. A. & Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behavioral Neuroscience, 106,* 731–738.

Anderson, G. M., Ross, D. L., Klykylo, W., Feibel, F. C. & Cohen, D. J. (1988). Cerebrospinal fluid indoleacetic acid in autistic subjects. *Journal of Autism and Developmental Disorders, 18,* 259–262.

Andreasen, N. C., Rezai, K., Alliger, R., Swayze, V.W., Flaum, M., Kirchner, P., Cohen, G. & O'Leary, D.S. (1992). Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia: Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. *Archives of General Psychiatry, 49,* 943–958.

Arin, D. M., Bauman, M. L. & Kemper, T.L. (1991). The distribution of Purkinje cell loss in the cerebellum in autism. *Neurology, 41,* 307.

Aussilloux, C., Collery, F. & Roy, J. (1989). Épidémiologie de l'autisme infantile dans le département de l'Hérault. *Revue Francaise de la Psychiatrie, 7,* 24–28.

Bailey, A. J. (1993). The biology of autism. Editorial. *Psychological Medicine, 23,* 7–11.

Balottin, U., Bejor, M., Cecchini, A., Martelli, A., Palazzi, S. & Lanzi, G. (1989). Infantile autism and computerized tomography brain-scan findings: Specific versus nonspecific abnormalities. *Journal of Autism and Developmental Disorders, 19,* 109–117.

Baron-Cohen, S., Leslie, A. & Frith, U. (1985). Does the autistic child have a "theory of mind"? *Cognition, 21,* 37–46.

Barry, R. J. & James, J. L. (1988). Coding of stimulus parameters in autistic, retarded and normal children; evidence for a two-factor theory of autism. *International Journal of Psychophysiology, 6,* 139–149.

Barthelemy, C., Bruneau, N., Jouve, J., Martineau, J., Muh, J. P. & Lelord, G. (1989). Urinary dopamine metabolites as indicators of the responsiveness to fenfluramine treatment in children with autistic behavior. *Journal of Autism and Developmental Disorders, 19,* 241–254.

Bauman, M. L. (1991). Microscopic neuroanatomic abnormalities in autism. *Pediatrics, 87,* 791–796.

Bauman, M. L. & Kemper, T. L. (1985). Histoanatomic observations of the brain in early infantile autism. *Neurology, 35,* 866–874.

Bishop, D. V. M. (1993). Annotation: Autism, executive functions and theory of mind: A neuropsychological perspective. *Journal of Child Psychology and Psychiatry, 34,* 279–293.

Boucher, J. (1981). Memory for recent events in autistic children. *Journal of Autism and Developmental Disorders, 11,* 293–303.

Bruneau, N., Arbeille, P., Dourneau, M-C., Garreau, B., Pourcelot, L. & Lelord, G. (1989). Evaluation du debit sanguin cerebral par Doppler transcranién chez les enfants presentant un comportement autistique. Resultats preliminaires. *Comptes Rendus de l'Academie des Sciences, Paris, 308,* 255–260.

Bruneau, N., Dourneau, M-C., Garreau, B., Pourcelot, L. & Lelord, G. (1992). Blood flow response to auditory stimulations in normal, mentally retarded and autistic children; a preliminary transcranial Doppler ultrasonographic study of the middle cerebral arteries. *Biological Psychiatry, 32,* 691–699.

Bryson, C. Q. (1970). Systematic identification of perceptual disabilities in autistic children. *Perceptual and Motor Skills, 31,* 239–246

Bryson, S. E., Clark, B.S. & Smith, I. M. (1988). First report of a Canadian epidemiological study of autistic syndromes. *Journal of Child Psychology and Psychiatry, 29,* 433–446.

Buitelaar, J. K., van Engeland, H., de Kogel, K. H., de Vries, H., van Hooff, J. & van Ree, J. M. (1992). The use of adrenocorticotrophic hormone (4–9) analog ORG 2766 in autistic children: Effects on the organization of behavior. *Biological Psychiatry, 31,* 1119–1129.

Burd, L. & Kerbeshian, J. (1988). Diagnosis of autism

and other pervasive developmental disorders. *Neuroscience and Biobehavioral Reviews, 12,* 275–282.

