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Three Diagnostic Approaches to Asperger Syndrome: Implications for Research

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Objective: To examine the implications for research of the use of three alternative definitions for Asperger syndrome (AS). Differences across the three nosologic systems were examined in terms of diagnostic assignment, IQ profiles, comorbid symptoms, and familial aggregation of social and other psychiatric symptoms. *Method*: Standard data on diagnosis, intellectual functioning, comorbidity patterns, and family history were obtained on 65 individuals screened for a very high probability of having autism without mental retardation (or higher functioning autism, HFA) or AS. Diagnoses of AS were established based on three different approaches: DSM-IV, presence/absence of communicative phrase speech by 3 years, and a system designed to highlight prototypical features of AS. *Results*: Agreement between the three diagnostic systems was poor. AS could be differentiated from HFA (but not from PDD-NOS) on the basis of IQ profiles in two of the three systems. Differences in patterns of comorbid symptomatology were obtained in two of the three systems, although differences were primarily driven by the PDD-NOS category. Only one of the approaches yielded differences relative to aggregation of the "broader phenotype" in family members. *Conclusions*: Diagnostic assignments of AS based on three commonly used approaches have low agreement and lead to different results in comparisons of IQ profiles, patterns of comorbidity, and familial aggregation of psychiatric symptoms across the approach-specific resultant groups of HFA, AS, and PDD-NOS.

KEY WORDS: Asperger syndrome; autism; diagnosis.

INTRODUCTION

Asperger syndrome (AS) was described over 50 years ago (Asperger, 1944) but was not officially recognized in the DSM system until DSM-IV (APA, 1994) where it was included as one of the pervasive developmental disorders (PDD). Inclusion in the DSM-IV followed limited evidence that it could be differentiated from autism unaccompanied by mental retardation, or higher functioning autism (HFA) (Volkmar *et al*., 1994). Its nosological status remains unclear, in part due to the adoption of varying diagnostic schemes in the research literature (Volkmar & Klin, 2000) and what appear to be significant limitations of the current DSM-IV definition (Miller and Ozonoff, 1997). Although the advent of the DSM-IV definition was intended to create a consensual diagnostic starting point for research, it has been consistently criticized as overly narrow (Eisenmajer *et al*., 1996; Szatmari, Archer, Fisman, Streiner, & Wilson, 1995), rendering the diagnostic assignment of AS improbable or even "virtually impossible" (Mayes,Calhoun, & Crites, 2001; Miller & Ozonoff, 2000).

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The introduction of AS in DSM-IV and ICD-10 (WHO, 1992) was prompted by the recognition that autism is a clinically heterogeneous disorder and that the characterization of subtypes of PDD/autism spectrum disorder might help behavioral and biological research by allowing the identification of clinically more homogeneous groups (Bailey, Palferman, Heavy, & Le couteur, 1998; Rutter, 1999; Volkmar, Klin, & Cohen, 1997). An awareness of the large number of individuals with serious social disability who did not meet strict criteria for autism was a further concern. For some disorders like Rett syndrome (Gura, 1999) this approach has already been productive in terms of neurobiological research; this has not yet been the case in AS. Published reports have modified DSM-IV or ICD-10 criteria (Klin, Volkomar, Sparrow, Cicchetti, & Rourke 1995; Ozonoff, Rogers, & Pennington, 1991), treated AS and HFA interchangeably (Gillberg, Gillberg, Rastam, & Wentz, 2001; Howlin, 2000), or used unique investigator-defined criteria (Gillberg, 1998), making it difficult to compare studies. Only two studies (Ghaziuddin, Tsai, & Ghazinddin, 1992a; Leekam, Libby, Wing, Gould, & Gillberg, 2000) have systematically compared different diagnostic schemes.

