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Autism and pervasive developmental disorders

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The quantity and quality of research into autism and related conditions have increased dramatically in recent years. Consequently we selectively review key accomplishments and highlight directions for future research. More consistent approaches to diagnosis and more rigorous assessment methods have significantly advanced research, although the boundaries of the 'broader phenotype' remain to be defined and the validity of Asperger's disorder as a discrete syndrome remains controversial. Recent epidemiological studies have shown that Autism Spectrum Disorders are common, but there continues to be debate about the causes of the increase in the frequency with which autism is diagnosed. Psychological research has helped to develop new developmental models for the disorder and there have also been significant advances in the molecular genetics of autism and understanding of the underlying neurobiological processes. Areas important for future research include the study of autism as it first develops, i.e., in infants and very young children, and of specific processes (psychological and neurobiological) which underlie the disorder. Significant challenges lie ahead in evaluating the growing number of treatments for autism and in integrating the results of research into treatment and educational settings. **Keywords:** Autistic disorder, Asperger's disorder, genetics, neuroimaging, neuropsychology.

Fourteen years have elapsed since the first review of autism in the Annual Research Review (Gillberg, 1990) and seven since the more recent review by Bailey, Phillips, and Rutter (1996). The pace of research has increased dramatically in recent years; this poses some difficult choices for reviewers. Search of standard databases such as Index Medicus reveals that in the years between Kanner's initial description of autism (1943) and 1989 approximately 2900 articles on autism were published; in contrast, in the years from 1990 to the present over 3700 articles have appeared – nearly 3000 of these in the last decade. While some of these articles were case reports, reviews, and non-empirical publications and so forth, other work reports much more substantive research and it clearly is impossible to be comprehensive in this review. Accordingly, we focus on what appear to us to have been the major findings and trends of the past decade. The primary focus of this review is on autism with occasional discussion of related conditions. In this review the terms autism, autistic disorder, and childhood autism are used interchangeably; similarly, the terms pervasive developmental disorder (PDD) and autism spectrum disorder (ASD) should be taken to have the same meaning.

Diagnosis and definition

Diagnostic instruments

The diagnosis of autism and related conditions (the PDDs or ASDs) has become increasingly standardized, and at the same time the conceptualization of these disorders has become broader. Identifying the defining deficits of autism has become easier with agreement between DSM-IV (APA, 1994) and ICD-10 (WHO, 1992) for most of the autism-related categories, access to standardized instruments such as the Autism Diagnostic Interview-Revised (ADI-R: Le Couteur, Lord & Rutter, 2003) and the Autism Diagnostic Observation Schedule (ADOS: Lord et al., 2000), and greater public awareness of these disorders (Lord & Corsello, in press). Standardized diagnostic measures for autism, when they are used and reported appropriately, mean that failures to replicate neurobiological or experimental results can less easily be attributed to obvious differences in how autism is defined. Fifteen years ago, participants in studies would have been classified as meeting or not meeting DSM III–R or ICD-9 criteria, without a standard method of clarifying the nature of differences between the groups. Now the ability to quantify diagnostic characteristics also allows comparison of nonstandardized measures to measures that are widely understood and accepted, and allows inclusion in samples of individuals who just miss categorical cut-offs. For example, some genetics studies (e.g., IMGSAC, 2001a) and neuropsychological research (Dawson et al., 2002a) have broadened samples by extending ADI-R criteria to include participants who miss ADI-R criteria by 1–2 points, without sacrificing the ability to describe the children's symptoms. In another example, both Howlin (2003) and Szatmari, Bryson, Boyle, Streiner, and Duku (2003) reported studies that compared the outcome of individuals with high-functioning autism to individuals with Asperger syndrome. Definitions of Asperger syndrome differed in the two studies, and it was difficult from a text description to

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determine what the implications of these differences would be. In Szatmari's sample, the ADI-R social scores for the individuals with Asperger syndrome were lower than those of the individuals with autism, suggesting possible differences in severity of social deficits, given that age and IQ were comparable. In contrast, the ADI-R scores for Asperger syndrome and autism did not differ in Howlin's samples and both of her samples had higher scores than both of Szatmari's groups. These findings give the reader important information about the differences between the Howlin and Szatmari samples overall and differences in the use of the terms autism and Asperger disorder.

Diagnosis and genetic studies

Findings on many levels currently lead investigators to the belief that what is transmitted familialy is not classic autism as described by Kanner (1943) but a more varied phenotype of social, communication and/or behavioral difficulties. It is somewhat ironic that having standardized measures based on narrow conceptualizations of these three domains of difficulty has also facilitated beginning well-controlled research about individuals who do not meet narrow classifications for autism. As etiological factors become better understood these systems seem very likely to change (Willemsen-Swinkels & Buitelaar, 2002). In this context it is important to understand both the limitations as well as the usefulness of standard diagnostic instruments.

Recently, there have been a number of genetic studies in which samples have been stratified according to ADI-R domain scores, ADI-R measures of language delay or specific factors generated through principal components analyses of the ADI-R (Shao et al., 2002: Tadevosyan-Leyfer et al., 2003). Consistently, factor analytic approaches have indicated that social and communication items as described in DSM-IV and ICD-10 and operationalized in the ADI-R do not load onto separate factors (Tanguay, Robertson, & Derrick, 1998; Tadevosyan-Leyfer et al., 2003; Lord, 1990), a finding also reported for the ADOS (Lord et al., 2000) and Social Reciprocity Scale (SRS) (Constantino et al., 2003) and the organization behind the Children's Communication Checklist (CCC) (Bishop, 1998). Researchers have also sought to define the dimension of repetitive behaviors and interests more explicitly than as done in ICD 10 and DSM IV, particularly given the interest of geneticists in serotonin transporters, which are targeted in the treatment of anxiety and rituals (McCauley et al., in press). However, the definitions yielded by cluster and factor analyses have varied considerably across groups (Silverman et al., 2002; Shao et al., 2002; McCauley et al., in press; Tadevosyan-Leyfer et al., 2003). Until there is replication across sites and samples, treating these factors as reliable dimensions of autism, beyond a single severity gradient, may be premature. However, these strategies hold promise for increasing homogeneity of samples both for genetics and for treatments, but also for their eventual use in identifying dimensions that may be useful in describing individuals with ASDs.

New instruments for identifying broader dimensions of behavior associated with ASD

Because most diagnostic measures for autism were designed specifically to characterize the core features of autism, not a broader phenotype, there is also the need for other instruments that provide more continuous measures of aspects of the ASD (see Bailey & Parr, 2003). The Social Responsiveness Scale, formerly known as the Social Reciprocity Scale (SRS) (Constantino, 2002; Constantino & Todd, 2003), and the Children's Communication Checklist (CCC) (Bishop, 1998) are two newer instruments that are intended to be used in the wider population of children beyond those with autism. The SRS is a 65-item questionnaire that has been used within populations of typically developing children, children with a range of psychiatric disorders and children with ASDs. It has yielded a single, continuously distributed factor that includes items representing social deficits, language difficulties and repetitive behaviors (Constantino et al., 2003). A twin study showed the overall score on the SRS to be highly heritable, influenced by the same additive genetic factors in boys and girls, and to be unrelated to IQ in children without ASDs (Constantino & Todd, 2003). For children with ASDs, the SRS score was inversely related to IQ for children with PDD-NOS and Asperger's syndrome in one study (Constantino, Przybeck, Friesen, & Todd, 2000) and not significantly related to IQ in another study (Constantino & Todd, 2003). Like the SRS, the CCC, another questionnaire that primarily covers pragmatic language difficulties, was also able to identify pragmatic impairment in children who had no evidence of autism on the ADOS, ADI-R and/or the SCQ (Bishop & Norbury, 2002).

The Social Communication Questionnaire or SCQ (Berument et al., 1999; Rutter, Bailey, & Lord, 2003), is a 40-item screening questionnaire based on questions from the original ADI. It has been shown to have very strong agreement with ADI-R diagnoses when families had been administered an ADI-R previously (Berument et al., 1999) and good categorical agreement with the ADI-R in families who completed the SCQ first (Bishop & Norbury, 2002). Its sensitivity in referred, but not yet diagnosed populations is not known. In a study reported by Bishop and Norbury (2002) that included children with high-functioning autism, pragmatic impairments or specific language impairment, the SCQ showed better agreement with children's school diagnostic category than did the ADOS, though without a standard clinical assessment, it is difficult

to fully evaluate the meaning of this finding. Unlike the SRS and CCC, the SCQ is not intended as a measure of milder autism-related difficulties in the more general population, but like the two other instruments, it is a questionnaire that can be completed relatively quickly and that yields a single overall score.

Scores on the CCC, SCQ and SRS do not map onto separate domain scores from the ADI-R or ICD-10/DSM-IV (Berument et al., 1999; Bishop & Norbury, 2002; Constantino et al., in press). Because many of the items from the three scales and the ADI-R are similar, this lack of agreement on the separate ICD-10/DSM-IV domains or items on the ADI-R is a little surprising, but seems likely related to how parents and teachers interpret questionnaires, in contrast to the clinician-investigator based scoring of the ADI-R. Because they do not represent the current multi-domain patterns required by ICD-10 or DSM-IV for a diagnosis of autism or other autistic spectrum disorders, these instruments cannot be used on their own to make a diagnosis. However, they can greatly increase efficiency of screening and, in the case of the CCC and SRS, have the potential to generate continuous scores in children who are sub-threshold for ASD diagnoses. In combination with the standard diagnostic instruments, the CCC and the SRS provide an opportunity to consider a wider range of behaviors associated with ASD that may be important in understanding both etiological heterogeneity and similarities in final common pathways.

Pervasive developmental disorders other than autism

The diagnosis of autism, and criteria for other disorders generally classified in the autistic spectrum, including Childhood Disintegrative Disorder (CDD) and Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS), have not changed much in the past 10 years within frameworks proposed in DSM-IV and ICD-10. Although the inclusion of Rett syndrome in DSM-IV was the object of some debate (Gillberg, 1994) given its tenuous relation with autism, it clearly was important that it be included somewhere (Rutter et al., 1994). The importance of including such conditions, even when relatively rare, was underscored by the discovery of mutations in the Methyl Cytosine Binding Protein 2 (MECP2) as the cause of a majority of cases of Rett's disorder (Amir, Van den Veyver et al., 1999) via an influence on chromatin remodeling. It remains unclear whether a similar finding may clarify the etiology of Childhood Disintegrative Disorder (CDD), the other syndrome within ASD characterized by very marked loss of skills. The unusual pattern of developmental regression in this condition is strongly suggestive of an underlying genetic etiology. The recent interest in autism associated with regression may also be important in clarifying areas of continuity/discontinuity with CDD.

Asperger syndrome has also been the focus of both considerable interest and disagreement. There are currently at least five different widely circulated definitions of Asperger syndrome, in addition to those provided in ICD-10 and DSM-IV (Ghazuiddin, Tsai, & Ghazzuiddin, 1992; Leekam, Libby, Wing, Gould, & Gillberg, 2000; Klin & Volkmar, 1997; Wing, 1981; Szatmari, Bryson, Boyle, Streiner, & Duku, 2003; Tsai, 1992). These definitions are difficult to operationalize and probably have limited agreement with each other. The two most obvious differences in systems have to do with exclusion criteria from Asperger syndrome. DSM-IV and ICD-10 both exclude individuals from having Asperger syndrome if they have ever met diagnostic criteria for autism (e.g., the 'precedence rule'), and if they had early language delay (often operationalized by whether they spontaneously used meaningful words by 24 months and phrases by 33 or 36 months, as specified in the ADI-R (Howlin, 2003; Klin et al., submitted). However, there are other differences across diagnostic systems, including whether Asperger is used as a term to denote milder difficulties than autism (Leekam et al., 2000), whether neuropsychological profiles are assumed to be important (e.g., poor visual-spatial skills in the presence of relatively intact verbal skills, as measured in an IQ test) (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995)), whether the nature of the social deficit is considered to be different to that in autism (Tsai, 1992) and whether motor skills are taken into account (Ghazuiddin & Butler, 1998). Even subtler differences emerge in whether abnormalities in communication, such as stereotyped speech, are considered an indicator of Asperger syndrome or an exclusionary factor (see Szatmari et al., 2003). In part, this differentiation depends on whether stereotyped speech is defined as very obvious delayed echolalia or in terms of more subtle 'pedantic' speech. In several observational studies, these difficulties, that is, delayed echolalia and pedantic speech, were found to lie on a continuum of unusual words and phrases, which depended in part on how well the examiner knew the participant and how much of the participant's language was observed (Volden & Lord, 1991). Distinctions among various aspects of odd or repetitive language can be difficult to make reliably, though Ghazuiddin and Gerstein (1996) were able to do so at least in part.