Burd, L., Fisher, W. & Kerbeshian, J. (1987). A prevalence study of pervasive development disorders in North Dakota. *Journal of the American Academy of Child and Adolescent Psychiatry, 26,* 700–703.

Campbell, M., Rosenbloom, S., Perry, R., George, A. E., Kricheff, I. I., Anderson, L., Small, A. M. & Jennings, S. (1982). Computerized axial tomography in young autistic children. *American Journal of Psychiatry, 139,* 510–512.

Campbell, M., Perry, R., Small, A. M. & Green, W. H. (1987). Overview of drug treatment in autism. In E. Schopler & G. B. Mesibov (Eds.) *Neurobiological Issues in Autism.* New York: Plenum Publishing Corp.

Campbell, M., Anderson, L. T., Small, A. M., Locascio, J. J., Lynch, N. S. & Choroco, M. C. (1990). Naltrexone in autistic children: A double-blind and placebo-controlled study. *Psychopharmacology Bulletin, 26,* 130–135.

Campbell, M., Anderson, L. T., Small, A. M., Adams, P., Gonzalez, N. M. & Ernst, M. (1993). Naltrexone in autistic children: Behavioral symptoms and attentional learning. *Journal of the American Academy of Child and Adolescent Psychiatry, 32,* 1283–1291.

Cantor, D. S., Thatcher, R. W., Hrybyk, M. & Kaye, H. (1986). Computerized EEG analyses of autistic children. *Journal of Autism and Developmental Disorders, 16,* 169–187.

Cegalis, J. A. & Deptula, D. (1981). Attention in schizophrenia: Signal detection in the visual periphery. *Journal of Nervous and Mental Disorders, 169,* 751–760.

Ciesielski, K. T., Courchesne, E. & Elmasian, R. (1990). Effects of focussed selective attention tasks on event-related potentials in autistic and normal individuals. *Electroencephalography and Clinical Neurophysiology, 75,* 207–220.

Coggins, T. E., Morisset, C., Krasney, L., Frederickson, R., Holm, V. A. & Raisys, V. A. (1988). Does fenfluramine treatment enhance the cognitive and communicative functioning of autistic children? *Journal of Autism and Developmental Disorders, 18,* 425–434.

Cohen, D. J. & Shaywitz, B. A. (1982). Preface: Neurobiological research in autism. *Journal of Autism and Developmental Disorders, 12,* 103–107.

Cohen, D. J., Caparulo, B. K., Shaywitz, B. A. & Bowers, M. B. (1977). Dopamine and serotonin metabolism in neuropsychiatrically disturbed children: CSG homovanillic acid and 5-hydroxyindole acetic acid. *Archives of General Psychiatry, 34,* 27–35.

Cook, E. H., Rowlett, R., Jaselskis, D. O. & Leventhal, B. L. (1992). Fluoxetine treatment of children and adults with autistic disorder and mental retardation. *Journal of the American Academy of Child and Adolescent Psychiatry, 31,* 739–745.

Corcoran, R. & Upton, D. (1993). A role for the hippocampus in card sorting? *Cortex, 29,* 293–304.

Courchesne, E., Lincoln, A. J., Kilman, B. A. & Galambos, R. (1985). Event-related brain potential correlates of the processing of novel visual and auditory information in autism. *Journal of Autism and Developmental Disorders, 15,* 55–76.

Courchesne, E., Yeung-Courchesne, R., Press, G. A., Hesselink, J. R. & Jernigan, T. L. (1988). Hypoplasia of cerebellar vermal lobules VI and VII in autism. *New England Journal of Medicine, 318,* 1349–1354.

Courchesne, E., Townsend, J., Akshoomoff, N. A., Yeung-Courchesne, R., Press, G. A., Murakami, J. W., Lincoln, A., James, H. E., Saitoh, O., Haas, R. H., Schreibman, L. & Lau, L. (1992). A new finding in autism: Impairment in shifting attention. In S. H. Broman and J. Grafman (Eds.) *Atypical Cognitive Deficits in Developmental Disorders: Implications for Brain Function.* Hillsdale, NJ: Lawrence Erlbaum.

Damasio, A. R. & Maurer, R. G. (1978). A neurological model for childhood autism. *Archives of Neurology, 35,* 777–786.

