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Neurodevelopmental processes and psychological functioning in autism

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Abstract
Autism is a developmental disorder with variable severity, occurring at all levels of cognitive ability and having a number of slightly different clinical presentations. It is associated with neuropsychological deficits that occur in other conditions also, but its *pattern* may be specific to autism. Genetic and environmental early insults to brain development are etiological determinants of the disorder. Brain circuitries important for social, communicative, and integrational purposes have been suggested to be dysfunctional in autism. There could be at least two different pathways to autism, one connected with primary temporofrontal dysfunction (and late prenatal–early postnatal origins) and another linked to primary brain-stem dysfunction (and early prenatal origins). Further study of neurodevelopmental and neuropsychological processes in autism will help elucidate not only the pathological mechanisms involved in the specific syndromes but also the underpinnings of normal brain development.

Autistic disorder (American Psychiatric Association, 1994), also referred to as childhood autism (World Health Organization, 1993), is a behaviorally defined syndrome, characterized by a triad of impairments hitting (a) reciprocal social interaction, (b) reciprocal verbal and nonverbal communication, and (c) imagination and behavior. The syndrome of autism with early childhood onset was first described by Leo Kanner (1943), but the particular variant that he delineated—characterized by aloofness and elaborate, repetitive routines (Kanner & Eisenberg, 1956)—is now considered only a portion of the autistic spectrum. This broader category also comprises, among other syndromes, the high-functioning variant described by Hans Asperger (1944) and referred to as Asperger's disorder (APA 1994) or Asperger syndrome (Gillberg, 1991a). With the inclusion of a broader phenotype of autism, it has become clear that disorders in the autism spectrum are quite common, affecting about 1 in 200 individuals (Gillberg & Wing, 1999). By and large, classic autism cases are usually associated with mild–moderate–severe mental retardation and onset of symptoms in the first 2 years of life, so that differential diagnosis is not a major problem. However, with respect to the small percentage of core autistic disorder cases with low-normal or normal intelligence (about 20% in most studies), the separation from Asperger syndrome may pose a challenging problem, perhaps particularly in research. On the basis of a factor analytic study of "social communication" in autism and autistic-like conditions, it has been suggested that there may not be a need for a separate category of Asperger's, and that the insistence in all diagnostic manuals that restrictive, repetitive, and stereotypic elements have to be present for a diagnosis along the "autism spectrum" may have to be reconsidered (Tanguay, Robertson, & Derrick, 1998).

Many more males than females are affected by autism spectrum disorders, the ratio usually reported as being in the range of 3–4 : 1 (males : females), higher still in Asperger syndrome and lower in other autistic-like con-

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ditions (Gillberg, 1992a). Recent reports (e.g., Kopp & Gillberg, 1992) have highlighted the possibility that girls with social deficit syndromes may be underdiagnosed because they are less aggressive, less hyperactive, and less typical of the autism prototype, which, since Kanner's first writings, has been described with affected males in mind.

Once thought to be a condition of the upper social classes, it is now accepted that autism occurs in all social classes and that the social class distribution is likely to be similar to that in the general population (Steffenburg & Gillberg, 1989; Wing, 1980).

A number of studies suggest that autism is more common in children born to parents born in cultures geographically distant from those being epidemiologically screened for autism (Akinsọla & Fryers, 1986; Gillberg, Steffenburg, Borjesson, & Andersson, 1987; Gillberg, Steffenburg, & Schaumann, 1991; Wing, 1980). The reason for this high rate is unclear, but could be either pregnancy viral infections in women who have arrived from foreign cultures, an increase in the number of, as yet, unidentified genetic disorders, an increased likelihood that men with Asperger syndrome might have children by women from faraway cultures, or other factors.

Autistic disorder and Asperger syndrome are the two disorders in the spectrum that have received the most attention in respect of research into underlying neurodevelopmental and neurobiological factors. Recent advances in these fields have made it clear that autism is a brain disorder, usually with roots in the prenatal period. There is good evidence that genetic factors (most likely polygenetic interactions) play a very important part in the causation of the disorder in a majority of cases (Bailey, Phillips, & Rutter, 1996). However, in a substantial minority of all cases, acquired brain damage or damage to certain brain regions during the course of another medical disorder—which may or may not be genetic—also may lead to autism (Gillberg & Coleman, 1996). Several strands of evidence suggest the possibility of critical periods during the early stages of the 1st trimester of intrauterine life, the middle of the 2nd trimester, and—in a minority of cases—the 2nd year of postnatal life, with a variety of mechanisms leading to abnormalities of preprogrammed intra- and extrauterine brain development. Certain frontotemporal neural circuitries appear to be crucial for the development of normal reciprocal communicative and social development, and these areas of the brain appear to be particularly often hit in autism. Brain-stem–cerebellar circuitries have also been found to be abnormal–dysfunctional in autism, and this would lead to secondary negative effects on frontotemporal functioning. Synapse dysregulation—with abnormalities of the normally occurring process of synapse pruning and nerve cell death around 12–24 months into postnatal life—in these areas is suggested by scattered research findings.

The underlying theme of this paper is that autism is a multifactorially determined biological disorder—caused by genetic brain dysfunction or acquired brain lesions—with a relatively characteristic neurocognitive test profile but no absolutely pathognomonic features. Autism spectrum disorders are suggested to be linked to temporofrontal brain dysfunction which may arise "in isolation" or as a consequence of very early prenatal abnormalities in the brain stem–cerebellum. There may be specific biochemical dysfunctions and abnormalities of synapse formation and regulation. It is further suggested that the higher functioning variants of autism spectrum disorders may exist on a continuum with "normality," representing the lowermost end of the normal distribution of "empathy skills" in the general population. Recent neuropsychological and neurobiological research data supporting—or contradicting—this view of the neurodevelopmental processes in autism spectrum disorders will be reviewed. The review will move from (a) focusing on phenomenological (clinical "surface") symptoms in a developmental perspective, to (b) assessing the neuropsychological and developmental cognitive dysfunctions that underlie these phenomena, and then on to (c) exploring the clinical and neurobiological data that suggest a brain problem which could account for the neuropsychological and cognitive characteristics of autism. The various strands of evidence will then be drawn together to suggest a hypotheti-

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cal model for the "neurodevelopment of autism."

Developmental Processes in Autism: The Clinical Surface

Classic autism may be symptomatic from the first few weeks of life or may become overtly symptomatic only after a period of 18–36 months of seemingly normal development (Gillberg & Coleman, 1992). It is not clear whether there might exist some fundamental differences between the early and late "onset" cases. A further distinction is sometimes made between classic autism and cases with even later symptom onset (usually after age 36 months), and these latter instances are sometimes referred to as childhood disintegrative disorder (formerly "disintegrative psychosis" or "Heller syndrome"; Volkmar, 1992). Interestingly, there have been several case reports demonstrating that classic autistic symptomatology can emerge in previously normal individuals who contract herpes brain infection at the age of 4, 14, and even 31 years (Gillberg, I. C., 1991).