The one consistent agreement across research teams about Asperger Disorder is that the current framework in DSM-IV and ICD-10 does not result in diagnoses which any of the research groups found helpful in creating reliable categorical diagnoses (Miller & Ozonoff, 1997, 2000). Even the usefulness of features such as the presence or absence of mental retardation or a history of language delay as exclusionary characteristics is under debate

(Eisenmajer et al., 1996; Howlin, 2003; Szatmari et al., 2003). On the other hand, several emerging lines of data are suggestive of some differences from higher-functioning autism in predictions of outcome (Szatmari et al., 2003), co-morbidity with other psychiatric disorders (Klin et al., submitted), neuropsychological profiles (Lincoln et al., 1998; Klin, Volkmar et al., 1995) and family genetics (Volkmar et al., 1998). Whether these findings are truly independent of the definitions and differences in recruitment for Asperger and autism samples will depend on researchers working together to create an operationalized set of diagnostic parameters that not only differentiate Asperger syndrome from autism but also from PDD-NOS. That is, the critical issue is whether Asperger's (as operationally and reliably defined) can be shown to differ in important respects from either autism or PDD-NOS beyond areas determined by the selection criteria in the different groups. Clearly it is crucial that such differences be truly independent of diagnosis, e.g., different patterns in family history, neuropsychological profiles, patterns of comorbidity, response to treatment would all be potential external validators if they were not used as part of selection criteria in the first place. The relationship of Asperger disorder to other diagnostic concepts, e.g., schizoid disorder, right hemisphere learning disability, and semantic pragmatic processing disorder also remains to be clarified (see Klin, Sparrow, & Volkmar, 2000 for a review). Replication of findings, based on the same diagnostic criteria used across sites, is critical for progress to be made in this area. If Asperger's and autism are to be mutually exclusive they need to share the level of detail and diagnostic description, e.g., in terms of behavioral features, early history, and so forth; the present situation, in which Asperger's is left as rather an afterthought (if the diagnosis of autism cannot be made), is clearly unsatisfactory.

Studies of PDD-NOS/atypical autism have been quite sparse (Towbin, 1997), though the newer instruments such as the SRS should allow more options for describing these groups (Constantino et al., 2003). The broadening conceptualization of ASDs and the lack of clear delineation of where the spectrum of autistic disorders begins and ends have made the categorical diagnosis of children and adults whose symptoms fall outside the boundaries of definite autism (Volkmar et al., 1994) more problematic, even while it has become easier within the boundaries (Mahoney et al., 1998). Measurements of severity that take into account chronological age, language level and cognitive skills are not yet available. Metrics of severity of autism or ASD, when used with a sample that covers the huge range of IQ and language functioning seen in autism, have typically, though not always, been strongly associated with IQ (Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002; Szatmari et al., 2003). However, it may be that the SRS will not show these effects. Spiker and colleagues (2002) and Szatmari and colleagues (2002) both proposed methods of quantifying general dimensions of autism using all three domains on the ADI-R within a single factor. This approach fits well with the results of the SRS, but differs considerably from the multi-domain pattern described in ICD-10 and DSM-IV and currently is under study by psychiatric geneticists (Tadevosyan-Leyfer et al., 2003).

Quantifying the severity of communication difficulties using standard measures such as the ADI-R is particularly complicated because the communication domain includes the absence of spoken language and limited use of gestures, which are strongly developmental items at least for younger and lower-functioning children (Charman & Baird, 2002), as well as deficits in pragmatic aspects of language, including both the presence of abnormalities such as delayed echolalia and the absence of typical development, such as conversational skills (Lord, Storoshuk, Rutter, & Pickles, 1993). A substantial number of individuals do not have enough language on which to judge abnormalities of speech or linguistic structure, and this proportion varies with chronological age and recruitment strategies. Because of this variation total scores of communication abnormality may be higher (i.e., indicating more impairment) for individuals who have more language (South et al., 2002) and children may receive higher ADI communication scores as they move from preschool to school age (Cox et al., 1999). On the other hand, structural aspects of language may contribute to an individual's ability to carry out tasks used in making diagnoses, such as answering the socio-emotional questions on the ADOS (see Bishop & Norbury, 2002). The availability of different modules in the ADOS was intended to limit the effects of nonsocial language ability on diagnostic codings of social behavior, but four modules that vary in language demands may not be sufficient (Joseph, Tager-Flusberg, & Lord, 2002).

Diagnosis in young children

There is now substantial evidence that autism can be reliably diagnosed in children as young as two years (Lord, 1995; Moore & Goodson, 2003), though there is more variability with children with early diagnoses of atypical autism or PDD-NOS (Charman & Baird, 2002; Cox et al., 1999; Stone et al., 1999). With evidence that most diagnoses of autism are stable from age two years onward, the opportunity to map trajectories of development and brain-behavior relationships has attracted the attention of many researchers (Courchesne, 2002; Dawson et al., 2002a; Rogers, 2001). Developmental changes in symptoms of autism and other ASDs are not always linear, and may be confounded by severity of other impairments (e.g., IQ) and differences in recruitment into research for children of different ages and/or in different sites (Szatmari et al., 2002). Thus, repetitive

behaviors are less common both in very young children with autism (Charman & Baird, 2002; Cox et al., 1999; Lord, 1995; Moore & Goodson, 2003; Stone et al., 1999) and in high-functioning adolescents and adults (Lord et al., 1997; Piven, Harper, Palmer, & Arndt, 1996b) than in older preschool or school age children. Social abnormalities, as reported by parents on the ADI-R, increase from early preschool to school age (Rutter et al., 1999) but then decrease from adolescence to adulthood (Seltzer et al., in press; Piven, Arndt, Bailey, & Andreasen, 1996a).

Much effort is currently being expended to identify characteristics of ASDs that are present in very young children that would allow early identification through screening of well-baby or high-risk populations, and then facilitating admission to treatment programs (Charman & Baird, 2002). The CHAT (Baird et al., 2000) was a creative attempt to use core features of autism to identify autism in toddlers. Its poor sensitivity in the general population reminds us that characteristics, such as joint attention, that are predictive of diagnostic stability within ASD may not necessarily be the most useful variables in screening out a population of children with ASD from other disorders or normal development, when informants are parents or non-experts in autism (Volkmar et al., 1994). Stronger results have been reported using the CHAT with a clinical population (Scambler, Rogers, & Wehner, 2001). The M-CHAT, a modified version of the CHAT, has also shown better predictive ability in 24-month-old children, though these children were mostly not identified in the general population, but from special education referrals (Robins, Fein, Barton, & Green, 2001). Whether this is the case because of difficulties with early diagnosis, with variability in the expression of autism or variability in typical development, or because of measurement issues is not clear (see Baird et al., 2000; Stone & Coonrod, in press).

As prevalence studies have yielded higher estimates of higher numbers of affected individuals (see below), the IQ distribution of ASD has also shifted, from earlier studies in which two-thirds or more children with autism were mentally retarded, to current estimates in which fewer than half of the children with more broadly defined ASD have had nonverbal IQs less than 70 (Chakrabarti & Fombonne, 2001). The outlook for children within the normal range of intelligence may be considerably more positive than prognosis in the past (Howlin, 2000; Tsatsanis, 2003). Yet which factors determine that outcome in groups where all individuals have fluent language and some academic skills is not yet entirely clear (Howlin, 2003; Pivern, Harpter, Palmer, & Arndt, 1996; Szatmari et al., 2003).

Finally, co-morbidity of other disorders and presence of nonspecific difficulties in individuals with ASD have become increasingly acknowledged as being important to outcome and to research (Howlin & Goode, 1998; Klin, Pauls, Schultz, & Volkmar, submitted; Szatmari, 2000). This is an area where much greater understanding will be needed as the field begins to address the higher proportion of non-retarded individuals with ASD. How to measure other disorders in individuals who may have relatively little insight into their own behavior or who have limited verbal skills is an ongoing question that is currently being addressed by a number of research groups.

Epidemiology

Prevalence and incidence

Since the mid-1960s, over 30 epidemiological studies of autism have been conducted. Several recent reviews of these studies are available (e.g., Baird et al., 2001; Wing & Potter, 2002; Fombonne, 2003a; Croen, Grether, Hoogstrate, & Selvin, 2002a). The most noteworthy aspect of recent epidemiological work has been the observation of an increase in prevalence. The rate for studies published between 1966 and 1991 was 4.4 cases per 10,000, while that for 1992–2001 was 12.7 (Fombonne, 2003b). The increase in rate has led to dramatic claims, particularly in the lay media, for an 'epidemic' of autism.

Several factors complicate the interpretation of the apparent increase, however, including changes in diagnostic practice, increased awareness of the disorder, earlier diagnosis, issues of study design and case ascertainment, and the problem of 'diagnostic substitution' (e.g., choosing to use a label of autism as opposed to a label of mental retardation for educational purposes; the latter problem may be a particular source of difficulties when investigators rely primarily on educational case records (Wing & Potter, 2002; Fombonne, 2001; Croen, Grether, & Selvin, 2002b). For Croen, Grether, and Selvin's example, the current (DSM-IV and ICD-10) approaches to diagnosis were specifically designed (Volkmar et al., 1994) to be applicable over the entire range of intellectual ability with a reasonable balance of sensitivity and specificity in both lower- and higher-functioning individuals. The importance of aspects of study design and methodology is also underscored by the observation that in eight recent studies reported from the UK and USA there were major variations in prevalence rates reported.

A common source of confusion has been the tendency to mistake prevalence for incidence; prevalence refers to cases with the disorder at a specified time whereas incidence refers to the rate of new cases of the disorder within a period of time (usually a year). Very few recent studies have assessed incidence (e.g., Powell et al., 2000) and the same problems with changes in diagnostic criteria and methods of case ascertainment apply here as well. One strategy for assessing changes in prevalence has been the examination of successive birth cohorts;

two studies completed in France in the same areas did not reveal statistically significant changes in rates of the disorder (Fombonne & du Mazubrun, 1992; Rumeau-Rouquette, Grandjean, Cans, du Mazaubrun, & Verrier, 1997), although rates of the disorder were relatively low in these studies, causing concern that cases may have been missed.

Presently available data suggest that a prevalence rate of 10 cases per 10,000 is a reasonable estimate for autistic disorder (Fombonne, 2003a). In general, epidemiological studies have focused on strictly defined autism, i.e., as opposed to other conditions included in the PDD category or potential variants of the broader PDD phenotype. However, the available (and limited) epidemiological data suggest that rates of Asperger's disorder are lower than those of autism (Fombonne, 2003a, suggests an estimate of 2.5/10,000 children). Rett's disorder and CDD are clearly less common than autism, with rates likely below 1 in 10,000 children with Rett's (Kozinetz et al., 1993) and about 1/50,000 for CDD (Fombonne, 2002). Clearly, cases of PDD-NOS (atypical autism or 'subthreshold autism') must be more common than autism, although, somewhat paradoxically, this population is only rarely studied in its own right (Towbin, 1997; Fombonne, 2003).

Demographic factors, race, and gender

Kanner's initial report (1943) of the syndrome of early infantile autism emphasized the unusual educational and professional achievement of parents; subsequent work, however, notably the reports of Schopler (Schopler, Andrews, & Strupp, 1979) and Wing (1980), strongly supported the idea that Kanner's original (1943) sample was atypical in this regard. In general, subsequent studies have supported this later view, with all recent epidemiological studies failing to find an association between autism and social class (Fombonne, 2003a).