Dawson, G., Finley, C., Phillips, S. & Lewy, A. (1989). A comparison of hemispheric asymmetries in speech-related brain potentials of autistic and dysphasic children. *Brain and Language, 37,* 26–41.

Deutsch, S. I. & Campbell, M. (1986). Relative affinities for different classes of neurotransmitter receptors predict neuroleptic efficacy in infantile autism: A hypothesis. *Neuropsychobiology, 15,* 160–164.

Deutsch, S. I., Milstoc, M., Platovsky, G., Wolsky, B.B., Perry, R. & Green, W. H. (1987). Cholinesterase activity in blood in infantile autism. *Biological Psychiatry, 22,* 228–234.

De Volder, A., Bol, A., Michel, C., Congneau, M. & Goffinet, A. M. (1987). Brain glucose metabolism in children with the autistic syndrome: Positron tomography analysis. *Brain and Development, 9,* 581–587.

Eggers, C. (1978). Zur nosologischen Abgrenzung zwischen frühkindlichem Autismus und kindlicher Schizophrenie. *Bibliotheca psychiatrica, 157,* 1–21.

Eggers, C. (1984). Neuroleptika. In Nissen, G., Eggers, C. & Martinius, J. *Kinder- und jugendpsychiatrische Pharmakotherapie in Klinik und Praxis.* Heidelberg: Springer-Verlag.

Eggers, C., Lempp, R., Nissen, G. & Strunk, P. (1994). *Kinder- und Jugendpsychiatrie* (Seventh edition). Heidelberg: Springer-Verlag.

Ekman, G., Miranda-Linne, F., Gillberg, C., Garle, M. & Wetterberg, L. (1989). Fenfluramine treatment of twenty children with autism. *Journal of Autism and Developmental Disorders, 19,* 511–532.

Ernst, M., Magee, H. J., Gonzalez, N. M., Locascio, J. J., Rosenberg, C. R. & Campbell, M. (1992). Pimozide in autistic children. *Psychopharmacology Bulletin, 28,* 187–191.

Erzegovesi, S., Ronchi, P. & Smeraldi, E. (1992). 5HT-2 receptor and fluvoxamine efect in obsessive-compulsive disorder. *Human Psychopharmacology, 7,* 287–289.

Fein, D., Skoff, B. & Mirsky, A. F. (1981). Clinical

correlates of brainstem dysfunction in autistic children. *Journal of Autism and Developmental Disorders, 11*, 303–315.

Frith, C. D. (1992). *The Cognitive Neuropsychology of Schizophrenia*. Hillsdale, NJ: Lawrence Erlbaum.

Frith, U. (1989). *Autism: Explaining the Enigma*. Oxford, UK: Basil Blackwell.

Gadow, K. D. (1992). Pediatric psychopharmacotherapy: A review of recent research. *Journal of Child Psychology and Psychiatry, 33*, 153–195.

Gaffney, G. R., Kuperman, S., Tsai, L. Y. & Minchin, S. (1989). Forebrain structure in infantile autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 28*, 534–537.

Garnier, C., Comoy, E., Barthelemy, C., Leddet, I., Garreau, B., Muh, J. P. & Lelord, G. (1986). Dopamine beta hydroxylase (DBH) and homovanillic acid (HVA) in autistic children. *Journal of Autism and Developmental Disorders, 16*, 23–29.

Garreau, B., Barthelemy, C., Martineau, J., Bruneau, J. & Lelord, G. (1985). Aspects electrophysiologiques de l'autisme de l'enfant. *L'Encephale, XI*, 145–155.

Garreau, B., Barthelemy, C., Jouve, J., Bruneau, J., Muh, J. P. & Lelord, G. (1988). Urinary homovanillic acid levels of autistic children. *Developmental Medicine and Child Neurology, 30*, 93–98.

George, M. S., Costa, D. C., Kouris, K., Ring, H. A. & Ell, P. J. (1993). Cerebral blood flow abnormalities in adults with infantile autism. *Journal of Nervous and Mental Disease, 180*, 413–417.

Geschwind, N. (1965). Disconnection syndromes in animals and man. *Brain, 88*, 237–294 & 585–644.