In this paper, we examined the implications for research of using three diagnostic approaches to AS. This study is necessary for several reasons. First, there is a need to gauge the extent to which available research data obtained using different diagnostic systems are comparable. Second, despite the upsurge in research and clinical interest in AS (Klin, Volkmar, & Sparrow, 2000), the absence of a validated definition prevents the development of standardized instrumentation that could enhance reliability of diagnostic assignment and make possible cross-site collaborations that are essential to both behavioral and biological research. Third, there are indications that the DSM-IV definition is being ignored in clinical practice (Mayes, Calhoun, & Crites, 2001), with the term being used as synonymous to HFA or, maybe even more commonly, to PDD-NOS (Volkmar & Klin, 2000), creating a rift between DSM-IV and research and clinical practice, thus confusing and alienating investigators, clinicians, and parents alike. And fourth, the scientifically interesting question as to whether or not there are qualitative discontinuities among the PDDs, or alternatively, whether the PDDs should be considered along a dimensional continuum (and what this dimension should be) is left unresolved without some resolution of the validity of the AS diagnosis.

Diagnostic Approaches

Asperger's (1944) original description emphasized a series of clinical features, including a later onset than is normally reported in autism and normative intelligence. The social disability is marked by a degree of social motivation but difficulty reading nonverbal cues, which in turn is compensated by one-sided verbosity. Verbal content is usually marked by an unrelenting focus on unusual or circumscribed factual topics about which the child learns a great deal. This style of social interaction results in alienation of others, particularly peers. Lack of understanding of social and conversational rules and expectations often lead to behavioral problems and social isolation. Although this profile can be easily distinguished from typical autism (Bosch, 1970; Van Krevelen, 1971), this is not so when compared to the presentation of the 30% (Fombonne, 1999) or so of non-retarded individuals with autism (Klin & Volkmar, 1997). Wing's (1981) influential case series, which effectively introduced the concept of Asperger syndrome to the investigators of autism in the US and UK, de-emphasized some of the more unique features of Asperger's account (relative to Kanner's autism) (1943), resulting in an usage of the term to capture, quite broadly, the more unique profiles of individuals with severe social disabilities despite normative IQ s (Wing, 1986).

The DSM-IV Approach

The DSM-IV approach to the definition of AS has been to adopt the triad of symptom clusters used for the definition of autism, namely qualitative impairments in social interaction and communication, and restricted repetitive and stereotyped patterns of behavior. Symptom requirements in the social and restrictive behaviors cluster are identical for AS as are for autism. In contrast to autism, there is no symptom requirement in the communication cluster, despite the fact that communication difficulties are universally reported in AS (Landa, 2000). In essence, therefore, DSM-IV makes a distinction between autism and AS solely on the basis of the onset criteria. In autism, any concerns prior to the age of 3 years involving social interaction, social communication, or symbolic/imaginative play are sufficient for the criteria to be met. In contrast, any concern involving cognitive development (in essence, typical exploration of and curiosity about the environment given that the majority of children are not developmentally assessed prior to age 3), self-help

skills or more broadly defined adaptive behavior (other than social interaction but including social communication) would rule out the diagnosis of AS. The possibly over-inclusive nature of onset criteria for autism and over-exclusive nature of onset criteria for AS (and any ambiguities left in the definition, e.g., how to distinguish social interaction from social communication) are resolved in terms of the "precedence rule", according to which if an individual meets criteria for autism he or she cannot be assigned the diagnosis of AS (Volkmar & Klin, 2000).

"Speech Delays" Approach

The stringency of the DSM-IV definition has prompted many investigators to modify, or re-define criteria for the diagnostic assignment of autism and AS. The most typical approach has been to divide children with a social disability but apparently normal cognitive development in terms of whether or not there were single words by age 2 years, and phrase speech (typically defined as non-echolalic 3-word combinations used meaningfully for communication) by the age of 3 years (i.e., AS is assigned if a child meets these criteria, and autism is assigned if the child does not) (Gilchrist *et al*., 2001; Szatmari 1995, 2000).