Immigrant status has been suggested as one potential risk for autism (Gillberg, Steffenburg, Borjesson, & Andersson, 1987; Gillberg & Gillberg, 1996). In the Camberwell study, Wing (1980) reported an excess of children with autism of Caribbean origin, although the entire sample of children with autism was relatively small so that this difference was not statistically significant. The suggestive data are, however, all based on small numbers of cases and are, as a result, not convincing. Few studies have specifically addressed the issue of race as such. In the Utah study (Ritvo et al., 1989) there was no difference in the distribution of races from that in the population of the state as a whole.

Studies based on both clinical and epidemiological samples find a higher incidence of autism in boys than in girls, with reported ratios averaging around 3.5 or 4.0 to 1 (Fombonne, 2003; Lord, Schopler, & Revicki, 1982; Volkmar, Szatmari, & Sparrow, 1993). There is a strong association of mental handicap and sex ratio; the highest male:female ratios are reported in individuals functioning in the normal range on cognitive assessment and the lowest male:female ratios found in individuals with autism and profound mental retardation (Lord et al., 1982). The cause of the observed sex difference remains the topic of debate. It is possible that males have a lower threshold for expressing the disorder and that more severe neurodevelopmental abnormalities are required to cause autism in a girl. Baron-Cohen (1997, 2003) has proposed a novel theory accounting for these differences, but supporting data are limited.

Cluster cases

Reports of 'outbreaks' or clusters of cases of autism have raised concern about the possibility that autism might be the result of some environmental risk or other factor. Such reports attract considerable attention in the lay media, although supporting data are limited. Baron-Cohen, Saunders, and Chakrabarti (1999) described a small group of children with either autism or PDD-NOS living near each other in a small town in the United Kingdom. As Fombonne (2003) notes, such a report does not, of itself, prove anything; one might expect a bias for reporting positive associations, e.g., one remains unaware of communities or neighborhoods where autism is not observed. A more rigorous study in the USA (Bertrand et al., 2001) examined the prevalence of autism in Brick Township, New Jersey, an area where an 'outbreak' of autism had been reported. The authors noted that the prevalence of autism was, in fact, within the range of other recent reports of studies using small populations and extensive case-finding. In summary, interest in possible environmental factors and autism has been stimulated, in part, by lay press reports of cluster cases but the available evidence for such etiologies is weak (Wing & Potter, 2002).

Autism and medical conditions

Beginning in the 1970s and 1980s and continuing to the present, associations with autism have been noted for numerous medical conditions (see Gillberg & Coleman, 2000). However, there are many problems in interpreting such reports, e.g., the bias for publication of positive case reports, duplicate publication of cases (e.g., as a case report and then within a case series), and many studies fail to provide evidence of association above the level predicted by chance for most disorders (Rutter et al., 1994). The available data on this issue are of variable quality, with studies ranging from questionnaires and retrospective parental reports to contemporaneous medical examinations. The strongest association with a medical condition is that of autism with epilepsy, with bimodal peaks of onset in both early childhood and adolescence (Rutter, 1970;

Deykin & MacMahon, 1979; Volkmar & Nelson, 1990). In his recent review Fombonne (2003) reports that across available epidemiological studies the mean rate of epilepsy was 16.8%, although this is likely an underestimate given the median age of available samples and the increased risk for onset of seizures throughout childhood and adolescence and early adult life.

The early suggestion that individuals with congenital rubella (Chess, 1971) and PKU (Knobloch & Pasamanick, 1975) were at increased risk for autism has not been supported by more recent studies (Fombonne, 2003). Indeed, as children with congenital rubella were followed over time it became clear that their 'autism' improved dramatically (Chess, 1977) suggesting a potential problem of misdiagnosis in a diagnostically challenging group of children. Although a veritable host of other medical conditions have been suggested to be associated with autism (Gillberg & Coleman, 2000), the available data support strong associations (i.e., above the expected rate of the disorder based on chance) for only a limited number of conditions – notably Fragile X syndrome and tuberous sclerosis (Rutter et al., 1994; Hagerman, Jackson et al., 1992; Smalley, 1998). The issue of more basic relationships between the disorders, e.g., is the risk for autism in tuberous sclerosis mediated by brain lesions or seizure disorder or some other effect, remains to be resolved.

In recent years considerable interest has centered on the notion that autism might be caused by immunization, either directly through some aspect of exposure to some pathogenic agent (such as measles virus; Wakefield, 1999) or some preservative (such as mercury containing thimerosal) in the vaccine (Bernard, Enayati, Roger, Binstock, & Redwood, 2002). As a result of this controversy rates of measles vaccination have fallen in both the USA and the UK, with a concomitant increase in the rate of measles infection and increased concern on the part of public health authorities (Ramsay, 2001). Reports from several groups question the link of autism with MMR vaccination and mercury, e.g., in Denmark rates of autism in relation to changes in the preparation (with and without thimerosal) are unchanged (Madsen, 2003) and expected changes in the prevalence of 'regressive autism' are not observed (Fombonne & Chakrabarti, 2001). Data on this issue continue to emerge but, at present, the putative link between measles vaccination and/or mercury to autism is highly suspect (Fombonne & Chakrabarti, 2001; Wilson, Mills, Ross, McGowen, & Jadad, 2003).

The topic of 'regressive' autism or 'late onset' autism has attracted attention, in part due to the interest in the putative link with measles. A series of studies, mostly of case series, have confirmed that in perhaps 20% of cases parents report normal development for 12 to 18 months before the development of more typical autistic features (e.g., Volkmar, Stier, & Cohen, 1985). In contrast to CDD (Volkmar, Klin, Marans, & Cohen, 1997), children with 'late onset' autism typically have minimal speech skills at the time of the regression (10 or fewer words). A major complication in this literature has been the understandable reliance on parental report; work using contemporaneous videotapes (e.g., Osterling, Dawson, & Munson, 2002) suggests that parents may not notice subtle abnormalities in the first year of life. A further complication is that in some cases the issue is more that of developmental stagnation (at least on the basis of parental report) rather than true regression of skills. In one recent paper (Siperstein & Volkmar, In press) in which parents provided reports both of early concern and developmental milestones, clear regression (i.e., without preexisting developmental delay or behavioral deterioration) was uncommon. The key here may separating the early presence of some delays or deficits from later specific losses of simple forms of communication and social interaction, both of which may occur (Luyster et al., in press). In addition, definitions of what constitutes regression vary widely.

In general, early apparent onset of autism has not been associated with greater severity of symptoms (Rogers & DiLalla, 1990); this is in contrast to CDD where, following the regression, outcome appears to be significantly worse than in autism (Volkmar & Cohen, 1989). It is likely that this group is etiologically heterogeneous. One recent paper reported no concordance for regression in families with more than one child with autism (Freitag et al., 2002) – the issue of late onset autism, and its relationship to CDD, remains an important topic of future research, perhaps as much to help us understand the nature of social and language learning in autism as to understand etiology.

Psychological models of autism

Psychological characterization of core deficits in individuals with autism plays an important role in the search for factors involved in the etiology and pathogenesis of the spectrum of conditions defined by early onset social disabilities. Variability in syndrome manifestation and the lack of established and specific etiologic factors have prompted the search for core psychological markers that could be used as endophenotypes in genetic research and as heuristic models guiding neuroimaging research. While early psychological research, from Scheerer, Rothman, and Goldstein's single-case study (1945) to the series of experiments by Hermelin and O'Connor (1970), had focused on disruptions of symbolic and conceptual development, the research that followed bifurcated into the study of specific social cognitive mechanisms (with the assumption that the social domain is the locus of the primary disability), and of more general perceptual and cognitive learning mechanisms (with the assumption that the social

disability is only an instance of a more generalized learning impairment) (Klin, Jones, Schultz, Cohen, & Volkmar, 2002a).

Since the early 1990s, the field has witnessed the emergence and consolidation of a few dominant psychological models of autism. These models were built around the constructs of 'theory of mind' skills, a cognitive drive for central coherence, and a group of neuropsychological skills clustered together by the term 'executive functions'. Despite this consolidation, however, work continues in other areas prompted by limitations of the prevailing theories. There are also constraints imposed by integration of neurobiological and, particularly, neuroimaging findings, which now point to the involvement of broader and developmentally interrelated neural systems that are less consistent with the notion of 'single core deficits'. One result of this debate has been the resurfacing of another model, in which derailment in normative social motivation processes leads to deficits in preferential orientation to, and engagement with, the social aspects of the child's early environment. This model is related to more established areas of research, including imitation, joint attention, and face processing, whose interrelationships remind us of the dangers of studying early social development as a composite of unrelated modular skills, a notion increasingly criticized on the basis of developmental and neuroscience evidence (see Geary & Huffman, 2002; Johnson, 2001; Plunkett, Karmiloff-Smith, Bates, Elman, & Johnson, 1997 for a sample of this important debate). The following is an overview of these various trends, their current limitations, and the lessons learned so far that help establish an agenda for the next 10 years.

In the social cognitive domain, the most influential framework emerging in the 1990s was the 'theory of mind' (ToM) hypothesis, which defines the social dysfunction in autism as the result of disruptions in processes leading to the acquisition of the capacity for conceiving of other people's and one's own mind (Baron-Cohen, 1995). Individuals with autism have difficulty in making attributions of mental states to others and to themselves, which result in an inability to construct a social world that is guided by intentions, desires, and beliefs (Baron-Cohen, Tager-Flusberg, & Cohen, 2000b). In the more general learning domain, two influential frameworks have guided thinking about the learning profiles of individuals with autism. One of them focuses on the tendency to process all stimuli in a fragmented fashion, focusing on details (localized processing) rather than integrated and meaningful wholes (configural processing) (Frith, 1989). This framework, termed the 'Weak Central Coherence' hypothesis (WCC) (Happé & Frith, 1996), delineates an internal social world that is piecemeal and disjointed, lacking the overall coherence that defines social context and meaning. Another framework focuses on the self-organizing elements required in general learning, which guide attention, inhibit irrelevant responses, abstract rules, and generate goals that are maintained 'on line' (in the mind) during task execution (Pennington & Ozonoff, 1996). This framework, termed the 'Executive Dysfunction' hypothesis (ED), defines general learning in autism as a process characterized by perseveration and poor self-regulation, which include difficulties with change, reduced forward planning, and ineffective problem-solving skills that lack in coordinated reasoning and ongoing adjustment to feedback (Ozonoff, 1997).

Alongside these prevailing theories, other psychological models continue to be studied. Replacing sensory and perceptual theories prevailing in the 1960s and 1970s which focused on brain stem abnormalities (Ornitz, 1985), new findings from psychological (e.g., Bertone, Mottron, Jelenic, & Faubert, 2003; Plaisted, Wettenham, & Rees, 1999) and neuroimaging research (Allen & Courchesne, 2003; Akshoomoff, Pierce, & Courchesne, 2002) have renewed interest in the role of basic processing models including motor, attentional, and perceptual functions in the pathogenesis of autism. The significance of this work to psychological models of autism is only beginning to be felt (e.g., Plaisted, Saksida, Alcántara, & Weisblatt, 2003), particularly as neurobehavioral systems traditionally thought to be circumscribed to motor control are found to interact with some higher cognitive functions (Allen, Buxton, Wong, & Courchesne, 1997).

It is still the case, however, that clinical face validity and research productivity have made the ToM, WCC, and ED frameworks the most active foci of psychological studies in the past decade (Happé & Frith, 1996), generating a large body of data that both support and refine them. The critique has focused on some limitations in their explanatory power and developmental modeling. For example, the ToM hypothesis has been criticized in terms of the lack of specificity to autism (Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998), a degree of association between ToM skills and more general verbal and cognitive levels (Buitelaar, van der Wees, Swaab-Barneveld et al., 1999), and the notion that the successful teaching of ToM skills does not necessarily lead to advancement in real-life social competence (Ozonoff & Miller, 1995). The WCC hypothesis has been questioned on the basis of some conflictual experimental findings (Mottron, Burack, Sauder, & Robaey, 1999; Mottron, Peretz, & Menard, 2000; Mottron, Burack, Iarocci, Belleville, & Enns, 2003), and the as yet limited number of perceptual and cognitive domains studied from the WCC perspective that would evaluate more directly its implications for social processing. The ED hypothesis has been criticized in terms of the lack of specificity to autism (Pennington & Ozonoff, 1996), possible social confounds involved in task administration (Ozonoff, 1995), the overly encompassing range of neuropsychological phenomena involved, and its yet

unproven relationship to degree of social disability. While these limitations do not invalidate the premises of these hypotheses, they do set the stage for the next decade of psychological research in autism. A number of advancements in clinical and cognitive science, from novel technologies to the opportunities provided by the study of very young children with autism, now make possible a more stringent agenda for future research in this area.