Gillberg, C. (1984). Infantile autism and other childhood psychoses in a Swedish urban region: Epidemiological aspects. *Journal of Child Psychology and Psychiatry, 25*, 35–43.

Gillberg, C. (1991). The treatment of epilepsy in autism. *Journal of Autism and Developmental Disorders, 21*, 61–77.

Gillberg, C. (1993). Autism and related behaviours. *Journal of Intellectual Disability Research, 37*, 343–372.

Gillberg, C. & Svennerholm, L. (1987). CSF monoamines in autistic syndromes and other pervasive disorders of early childhood. *British Journal of Psychiatry, 151*, 89–94.

Gillberg, C., Steffenburg, S. & Jakobsson, G. (1987). Neurobiological findings in 20 relatively gifted children with Kanner-type autism or Asperger syndrome. *Developmental Medicine and Child Neurology, 29*, 641–649.

Gillberg, I. C., Bjure, J., Uvebrant, P., Vestergren, E. & Gillberg, C. (1993). SPECT (single photon emission computed tomography) in 31 children and adolescents with autism and autistic-like conditions. *European Child and Adolescent Psychiatry, 2*, 50–59.

Gordon, C. T., State, R. C., Nelson, J. E., Hamburger, S. D. & Rapoport, J. L. (1993). A double-blind comparison of clomipramine, desipramine and placebo in the treatment of autistic disorder. *Archives of General Psychiatry, 50*, 441–447.

Green, W. H., Padron-Gyol, M., Hardesty, A. S. & Bassiri, M. (1992). Schizophrenia with childhood onset: A phenomenological study of 38 cases. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*, 968–976.

Grillon, C., Courchesne, E. & Akshoomoff, N. (1989). Brainstem and middle latency auditory evoked potentials in autism and developmental language disorder. *Journal of Autism and Developmental Disorders, 19*, 255–269.

Gruesser, O-J. (1991). Impairment of perception and recognition of faces, facial expression and gestures in schizophrenic children and adolescents. In C. Eggers (Ed.) *Schizophrenia and Youth*. Heidelberg: Springer-Verlag.

Guilarte, T. R., Wagner, H. N. & Frost, J. J. (1987). Effects of perinatal vitamin B6 deficiency on dopaminergic neurochemistry. *Journal of Neurochemistry, 48*, 432–439.

Happe, F. & Frith, U. (1991). Debate and argument: How useful is the "PDD" label? *Journal of Child Psychology and Psychiatry, 32*, 1167–1168.

Hashimoto, T., Tayama, M., Mori, K., Fujino, K., Miyazaki, M. & Kuroda, Y. (1989). Magnetic resonance imaging in autism: Preliminary report. *Neuropediatrics, 20*, 142–146.

Hauser, S. L., De Long, G. R. & Rosman, N. P. (1975). Pneumographic findings in the infantile autism syndrome. A correlation with temporal lobe disease. *Brain, 98*, 667–688.

Heh, C. W., Smith, R., Wu, J., Hazlett, E., Russell, A., Asarnow, R., Tanguay, P. & Buchsbaum, M. S. (1988). Positron emission tomography of the cerebellum in autism. *American Journal of Psychiatry, 146*, 242–245.

Herault, J., Martineau, J., Perrot-Beaugerie, A., Jouve, J., Tournade, H., Barthelemy, C., Lelord, G. & Muh, J-J. (1993). Investigation of whole blood and urine monoamines in autism. *European Child and Adolescent Psychiatry, 2*, 211–220.

Hermelin, B. & O'Connor, N. (1970). *Psychological Experiments with Autistic Children*. Oxford, UK: Pergamon Press.

Herold, S., Frackowiak, R. S. J., Le Couteur, A., Rutter, M. & Howlin, P. (1988). Cerebral blood flow and metabolism of oxygen and glucose in young autistic adults. *Psychological Medicine, 18*, 823–831.

Hertzig, M. E., Snow, M. E. & Sherman, M. (1989). Affect and cognition in autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 28*, 195–199.

Hier, D. B., LeMay, M. & Rosenberger, P. B. (1979). Autism and unfavorable left-right asymmetries of the brain. *Journal of Autism and Developmental Disorders, 9*, 153–159.