The first symptoms of autism may be unspecific and show as sleep problems and developmental or language delay (Wing, 1996). However, there is growing evidence that with more specific tools for evaluation more specific symptoms will be delineated. For instance, in a prospective study of 20-month-old infants, children who later met full criteria for autism were specifically impaired in the use of social gaze in empathy and joint attention tasks. Marked absence of spontaneous pretend play was typical of autism and mental retardation, but pretend play did emerge after prompting in the retarded group but not in the autism group (Charman, Swettenham, Baron–Cohen, Cox, Baird, & Drew, 1997). An early prospective study of infants has identified failure to react to auditory stimuli and lack of pretend play as salient features of autism (Gillberg et al., 1990), very often present in the first 10 months of life. An early retrospective study showed empty gaze and strange reactions to auditory stimuli to be items that clearly discriminated autism from mental retardation and normalcy (Dahlgren & Gillberg, 1989). Baron–Cohen has suggested that infants who develop the symptoms of autism may have a failure in the development of an "eye-direction detector" which is present in normal children in the 1st year of life (Baron–Cohen, Baldwin, & Crowson, 1997). Thus, the clinical evidence relating to early symptoms of autism tend to suggest brain-stem and midbrain problems (auditory and gaze abnormalities and sleep problems). One study found that autism and mental retardation can be reliably differentiated on electrophysiological measures; intellectual impairment was associated with centroparietal electrophysiological reactivity, whereas autism was linked to temporal lobe reactivity (Roux et al., 1997).

Asperger syndrome, unlike autistic disorder, is not usually suspected or diagnosed in the preschool years (Gillberg, 1991a). Instead, most of the individuals who are significantly impaired by their problems receive their diagnosis in the 7- to 12-year-old age range. However, it seems that, even though their abnormalities are less striking in the first few years of life, they do have mild problems in the social, communication, and imagination–behavior areas early on. A few appear to be cases of classic autism but later develop into such high-functioning individuals—both verbally and nonverbally—that a clinical diagnosis of Asperger's seems much more appropriate (Wing, 1996). Conversely, there are those who appear to "start out" as typical Asperger cases but who later are so handicapped that a diagnosis of autistic disorder is considered instead. There is often a problem—even when using manuals that were developed for this particular purpose, such as the ADI-R (Lord, Storoschuk, Rutter, & Pickles, 1993)—in determining whether there were clear problems in the triad domain before the age of 3 years, when a child (or an adult for that matter) is seen many years later. This contributes to the problems that are associated with separating some cases of Asperger syndrome from autistic disorder. It also underscores the need to continue to keep an open mind with respect to Asperger syndrome: sometimes it does represent a variant of the autistic syndromes, qualitatively closely linked to autistic disorder, but at other times it *may* represent a con-

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dition which is not so intimately connected with autism.

Neuropsychological and Cognitive Functioning in Autism Spectrum Disorders

Recent years have witnessed a veritable explosion in the fields of cognitive psychology and neuropsychology in relation to autism. There is now a considerable autism literature documenting deficits in (a) executive functions, (b) mentalizing or "theory of mind," and (c) drive for central coherence. Autistic disorder shows a fairly characteristic pattern on neuropsychological tests such as the Wechsler scales (Frith, 1989), the Tower of Hanoi or Tower of London tests, and other so-called executive function tests (Ozonoff & Miller, 1995). Individuals with autism often fail on specific mentalizing tests, such as the "Sally-Anne" and "Smarties" tasks (Happe, 1994), and on tasks aimed at measuring drive for central coherence, such as elaborate versions of the WISC/WAIS (Wechsler, 1974, 1981) Block Design subtest (Happe, 1996). Not all people with autism are impaired in all of these fields, but there is usually evidence of dysfunction in at least one of the areas outlined.

Global cognitive deficits

There is always evidence of cognitive dysfunction in autism (Rutter, 1983). In most studies of autistic disorder and classic autism, mental retardation (in which the IQ is 70 or below) is present in 65–85% of cases examined. There is usually, but not invariably, poorer performance on verbal than on performance tests and evidence of relatively spared functions in the visuospatial domains (Frith, 1989). The subtest profile on the WISC/WAIS is often characterized by troughs on comprehension and picture arrangement and a peak on block design.

The picture is different in Asperger syndrome, where most individuals have IQs above 70 and the verbal scores often exceed those of the performance parts of the test. There are often WISC/WAIS troughs on picture arrangement (possibly as a marker of mentalizing deficits) and object assembly (a possible indication of weak central coherence) and quite commonly also in areas that are usually dysfunctional in attention disorders (i.e., arithmetics, digit span, and digit symbol; Ehlers et al., 1997).

Executive function deficits

There is widespread acceptance that executive functions—usually believed to reflect prefrontal brain activity—are dysfunctional in autism (Ozonoff & Strayer, 1997). However, the issue of whether or not there are *specific* executive function deficits in autism has yet to be resolved. One study comparing school-age children with a variety of neuropsychiatric disorders to normal children found that high-functioning autism, ADHD, and dyslexia were all markedly different from normality, but not significantly different from each other in terms of executive functions (Nyden, Gillberg, Hjelmquist, & Heiman, 1999). Children—and adults—with autism show impairments in respect of working memory, ability to inhibit, plan, organize, and to flexibly shift from one cognitive set to another (Dawson, 1996). Attentional abilities—accepted by some researchers as markers of executive function, considered by others to be a different set of neuropsychological–cognitive functions—are impaired with regard to orienting, disengaging, and selection, but usually spared in terms of the category named "sustained attention."

Mentalizing deficits

There is general agreement that young children with autism—across the board of intellectual functioning and severity—have severe problems in the area of mentalizing or "theory of mind" (Baron–Cohen, 1995; Frith, 1989). They have severe problems taking another person's social point of view and, at least when young or of low mental age, understanding that other people have thoughts and beliefs and other mental states that do not necessarily show on the outside in mimicry or gesture. There has been some doubt as to

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whether the mentalizing deficits are linked to autism or mental retardation or low language competence (Prior, Dahlstrom, & Squires, 1990), since a number of individuals with autism pass theory of mind tests. It now appears that older mildly retarded or normally intelligent individuals with autism pass such tests in a majority of all cases, and that those diagnosed as having Asperger syndrome do so even from around early school age. It appears that the emergence of mentalizing skills may be greatly delayed in autism, and that in the most severely handicapped group with severe and profound levels of mental retardation, such skills may never develop at all (Baron–Cohen, 1995). Reaction times to so-called false-belief tasks tend to be delayed in autism even in cases who actually formally pass the tasks per se (Bowler, 1997). Theory-of-mind skills can be trained successfully in young children (Howlin 1998), but such training does not appear to affect their everyday social behavior. However, unfortunately, there is good correspondence between poor theory of mind skills and impairments in everyday social behavior (Hughes, Soares–Boucaud, Hochmann, & Frith, 1997).