First, the onset of autism is by all accounts in the first two years of life. By the age of two, typically developing children are accomplished social interactionists, while children with autism can now be reliably identified at that age. There is a need, therefore, for any psychological theory to set forth a model of its developmental psychopathology, which should focus on skills and processes that both emerge early and that could eventually lead to deficits in theory of mind skills, drive for central coherence, or executive functions in older individuals with autism. Several candidates have shown promise. Chief among these are deficits in joint attention skills (Mundy, Sigman, & Kasari, 1990; Tomasello, 1995; Mundy, 2003), which refer to the ability to share a common focus of attention with another person (e.g., looking in the direction that another person is looking, following a pointing gesture). Deficits in joint attention are central in the characterization of toddlers with autism (Lord, 1995), play a crucial role in the subsequent development of language and social communication (Mundy & Neal, 2001), and have been identified as the main precursor of subsequent ToM disabilities in autism (Charman, Baron-Cohen, Swettenham et al., 2001). Another central deficit in young children with autism involves imitation (Rogers, 1999), a key component of social learning that is also thought to be an important mechanism facilitating intersubjectivity (Rogers & Bennetto, 2000). A still more basic group of skills involve the *sine qua non* of all kinds of processes involved in social development, namely the infant's preferential orientation to social stimuli (relative to the surrounding inanimate environment) (Mundy & Neal, 2001; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Klin, 1991), and the infant's drive or motivation for social engagement (Dawson, Webb, Schellenberg et al., 2002c; Klin, Jones, Schultz, & Volkmar, 2003; Mundy, 2003). Although these various trends have not fully coalesced around a single construct, as has happened with ToM, WCC, and ED, it is possible that their common focus on very early emerging social motivation and orientation skills will lead to an integrated psychological model offering an alternative to the prevailing ones.

In the interim, however, the focus on early development has already shown some benefits. For example, while executive dysfunction characterizes older individuals with autism, this is not the case with younger children (Rogers & Bennetto, 2000; Dawson, Munson, Estes et al., 2002a). Equally interesting, deficits in early imitation seem to disrupt aspects of executive functions later in life (Rogers, 1999). These examples illustrate the need not only to intensify the study of early emerging skills but to document their longitudinal association with later developmental accomplishments or disabilities. The study of the interrelationships among these skills is equally crucial because it is unlikely that any of these candidate early-emerging processes follow independent developmental courses.

A second element of the agenda of research for the next decade involves the need to relate levels of putative 'core' impairments to levels of 'core' outcomes. It is a reasonable expectation to assume that if a psychological process is hypothesized to be causatively linked to autism, then levels of disruption in the given skill should hold a quantified and proportional relationship to levels of social competence in real life. And yet, to date only very few studies have attempted to measure this predictive relationship (Dawson, Munson, Estes et al., 2002a; Klin, Jones, Schultz et al., 2002b). Typical research designs involve a simple comparison between a group with autism and a control group on the measure of interest. Significant results in such comparisons have generated sweeping theories of autism in the past, regardless of effect sizes obtained or the extent to which the variable of interest could be directly related to social adaptive functioning. The social disabilities in autism are both extremely variable and severe. Thus it will be important to assess the 'core-ness' of a given construct in terms of its predictive value relative to social outcome measures (so that one can think of it as a dimension contributing to the spectrum of autistic social dysfunction), and in terms of proportionality in effect size relative to real-life measures of social adaptive functioning (or, in other words, small effect sizes are unlikely to account for the very large gaps in social abilities and disabilities separating individuals with autism from their peers).

A third element in the agenda of research concerns the need to focus on processes used by, and not only on results obtained for individuals with autism when completing experimental tasks. A number of studies are showing that individuals with autism may achieve higher than expected results on a given task, but are found to be achieving these results using processes that contrast markedly from their typical peers. For example, a small number of functional neuroimaging studies are suggesting that higher-functioning adolescents with autism may achieve less impaired levels of face recognition skills using compensatory strategies rather than normative neurobehavioral mechanisms (Pierce, Muller, Ambrose et al., 2001; Schultz, Gauthier, Klin et al., 2000a). Devoid of a preferential neurosystem for specialization in faces, it is likely that the obtained performance in judging static faces as 'same' or 'different' (as shown in a standard functional MRI

experiment) may not translate into the proficiency and automaticity required for fast processing of dynamic faces in natural environments. Consistent with this notion, more normative face-scanning patterns are obtained for static (i.e., photographs; Van der Geest, Kemner, Verbaten et al., 2002) rather than moving (i.e., video; Klin et al., 2002b) face stimuli. Similarly, some mastery of fairly complex theory of mind tasks may be observed in higher-functioning individuals with autism if the tasks are explicitly and verbally defined to them (e.g., Dahlgren & Trillingsgaard, 1996), and yet they may fail to attribute social meaning to ambiguous visual displays at a level shown by much younger typically developing children (Abell, Happé, & Frith, 2000; Bowler & Thommen, 2000; Klin, 2000). From a clinical standpoint, this pattern of higher performance in explicit and structured situations relative to the lower performance in spontaneous and unstructured situations is of great importance. The most entrenched challenge to interventions in autism is the core difficulty with generalization of skills, from explicit and structured settings to naturalistic environments. Typically, the greater the demands on spontaneous use of social skills (e.g., lunch, recess), the greater the level of social disability evidenced in individuals with autism. From a scientific standpoint, there is a need to address this issue by ensuring that the rigor of experimentation does not alter the essence of social phenomena studied. While the typical approach has been to highly constrain presentation stimuli in social experiments (making tasks explicit and well defined, thus avoiding complexity and confounds), there is concern that such abstractions of social situations may change the nature of what is needed to perform well (or, in other words, the task ends up measuring problem-solving abilities on explicit tasks rather than what is needed for social competence in real life). This distinction is particularly important in newer frameworks of social neuroscience that see social action (rather than social problem-solving) as the cornerstone of real-life social competence (Clark, 1999; Varela, Thompson, & Rosch, 1991). Enhanced ecological validity and greater attention to processes of learning and execution (including compensatory strategies) remain, therefore, important goals in the effort to bridge the gap between knowledge accrued through rigorous experimentation and the pronounced social challenges faced by individuals with autism in their daily lives.

The fourth mandate for future psychological research is to fully incorporate the various tools of genetic and brain research in the building of integrated brain–behavior models of psychological constructs and mechanisms deemed to play a role in the pathogenesis of autism. To date, these two levels of discourse and scientific methodology – psychological constructs and neurobiological processes – have yielded only a limited amount of overlap and synergy in autism research. In general, genetic and structural brain findings have not been sufficiently specific to inform the discussion on neural or psychological systems involved in autism. And functional neuroimaging technology still lacks the power to rigorously measure temporal and spatial connectivity, a crucial requirement in more detailed studies of functional interactions in the brain (Johnson, Halit, Grice et al., 2002), although the increasing availability of magnetoencephalography opens new avenues to exploring brain dynamics (see for instance Bräutigam, Bailey, & Swithenby, 2001). Still, the preliminary knowledge that is available provides an exciting prelude to the future benefits of greater integration of psychological and biological models and methodologies to be achieved in the next decade.

Though still a longer-term goal, the translation of susceptibility regions into candidate genes will likely inform the debate on affected neural mechanisms, which in turn may constrain the discussion of psychological constructs involved in pathogenesis. Preliminary work on candidate psychological endophenotypes, including ToM (Baron-Cohen & Hammer, 1997), WCC (Baron-Cohen & Hammer, 1997; Happé, Briskman, & Frith, 2001) and ED (Hughes, Plumet, & Leboyer, 1999), have so far validated these psychological hypotheses of autism, although it is too early to evaluate the utility of these findings for studies of heritability patterns in autism. Additional candidate traits characterizing the broader phenotype of autism have been offered (Dawson et al., 2002c), including face processing, social motivation, motor imitation, specific memory processes, and some aspects of language ability (but not others; see Pilowsky, Yirmiya, Shalev et al., 2003). Findings on structural brain abnormalities continue to raise the intriguing hypothesis of reduced connectivity in the autistic brain (e.g., Courchesne, Karns, Davis et al., 2001), with accelerated overgrowth occurring in the first 2 years of life (Courchesne, Carper, & Akshoomoff, 2003), a time period coinciding with the emergence of core symptomatology in autism.

In contrast to the less specific findings of molecular genetic and brain structure research, functional neuroimaging studies in the past decade have mostly been conceived to test a small number of psychological hypotheses (see next section for detailed descriptions and findings). The majority of studies have focused on mentalizing and face recognition abilities. Although one may argue that these studies have provided validation of the psychological models of autism involving ToM and face processing deficits, it is possible that another important finding of these studies was the discovery of generalized hypoactivation of an entire social processing brain network in individuals with autism. This pattern of results has been obtained with different social perceptual and social cognitive paradigms, encompassing a highly interrelated neural system consisting of medial and

orbital prefrontal cortex, the superior temporal sulcus, the fusiform gyrus, and medial temporal lobe limbic areas (see Dawson et al., 2002c, and Schultz, Romanski, & Tsatsanis, 2000b for reviews). These structures are connected to a great number of early-emerging social mechanisms, some of which are likely forerunners of ToM skills, whereas others correspond to phenomena associated but not identical to face recognition skills. For psychological research, the implication is that these skills deserve further investigation. Examples are the effects of familiarity in face processing (Dawson, Carver, Meltzoff et al., 2002b), the role of perception of biological movement in the acquisition of theory of mind skills (Blake, Turner, Smoski, Pozdol, & Stone, 2003; Frith & Frith, 1999; Klin, Jones, Schultz, & Volkmar, 2003; Moore, Hobson, & Lee, 1997), the relationship between sensitivity to gaze direction and joint attention skills (Chawarska, Klin, & Volkmar, 2003; Swettenham, Condie, Campbell, Milne, & Coleman, 2003), and specific forms of joint attention skills (Mundy, 2003). For functional neuroimaging research, the implication is that a more concerted effort is needed to investigate what can be called the developmental connectivity of the social brain (Iacoboni, 2000a, b), or the ways in which different brain areas interrelate and act synergistically, temporally (when someone is performing a task) and developmentally (in the process of postnatal organization), to perform a social function. Still, the generalized hypoactivation finding could be indicative of a pervasive lack of social interest, engagement, motivation, or reactivity (Schultz, Grelotti, Klin et al., 2003). If so, Kanner's (1943) original hypothesis of reduced 'affective contact' could become once again the driving hypothesis in the field.

Brain mechanisms in autism

Changes in the areas of neuroimaging and neuropathology research in autism spectrum disorders since the last *JCPP* review have been dramatic. There has been an enormous increase in the number and quality of studies, such that contemporary reviews on brain mechanisms in autism seldom cite papers before 1990. Prior to 1990, neuroimaging studies of autism were largely restricted to lower-resolution techniques such as computed tomography (CT) and single-photon emission computed tomography (SPECT), or from techniques such as positron emission tomography (PET) that typically cannot be applied to the study of children because of ethical concerns about exposure to radioactive tracers. In recent years each of these techniques has undergone considerable methodological development, allowing greater resolution for imaging the brain. Magnetic resonance imaging (MRI) has come of age in the past decade as a technique for measuring brain morphology with resolution at or below 1 mm^3. Advances have been especially dramatic in the post-processing of image data, allowing much more precise definition and measurement of neural structures. Perhaps the most promising development has been the exploitation of MRI for studying brain function. Functional MRI (fMRI) allows for the study of discrete brain systems that underlie the cognitive, behavioral and social-emotional deficits that define autism. Neuroimaging research prior to 1990 was also distinguished by a frequent lack of hypotheses about what brain structures or neural systems would be impaired in autism. This was appropriate to that era, as it was not at all clear until these studies were done whether consistent gross anatomical and functional differences would emerge from more casual inspection. In the past decade, neuroimaging research in autism has become much more sophisticated both in terms of methods and the specificity of the hypotheses about the underlying impairment. For example, fMRI studies are now testing the role of specific perceptual, motor, attentional, and affective systems in autism, often with activation paradigms that have been developed and well replicated in the field of normative cognitive neuroscience. This is a tremendous advance, as we can now draw on fairly precise data from the cognitive neurosciences to hypothesize with good specificity about the localization of brain functions that might be aberrant in autism.