Holtum, J. R., Minshew, N. J., Sanders, R. S. & Phil-

lips, N. E. (1992). Magnetic resonance imaging of the posterior fossa in autism. *Biological Psychiatry, 32,* 1091–1101.

Horwitz, B., Rumsey, J. M., Grady, C. & Rapoport, S. I. (1987). Interregional correlations of glucose utilization among brain regions in autistic adults. *Annals of Neurology, 22,* 118.

Horwitz, B., Rumsey, J. M., Grady, C. L. & Rapoport, S. I. (1988). The cerebral metabolic landscape in autism: Intercorrelations of regional glucose utilization. *Archives of Neurology, 45,* 749–755.

James, A. L. & Barry, R. J. (1980). A review of psychophysiology in early onset psychosis. *Schizophrenia Bulletin, 6,* 506–524.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child, 2,* 217–250.

Kasari, C., Sigman, M. & Yirmiya, N. (1993). Focused and social attention of autistic children in interactions with familiar and unfamiliar adults: A comparison of autistic, mentally retarded and normal children. *Development and Psychopathology, 5,* 403–414.

Kemner, C. (1992). *Event-Related Brain Potentials: A Window on Stimulus Processing in Autistic Children.* Proefschrift, Rijksuniversiteit te Utrecht.

Launay, J. M., Ferrari, P., Haimart, M., Bursztejn, C., Tabuteau, F., Braconnier, A., Pasques-Bondoux, D., Luong, C. & Dreux, C. (1988). Serotonin metabolism and other biochemical parameters in infantile autism: A controlled study of 22 autistic children. *Neuropsychobiology, 20,* 1–11.

Le Couteur, A., Trygstad, O., Evered, C., Gillberg, C. & Rutter, M. (1988). Infantile autism and urinary excretion of peptides and protein-associated peptide complexes. *Journal of Autism and Developmental Disorders, 18,* 181–190.

Leekam, S. R. & Perner, J. (1991). Does the autistic child have a metarepresentational deficit? *Cognition, 40,* 203–218.

Leslie, A. (1987). Pretense and representation: The origins of "theory of mind". *Psychological Review, 94,* 412–426.

Lincoln, A. J., Courchesne, E., Harms, L. & Allen, M. (1993). Contextual probability evaluation in autistic, receptive developmental language disorder and control children: Event-related brain potential evidence. *Journal of Autism and Developmental Disorders, 23,* 37–58.

Loge, D. V., Staton, R. D. & Beatty, W. W. (1990). Performance of children with ADHD on tests sensitive to frontal lobe dysfunction. *Journal of the American Academy of Child and Adolescent Psychiatry, 29,* 540–545.

Martineau, J., Garreau, B., Barthelemy, C., & Lelord, G. (1984). Evoked potentials, P300 during sensory conditioning in autistic children. *Annals of the New York Academy of Sciences, 425,* 362–369.

Martineau, J., Barthelemy, C., Garreau, B. & Lelord, G. (1985). Vitamin B6, magnesium and combined B6-Mg: Therapeutic effects in childhood autism. *Biological Psychiatry, 20,* 467–478.

Martineau, J., Roux, S., Garreau, B., Adrien, J. L. & Lelord, G. (1992). Unimodal and crossmodal reactivity in autism: Presence of auditory evoked reponses and effect of the repetition of auditory stimuli. *Biological Psychiatry, 31,* 1190–1203.

McBride, P. A., Anderson, G. M., Hertzig, M. E., Sweeney, J. A., Kream, J., Cohen, D. J. & Mann, J. J. (1989). Serotonergic responsivity in male young adults with autistic disorder: Results of a pilot study. *Archives of General Psychiatry, 46,* 213–221.

McClelland, R. J., Eyre, D. G., Watson, D., Calvert, G. J. & Sherrard, E. (1992). Central conduction time in childhood autism. *British Journal of Psychiatry, 160,* 659–663.

Minshew, N. J., Goldstein, G., Dombrowski, S. M., Panchalingam, K. & Pettegrew, J. W. (1993). A preliminary 31-P MRS study of autism: Evidence for undersynthesis and increased degradation of brain membranes. *Biological Psychiatry, 33,* 762–773.