There is now also a growing literature showing that difficulties in understanding mental states are not specific to autism but also occur in other conditions, such as schizophrenia (Frith & Corcoran, 1996) and "social immaturity" (Muris, Steerneman, & Merchelbach, 1998). These findings do not contradict the broader concept of autism, but are compatible with findings that schizophrenia may be anteceded by autistic-type problems (Asarnow, Goldstein, Carlson, Perdue, Bates, & Keller, 1988) and that the broader phenotype of autism may well include variants reflecting mainly as social immaturity (Le Couteur et al., 1996). However, they are also well fitted to a model suggesting that genes and environmental hazards act in concert to only rarely produce the (arbitrarily defined) "syndrome" of autism and to more often cause "spectrum" problems and "similar" problems or disorders depending on which genes or hazards and neuropsychological functions are most severely affected.

Originally being conceptualized as an all-or-nothing phenomenon (Baron–Cohen, Leslie, & Frith, 1985), theory-of-mind skills are now regarded as the result of gradual emergence and molding of developmentally more primitive skills such as "eye-direction detection" (Baron–Cohen, 1995) and joint attention (Sigman, Ungerer, & Russell, 1983). Both of these functions appear to be impaired very early in the lives of children with autism (Baron–Cohen, 1995; Mundy & Crowson, 1997).

Gillberg (1992a) has suggested that poorly developed theory of mind skills might be equivalent to having poor empathy (although not necessarily to having poor sympathy) and has launched the concept of "disorders of empathy" for the broader group of individuals who have mentalizing deficits. He has argued that in an older person who had such problems as a child there may be an inability to react quickly enough to social stimuli, and, hence, the striking quality of lack of intuition and common sense. His model also suggests that the ability to mentalize may be normally distributed in the general population and that individuals diagnosed as having an autism spectrum disorder may either represent cases on the lowermost tail of the normal distribution curve or have severely deficient empathy skills because of an acquired brain lesion hitting neural circuitries that subserve empathy.

Central coherence deficits

There is mounting support for the notion that individuals with autism are characterized by their "weak drive for central coherence" (Happe, 1994). Such a deficit biases them towards processing information at an analytic rather than global level, and they have difficulty switching from details to concepts of whole gestalts or vice versa. Both children and adults with autism and Asperger syndrome perform better on the so-called Embedded Figures Test than do normal controls (Jolliffe & Baron–Cohen, 1997), but they do not differ significantly from each other. Counting abilities differentiated children with autism from those with moderate learning difficulties and from normally developing children (Jarrold & Russell, 1997). These findings, along

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with the well-known tendency for individuals with autism to score relatively high or very high on the Block Design subtest of the WISC or WAIS (Frith, 1989)—and the suggestion that those with Asperger syndrome score low on the Object Assembly subtest (Ehlers et al., 1997)—have been taken as evidence of "lack of a drive for" or "weak" central coherence in autism and autistic-like conditions.

Other neuropsychological characteristics of autism

Several other neuropsychological domains have been studied in the pathogenesis of autism. Some of these may be seen to represent functions overlapping or even synonymous with those referred to in the previous three sections. Deficits in social perception, in symbolic play, and in memory are examples of such domains. Other functions that have been suggested to be impaired in autism comprise motor performance, some visually related abilities (in spite of the fact that other aspects of visuospatial functions appear to be spared or even hyperfunctioning in many cases of autism), facial recognition, and interhemispheric transfer. These areas appear to be slightly more clearly separated from executive functions, mentalizing, and drive for central coherence. Language is a tricky area in autism research, given that communication deficits (verbal and nonverbal) are a defining feature of the syndrome. Nevertheless, there is evidence that the nonverbal communication deficit resulting from impairment in mentalizing ability might be of greater importance than specific language dysfunction in autism, meaning that the language deficits observed in the syndrome may also be best interpreted in the light of knowledge that has accumulated on the basis of research into theory of mind.

Social perception, symbolic play, and attentional deficits. In a well-controlled study, children with autism were unimpaired on social perception tasks that involved only one cue (Pierce, Glad, & Schreibman, 1997), but failed when more cues were involved. The findings were interpreted as possibly reflecting attentional rather than primarily social deficits. Symbolic play and memory were delayed rather than deviant in an experimental setting in which children with autism and children matched for receptive language and others matched for nonverbal IQ were compared with one another (McDonough, Stahmer, Schreibman, & Thompson, 1997). These findings—sharply contrasting with the impairments in these areas found when children with autism are observed in naturalistic settings—again were taken to suggest attentional deficits in autism: distractions typically occur in naturalistic settings, but experimental settings tend to minimize disruptions of this kind. However, even in highly structured settings with a familiar partner at home, attentional deficits and low affective responsiveness tend to persist, albeit at a less striking level than in unstructured situations (Joseph & Tager–Flusberg, 1997).

Adults with autism were much delayed compared with normal controls in orienting their attention on a traditional spacial cuing task. This sluggishness of shifting attention between and within modalities was interpreted as a sign of cerebellar dysfunction (Townsend, Harris, & Courchesne, 1996).

Motor deficits. There is a small literature on motor problems in autism and autistic-like conditions, including Asperger syndrome (e.g., DeMyer, 1978; Ghaziuddin, Tsai, & Ghaziuddin, 1992; Gillberg, 1989). It now seems clear that such disorders are associated with minor–moderate motor problems. It is unclear whether there is anything in the motor domain which might separate Asperger syndrome from high-functioning autism (Gillberg, 1998). Motor imitation is impaired in autism (Heiman, Nelson, Tjus, & Gillberg, 1995; Stone, Ousley, & Littleford, 1997), but whether or not this deficiency is responsible for the clumsy and ill-coordinated movements is not known. Coordination problems are often most evident in the high-functioning individuals with autism or Asperger syndrome, but this might be because the most high-functioning people have a greater repertoire of activities and, hence, get to show their awkward and clumsy motor skills much more often and in many more settings than those who are

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lower functioning (who are usually not *perceived* as motor clumsy, even though on formal testing they may well be; Miyahara, Tsujii, Hori, Nakanishi, Kageyama, & Sugiyama, 1997).

Visuospatial problems and strengths. It has been known for more than half a century that children with autism have some relatively superior visuospatial skills (Kanner, 1943). Whether this should be seen as merely reflecting an area of intact functioning—and hence an impression that such skills are "superior" to other impaired functions—or as an association with a more fundamental characteristic of the core impairment in autism is debatable. The lack or delayed development of an eye-direction detector (see above) could be taken as a symptom of impaired visuospatial functioning but is probably best understood in the context of a joint attention–theory of mind framework. It is quite possible that individuals with autism have similar attention deficits in the auditory domain.

Specific localizing neuropsychological dysfunctions in autism

Medial temporal lobe and dorsolateral frontal lobe dysfunction. Dawson and coworkers compared young children with autism with developmentally matched groups of children with Down syndrome and with typical development on neuropsychological tests purportedly tapping specific medial temporal lobe functions and dorsolateral frontal lobe functions. Children with autism scored persistently worse than the other two groups, and severity of autistic symptoms was strongly correlated with poor performance on the medial temporal lobe task (Dawson, Meltzoff, Osterling, & Rinaldi, 1998).