The social, language, and behavioral problems that occur with autism suggest that the syndrome affects a functionally diverse and widely distributed set of neural systems. At the same time, however, the pathophysiology must involve only selected systems, sparing others, because autism is not incompatible with normative intelligence and domains of superior functioning. At one point or another, malfunction of nearly every neural system in the brain has been proposed as central to the pathobiology of autism. Theories typically derive from beliefs about the most salient behavioral and psychological features of the disorder. For example, models that emphasize difficulty with complex information processing as the principal characteristic of autism postulate widespread cortical abnormalities sparing early sensory processes as the neural basis of autism (e.g., Minshew, Sweeney, & Bauman, 1997). Models that focus on the emotional deficits and their role in social difficulties often highlight the limbic system in the pathogenesis of autism (e.g., Bachevalier, 1994; Baron-Cohen et al., 2000a; Schultz, Romanski, & Tsatsanis, 2000b).

This section of the review will attempt to highlight the most promising findings, devoting more attention to those that have been replicated. There is now consistent evidence for abnormalities in overall brain size, with developmental differences that may point to specific growth processes that have gone awry. Data also continue to accumulate from structural MRI, postmortem and animal lesion models on the role of specific brain structures in the pathobiology

of autism, particularly the medial temporal lobe structures and the cerebellum. Unfortunately, these have yet to show completely consistent and coherent patterns of results. FMRI studies that have focused on aspects of the 'social brain' seem to show much early promise. However, fMRI studies of other areas of functioning, such as language, working memory, attention and motor functioning also show promise, but by comparison work in those areas currently lags behind.

Kanner's seminal paper (1943) noted that children with autism had enlarged heads. Although subsequent studies of external head circumference confirmed this observation (e.g., Steg & Rapoport, 1975; Walker, 1977), it did not receive much attention until the past decade when support for this finding began to accumulate via MRI (Aylward, Minshew, Field, Sparks, & Singh, 2002; Courchesne et al., 2001; Piven et al., 1995; Sparks et al., 2002), postmortem studies (Bailey et al., 1993; Bailey, Luthert et al., 1998; Kemper & Bauman, 1998), and additional head circumference studies (Aylward et al., 2002; Bolton et al., 2001; Davidovitch, Patterson, & Gartside, 1996; Fidler, Bailey, & Smalley, 2000; Fombonne, Roge, Claverie, Courty, & Fremolle, 1999; Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Stevenson, Schroer, Skinner, Fender, & Simensen, 1997; Woodhouse et al., 1996). The size increase appears to be a shifting of the entire autism brain and head size distribution (Aylward et al., 2002; Courchesne et al., 2003; Fombonne et al., 1999) rather than merely an excess of megalencephaly among a minority of cases that elevates what would otherwise be a normal autism population mean size. While there are a few studies that have failed to find significant increases in brain or head size, these seem to be a result of insufficient statistical power or specific sample characteristics (e.g., Herbert et al., 2003).

Recent findings suggest that the brain may be enlarged by as much as 10% in volume in toddlers with autism (Courchesne et al., 2001; Sparks et al., 2002). However, the magnitude of the effect appears to diminish with age. In adolescence and adulthood the effect is less consistently found across studies (Aylward et al., 2002; Courchesne et al., 2001; Herbert et al., 2003; Kemper & Bauman, 1998; Piven et al., 1995), and the size of the effect is diminished to a few percent increase at most. Interestingly, studies of head circumference have consistently found size increases in autism, regardless of the age of the participants. While head circumference lacks precision and correlates only about .50 with brain size, it has the advantage of being noninvasive and thus easily obtained on persons for whom it would be difficult or impossible to obtain MRI data. This advantage is especially important for localizing the time of onset for the growth abnormality. Several studies have now shown that the head is not significantly enlarged at birth (e.g., Lainhart et al., 1997; Courchesne et al., 2003, but see Mason-Brothers et al., 1987 and Gillberg, 2002), leading to the proposal that there are specific events in the first months of life that are responsible for the brain enlargement. Since different factors affect brain growth during different developmental stages, this proposal promises to allow the field to identify specific causal mechanisms for this early overgrowth, e.g., specific neuotrophins and neuropeptides (Nelson et al., 2001), excessive production of glial and/or neuronal synapses, dysregulation of programmed cell death, and synaptic pruning. While the current data support a model of early overgrowth of the brain in autism followed by a tendency toward size normalization, caution is warranted as these studies are all cross-sectional, and true longitudinal studies will be needed to confirm these observations.

It is not yet clear whether all neural systems are equally affected by the volume expansion, nor is it clear what the functional significance of the expansion may be. Variance in head size or brain size within samples of autism does not appear correlated with autism symptom severity or other measures of disability. However, increased brain size in autism appears to disrupt at least one typical brain size correlate; there is now good evidence that in typically developing persons there is a modest, positive correlation of brain size with IQ (e.g., Reiss, Abrams, Singer, Ross, & Denkla, 1996; Willerman, Schultz, Rutledge, & Bigler, 1991), but in autism this correlation is smaller (Aylward et al., 2002), suggesting that the extra tissue is not functionally well integrated. Results concerning enlargement of individual lobes are thus far contradictory, with one study finding a selective enlargement of occipital, parietal and temporal lobes, but not frontal cortex (Piven et al., 1995), and the other an opposite pattern of results with the frontal lobe being most enlarged (Carper, Moses, Tigue, & Courchesne, 2002). Finer parcellations of the cortex into more functionally homogenous units are just now appearing with promising results implicating gray matter volume changes in language-related cortices (Herbert et al., 2002; Rojas et al., 2002). One postmortem study of the cyto architecture of the cerebral cortex has garnered much excitement. Casanova, Buxhoeveden, Switala, and Roy (2002) examined the cortical minicolumns (a basic functional unit) in temporal and frontal tissue samples of 9 brains of persons with autism, and found them to be significantly smaller in width and to have cells which were more dispersed. This type of neuropathology could be consistent with a reduction of inhibitory neuronal activity at the boundaries of each column, causing a type of 'cortical noise' and widespread cognitive and behavioral dysfunction.

Courchesne and colleagues (2001) found the volume of the cerebral white matter to be disproportionately enlarged in toddlers relative to the cortical gray matter; in a separate adolescent sample, white

matter was significantly diminished in volume, with no significant differences in gray matter. Another study of children with an average age of 7 years found a trend for cerebral white matter to be disproportionately larger in autistic boys (Herbert et al., 2003). Courchesne and colleagues' observation of a decrease in white matter by adolescence is consistent with many other studies of older participants with autism showing size reductions in the cross-sectional area of the corpus callosum (CC) measured at midline (Berthier, Bayes, & Tolosa, 1993; Egaas, Courchesne, & Saitoh, 1995; Hardan, Minshew, & Keshavan, 2000; Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997). Reductions in white matter may also be consistent with an older PET study that showed reduced inter-regional correlations in persons with autism, suggesting reduced functional integration and connectivity (Horwitz, Rumsey, Grady, & Rapoport, 1988). Co-occurrence of reduced white matter and reduced functional connectivity makes some sense, given the physical constraints on how large the brain can grow while still maintaining adequate levels of connectivity (Ringo, 1991). Schultz and colleagues (2000b) have suggested that one consequence of reduced interconnectivity in the autistic brain might be increased modularity and reduced integration of functions. Such a reduction in neural integration would be consistent with one influential theory that attributes autistic symptoms to a lack of 'central coherence' (Frith, 1989), a cognitive processing style that makes integration of parts into wholes problematic. One new MRI technique, diffusion tensor imaging, is currently being used in many labs and promises to shed additional light on the structural connectivity and integrity of the cerebral white matter and autism.

There is also significant interest in the role of limbic system circuitry, particularly the amygdala and hippocampus, in causal models of autism (e.g., Baron-Cohen et al., 2000a; Saitoh, Karns, & Courchesne, 2001). Postmortem studies have repeatedly noted abnormalities in these areas, including reduced density, cell size, and dendritic arborization in structures such as the amygdala, hippocampus, septum, anterior cingulate and mammillary bodies (Bauman, 1996; Kemper, & Bauman, 1998). The amygdala, in particular, plays a critical role in emotional arousal, assigning significance to environmental stimuli and mediating emotional learning (LeDoux, 1996), and thus it is often highlighted as a core structure in models of autism pathobiology. Although of great theoretical interest, animal models of autism have, in general, been difficult to produce. One animal model involving bilateral surgical aspiration of the amygdala shortly after birth in monkeys has produced patterns of behavior similar to those of autism, such as social isolation, lack of eye contact, and motor stereotypies (Bachevalier, 1994). The early postnatal lesions did not immediately produce the signs characteristic of autism spectrum disorders. Rather, the deficits emerged during development, suggesting that faulty emotional learning is an important consequence. In fact, similar lesions in adulthood fail to produce these behaviors (Emery et al., 2001). The neonatal lesions also produced abnormalities of the frontal cortex in later development (Bertolino et al., 1997; Saunders et al., 1998). While an attractive model, one recent attempt to replicate these findings with three neonatally lesioned macque monkeys failed to re-create the autistic type of behaviors found by Bachevalier and colleagues (Prather et al., 2001). At age 8 to 9 months, the monkeys were attentive to social communications, but nevertheless showed a complex pattern of changed social behaviors that included increased fear during dyadic social interactions (Amaral et al., 2003; Prather et al., 2001). There were several important differences between this study and earlier ones that might explain the conflicting results, including the use of an ibotenic acid lesioning technique, which, compared to aspiration lesions, will spare fibers of passage in the amygdala, allowing more carefully specified interpretations (Amaral et al., 2003; Prather et al., 2001). These monkeys were also raised in a natural environment, with their mothers and peers, as opposed to more isolated single-cage rearing, which by itself might be expected to influence social behavior. This area is clearly very important and more studies, with larger samples, are now needed to clarify the effects of early amgydala damage.

Interest in the amygdala also stems from its role in perceptual processing of social stimuli (Adolphs, Tranel, & Damasio, 1998; Castelli et al., 2000; Schultz et al., 2003). Several studies have now found hypoactivation of the amygdala in autism during tasks involving the perception of facial expressions and during theory of mind (ToM) type tasks (Baron-Cohen et al., 1999; Castelli, Frith, Happe, & Frith, 2002; Critchley et al., 2000; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001). New data suggest that the amygdala's role in these social cognitive and perceptual processes might largely be one of mediating physiological arousal (e.g., Anderson & Sobel, 2003). Thus, hypoactivation of the amygdala in autism may reflect nonspecific tasks effects, i.e., less interest in or emotional arousal by task stimuli. This view provides good support for social motivation hypotheses of autism pathobiology (e.g., Dawson et al., 1998; Klin et al., 2003). MRI studies of amygdala volume, on the other hand, have produced many conflicting results (for a review, see Sweeten et al., 2002). Although less extensively studied, no clear picture of the hippocampal morphology has emerged (Aylward et al., 1999; Piven et al., 1998; Saitoh et al., 2001).

Functional imaging studies have also begun to highlight the role of several specific cortical areas in the pathobiology of autism. The older resting blood flow literature found global hypoactivation of frontal

and temporal areas (e.g., for a recent review see Boddaert & Zilbovicius, 2002). Newer activation studies with fMRI are highlighting discrete cortical regions that might be impaired in autism. One basal temporal lobe region along the lateral aspect of the fusiform gyrus is more engaged by human faces than any other category of image (Kanwisher, McDermott, & Chun, 1997). Given the known face recognition deficits in autism (reviewed in Grelotti et al., 2002), several groups have now used face perception tasks to evaluate this so-called fusiform face area (FFA). Three independent labs have now published data showing that the FFA is hypoactive in autism (Critchley et al., 2000; Pierce et al., 2001; Schultz et al., 2000a). Moreover, unlike other brain markers of autism pathobiology, degree of hypoactivation in the FFA appears to be strongly correlated to degree of social disability (Schultz et al., 2001). These data and related work showing that the FFA is also engaged by ToM type tasks (Castelli et al., 2000; Martin & Weisberg, 2003; Schultz et al., 2003) suggest that the FFA region is one of the more important cortical areas in the pathobiology of autism.