Moll, G. H. & Schmidt, M. H. (1991). Entwicklungen in der Therapie des frühkindlichen Autismus – Ergebnisse der Therapieforschung. *Zeitschrift für Kinder- und Jugendpsychiatrie, 19,* 182–203.

Murakami, J. W., Courchesne, E., Press, G. A., Yeung-Corchesne, R. & Hesselink, J. R. (1989). Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism. *Archives of Neurology, 46,* 689–694.

Niwa, S., Ohta, M. & Yamazaki, K. (1983). P300 and stimulus evaluation process in autistic subjects. *Journal of Autism and Developmental Disorders, 13,* 33–42.

Novick, B., Vaughan, H. G., Kurtzberg, D. & Simson, R. (1980). An electrophysiologic indication of auditory processing deficits in autism. *Psychiatry Research, 3,* 107–114.

Oades, R. D. (1985). The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. *Neuroscience and Biobehavioral Reviews, 9,* 261–282.

Oades, R. D. (1989). Attention deficit disorder and hyperkinetic syndrome: Biological perspectives. In T. Sagvolden & T. Archer (Eds.) *Attention Deficit Disorder: Clinical and Basic Research* (pp. 353–369). Hillsdale, NJ: Lawrence Erlbaum.

Oades, R. D. (1994). Connections between studies of the neurobiology of attention, psychotic processes and event-related potentials. *Electroencephalography and clinical Neurophysiology,* in press.

Oades, R. D. & Zerbin, D. (1991). Signs of differential stimulus processing problems: A comment on event-related potentials in young schizophrenic and autistic subjects. In C. Eggers (Ed.) *Schizophrenia and Youth,* Heidelberg: Springer-Verlag.

Oades, R. D., Röpcke, B. & Eggers, C. (1994). Monoamine activity reflected in urine of young patients with obsessive compulsive disorder, psychosis with

and without reality distortion and healthy subjects: An explorative analysis. *Journal of Neural Transmission*, in press.

Oades, R. D., Walker, M. K., Geffen, L. B. & Stern, L. (1988). Event-related potentials in autistic and healthy children on an auditory choice reaction time task. *International Journal of Psychophysiology, 6*, 25–37.

Oades, R.D., Stern, L. M., Walker, M. K., Clark, C. R. & Kapoor, V. (1990). Event-related potentials in autistic children on a clinical trial of fenfluramine. *International Journal of Psychophysiology, 8*, 197–212.

Ornitz, E. M. (1985). Neurophysiology of infantile autism. *Journal of the American Academy of Child Psychiatry, 24*, 251–262.

Ozonoff, S., Pennington, B. F. & Rogers, S. J. (1991a). Executive function deficits in high-functioning autistic children: Relationship to theory of mind. *Journal of Child Psychology and Psychiatry, 32*, 1081–1105.

Ozonoff, E. M., Rogers, S. J. & Pennington, B. F. (1991b). Asperger's syndrome: Evidence of an empirical distinction from high-functioning autism. *Journal of Child Psychology and Psychiatry, 32*, 1107–1122.

Panksepp, J. (1979). A neurochemical theory of autism. *Trends in the Neurosciences, 2*, 174–177.

Panksepp, J. & Sahley, T. L. (1987). Possible brain opioid involvement in disrupted social intent and language development in autism. In E. Schopler & B.G.Mesibov (Eds.) *Neurobiological Issues in Autism* (Second edition, pp 357–37). New York: Plenum Press.

Pelligra, R., Norton, R. D., Wilkinson, R., Leon, H. A. & Matson, W. R. (1992). Rett syndrome: Stimulation of endogenous biogenic amines. *Neuropediatrics, 23*, 131–137.

Piven, J., Nehme, E., Simon, J., Barta, P., Pearlson, G. D. & Folstein, S. E. (1992). Magnetic resonance imaging in autism: Measurement of the cerebellum, pons and fourth ventricle. *Biological Psychiatry, 31*, 491–504.

Piven, J., Simon, J., Chase, G. A., Wzorek, M., Landa, R., Gayle, J. & Folstein, S. (1993). The etiology of autism: Pre-, peri- and neonatal factors. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*, 1256–1263.