Interhemispheric transfer dysfunction. The prevalence of non-right-handedness is increased in autism (Gillberg, 1983). A SPECT study revealed autism to be associated with low regional cerebral blood flow in the left hemisphere, particularly in sensorimotor and language areas (Chiron, Leboyer, Leon, Jambaque, Nuttin, & Syrota, 1995). This was regardless of handedness, which was often "non-right" in autism. The results support anomalous hemispheric specialization or interhemispheric transfer dysfunction in autism.

One study examined the potential contribution of right hemisphere dysfunction to the communicative impairments of autism. Pragmatic language measures sensitive to right hemisphere damage were administered to nonretarded adults with autism and to controls matched on age and intellectual ability. Individuals with autism performed significantly less well than controls on all measures, replicating results of an earlier investigation by Rumsey and Hanahan (1990). The performance of the autism group on the three tasks was also similar to that of right-hemisphere stroke patients reported previously (Molloy, Brownell, & Gardner, 1990).

Language, speech, and voice problems. About half of all children with classic autism are functionally mute (Wing, 1996). The other half have delayed and deviant language, hallmarked by reversal of pronouns, immediate and delayed echolalia, and repetitive questioning with insistence on standard answers (Rapin & Dunn, 1997). There are major receptive language problems, even though concrete words like nouns and verbs are usually well understood. Phonology, syntax, morphology, and semantics may be impaired, but not specifically so (Tager–Flusberg, 1996). Pragmatics, on the other hand, is one area of language that is always seriously impaired in autism—and in autistic-like conditions, including Asperger syndrome. Problems in nonverbal communication (pointing, showing objects, eye gaze to regulate contact) are present from very early on in the lives of individuals with autism (Stone, Ousley, Yoder, Hogan, & Hepburn, 1997). Such problems are to be expected if mentalizing deficits are at the core of the autistic syndrome. At the nonverbal level, the monotonic prosody and paucity of gesture are characteristic features that suggest right hemisphere dysfunction. At the verbal level, problems with narrative discourse (including impoverished stories), difficulties in understanding and using abstract language, and difficulties providing the appropriate

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level of relevant information are striking (Loveland & Tunali, 1991). The use of social conventional language, such as greetings and polite forms, is also limited.

The question arises as to whether people with autism also have "dysphasia" (Rapin & Dunn, 1997), which would suggest left temporofrontal dysfunction. It is clear that a proportion of all individuals diagnosed as having a disorder in the "autism spectrum" do have expressive language problems that merit the diagnosis of dysphasia. However, it is equally clear that many of those with high-functioning autism and Asperger syndrome have excellent expressive language skills, and that if autism is conceptualized as a spectrum disorder, then dysphasia cannot be an inclusion criterion but should be coded separately under developmental language disorder (Tanguay et al., 1998). Nevertheless, it is interesting to speculate about the links of language disorders to autism, particularly given the recent finding of genes on chromosome 7q being abnormal both in autism and severe expressive language disorders.

Preliminary conclusion

The neuropsychological profile in autism is not consistent with that seen in mental retardation or in any other general deficit syndrome. Rather, it appears to involve a selective impairment in complex information processing that does not usually affect visuospatial processing. The profile is not consistent with a single primary deficit, but with a multiple primary deficit model (Minshew, Goldstein, & Siegel, 1997). Several theories have been proposed that might "explain" how the multiple primary deficits combine to produce the syndrome of autism. Among the more interesting of these is the neural circuit–neural network theory (Cohen, 1994; Gustafsson, 1997), which proposes that there may be inadequate cortical feature maps in autism, making it difficult for affected individuals to use previous sensory impressions when processing current information.

Neurobiology of Autism: Associated Impairments, Disorders, and Diseases

Autism is associated with a range of other impairments, disorders, and medical diseases. Intellectual impairment and epilepsy are among the best known and validated associations, but hearing, visual, and language impairments are also common.

There is now strong evidence that genetic factors are of major importance in a majority of all cases of autism (Bailey et al., 1996). Twin and family studies have put autism on the map as one of the most strongly genetic disorders in psychiatry and developmental medicine. A considerable proportion of classic autism cases in the general population, about 25% according to a recent review (Gillberg & Coleman, 1996), are associated with other medical disorders such as tuberous sclerosis, the Fragile X syndrome, and certain intrauterine infections. Many of these are themselves genetic. The study of these disorders and their links with autistic behavior has provided valuable insight into the neurobiological processes that underlie the development of the specific symptoms of autism.

Epilepsy

Epilepsy is much more common in people with autism than in the general population (Gillberg, 1991b). Conversely, it appears that autism and autistic-like conditions are considerably more common in people with epilepsy than in those without (Steffenburg, Gillberg, & Steffenburg, 1996).

About 20% of all people with autism have developed nonfebrile seizure before the age of about 3 years. Another 15–20% develop seizures around the time of puberty or later (Gillberg & Coleman, 1992; Olsson, Steffenburg, & Gillberg, 1988; Volkmar & Nelson, 1990). It is possible that in early studies, a number of classic autism cases were excluded from the diagnostic category of autism because they showed early onset epilepsy, which then became their main (and often only) diagnosis. This is supported by findings from a recent study of psychiatric disorder in children with the combination of epilepsy and mental retardation, in which many children meeting full criteria for autistic disorder had never received that diagnosis because physicians in charge of treatment of their epilepsy felt there were already "appropriate" diagnoses (epilepsy and mental retardation; Steffen-

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burg et al., 1996). It seems that complex partial seizures (signaling temporofrontal brain abnormality) and infantile spasms are overrepresented in people with autism as compared with other individuals with seizure disorders. In the study by Olsson et al. (1988), three quarters of all children with autism who also had epilepsy suffered from partial complex seizures (solely or in combination with other types of seizures). Conversely, the rate of autism and Asperger syndrome was much greater than expected in children with complex partial seizures undergoing workup for epilepsy surgery (Taylor et al., in press). This, again, would favor a connection between temporofrontal abnormality and autism. Right-sided lesions tended to be associated with Asperger syndrome, whereas autism was not clearly linked to lateralized pathology.

Infantile spasms are strongly associated with autistic behavior. More than one third of all cases with infantile spasms (regardless of the presence or not of other signs of tuberous sclerosis) show autistic behavior, and at least one in six of all cases meet criteria for autism during one phase of development (Riikonen & Amnell, 1981). The brain dysfunction in infantile spasms is often diffuse, but temporal lobe–middle cerebral artery territory pathology is often inferred (Aicardi, 1998).

Seizures with adolescent onset in autism are quite often of the benign focal type with centrotemporal Rolandic spikes and tend to occur in the early morning hours just before or after the termination of sleep.

A rare, but important, phenomenon is the occurrence of absence epilepsy in autism. Petit mal status can be obscured by autistic behavior, and appropriate anticonvulsant medication can lead to disappearance of autistic symptoms (Gillberg & Schaumann, 1983).

Hearing deficits

It now seems clear that moderate and severe hearing deficits are uncommon in autism, even though the rate is markedly increased above that in the general population (Jure, Rapin, & Tuchman, 1991; Rosenhall, Sandstrom, Nordin, & Gillberg, 1999; Steffenburg, 1991). The rate is increased even in those who are not mentally retarded.