Although this approach allows for important research (e.g., on developmental paths and outcome) to be conducted on higher functioning individuals with PDDs on the basis of presence/absence of speech delays and non-echolalic phrase speech before the age of 3 years, it greatly narrows the potential lines of distinction between autism and AS in that other aspects of onset as well as any unique features in current presentation are disregarded (Volkmar & Klin, 2000). In essence, given that individuals with HFA may not present with speech delays as defined here, there is a potential for the resultant samples (of individuals with HFA and AS) to overlap considerably in terms of other symptomatology, thus increasing the potential for type II errors (i.e., not finding differences) in research studies of HFA and AS using this diagnostic scheme.

New System

In this paper another diagnostic approach is proposed in which the more unique features of AS described by Asperger (1944) (see also Hippler and Klicpera, 2003; Volkmar & Klin, 2000) are emphasized. These features are in the narrative text accompanying the ICD-10 (WHO, 1992) and DSM-IV TR edition (APA, 2000) definitions but are not included as essential defining criteria. In this approach, onset criteria are given in more detail. For example, in regards to onset, distinctions are made between children who isolate themselves (more typical of autism) and those who seek others, sometimes incessantly, but in a socially insensitive manner (more typical of AS); between children whose language is delayed, echolalic, or otherwise stereotyped(more typical of autism) and those whose language is adequate or even precocious, and whose difficulties in this area are constrained to the communicative use of language (i.e., pragmatics) (more typical of AS). The greater detail added in this diagnostic scheme is meant to facilitate research into developmental paths of social disabilities with a greater degree of specificity. Additional modifications introduced in the new diagnostic scheme include the inclusion of one-sided verbosity as a necessary communication criterion in AS, and of the presence of factual, circumscribed interests that interferes with both general learning and with reciprocal social conversation. These communication symptoms were introduced with a view to capture the observed greater social motivation seen in individuals with AS (relative to HFA).

This study was intended to operationalize these three diagnostic schemes – DSM-IV, (presence/absence of) Speech Delays, and the (more detailed) New System, and then to verify the implications for research of three clinically important variables external to the nosologic schemes, namely learning style as reflected in IQ profiles, comorbid psychiatric symptoms, and genetic vulnerability as expressed in the aggregation of social and other psychiatric symptoms in immediate relatives of the probands.

IQ Profiles

Learning profiles of assets and deficits are of great importance in educational treatment planning for individuals with PDDs (Klin *et al*., 1997), particularly in individuals with normative IQs (Klin, Sparrow, Marans, Carter, & Volkmar, 2000). And yet, neuropsychological research of AS is extremely equivocal to date. In 1995, we (Klin *et al*., 1995) documented considerable differences between individuals with HFA and AS. Specifically, individuals with AS showed a profile of assets and deficits consistent with a nonverbal learning disability (NLD) (Rourke, 1989). NLD is characterized by strengths in verbally mediated skills (e.g., vocabulary, rote knowledge, verbal memory, verbal output) and deficits in nonverbal skills (e.g., visual-spatial problem solving, visual-motor coordination). Individuals with HFA exhibited the opposite

profile. Such "double dissociation" has been shown to be one of the most powerful external validators of specific subtypes of syndromes (Fletcher, 1985). These findings have been supported by a number of studies focused on IQ profiles (Ehlers, Nyden, Gillberg, & Dahlgren Sandberg, 1997; Lincoln, Allen, & Kilman, 1995; Lincoln, Courchesne, Allen, Hanson, & Ene,1998), although several other groups have failed to replicate them (Szatmari *et al*., 1995; Ozonoff, 2000). However, direct comparison across studies is not possible since different approaches were used (Ozonoff, 2000); i.e., failures in replication may relate primary to fundamental differences in diagnostic approach.

Patterns of Comorbidity

Research on the psychiatric difficulties associated with the PDDs is of great importance for treatment planning given that these symptoms may have the potential of being extremely debilitating, e.g., limiting the effectiveness of educational interventions, posing further limitations on the individual's ability to utilize his or her internal coping resources. Documentation of these difficulties can lead to psychopharmacological approaches that can greatly alleviate such symptoms, thus making the student more available to other forms of intervention, e.g., educational (Towbin, 2003).