Aside from the FFA and amygdala, other key nodes in the emerging model of the social brain include orbital and medial prefrontal cortices and posterior aspects of the superior temporal sulci (STS) and adjacent cortex. The STS is involved in perception of dynamic social signals, such as facial expressions, social gestures, and interpretation of direction of eye gaze (Allison, Puce, & McCarthy, 2000; Schultz et al., 2003). The dorsomedial prefrontal cortex (PFC), on the other hand, appears critical for 'social cognition', i.e., for thinking about others' thoughts, feelings, and intentions (Castelli et al., 2000; Schultz et al., 2003). In addition, the ventromedial prefrontal cortex has been implicated in processing normal affects (Lane, Reiman, & Ahern, 1997). These medial PFCs have dense reciprocal connections with medial temporal areas, forming a system for regulating social-emotional processes (Carmichael & Price, 1995). Function of prefrontal cortices seems to be disturbed in persons with autism spectrum conditions. A PET study, for instance, reported reduced dopaminergic activity in the medial prefrontal cortex of autistic subjects (Ernst, Zametkin, Matochik, Pascualvaca, & Cohen, 1997). Reduced glucose metabolism has also been reported in a subdivision of the anterior cingulate gyrus in persons with autism engaged in a verbal memory task (Haznedar et al., 2000). A small PET study of Asperger's syndrome using a ToM task showed specific engagement of the medial PFC, except that the center of activation was displaced below and anterior in patients compared with controls (Happé et al., 1996). More recently, Castelli et al. (2002) showed reduced dorsomedial PFC activation in ASDs during a social ToM task. The dorsal lateral prefrontal cortex is critical for working memory and executive functioning. One recent fMRI study found decreased task-related activity in this region (Luna et al., 2002). In addition to these localized findings, other data call attention to the possibility that functions may be less consistently localized to specific regions across any sample of persons with autism (Pierce et al., 2001; Muller, Pierce, Ambrose, Allen, & Courchesne, 2001).

The cerebellum has been perhaps the most active area of study during the past 14 years. Postmortem neuropathology studies have revealed very consistent reductions in the number of Purkinje neurons and in the cerebellum (Bauman, 1996; Kemper & Bauman, 1998). The precise nature of these abnormalities, including a lack of gliosis, suggests a prenatal origin. Although classical neuropsychological models see the cerebellum as strictly a motor system, some evidence finds a role for it in cognition, sensation and attention (Allen, Buxton, Wong, & Courchesne, 1997; Schmahmann & Sherman, 1998), especially as it participates as part of larger cerebellar-cortical systems. In autism, dysfunction of cerebellar-cortical serotonergic pathways has been noted (Chugani et al., 1997), and fMRI evidence implicates the cerbellum in attention difficulties seen in autism (Allen & Courchesne, 2003). Structural MRI studies have usually found the cerebellum to be enlarged in autism, but this enlargement appears proportional to overall brain enlargement (Courchesne et al., 2001; Herbert et al., 2003; Piven et al., 1997; Sparks et al., 2002). Morphology of the cerebellar vermis has been the focus of many MRI studies, with some studies reporting evidence of hypoplasia of the vermian lobules VI and VII (Ciesielskia, Harris, Hart, & Pabst, 1997; Courchesne et al., 1988, 1994a, b; 2001; Hashimoto et al., 1993, 1995). Other studies, however, have failed to replicate these findings (Filipek, 1995; Hardan, Minshew, Harenski, & Keshavan, 2001; Holttum, Minshew, Sanders, & Phillips, 1992; Kleinman, Neff, & Rosman, 1992; Levitt et al., 1999; Manes et al., 1999; Piven et al., 1992, 1997). One issue here seems to be the level of impairment of the participants and the control groups, with hypoplasia of the neocerebellar vermis being more common among those with mental retardation and autism, but not higher-functioning autism (Piven et al., 1992, 1997; Filipek, 1995; Levitt et al., 1999; Manes et al., 1999).

Various neurochemical systems are of interest in autism. Without a doubt the most replicated finding has been that of high peripheral serotonin levels in about a third of children with autism (Anderson & Hoshiono, 1997). The significance of this finding remains somewhat unclear, although studies of basic genetic mechanisms may help to clarify its significance (Veenstra-VanderWeele et al., 2002). Dopaminergic systems are of interest given the role of dopamine in movement problems and of dopamine-blocking agents in the treatment of autism (Anderson & Hoshino, 1997), but results of studies of both dopaminergic and catecholaminergic systems in autism have not yet produced consistent

results. The endogenous opioid system was of interest as part of the hypothesis that abnormalities in this system might account for certain maladaptive behaviors in autism such as self-injury (Gillberg, 1995), while early reports suggested the potential effectiveness of the opiate antagonists in the treatment of self-injury. Subsequent, controlled, research has been much less positive in treatment of autistic children; while early case reports were positive, subsequent controlled studies have been much less so (Buitellaar et al., 1998).

Genetic influences in autism

Over the past 10–15 years the focus of genetic research into autism spectrum disorders has shifted from establishing the strength of specific genetic influences and clarifying the range of phenotypic expression (reviewed by Bailey, Palferman, Heavey, & Le Couteur, 1998; Szatmari, Jones, Zwaigenbaum, & MacLean, 1998; Folstein & Rosen-Sheidley, 2001) to systematic attempts to identify susceptibility loci. This changed emphasis has been prompted both by the general acceptance of the role of genetic factors and by technological developments that have enabled the molecular investigation of complex genetic diseases. The current high priority given to the identification of susceptibility alleles for ASDs arises for several reasons. First, together, epidemiological, twin and family data suggest that the vast majority of cases of ASD arise on the basis of a complex genetic predisposition, perhaps involving interactions between as few as 3–4 susceptibility loci, although the involvement of as many as 10 loci cannot be discounted (Pickles et al., 1995). Secondly, identifying susceptibility alleles and the proteins they encode will provide clues to the biochemical and pathophysiological processes underlying ASDs. Thirdly, knowledge about the relevant neurobiological mechanisms (and their timing during development) should optimize the search for any environmental factors influencing phenotypic expression, which otherwise might be hard to identify. Fourthly, identifying susceptibility loci will enable genetic counseling to be based on knowledge of individuals' genotypes, rather than group-based recurrence estimates (typically of the order of 5–6% for an ASD); nevertheless, genotype information alone may be insufficient to predict phenotypic severity. Lastly, advances in the molecular biology of ASDs seems likely to be relevant to a greater understanding of related behaviorial/personality traits and developmental psychopathology more generally.

Given the importance of the endeavor, what approaches are currently being used to identify susceptibility genes? When there is already knowledge about the pathophysiological processes underlying a disease, it is possible to analyse those genes encoding proteins involved in the relevant neurobiological pathways: a functional candidate gene approach. The strategy can involve identifying alleles (versions) of a gene that occur at significantly different frequencies in samples of affected and control individuals, whereas family-based association designs, such as the Transmission Disequilibrium Test (TDT), use the frequencies of parental alleles that are not transmitted to affected offspring as internal controls. Alternatively, candidate genes may be screened for novel mutations not found in a control population. Because of limited knowledge about the relevant neurobiology and the lack of specific drug effects, there have been few true functional candidate gene studies of ASD. Most attention has focused on the serotonergic system and several groups have examined allelic variation in the promoter of the serotonin transporter gene (5-HTT), but the data remain contradictory (Cook et al., 1997a; IMGSAC, 1998; Kim et al., 2002), while studies of various serotonin receptor genes are also equivocal (reviewed by Lamb, Moore, Bailey, & Monaco, 2000). Studies of the HOX genes (Ingram et al., 2000; Li et al., 2002), tuberous sclerosis type 2 (TSC2) gene (Brandt et al., 2002), neurofibromatosis type 1 gene (Mbarek et al., 1999; Plank et al., 2001), adenosine deaminase (Persico et al., 2000a,b; Bottini et al., 2001), and others have also produced inconsistent results.

Another strategy is to test positional candidate genes: brain-expressed genes that are potentially implicated in idiopathic cases because of their proximity to chromosomal abnormalities associated with autistic spectrum disorders (reviewed by Gillberg, 1998). The most common association is with interstitial duplications or a supernumerary pseudodicentric chromosome 15 (inv-dup[15]) (Rineer, Finucane, & Simon, 1998; Buoni et al., 2000; Wolpert, Pericak-Vance, Abramson, Wright, & Cuccaro, 2000). These individuals with ASD usually also have mental retardation and seizures and when parental origin has been investigated, all of the 15q interstitial duplications have been derived from the mother (Cook et al., 1997b; Repetto, White, Bader, Johnson, & Knoll, 1998; Schroer et al., 1998), raising the possibility of imprinting effects. The GABAA receptor gene cluster – containing several genes of interest – lies in this region and remains of interest, although the evidence for association remains contradictory (Cook et al., 1998; IMGSAC, 1998). There have also been reports of autistic features in females showing whole or partial deletion of one X chromosome (Skuse et al., 1997; Thomas et al., 1999; Donnelly et al., 2000), with claims (Skuse et al., 1997) that these are most obvious in individuals with a single maternally derived X chromosome, suggesting that there may be a maternally imprinted locus for social cognition that is expressed only by the paternal X chromosome. Skuse (2000) suggests that the protective locus explains the higher threshold for

phenotypic expression in females than in males, and the higher incidence of autism in males; an interesting hypothesis that awaits independent verification.

Although some groups are engaged in functional and positional candidate gene analysis, most effort has been expended on linkage approaches that make no prior assumptions about gene function or position. Because the mode of inheritance of autism is not known and extended pedigrees of affected individuals are not available, most researchers have used linkage methods that rely on determining allele sharing between two or more affected individuals in large numbers of nuclear multiplex families. The goal is to identify markers at which affected pairs of individuals share alleles more often than expected by chance, indicating that the marker may be linked to a susceptibility gene (see Turner, Barnby, & Bailey, 2000 for a more detailed explanation).

To date, 8 genome screens for autism susceptibility loci in affected relative pair families have been published, identifying several chromosomal regions of interest (IMGSAC, 1998; Barrett et al., 1999; Philippe et al., 1999; Risch et al., 1999; Auranen et al., 2002; Buxbaum et al., 2001; IMGSAC, 2001b; Liu et al., 2001; Pericak-Vance et al., 2001; Shao et al., 2002). The results have been reviewed in detail (see Lamb, Moore, Bailey, & Monaco, 2000; Gutknecht, 2001, Lamb, Parr, Bailey, & Monaco, 2002). The first identified susceptibility region in 7q21–q32 (designated AUTS1 OMIM #209850; IMGSAC, 1998) has been supported by the addition of further families (IMGSAC, 2001a) and has subsequently shown possible evidence of linkage in three other independent multiplex samples (Shao et al., 2002; CLSA, 1999; Philippe et al., 1999) and in a meta-analysis (Badner & Gershon, 2002). The enlarged study by the International Molecular Genetic Study of Autism Consortium (IMGSAC) identified three other loci on chromosomes 2,16 and 17 with a multipoint maximum LOD score (MLS) greater than 2 (IMGSAC, 2001b). The locus on chromosome 2q with a multipoint MLS of 3.74 at marker D2S2188 reached genome-wide significance, and has also possibly been identified by Buxbaum et al. (2001) and by Shao et al. (2002). Other studies have also identified additional regions suggestive of linkage on chromosome 6 (Philippe et al., 1999), chromosome 13 (Barrett et al., 1999), chromosome 1 (Risch et al., 1999), chromosomes 5, 19 and X (Liu et al., 2001), chromosomes 3 and X (Pericak-Vance et al., 2001; Shao et al., 2002) and chromosomes 1,4 and X (Auranen et al., 2001).

Once regions of suggestive linkage have been identified, it is then possible to test plausible functional candidate genes in the region. Claims have been made for the involvement of WNT2 (Wassink et al., 2001) and reelin (Persico et al., 2001) in the susceptibility region on chromosome 7, but currently the possible involvement of reelin remains unclear (Bonora et al., in press). The susceptibility region also contains the forkhead domain gene FOXP2, which is implicated in a family with a severe speech and language disorder (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001), but there is no evidence so far that this gene is also implicated in susceptibility to ASDs (Newbury et al., 2002).