Speech and language impairments

It is not that the majority of people with autism cannot speak but that they do not understand the meaning of language use. In other words, their failure is more in the pragmatics than in the execution of speech and language. However, a minority of children with autism (perhaps about one in five, according to the present author's experience) have specific language impairment *in addition* to their autism-inherent language problems.

Ophthalmological problems

At least one in five of all children with autism have reduced visual acuity (Steffenburg, 1991). This is probably higher than in the general population, although no exactly comparable figures are available. Many children with autism have a squint or other abnormalities of eye movements (Steffenburg, 1991). Congenitally blind children have a high rate of autistic features (Brown, Hobson, Lee, & Stevenson, 1997). The descriptions of autism associated with Moebius syndrome (Gillberg & Steffenburg, 1989), Goldenhar syndrome (Landgren, Gillberg, & Stromland, 1992), and thalidomide embryopathy (Stromland, Nordin, Miller, Akerstrom, & Gillberg, 1994)—all of which also signal brain-stem abnormality, and fetal alcohol syndrome (Aronson, Hagberg, & Gillberg, 1997) and retinopathy of prematurity (Ek, Fernell, Jacobsson, & Gillberg, 1998) highlight the need for ophthalmologic examination in cases of autism.

Associated medical disorders

According to population studies, about 25% of all autism cases have an associated major medical disorder (Gillberg & Coleman, 1996). In clinical reports, mostly from child psychiatric clinics, the rate appears to be about half of that reported from the community samples. The disorders range from chromosomal to neurocutaneous disorders and metabolic and infectious diseases.

Chromosomal abnormalities. The Fragile X syndrome is associated with frontal lobe dys-

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function (and possibly also brain-stem abnormality) *and* with autism. According to a review of all the available literature in the field, Hagerman (1989) concluded that 8% of all cases with autistic disorder suffered from the Fragile X chromosomal abnormality. This conclusion was based on light microscopy chromosomal studies that could not differentiate the various types of Fragile X abnormalities that occur (A, E, F, etc.) from each other. It now appears that Fragile X A (with abnormality of the so called FMR-1 gene) cannot account for any large fraction of all autism cases. However, the majority of males with the Fragile X syndrome show moderate or severe degrees of autistic behavior, even though it may be that only a (considerable) minority meets all the diagnostic criteria for autistic disorder. Autism symptoms may subside with age in this syndrome (as they do in many other) and this may lead to an underestimation of the true rate of autistic disorder in the Fragile X syndrome if only cases older than, say, 8 years are included (Percy, Gillberg, Hagberg, & Witt–Engerstrom, 1990).

A number of other chromosomal disorders have been described to be associated with autism (Gillberg & Coleman, 1992). These include the XYY, XXY, and XXX syndromes (Hagerman, 1989). Interestingly, Turner syndrome (XO), although only rarely linked with full-blown autistic disorder, is often associated with social interaction problems. This seems to be the case only if the X chromosome is maternally derived (Skuse et al., 1997), indicating that there is an imprinted locus important for social interaction on the X chromosome. Because boys usually have only one X chromosome and this is inherited from the mother, boys (but not girls) would be at high risk of social interaction problems.

Down syndrome with trisomy 21 has been reported in several cases of autism (Ghaziuddin, 1997; Howlin, Wing, & Gould, 1994), but it does not seem, at the present stage, that Down syndrome as such predisposes to the development of autistic behavior. It could be that additional brain damage, hypothyroidism, or other genetic factors could increase the risk of autism symptoms (Gillberg, Persson, & Wahlstrom, 1986).

A marker chromosome syndrome involving tetrasomy of the same portion of chromosome 15 which is involved in Prader–Willi syndrome (and Angelman syndrome) has been shown to be associated with autism (Cook et al., 1997; Gillberg et al., 1991b).

Chromosomal disorders involving almost all the other chromosomes of the human karyotype have been reported in single cases of autism. Whether or not they are associated with autistic behavior by chance alone remains to be established (Gillberg & Coleman, 1992).

Teratologic syndromes. A number of teratologic syndromes, such as fetal alcohol syndrome (Aronsson et al., 1997) and fetal valproate syndrome (Williams & Hersh, 1997), have been described in connection with autism. Some of these associations suggest that 1st-trimester injury to the developing nervous system might be important in the origin of autism in some cases.

Thalidomide has been shown to lead to a high rate of autism when exposure occurs during the 20th–24th day of gestation (Stromland et al., 1994). Both the critical period and the neurological deficits of the autistic cases indicate that they have sustained injuries to the cranial nerve motor nuclei. Interestingly, Moebius syndrome, with bilateral facial nerve palsies, is associated with a high rate of autistic symptoms (Gillberg & Coleman, 1992). To determine whether brain-stem lesions characterize other cases of autism, the brain stem of a case with autism was compared to that of a control. The autopsy case showed abnormalities predicted by the thalidomide cases (near-complete absence of the facial nucleus and superior olive) and evidence of shortening of the brain stem between the trapezoid body and the inferior olive, a defect that could have occurred only during neural tube closure. A similar deficit has been reported in *Hoxa*-1 gene knockout mice in which pattern formation of the hindbrain is disrupted during neurulation. To test whether animals can be similarly injured but remain viable, rats were treated with 350 mg/kg of valproic acid on day 11.5, 12, or 12.5 of gestation. Neuron counts showed reductions of cell numbers in the cranial nerve motor nuclei. Rats with motor neuron deficits also had cerebellar anoma-

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lies like those reported in studies of autistic cases, supporting the idea that these animals may be a useful model of the developmental injury that initiates autism (Rodier, Ingram, Tisdale, & Croog, 1997). The autopsy data and experimental data from rats confirmed that CNS injuries occurring during or just after neural tube closure can lead to a selective loss of neurons derived from the basal plate of the rhombencephalon. The results add two new lines of evidence that place the initiating injury for autism around the time of neural tube closure (Rodier, Ingram, Tisdale, Nelson, & Romano, 1996). Several studies have shown abnormal ear configuration to be markedly overrepresented in autism (e.g., Rodier, Bryson, & Welch, 1997). These results would also be compatible with a model of 1st-trimester injury in the etiology of some cases of autism. Otherwise, much of the literature on causes of autism suggests 2nd-trimester damage (Gillberg & Coleman, 1992).

Neurocutaneous disorders. Tuberous sclerosis, neurofibromatosis, and hypomelanosis of Ito have been described to be associated with autism or autistic symptomatology (Gillberg & Coleman, 1992). Each of these seems to account for 2–5% of all autism cases, implying that at least about 6–15% of all autism cases can be accounted for by neurocutaneous disorders. These disorders can be difficult to diagnose unless the clinician is aware of the existence and diagnostic hallmarks of these conditions. The study of tuberous sclerosis and its association with autism has been particularly enlightening for understanding autism pathophysiology. It appears that the vast majority of individuals with autism and tuberous sclerosis have temporal lobe pathology, whereas few, if any, of those with tuberous sclerosis without autism do (Bolton & Griffiths, 1997). Also, one of the susceptibility genes suggested for autism is in the same region on chromosme 16 as one of the two identified tuberous sclerosis genes (see further in Where in the Brain Is Autism and Asperger Syndrome?).