AS has been associated with a host of comorbid conditions, including schizophrenia (Clarke,Little Johns, Corbett, & Joseph, 1989; Tantam, 1988), Tourette's syndrome (Kerbeshian & Burd, 1986), attentional, affective, and obsessional disorders (Ghaziuddin, Tsai, & Ghaziuddin, 1992b; Thomsen, 1994). More recent research has emphasized anxiety, mood and obsessional disorders to be particularly prevalent in this population (Green, Gilchrist, Burton, & Cox, 2000; Kim, Szatmari, Bryson, Streiner, & Wilson, 2000). Typically there has been no attempt to study patterns of comorbidity that may be specific to HFA and AS, with most studies using the two diagnoses interchangeably.

Aggregation of Social and Other Psychiatric Disorders in Family Relatives

Research into patterns of genetic liability associated with the PDDs has been one of the most active areas of investigation in autism and related conditions (Rutter, 2000). Studies have consistently shown higher rates of social disabilities or difficulties in family members of individuals with autism (Murphy *et al*., 2000; Piven, Palmer, Jacobi, childress, & Arndt, 1997), given rise to the term "Broader Autism Phenotype", as well as of other psychiatric symptoms including anxiety, mood, and obsessional disorders (Bolton, Pickles, Murphy, & Rutter, 1998; Murphy *et al*., 2000; Piven & Palmer, 1999).

None of these studies, however, has made the attempt to assess the utility of separating families of probands with HFA from those of probands with AS. The available data on the familiality of AS are essentially limited to a handful of case reports and some preliminary studies (Folstein & Santangelo, 2000; Volkmar, Klin, & Pauls, 1998). Many case reports have been consistent with Asperger's original observation (1944) of similar traits in family members, particularly fathers or male relatives (Bowman, 1998; DeLong & Dwyer, 1988; Gillberg, Gillberg, & Steffenbufg, 1992).

METHOD

Participants and Standardized Procedures

Sixty-five individuals, 61 males and 4 females, were evaluated using standardized diagnostic instruments, neuropsychological, communication, and adaptive functioning assessments as part of a large federally- funded project on the neurobiology of autism and related conditions. Prior to participation, all participants or their legal guardians were able to supply informed, written consent after a thorough explanation and discussion of the research procedures. Assent was obtained for the children among the participants. The protocol was approved by the Human Investigations Committee of the Yale University School of Medicine.

Characterization data are presented in Table I. The sample consisted primarily of adolescents and young adults. The mean Full Scale IQ was 98, and yet these individuals were quite socially disabled. The socialization scores on the Vineland Adaptive Behavior Scales, Expanded Edition (Sparrow, Balla, & Cicchetti, 1984) were more than 2 SDs below the mean. Of interest is that there was a mean difference between Verbal IQ and Performance IQ of close to 1 SD. Special care was taken to avoid recruitment bias on the basis of IQ profiles (see below), thus this finding seems to suggest that a considerable number of higher functioning individuals with severe social disabilities exhibit verbal IQs greater than performance IQs.

Table I. Sample characterization ($N = 65$)

	Mean (SD)	Range
Age[a]	16.75 (8.73)	8–32
FSIQ[b]	97.86 (23.89)	50–144
VIQ[c]	104.78 (24.73)	62–153
PIQ[d]	90.28 (21.62)	46–136
Vineland socialization[e]	59.20 (15.82)	25–86

[a] Years.
[b] Full Scale IQ.
[c] Verbal IQ.
[d] Performance IQ.
[e] Standard score on the Socialization Domain of the Vineland. All standard scores have a mean of 100 and SD of 15.