Plioplys, A. V., Hemmens, S. E. & Regan, C. M. (1990). Expression of a neural cell adhesion molecule serum fragment is depressed in autism. *Journal of Neuropsychiatry, 2*, 413–417.

Prior, M. (1979). Learning abilities and disabilities in childhood autism: A review. *Journal of abnormal Child Psychology, 7*, 357–380.

Prior, M. R. & Hoffmann, W. (1990). Brief report: Neuropsychological testing of autistic children through an exploration with frontal lobe tests. *Journal of Autism and Developmental Disorders, 20*, 581–590.

Prior, M., Dahlstrom, B. & Squires, T-L. (1990). Autistic children's knowledge of thinking and feeling states in other people. *Journal of Child Psychology and Psychiatry, 31*, 587–601.

Raymond, G., Bauman, M. & Kemper, T. (1989). The hippocampus in autism: Golgi analysis. *Annals of Neurology, 26*, 483–484.

Reichelt, K. L., Saelid, G., Lindback, T. & Boler, J. B. (1986). Childhood autism: A complex disorder. *Biological Psychiatry, 21*, 1279–1290.

Reiss, A. L., Faruque, F., Naidu, S., Abrams, M., Beaty, T., Bryan, R. N. & Moser, H. (1993). Neuroanatomy of Rett syndrome: A volumetric imaging study. *Annals of Neurology, 34*, 227–234.

Riikonen, R. & Amnell, G. (1981). Psychiatric disorders in children with earlier infantile spasms. *Developmental Medicine and Child Neurology, 23*, 747–760.

Rimland, B., Callaway, E. & Dreyfus, P. (1978). The effect of high doses of vitamin B6 on autistic children: A double-blind crossover study. *American Journal of Psychiatry, 135*, 472–475.

Ritvo, E. R. & Freeman, B. J. (1978). National society for autistic children: Definition of the syndrome of autism. *Journal of the American Academy of Child Psychiatry, 17*, 565–576.

Ritvo, E. R., Freeman, B. J., Geller, E. & Yuweiler, A. (1983). Effects of fenfluramine on 14 outpatients with the syndrome of autism. *Journal of the American Academy of Child Psychiatry, 22*, 549–558.

Ritvo, E. R., Freeman, B. J., Pingree, C., Mason-Brothers, A., Jorde, L., Jenson, W. R., McMahon, W. M., Peterson, P. B., Mo, A. & Ritvo, A. (1989). The UCLA – University of Utah epidemiological study of autism: Prevalence. *American Journal of Psychiatry, 146*, 194–245.

Rumsey, J. M. & Hamburger, S. (1990). Neuropsychological divergence of high-level autism and severe dyslexia. *Journal of Autism and Developmental Disorders, 20*, 155–168.

Rutter, M. (1972). Childhood schizophrenia reconsidered. *Journal of Autism and Childhood Schizophrenia, 2*, 315–337.

Rutter, M. (1983). Cognitive deficits in the pathogenesis of autism. *Journal of Child Psychology and Psychiatry, 24*, 513–531.

Rutter, M. (1991). Nature, nurture and psychopathology: A new look at an old topic. *Development and Psychopathology, 3*, 125–136.

Sandberg, A. D., Nyden, A., Gillberg, C. & Hjelmquist, E. (1993). The cognitive profile in infantile autism – A study of 70 children and adolescents using the Griffiths Mental Development Scale. *British Journal of Psychology, 84*, 365–373.

Sandyk, R. & Gillman, M. A. (1986). Infantile autism: A dysfunction of the opioids? *Medical Hypotheses, 19*, 41–45.

Schain, R. & Freedman, D. X. (1961). Studies on 5-hydoxyindole metabolism in autistic and other men-

tally retarded children. *Journal of Pediatrics, 58,* 315–320.

Schwartz-Place, E. J. & Gilmore, G. C. (1980). Perceptual organization in schizophrenia. *Journal of Abnormal Psychology, 89,* 409–418.

Sherman, J., Factor, D. C., Swinson, R. & Darjes, R. W. (1989). The effects of fenfluramien (hydrochloride) on the behaviors of fifteen autistic children. *Journal of Autism and Developmental Disorders, 19,* 533–543.