Metabolic disorders. A number of conditions with a known metabolic deficit, such as PKU (Friedmann 1969), lactic acidosis (Coleman & Blass, 1985), and hypothyroidism (Gillberg, Gillberg, & Steffenburg 1992), have been shown to be associated with autism at a level which is possibly over and above that suggested by chance alone.

Infectious disorders. Postnatal herpes encephalitis and intrauterine rubella infection are the two best known infectious disorders which have been described to be associated with autism (Gillberg & Coleman, 1992). Apart from these, a number of infectious disorders affecting the child in early life have been described in connection with autism. However, for all of these, including CMV infection (Stubbs, 1978), the evidence is less convincing than for the two mentioned.

Neurobiology of Autism: Genetics

There is now strong evidence that in many cases autism has genetic roots (Bolton & Rutter, 1990). In order to analyze this issue properly, one has to subdivide autism cases according to proposed or demonstrated etiology. A number of cases of autism are genetic in the sense that they are due to medical disorders with a genetic background (tuberous sclerosis, the Fragile X syndrome, PKU, etc.). There is still considerable uncertainty as to what proportion of autism cases generally and what proportion of those autism cases without demonstrable associated medical disorders have a genetic basis. Three sets of published twin studies (Bailey et al., 1996; Folstein & Rutter, 1977; Steffenburg et al., 1989) on population-based samples of same-sexed twins without a known associated medical disorder have shown that in identical twins concordance is at a very high rate (36–89%), whereas in nonidentical twin pairs it is low (under 5%), indicating heritability indices of about 70–90%. The rate of autism in siblings is much raised compared with the general population. Most of the available evidence suggests a 50- to 100-fold increase (Bolton & Rutter, 1990, Gillberg et al., 1992). There appears to be an accumulation of other neuropsychiatric disorders in families with children with autism and Asperger syndrome. Tourette syndrome (Comings & Comings, 1990; Ehlers et al., 1997), DAMP (Gillberg et al., 1992), dyslexia, and other specific language

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impairments (Bolton & Rutter, 1990), affective disorders (DeLong, 1994), and anorexia nervosa (Comings & Comings, 1990; Gillberg & Rastam, 1992) have all been reported to cluster in families in which at least one member has been diagnosed as suffering from infantile autism or autistic disorder. Schizoaffective disorder (or cycloid psychosis) has been diagnosed in a number of families in which the diagnosis of autism and the Fragile X syndrome has been made (Hagerman, 1989; Gillberg, 1992b). Several reports have documented the coexistence of autism and elective mutism within one and the same family tree (Gillberg, 1989; Gillberg, 1992b).

It remains unclear what it is that might be inherited in autism. Several studies suggest that a "personality style" or "disorder" resembling or identical with Asperger syndrome might be the best phenotypical approximation of the crucial genotype, if such a specific genotype exists (Gillberg et al., 1992; Szatmari, Boyler, & Offord, 1993). Other authors highlight a cognitive disorder showing as mental retardation or as dyslexia or language and speech problems rather than a specific social disorder as being at the genetic root of autism in many cases (Folstein & Rutter, 1977). The concept of "a broader autism phenotype" has emerged, and it is possible that this extends to mild social and communication deficits and to obsessions–compulsions, rigidity, and stereotyped behaviors (Bolton, Pickles, Murphy, & Rutter, 1998; Le Couteur et al., 1996; Piven, Palmer, Jacobi, Childress, & Arndt, 1997). Since such characteristics are common in the general population, the genes that precipitate autism would have to be prevalent in the general population. At least one study produced results suggesting that impaired executive functions might be more specifically what it is that is inherited in autism (Hughes, Leboyer, & Bouvard, 1997). Even so, impaired executive functions are common in all sorts of neuropsychiatric disorders in childhood and are not specifically linked with autism, meaning that it would have to be particular aspects of executive functions that were impaired or that the executive function deficits were combined with other impairments (inherited or acquired) for autism to occur.

Some studies (International Molecular Genetic Study of Autism Consortium, 1998; Philippe et al., 1999) have found evidence of linkage to a region on chromosome 7q. Several other genes (e.g., on chromosomes 15, 16, and 22) were identified as possible susceptibility genes. Interestingly, a genome screen of a large three-generation family with severe speech and language disorder found linkage to an overlapping area of chromosome 7q (Fisher, Khadem, Watkins, Monaco, & Pembrey, 1998). Also, the possible susceptibility region on chromosome 15 is identical to that involved in Angelman syndrome and the partial tetrasomy 15 syndrome (Gillberg et al., 1991b), both of which demonstrate high levels of autistic behaviors, including marked ritualism and desire for sameness. The region on chromosome 16 overlaps with one of the two genes identified in tuberous sclerosis, another disorder with a very high rate of autism and autistic behaviors (Hunt & Shepherd, 1993). The finding that girls with Turner syndrome have different social styles depending on whom they inherited their only X chromosome from (Skuse et al., 1997) is also important and suggestive of one or several loci influencing social cognition being located on the X chromosome. These findings again suggest that several genes are likely to be involved in the pathogenesis of autism and that these genes will *not* turn out to be specific to autism. It is possible that genes predisposing to communication dysfunction (hypothetical link to chromosome 7), ritualism, and OCD (hypothetical link to chromosome 15) and social reciprocity deficits (hypothetical links to chromosme 16 and X) interact in ways that sometimes evoke the (arbitrarily defined) "clinical autism." It is likely that these susceptibility genes exist at relatively high population base rates.

Neurobiology of Autism: Specific Laboratory Findings

Many neurobiological correlations have been demonstrated in autism. Only some recent developments in this field will be highlighted in the present context.

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Neurochemical findings

Monoamines. Serotonin in the blood is raised in one-third of patients with autism (Gillberg & Coleman, 1992). It is still not clear whether this finding obtains only in autism with mental retardation. The serotonin transporter gene has been suggested to be specifically correlated with autism (Cook et al., 1997).

There is evidence that cerebrospinal dopamine turnover in autism may be altered, regardless of concomitant mental retardation (Cook, 1990; Gillberg & Coleman, 1992; Gillberg & Svennerholm, 1987). There is also evidence that urinary HVA excretion may be altered in young patients with autism. Finally, a deficiency of dopamine β-hydroxylase has been demonstrated in autism in a few studies. Major dysfunction of the dopamine system would be consistent with the model for the development of autism proposed by Maurer and Damasio (1982).

In the study by Gillberg and Svennerholm (1987), it appeared that it could be the ratio of HVA to HMPG (the major metabolite in the norepinehprine breakdown process), rather than the level of HVA as such, which was specifically increased in autism. Also, some authors (e.g., Dahlstrom, 1989) have proposed that many of the symptoms typical of autism could result from dysfunction of the locus ceruleus, the small mass of norepinephrine-containing cell bodies in the brain stem.