Treatment and intervention

Psychosocial and educational interventions

By far the most commonly studied treatment, both in terms of specific interventions and comprehensive programs, has been Applied Behavior Analysis (ABA) (Smith, Groen, & Wynn, 2000). However, the past five years have yielded both a 'practical consensus' (Dunlap, 1999) and a formal consensus from the National Academy of Science in the USA (NRC, 2001) that no single approach is the best for all individuals or even across time for the same individual with ASD. Greater recognition of the interplay between different treatments, such as use of social stories and written cues (Thiemann & Goldstein, 2001) and/or modifications or expansions of behavioral treatments, such as incidental teaching (McGee, Morrier, & Daly, 1999) or Pivotal Response Intervention (Koegel, Koegel, Harrower, & Carter, 1999) and the TEACCH (Treatment and Education of Children and Adults with Communication Handicaps: Ozonoff & Cathcart, 1998) program may portend the end of the divisiveness in treatment advocacy that affected educational and parents' groups throughout the 1990s. Treatment research for children and adults with autistic spectrum disorders tends to be inspired by various psychological models, i.e., rather than focusing primarily on empirical work on current treatments. There have been emerging attempts to treat 'core' deficits of ASD (Kasari, 2002; Baron-Cohen & Howlin, 1994), and children's response to treatment has contributed to some neuropsychological models, such as Mundy's conception of neuroplasticity (Mundy, 2003).

Besides a study by Jocelyn and colleagues (1998) that looked at the effects of a caregiver-based program for children with autism in community daycare centers, the first randomized control trial of ABA was published in 2000, by Smith, Groen, and Wynn. It compared two groups of 15 children who were randomly assigned either to a year of 24 hours a week of ABA carried out by skilled therapists plus follow-up, or 3–9 months of parent training several hours a week. The children who received ABA made greater gains than the children in the parent training control group, but none changed diagnosis and the gains were not as dramatic as those reported in the Lovaas (1987) paper. Children with PDD-NOS and higher IQs at entry made greater gains than children with autism diagnoses.

A second study comparing two groups of children in a specialized school, without randomization but using a control group, compared children who received 29 hours a week of skilled IBT (Individualized Behavior Treatment) and consultation to children who received eclectic therapy, in which teachers received substantially less training and support, for an equal number of total hours (Eikeseth, Smith, Jahr, & Eldevik, 2002). The children were 4 to 7 years old. Children who received IBT made significantly greater gains than the children who did not. Thus, while age at the start of treatment may be a factor (Harris & Handleman, 2000), response to behavioral treatment is not limited to very young preschool children.

Drew and colleagues (Drew et al., 2002) also reported on a pilot randomized control trial of a parent training intervention for preschool children with autism. They compared 24 children identified at around 24 months by the CHAT, randomly assigned to a parent training group and a local services control group. Children were followed up a year later. These authors highlighted the methodological complexities of carrying out an RCT on a small group of children with a wide range of skills. The intervention focused on parent training to elicit social pragmatic skills, including joint attention and engagement. The parent training group made more progress in some measures of language development than the local services group, though major methodological challenges were highlighted. These included nonmatching of the groups on initial IQ, lack of fidelity measures, reliance on parent report for outcome and the decision by parents of 3 out of 12 children in the local services group to seek home-based intervention that was more intensive than what the parent training group was receiving.

Several studies have looked at measures related to the effectiveness of comprehensive treatment programs, particularly ABA or EIBI (Early Individualized Behavioral Intervention) (terms used interchangeably here). Sustaining the originally proposed 40 hours a week (see Lovaas, 1987) has been difficult in many cases, with Smith and colleagues' (Smith, Buch, & Gaamby, 2000) participants receiving an average of 24 hours a week and the families in home-based behavioral interventions in the Drew et al. study averaging 33 hours a week (Drew et al., 2002). Smith and Antolovich (2000) reported that families participated in an average of seven additional treatments, most commonly speech therapy, sensory integration, multivitamins and elimination diets. In one survey of families managing their own ABA programs in Surrey, Mudford and colleagues (Mudford, Martin, Eikeseth, & Bibby, 2001) found that none of 75 children in behavioral treatment met the criteria defined in Lovaas' original study in terms of age, IQ, or level of skill of therapist. Another study of parent-managed behavioral interventions for 66 children reported that no gains in IQ were observed and no child functioned unassisted in a mainstream program beyond 6 years of age (Bibby, Eikeseth, Martin, Mudford, & Reeves, 2001). Several research groups found that parent satisfaction with ABA programs was very high, even though the studies were not able to replicate the amount of progress previously reported (Bibby, Eikeseth, Martin, Mudford, & Reeves, 2002; Boyd & Corley, 2001; Smith et al., 2000) in modified versions of behavioral interventions. In one study of parent-directed treatment, parents were given six 1-day workshops and then consultation. Five out of six children rapidly acquired new skills, and all parents reported high satisfaction, but only two out of six children showed significant gains in standard test scores two or three years later.

Awareness of this variability in effectiveness has resulted in increasing interest in factors that lead to successful treatment, and in defining the parameters of successful treatment of a child or adult with ASD (Howlin, 1998). In the past, outcomes were often defined by IQ or placement or by changes in very specific behaviors (Smith et al., 2000; Siller & Sigman, 2002). Several recent authors, including Rogers (2000) and Wolery and Garfinkle (2002), have argued that the child's engagement in tasks may be the most important feature of intervention, and that this requires attention, not just to the child's interests and skills (Moes, 1998), but also to the family system (Dunlap, 1999; see Lord & McGee, 2001). Pivotal Response Treatment (Koegel, Koegel, Harrower, & Carter, 1999) emphasizes supporting behaviors that themselves lead to greater engagement. Similarly, several treatments have emphasized teaching joint attention skills (see Charman, 1999; Drew et al., 2002; Kasari, Freeman, & Paparella, 2001; Whalen & Schreibman, 2003). Initial learning rates have been shown to be moderately correlated with treatment outcomes after two years (Weiss, 1999). Studies have also shown that, even with the most ecologically valid treatments, generalization needs to be specifically addressed or it will very rarely happen (Hwang & Hughes, 2000; Strain & Hoyson, 2000).

The reemergence of notions of 'Verbal Behavior' in which the purpose of the communicative behavior is the focus rather than the content also attests to the growing awareness of the need for research to address the appropriateness of goals of treatment and how methods address them, moving beyond evaluating the methods themselves (Sundberg & Michael, 2001). Delprato (2001) reviewed 10 studies of communication interventions and reported that those that encouraged children's initiations and were more loosely structured around everyday situations, with looser contingencies and more natural reinforcements, resulted in greater improvements in language and more positive affect. Siller and Sigman (2002) found that mothers' synchronized attention to toys of interest to their children, accompanied by undemanding statements, predicted language gains years

later. This is similar to the best practice proposed by Wetherby and Prizant (1999). On the other hand, Kok, Kong, and Bernard-Opitz (2002) compared play interventions that structured children's play or facilitated it (without directing it) and found that both strategies were effective, but that more communication occurred by both parties during the more structured play. These different findings support Smith et al. (2000) and the National Research Council committee's (2001) conclusion that number of hours in treatment and training of therapists or teachers are important for progress in any child, but that optimal strategies may be different depending on whether a new behavior is being taught or an existing behavior generalized and whether the focus is on child initiation or response. Flexibility that allows for individual differences in abilities, contexts, and needs is necessary for the success of any approach (Anderson & Romancyzk, 1999).

Interventions emphasizing social skills in children, usually from later preschool through school age and in adolescents and adults, have emerged as a major theme of the treatment literature in the past few years. A number of innovative approaches to peer interactions, including integrated peer groups (Wolfberg & Schuler, 1999), class-wide interventions (Weiss & Harris, 2001) and adult social groups (Howlin & Yates, 1999), have been proposed, as well as continuing discussion of peers as direct agents of behavior change (Strain & Schwartz, 2001). The limitations of full inclusion in a regular classroom without systematic or skilled support for young children with ASDs have also continued to be documented (Gena & Kymissis, 2001). Several authors have combined specific approaches, such as social stories, with other problem-solving, affect training and more interactive methods to achieve positive changes (Bauminger, 2002; Krasny, Williams, Provencal, & Ozonoff, 2003), though with continued warnings that comprehensive programs for social development must include follow-up and multi-site support for maintenance (Strain & Hoyson, 2000). Social stories have also been employed to decrease temper tantrums (Lorimer, Simpson, Myles, & Ganz, 2002).

A number of recent studies have used videotapes to help children and adults acquire or use social behaviors in everyday contexts, such as within complex play schemes (D'Ateno, Mangiapenello, & Taylor, 2003), transitions (Schreibman, Whalen, & Stahmer, 2000), and play with siblings (Taylor, Levin, & Jasper, 1999). Procedures that involve both the child viewing himself and viewing other people were shown to be effective (Sherer et al., 2001). Attempts to teach 'theory of mind' successfully improved children's ability to do tasks within the teaching environment, but did not generalize (Howlin, Baron-Cohen, & Hadwin, 1999).

Overall, research continues to amass information about specific strategies determined to be effective primarily through single subject designs, often replicated across several other study participants. There is a tremendous amount of information about different techniques that have successfully changed the behavior of children and adults with ASDs. Developmental and behavioral therapies, as well as specific techniques, appear to be becoming increasingly integrated; however, randomized controlled studies comparing alternative treatments are nonexistent and few studies addressed the most important issues of treatment as defined by parents, educational systems, or scientific review panels (see Lord & McGee, 2001, and Howlin, 1998). Few studies have addressed interventions in public schools, which are the major sources of intervention in almost all countries; psychosocial treatment studies of adolescents and adults are also few and far between (see Howlin & Yates, 1999; Van Bourgondien, Reichle, & Schopler, 2003 for exceptions). There is a clear need to begin to integrate findings from single subject to group designs and to address questions of mechanisms, moderators and individual differences in response to different interventions (Paul, 2003).

Pharmacological treatments

Pharmacological treatment of children, adolescents, and adults is common in clinical practice but empirical research, particularly well-designed, placebo-controlled studies, have been uncommon – especially for children (Martin, Scahill, Klin, & Volkmar, 1999). Although in no sense curative, such intervention may be of great benefit to children with autism and their families both directly, relative to symptom reduction, and indirectly, in helping the child profit from behavioral and educational interventions (Volkmar, 2001). Unfortunately, clinical trials have tended, with some important exceptions, to include small numbers of subjects who are often not well characterized; given the difficulties of study design and completion, it is not surprising that few studies are well replicated.

Over the past decade there has been a shift in interest from the first-generation neuroleptics to the newer, atypical, neuroleptics as well as to the use of the serotonin-blocking agents. Until recently, the most extensive body of well-conducted pharmacological research in autism was that of Campbell and colleagues (see Campbell & Cueva, 1995), which evaluated a range of agents but with a special focus on neuroleptics. The latter agents were shown, in a series of studies, to have positive benefits in terms of lower levels of stereotyped and other problematic behaviors and increased engagement. Unfortunately, side effects, such as sedation, withdrawal, and tardive dyskinesia, limited the usefulness of these agents (Campbell et al., 1997).

The advent of atypical neuroleptics, and the promise of more favorable side-effect profiles, generated considerable interest and these agents have

now largely replaced the use of first-generation neuroleptics in this population. Typical target symptoms for treatment include self-injury, severe agitation or stereotyped movements, self-injury, and severe behavior problems (McDougle et al., 2000). Advantages of these agents include the decreased risk of extra pyramidal side effects and presumably the risk for tardive dyskinesia. Some investigators have also speculated that an additional potential benefit may be improvement in social withdrawal, i.e., similar to the improvement in the 'negative' core symptoms of schizophrenia. Although various of these newer atypical neuroleptics have been studied in the treatment of autism, the most extensive body of work has developed on risperidone; case series, open-label trials, and, more recently, well-designed double-blind, placebo-controlled trials in individuals with autism have documented significant benefits (McDougle et al., 2000).