Diagnostic Instruments

Diagnostic procedures included (a) the Autism Diagnostic Interview – Revised (ADI-R) (Lord, Rutter, & Le Coutem, 1994): a semi-structured interview with the parent providing historical and current information about autism-related symptoms and developmental data; (b) the Autism Diagnostic Observation Schedule – Generic (ADOS) (Lord, Rutter, & De Lavore, 1996): a semi-structured interview with the participant that generates a sample of behaviors that are relevant to the diagnosis of autism and related conditions; (c) the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS-NP) (Orvaschel & Puig-Antich, 1987) or the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1996): a semi-structured interview covering a wide range of psychiatric symptomatology in children and adults, respectively; and (d) the UCLA modification (Smalley, Mc Cracken, & Tanguay, 1995) of the Folstein/Rutter Family History Interview (FHI): a semi-structured interview covering social and other psychiatric symptomatology in family members.

Intellectual Functioning

All participants were administered the Wechsler Intelligence Scale for Children – Third Edition (WISC-III) (Wechsler, 1992) or the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997).

Diagnostic Assignment Procedures: Autism, AS, and PDD-NOS

Diagnostic procedures for case assignment of autism, AS, and PDD-NOS varied across the three competing diagnostic schemes as follows (see Table II for summary):

DSM-IV

As both the ADI-R and ADOS are keyed to DSM-IV, case assignment was entirely derived from results obtained with these instruments. Nevertheless, The ADI-R provides a diagnosis of "autism" or of "not autism" only (i.e., there are no algorithms for AS or PDD-NOS). Therefore, additional algorithms were required for case assignment of AS and PDD-NOS. The ADOS provides a diagnosis of "autism" and of "PDD-NOS", but not of AS. Therefore, additional algorithms were also required for case assignment of AS. The following are the case-assignment procedures adopted for this study. Autism: participant meets ADI-R criteria for autism in all domains (onset, social, communication, interests/behaviors), and meets all criteria for autism in the ADOS (social and communication). AS: participant meets ADI-R criteria for social and interests/behaviors, may or may not for communication, and does not meet onset criteria; on the ADOS, participant meets criteria for social but may or may not for communication. PDD-NOS: by exclusion, all participants who did not fulfill criteria for the diagnoses of autism or AS, and did not receive a diagnosis of a "non-PDD condition". Non-PDD condition: participant does not meet criteria in the social domain of the ADI-R.

Speech Delays

As noted, this diagnostic scheme highlights whether or not a person had single words before the age of 24 months and phrase speech (defined as two words including a verb, not echolalic, used meaningfully) before the age of 36 months. Case assignment was entirely derived from ADI-R and ADOS results and protocols. Autism: participant meets ADI-R criteria for autism in all four domains, and meets ADOS criteria in the two domains. Additionally, as assessed in the ADI-R, single words are not acquired before 24 months and phrase speech is not exhibited before 36 months. AS: participant meets ADI-R criteria for autism in all four domains or fails to meet criteria in the onset domain only, and meets ADOS criteria for social but may or may not meet criteria for communication. Additionally, as assessed in the ADI-R, single words are acquired before 24 months and phrase speech is exhibited before 36 months. PDD-NOS: by exclusion, all participants who did not fulfill criteria for the diagnoses of autism or AS, and did not receive a diagnosis of a "non-PDD condition". *Non-PDD condition:* participant does not meet criteria in the social domain of the ADI-R.

Table II. Operationalization of Asperger syndrome (AS) diagnostic assignment according to each of the three diagnostic systems

DSM-IV	Meets ADI-R criteria for social and stereotyped behaviors clusters
	Does not meet ADI-R criteria for onset
	Meets ADOS criteria for social cluster
Speech delays	Meets ADI-R criteria for social, communication, and stereotyped behaviors clusters
	Meets ADOS criteria for social cluster
	Single words by age 2 years and communicative phrase speech by 3 years
New system	Meets ADI-R criteria for social cluster
	Presence of social motivation, verbosity, and pragmatic deficits
	Circumscribed and socially interfering interest based on gathering of facts and information
	New onset criteria: presence of social approaches but awkward; formal language skills are adequate or precocious (e.g., "adult vocabulary) but presence of pragmatic deficits; presence of pretend play but unusual content (e.g., focused on specific topics of interest rather than age-appropriate social routines)
	Meets ADOS criteria for social cluster
	Precedence rule: AS over autism