Endogenous opioids. Several of the components of the human endogenous opioid system have been suggested to be involved in the pathogenesis of autism (Panksepp, 1979). A number of blood and CSF studies have shown abnormalities of endorphins in autism (Gillberg & Coleman, 1992), but the picture, so far, is not consistent (Gillberg, 1995).

Glial proteins and gangliosides. In one study CSF glial fibrillary acidic protein (GFA-p) in autism was 3 times higher than in a group of normal children (Ahlsen et al., 1993). This finding could reflect abnormal synapse turnover in autism, which, in turn, might result from autoimmune pathology. Circulating autoantibodies to GFA-p characterized subjects with autism—but not subjects with mental retardation—in another study (Singh, Singh, & Warren, 1997). Unspecifically raised levels of gangliosides in the CSF of young people with autism (Nordin, Lekman, Johansson, Fredman, & Gillberg, 1998) could also reflect abnormal synapse turnover.

Neurophysiological findings

There have been a large number of reports on evoked response examinations in autism. The majority have included auditory brain-stem response (ABR) examinations, and the majority of these have shown abnormal prolongation of brain-stem transmission time and abnormal interrelationships between the brain-stem waves (Gillberg & Coleman, 1992). However, the pattern is not quite consistent in this respect and there are some reports that do not support the notion of brain-stem abnormality in a subgroup of patients with autism. Nevertheless, the larger studies tend to show the clearest signs of abnormal brain-stem function (Klin, 1993; Rosenhall et al., 1999).

EEG studies have consistently shown a high rate of abnormalities in autism, but it is not quite clear to what extent this increase is accounted for by the high prevalence of epilepsy in autism. Paroxysmal activity has been reported in 17–61% of cases in the studies published to date. A particularly interesting finding comes from a Japanese study of a large group of individuals with autistic disorder who had EEGs on several occasions during childhood, adolescence, and young-adult age. In adolescence, frontal paroxysmal activity *emerged* in about half the group, a finding that was not replicated in a mentally retarded control group (Kawasaki, Yokota, Shinomiya, Shimizu, & Niwa, 1997). The results of this study adds support to the notion of frontal lobe dysfunction being crucial in a large proportion of cases with autism.

Neuroimaging findings

The majority of neuroimaging studies (pneumoencephalography, CAT-scan, and MRI-

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scan examinations of the brain) in autism have shown abnormalities in autism, but no typical pattern has emerged. However, structural abnormalities in the region of the brain stem and pons have been most often reported (Gillberg & Coleman, 1992). Also, the ventricular system has been enlarged according to several studies. The temporal lobes have been implicated in a number of studies. The cerebellum was described as rather specifically affected in one autism study (Courchesne, Yeung–Courchesne, Press, Hesselink, & Jernigan, 1988), but so far no other group has been able to replicate the results of that report. Also, in one study (Herold, Frackowiak, Le Couteur, Rutter, & Howlin, 1988), it appeared that the caudate nucleus might be specifically affected. According to an MRI study, after controlling for brain volume (which is often high in autism, see below), gender and performance IQ, the body and posterior regions of the corpus callosum may be smaller in autism (Piven, Palmer, Landa, Santangelo, Jacobi, & Childress, 1997). Similar findings have been reported in attention disorders.

Recent PET-scan and single photon emmision computed tomography (SPECT) studies of autism have also shown abnormalities, both in the distribution of interactional patterns across various parts of the brain and specifically in blood-flow reduction in the temporal lobes. In the SPECT study from our own group (Gillberg, Bjure, Uvebrant, & Gillberg, 1993), both temporal lobes showed reduced activity in autism, regardless of whether the child also had epilepsy or not. In a study looking at PET scans of adults undergoing mentalizing tasks, it was found that normal men ($n = 6$) activate Broddman's areas 8 and 9 in the medial portion of the left frontal lobe but that these areas were not activated at all by young men with Asperger syndrome ($n = 5$) while undergoing these same tasks (Happe et al., 1996).

In a pilot study, brain high-energy phosphate and membrane phospholipid metabolism were investigated in the dorsal prefrontal cortex of 11 high-functioning adolescent and young adult men with autism aged 12–36 years and an equal-size normal comparison group, using in vivo 31P nuclear magnetic resonance spectroscopy (MRS). The group with autism had decreased levels of phosphocreatine and esterified ends. As test performance declined in the autistic subjects, levels of the most labile high-energy phosphate compound and of membrane building blocks decreased, and levels of membrane breakdown products increased. This pilot study provided tentative evidence of alterations in brain energy and phospholipid metabolism in autism that correlate with the neuropsychologic and language deficits. The findings could be taken to imply a hypermetabolic energy state and undersynthesis of brain membranes and may relate to the neurophysiologic and neuropathologic abnormalities in autism (Minshew, Goldstein, Dombrowski, Panchalingam, & Pettegrew, 1993). They are also compatible with the increase in synapse turnover suggested by the studies of GFA-p and gangliosides described earlier in the Neurochemical Findings.

Autopsy findings

Fewer than 35 autism brain autopsy reports exist in the literature (Rapin & Katzman, 1998). The findings show no consistent pattern. Dense cell packing (suggestive of synapse production dysregulation consistent with GFA abnormalities and abnormalities of membrane production), low counts and abnormal histoanatomy of Purkinje cell fibers, hypoplasia of the brain stem and posterior cerebellum, gliosis (consistent with GFA abnormalities), abnormal anatomy in the amygdala ("too many cells too small" or "crowding"), and unspecific general atrophy have all been reported (Bauman, 1991; Gillberg & Coleman, 1992; Oldfors, Sourander, & Percy, 1993).

Clinical findings

Macrocephalus has been shown repeatedly to be associated with autism in some cases. About one in seven to one in three of all individuals with autism have macrocephalus (Lainhart et al., 1997), a finding which could

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support the notion of synapse overproduction and crowding referred to above.

Where in the Brain Is Autism and Asperger Syndrome?

It is likely that autistic behavior can arise on the basis of abnormal function in several different parts of the brain. The brain stem, cerebellum, medial temporal lobes, and frontal lobes have been the areas most often found to be dysfunctional in autism. With social functioning being a very complex process, it should not be unexpected that abnormality in this domain can result from problems in several different parts of the brain.

Obviously, the underlying anatomical problems in autism will vary with the underlying medical disorder (such as tuberous sclerosis and the Fragile X syndrome). Most of the disorders known to be associated with autism affect many different parts of the brain. However, many of them have fairly distinct patterns or "predilection." Thus, for instance, it appears that the frontal lobes may be crucially impaired in the Fragile X syndrome, the temporal lobes and diencephalon in tuberous sclerosis, and the brain stem in Moebius syndrome. All of these conditions are associated with autism at a rate considerably higher than that suggested by chance alone (Gillberg & Coleman, 1992; Hagerman, 1989; Ornitz, Guthrie, & Farley, 1977). It appears then that autism could result from abnormality in the brain stem, the temporal lobes, and the frontal lobes. Are these parts of the brain specifically functionally or neurochemically related?