The US Research Units in Pediatric Psychopharmacology (RUPP) Autism Network completed (RUPP, 2002) a large, multi-site trial of the short- and long-term safety and efficacy of risperidone in a group of over 100 children and adolescents with autism. The first phase of the study included an eight-week, randomized, double-blind trial of placebo vs. risperidone; outcome measurers included the Aberrant Behavior Checklist (ABC) and Clinical Global Impression (CGI) scale (Aman & Singh, 1986). The mean dose of risperidone was 2.0 mg per day (divided doses) and was associated with a significant reduction in irritability scale of the ABC, with nearly 70% of cases being rated as much or very much improved on the CGI (as opposed to 12% on placebo). The most significant side effect was weight gain (average of 2.7 kg vs. .8 kg for the placebo group). Other side effects included drowsiness, fatigue, tremor, and drooling but these were generally transient and mild to moderate in severity. Placebo nonresponders were treated openly with Risperidone and could then join the second-phase, 4-month open-label extension of the study. The benefits of Risperidone were sustained at a stable dose. In the final, third phase of the study subjects were randomly assigned to continue the active agent or to gradual withdrawal to placebo. The relapse rate was significantly greater in the placebo group, although the authors also noted that a significant proportion of subjects who withdrew to placebo did not relapse (suggesting that some children could be safely withdrawn from the agent). Several aspects of this study are noteworthy. The magnitude of the treatment effect was large, indeed larger than previous responses to first-generation neuroleptics, but with significantly fewer side effects. In this study there were no major effects on adaptive skills, although it is possible that the addition of a behavioral component would further increase the benefit of this agent. The study represents an important advance in evaluation of drug treatments for autism, i.e., its use of a multi-site protocol (with careful attention to aspects of site consistency), careful design and subject assessment.

The serotonin reuptake inhibitors (SRIs) are of interest given both the observation of high peripheral serotonin levels in autism and the observation that these agents may be helpful with many of the repetitive behaviors reminiscent of obsessive compulsive disorder (McDougle, 1997). Clomipramine, a tricyclic antidepressant, inhibits the reuptake of both norepinephrine and serotonin, while the other agents in this group are more selective for serotonin. Although not yet extensively studied, these agents have commonly been used for treatment of behavioral difficulties in autism, particularly for difficulties with repetitive behaviors, stereotyped mannerisms, and difficulties with anxiety and dealing with change (Martin et al., 1999). Unfortunately, most of the available data on the use of these agents is based on small samples with variable characterization and sometimes poorly defined target symptoms. In one early study of 7 individuals, Gordon, Rapoport, Hamburger, State, and Mannheim (1992) reported that clomipramie was superior to desipramine in reducing stereotyped and repetitive behaviors; in a second double-blind crossover study clomipramine was compared to desipramine and to placebo (Gordon, State, Nelson, Hamburger, & Rapoport, 1993) and clomipramine was superior to both placebo and desipramine in reducing repetitive ('obsessive like') behaviors. In this relatively small sample some adverse effects were noted, with ECG changes noted and one individual suffering a seizure. Other studies have similarly shown some benefit in small groups of individuals (Brodkin, McDougle, Naylor, Cohen, & Price, 1997; Garber et al., 1992; McDougle et al., 1992), although one study of prepubertal children showed general poor response (Sanchez et al., 1996). Cook, Rowlett, Jaselskis, and Leventhal (1992) conducted an open-label study of fluoxetine in 23 individuals with autism (children to adults) and noted that over half the patients responded – this was particularly true for older subjects. The issue of potential developmental changes in drug efficacy remains an open one. In a study of prepubertal children, DeLong, Teague, and McSwain Kamran (1998) reported improvement in a substantial number of cases treated with fluoxetine; unfortunately, the sample was not well described and the dose was not reported. Some of the nonresponders did exhibit behavioral activation. Double-blind, placebo-controlled studies of small samples of adults with autism using fluvoxamine have also noted improvement in many instances, particularly relative to reduced levels of compulsive behavior and aggression (McDougle et al., 1996). Martin, Koenig, Anderson, and Scahill (2003) have completed a pilot study of age-related differences in response to fluvoxamine and found that the potential for untoward side effects (particularly behavioral activation) could be

minimized by use of a low initial dose with gradual increases; therapeutic response was, however, inconsistent overall. Although the SSRIs are frequently used in the treatment of individuals with autism and related conditions, the body of available data is relatively weak. Larger, better designed studies which include subjects with a range of ages and with better characterization and outcome measures are needed.

The utility of various other agents has been studied, although not as intensively or as systematically as either the atypical neuroleptics or SSRIs. The symptoms of overactivity and inattention commonly seen in children with autism spectrum disorders suggest to many clinicians the potential usefulness of stimulant medications. In the past, the impression, particularly for more children with more 'classical' autism, was that stimulants could result in behavioral activation, increased stereotyped movements, or tics; data to address this issue are relatively sparse, although there is some suggestion that higher-functioning children may be more likely to respond positively (Aman, Buican, & Arnold, 2003; Handen, Johnson, & Lubetsky, 2000). Other agents studied have included anticonvulsants (used as mood stabilizers) and naltrexone. Studies of the mood stabilizers are quite limited, although one recent study showed no benefit of lamotrigine relative to placebo (Belsito, Law, Kirk, Landa, & Zimmerman, 2001); additional concerns have to do with the potential for serious side effects (Messenheimer, 1998). Initial open-label studies of naltrexone were promising (e.g., Panksepp & Lensing, 1991; Campbell et al., 1989); unfortunately, placebo-controlled studies have been disappointing (Campbell et al., 1993; Kolmen, Feldman, Handen, & Janosky, 1997), with some, modest, effects seen only on levels of hyperactivity.

Although alternative (non-established) treatments are generally outside the scope of this review, it is worth noting the considerable attention that one putative pharmacological treatment received. In a small, uncontrolled study Horvath and colleagues (1998) reported improvement in three children with autism spectrum disorder who were administered the gut hormone secretin (a substance used to stimulate pancreaticobiliary secretion). Coverage of this paper in the national print and television media in the USA and anecdotal claims for improvement prompted a flurry of interest on the part of parents; a black market in this agent developed in the USA as parents scrambled to secure a supply. However, a series of randomized, double-blind, placebo-controlled trials have been remarkably consistent in failing to demonstrate a significant benefit over placebo (e.g., Sandler et al., 1999; Dunn-Geier et al., 2000; Owley et al., 2001; Unis et al., 2002). The major placebo effect repeatedly noted in these studies is, in some respects, the most important finding and underscores the crucial importance of double-blind, randomized, placebo-controlled trials in evaluating potential treatments (Volkmar, 1999).

Important aspects of pharmacotherapy in autism remain to be addressed. For example, Honomichi, Goodlin-Jones, Burnham, Gaylor, and Anders (2002) collected data on the sleeping patterns of 100 children with PDD, using a series of measures. Prior to data collection, over half of parents reported sleep problems in their child; sleep diary and questionnaire data confirmed this impression. Fragmentation of sleep and longer onset of sleep (as compared to community norms) were very frequent. Sleep problems pose major difficulties for the child and his or her family. Unfortunately, the treatment literature (either pharmacological or behavioral) is quite limited, apart from a few reports on the use of melatonin (see Lord, 1998).

Directions for the future

The past decade has witnessed tremendous progress in the field. Advances in diagnosis and assessment have been central to facilitating work on the genetics of autism and other neurobiological processes. Increasingly, studies have focused on bringing together work from diverse areas, e.g., psychological and brain mechanisms and the social deficit of autism, the broader phenotype of autism and core aspects of the disorder. Another positive development has been the increasing number of collaborative studies – on diagnosis, genetics, psychopharmacology, treatment, and even neuroimaging. Official and semi-official guidelines have now appeared in which empirical research has been used to document effective methods of diagnosis and treatment (Volkmar et al., 1999; Filipek et al., 2000; National Research Council, 2001). The support of parent groups for research has been critical in this effort. Despite these accomplishments, however, much is left to do. In closing, we wish to highlight some of the issues which seem to us the most critical for the future.

Studies of early development

The early onset of autism and the evidence showing the considerable benefits of early intervention highlight the need for prospective studies (from birth or earlier) of high-risk populations (e.g., siblings, children in affected families). These studies are likely to shed light on the emergence and natural course of the condition, to clarify issues related to regression phenomena, and to make possible models of the effects of autism on a wide range of pertinent developmental processes. At both the behavioral and brain levels, developmental processes are highly interrelated and synergistic. Behavioral and brain organization reflects both predisposing disabilities and the effect of profoundly atypical experiences of the environment. Longitudinal follow-up studies of

children seen from birth are likely to help us disentangle what leads to early-onset social disabilities from the effects of having such disabilities. This is critical information for studies focusing of what is inheritable in autism, and for interpretation of functional neuroimaging findings.

Focus on processes

Individuals with autism not only fail to acquire important skills; they also acquire a very distinct learning style. There is evidence that they learn differently, likely compensating, to some degree, for their deficits. Cross-sectional studies focusing on results, therefore, may miss the all-important processes used to achieve a given result. The gaps between performance on explicit tasks and real-life adaptation, and between circumscribed learning and generalization, thus set the goal for improved methods that will both simulate the everyday challenges of individuals with autism, and capture the atypical ways in which they try to meet these challenges. In other words, the characterization of compensatory strategies can be as enlightening (and practically beneficial) as findings on the breakdown of normative processes. Equally important is the need to evaluate hypotheses of this breakdown relative to outcomes in a quantified manner, so as to delineate what are the critical dimensions creating the spectrum and broader forms of autism-related disorders.

Integrating research

Autism has been studied through different disciplines, conceptual and technical tools, and levels of gene–brain–behavior analysis. Although integration of research is still in its infancy, the benefits of this effort are considerable. A new, fully integrated social neuroscience of autism will entail not only cross-disciplinary fertilization but also helpful mutual constraints and demands. While experimental psychology and functional neuroimaging are spearheading this trend, new findings in one area (e.g., the hypothesis of postnatal accelerated brain growth) pose challenges to other areas (e.g., the need for a developmental psychopathology model of the behavioral and brain organization patterns in the first two years of life). These connections will be critical for the field to derive full benefits from isolated breakthroughs. An example might be the possible relationship between the recently reported mutations of the X-linked genes associated with synaptogenesis (Jamain et al., 2003) and accelerated brain growth in infants with autism (Courchesne et al., 2003).

Diagnostic issues

Although considerable advances in diagnosis have been made, research is still needed in a number of areas. These include better methods for early diagnosis, involving approaches based on symptom characterization and on the description and operationalization of specific psychological and neurobiological processes that may precede the onset of symptoms. Nosologic issues related to the boundaries and validity of different diagnostic categories of the PDDs, particularly Asperger's disorder and PDD-NOS, are far from resolved. As most studies to date are cross-sectional, there is a great need for longitudinal follow-up studies of infants, as these are likely to shed light on the factors that may result in different profiles later in life. Findings may indicate the need for modification of diagnostic categories (merging them on the basis of identified dimensions), or, equally possible, they may indicate the need for further separation of the categories (on the basis that similar outcomes originate from different developmental processes). Clearly, nosology serves a number of roles (e.g., eligibility for services, creating more homogeneous groups for neurobiological studies), and different classifications may have to be adopted for different purposes. It is critical, however, that in the absence of consensual evidence and definitions, an effort is made to provide as much standardized information about participating subjects as is necessary for replication studies (with a very similar population) to take place.

For the very rare condition of CDD it will be important to develop registries and/or collaborative, multi-site projects in an effort to identify etiological mechanisms. Efforts to more fully understand the broader phenotype of autism and related conditions, as well as comorbid symptomatology contributing to social difficulties in autism-related disorders, will have to include the attempt to better specify the relationship of PDD-NOS to other conditions and to autism.

Treatment studies

Treatment studies are both the most important and also the most difficult to conduct (and fund). The recent National Academy of Science review (2001) underscores these issues. A number of innovative behavioral and educational interventions have been developed, but often solid data on efficacy and cost-effectiveness are lacking. A major concern is the large, and possible growing, gap between what science can show is effective, on the one hand, and what treatments parents actually pursue. Another concern is the extent to which the full benefit of scientific research is translated into best practices in actual classroom settings.

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