Siegel, B. V., Asarnow, R., Tanguay, P., Call, J. D., Abel, L., Ho, A., Lott, I. & Buchsbaum, M. S. (1992). Regional cerebral glucose metabolism and attention in adults with a history of childhood autism. *Journal of Neuropsychiatry, 4,* 406–414.

Small, J. G. (1975). EEG and neurophysiological studies of early infantile autism. *Biological Psychiatry, 10,* 385–395.

Sodian, B. & Frith, U. (1992). Deception and sabotage in autistic, retarded and normal children. *Journal of Child Psychology and Psychiatry, 33,* 591–605.

Steffenburg, S. (1991). Neuropsychiatric assessment of children with autism: A population based study. *Developmental Medicine and Child Neurology, 33,* 495–511.

Steinhausen, H., Göbel, D., Breinlinger, M & Wohlleben, B. (1986). A community survey of infantile autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 25,* 186–189.

Stern, L. M., Walker, M. K., Sawyer, M. G., Oades, R. D. Badcock, N. R. & Spence, J. G. (1990). A controlled crossover trial of fenfluramine in autism. *Journal of Child Psychology and Psychiatry, 31,* 569–585.

Stevens, S. & Gruzelier, J. (1984). Electrodermal activity to auditory stimuli in autistic, retarded and normal children. *Journal of Autism and Developmental Disorders, 14,* 245–260.

Straube, E. R. & Oades, R. D. (1992). *Schizophrenia: Empirical Research and Findings.* New York: Academic Press.

Sugiyama, T. & Abe, T. (1989). The prevalence of autism in Nagoya, Japan: A total population study. *Journal of Autism and Developmental Studies, 19,* 87–96.

Sutton, S., Hakerem, G., Zubin, J. & Portnoy, M. (1961). The effect of shift of sensory modality on serial reaction time: A comparison of schizophrenics and normals. *American Journal of Psychology, 74,* 224–232.

Tamlyn, D., McKenna, P. J., Mortimer, A. M., Lund, C. E., Hammond, S. & Baddeley, A. D. (1992). Memory impairment in schizophrenia: Its extent, affiliations and neuropsychological character. *Psychological Medicine, 22,* 101–111.

Tanguay, P. E., Edwards, R. M., Buchwald, J., Schwafel, J. & Allen, V. (1982). Auditory brainstem responses in autistic children. *Archives of General Psychiatry, 39,* 174–180.

van Engeland, H., Roelofs, J. W., Verbaten, M. N. & Slangen, J. L. (1991). Abnormal electrodermal reactivity to novel visual stimuli in autistic children. *Psychiatry Research, 38,* 27–38.

Weinberger, D. R., Berman, K. F. & Zec, R. F. (1986). Physiologic dysfunction of dorsolateral prefronatl cortex in schizophrenia: I. regional cerebral blood flow evidence. *Archives of General Psychiatry, 43,* 114–124.

Wing, L. (1979). Mentally retarded children in Camberwell (London). In H. Häfner (Ed.) *Estimating Needs for Mental Health Care* (pp. 107–112). Berlin: Springer-Verlag.

Wing, L. (1993). The definition and prevalence of autism: A review. *European Child and Adolescent Psychiatry, 2,* 61–74.

Wing, L. & Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *Journal of Autism and Developmental Disorders, 9,* 11–30.

World Health Organization. (1991). *Tenth revision of the International Classification of Diseases, Chapter V (F): Mental and Behavioural Disorders (including disorders of psychological development). Clinical Descriptions and Guidelines.* Geneva: World Health Organization.

Yates, A. (1984). Autism: The case for left hemisphere damage. *Arizona Medicine, 41,* 395–397.

Yuwiler, A., Shih, J. C., Chen, C-H., Ritvo, E. R., Hanna, G., Ellison, G. W. & King, B. H. (1992). Hyperserotonemia and antiserotonin antibodies in autism and other disorders. *Journal of Autism and Developmental Disorders, 22,* 33–45.

Zilbovicius, M., Garreau, B., Tzourio, N., Mazoyer, B., Bruck, B., Martinot, J. L., Raynaud, C., Samson, Y., Syrota, A. & Lelord, G. (1992). Regional cerebral blood flow in childhood autism. A SPECT study. *American Journal of Psychiatry, 149,* 924–930.