The dopamine neurons arising in the brain stem and projecting onto target areas in the temporal and frontal lobes might well be particularly important in autism (Maurer & Damasio, 1982). The abnormally high ratio of HVA to HMPG (Gillberg & Svennerholm, 1987), the urinary dopamine abnormalities suggested by some studies (Barthelemy, Bruneay, Jouve, Martineay, Muh, & Lelord, 1989), the abnormal level of dopamine β-hydroxylase (Gillberg & Coleman, 1992), the positive effect of dopamine blockers in autism (Campbell, 1989), the possible association of autism with PKU, and the relationship of tuberous sclerosis to autism (a genetic disorder believed to be located on chromosomes 9 and 16, very close to genes regulating dopamine turnover, and one whose autistic symptomatology is clearly linked to temporal lobe pathology; Bolton & Griffiths, 1997) are all points which favor a dopamine hypothesis for the development of autism in some cases. Finally, the prevalence of motor stereotypies and other movement disorders often encountered in autism are also suggestive of dopamine hyperfunction. However, it seems unlikely that autism would be the result of *just* dopamine dysfunction. The brain stem is also where the serotonergic and noradrenergic neurons originate, and several lines of evidence suggest that these two transmitters may also be dysfunctional in autism (Gillberg & Coleman, 1992).

Disorders of empathy other than autism (e.g., the Kluver–Bucy syndrome) can result from bilateral temporal lobe dysfunction, perhaps specifically bilateral dysfunction of the amygdala. Herpes encephalitis destroying the amygdala on both sides can result in a syndrome indistinguishable from autism (DeLong, Beau, & Brown, 1981; Gillberg, 1986; Gillberg, 1991a).

The SPECT studies performed in our center point to a bilateral temporal lobe dysfunction in autism. Asperger syndrome has been suggested to be confined to unilateral frontal lobe dysfunction (e.g., in the PET study referred to above). These, and other studies, fit a model for the development of autism involving temporal and frontal lobe dysfunction, with the amygdala and areas in the left frontal lobe possibly being crucial. The findings implicating the cerebellum and brain stem also fit this hypothesis. The temporal lobes could be dysfunctional because of primary damage to the temporal regions of the brain or, secondarily, because of problems in the cerebellum and brain stem. If both temporal lobes are affected, communication and social skills will suffer equally and autism could result. If only one temporal lobe is dysfunctional, social and communication skills will suffer, but not to the extent encountered in

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classic autism; in such cases, Asperger syndrome might seem to be a more appropriate diagnosis (Goodman, 1990).

A developmental chronometry hypothesis of early brain damage has also been suggested (Ciesielski, Harris, Hart, & Pabst, 1997) "in which regions with a protracted course of postnatal development will be more vulnerable than earlier maturing areas to deleterious effects of early insult, and therefore, may become common sites of abnormality across many disorders originating in early childhood." In one study, cerebellar and frontal lobe abnormalities occurred together in individuals with autism, in agreement with the theory that cerebellar abnormality might be of crucial importance for the development of higher cognitive dysfunction (Cieseielski et al., 1997). Autopsy and quantitative MRI studies in autism have identified agenesis of the superior olive, dysgenesis of the facial nucleus, reduced numbers of Purkinje neurons, hypoplasia of the brain stem and posterior cerebellum, and increased neuron-packing density of the medial, cortical, and central nuclei of the amygdala and the medial septum. As neurogenesis occurs for these different neuron types during approximately the 4th to 5th weeks of gestation, the possibility is raised that this may be a "window of vulnerability" for autism (Courchesne, 1997). This is also compatible with the thalidomide findings of damage occurring early in the 4th week of gestation in those embryopathy cases who develop autism (Rodier et al., 1997; Stromland et al., 1994). However, the etiologic heterogeneity of autism suggests that other windows of vulnerability are possible. Second-trimester bleedings, intrauterine infections, cortical malformations related to neuronal migration abnormalities, and the generally normal physical appearance of most individuals with autism are some of the factors that have been highlighted by Gillberg and Coleman (1992), when proposing that many cases of autism represent 2nd-trimester syndromes. It is also possible that autistic behavior could arise on the basis of something going wrong in preprogrammed synapse development and pruning in the 2nd year of postnatal life. This would be supported by the cases (about one in five of all autism cases) with a setback or symptom onset around age 18 months—even though this could have been caused by a primary genetic defect—and by the emergence of autistic symptoms in connection with epilepsy beginning around this age (Rapin & Katzman, 1998), or in the aftermath of herpes encephalitis.

Concluding remarks

Thus, the answer to the question "Where in the brain is autism?" might well be that autism could result from damage or dysfunction in several different brain areas, even though one particular, functionally interconnected system might be more frequently involved than others. Timing may be essential, and there may be a least two (possibly three) vulnerability windows, one in the 4th to 5th weeks of gestation and another towards the middle of intrauterine life (and one in the 2nd year of life?). It is likely that for the full syndrome of autism to occur there has to be temporofrontal involvement (leading to a variety of neuropsychological and cognitive dysfunctions, which, in turn, underlie the specific autism "surface" symptoms), but this could arise "per se" or as a consequence of damage or dysfunction in brain-stem–cerebellar systems. The possibility exists that increased synapse turnover (specifically in the areas mentioned?) may play an important role. The underlying causes of dysfunction or damage are manifold, ranging from the interaction of susceptibility genes to teratogenic factors and acquired lesions of other kinds.

Summary

Autism is a behaviorally defined syndrome with a fairly specific neuropsychological profile resulting from genetically programmed abnormal brain development or environmentally induced abnormal brain functioning arising in the antenatal period or the first few years of life. The brain dysfunction appears to be located particularly often in the medial portions of the temporal and frontal lobes,

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possibly also in the cerebellum and brain stem. Neuropsychological impairments include executive function deficits, mentalizing problems, and lack of drive for central coherence. The defining phenomenological features comprise a triad of impairments affecting (a) reciprocal social interaction, (b) two-way communication including language, and (c) imagination–behavior. The triad in its classic form is usually a severely disabling condition, symptomatic in the first few years of life, and affecting about one in a thousand individuals, males more often than females. There are closely related syndromes, including some cases of so-called Asperger's disorder, which are less disabling and more prevalent. It is likely that many cases of Asperger's represent so-called lesser variants of autism—genetically linked to autism—but these may also include even milder conditions (including obsessiveness, social gaucheness, social immaturity, and mild communication problems) not amounting to clinically significant disorder. Some of these Asperger's cases may go unrecognized into the school years or even adult age. It has been suggested that some cases of high-functioning autism or Asperger's disorder might best be conceptualized as belonging on the lowermost tail of the normal distribution of empathy skills in the general population and, hence, not being strictly examples of brain "abnormality" but rather of brain "variation."

Concluding Remarks

Autism is a developmental disorder with variable severity and occurring at all levels of cognitive ability. It is associated with neuropsychological deficits that occur in other conditions also, but its pattern may be specific to autism. Genetic and environmental early insults to brain development are etiological determinants of the disorder. Further study of neurodevelopmental and neuropsychological processes in autism will help elucidate not only the pathological mechanisms involved in the specific syndromes but also the underpinnings of normal brain development.

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