ADI-R: *Autism Diagnostic Interview – Revised* (semi-structured parent interview) (Lord *et al.*, 1994).
ADOS: *Autism Diagnostic Observation Schedule* (semi-structured interview with individual with social disabilities) (Lord Rutter, & Di Lavae, 1996).
"Meets criteria": Meets criteria for autism as per standardized coding in ADI-R or ADOS.
"Clusters": four clusters of behaviors defining autism in DSM-IV (APA, 2000), namely "social" (qualitative impairment in social interaction), "communication" (qualitative impairments in communication), "stereotyped behaviors" (restricted repetitive and stereotyped patterns of behavior, interests, and activities), and "onset" (abnormal functioning prior to age 3 years in social interaction, language as used in social communication), or symbolic/imaginative play).
"Precedence Rule": Meeting criteria for autism precludes the diagnosis of AS.

New System

As noted, this system was meant to capture the more prototypical aspects of AS with a view to define it more narrowly, while explicating the onset criteria used to make a diagnosis of autism, thus making it less overly inclusive. In this system, case assignment was derived from both the ADI-R and ADOS as well as a review and coding of onset information generated through the ADI-R and additional clinical materials (e.g., clinical reports) made available by the families to the research team. In addition, parents completed a detailed "special interests" form that focused on the nature of special interests (e.g., how intense and unusual for the person's age and developmental level) and how interfering or disruptive the special interest was in the person's conversations with others (e.g., how often the person talks about the special interest with others). Case assignment was made according to the following algorithms: Autism: participant meets ADI-R criteria for autism in all domains (onset, social, communication, interests/behaviors), and meets all criteria for autism in the ADOS (social and communication). However, the "precedence" rule is reversed, i.e., if the participant meets criteria for AS, the diagnosis of AS is made rather than autism. AS: participant meets criteria in the social domain of the ADI-R, and is reported to be socially motivated during the "most abnormal period" (defined in the ADI-R as between the ages of 4–5 years). Social motivation is defined as absence of social isolation and presence of frequent verbal social approaches to adults or peers regardless of social appropriateness or effectiveness; participant may or may not meet criteria in the communication domain of the ADI-R, but there is presence of verbosity (e.g., reports that the child "talks too much") and pragmatic deficits (e.g., one-sided style, tangential content); participant also may or may not meet criteria in the interests/behavior domain of the ADI-R, but there is presence of a circumscribed interest of a factual nature (e.g., a topic about which one can acquire a great deal of factual information), that is all-absorbing (e.g., the person spends a great portion of free time involved with the topic) thus interfering with learning of other things, and which has a deleterious impact on reciprocal conversation because the person tends to frequently insert it in conversation with others. The onset algorithm of the ADI-R was replaced by a coding form that summarized all materials available on the participant's first 3 years of life. The participant met onset criteria for AS only if language concerns were restricted to pragmatic deficits (i.e., speech and formal language skill acquisition was intact) or language patterns are reported to have been precocious, with early achievement of milestones; if child was not socially isolated

(e.g., seeking and relating with family members), although may have avoided peers or approached them in inappropriate ways; if problems in pretend play were restricted to the content of play (i.e., pretend play is observed but it involves unusual objects or themes); and there is an absence of unusual sensory seeking/reactions and of motor stereotypies. Onset information was reviewed blind to participant's identity by two of the investigators (AK and FV), who coded onset patterns as consistent with autism or AS as defined above. An agreement of 89.23% was achieved, corresponding to a Kappa of .771 (''excellent agreement'') (Cicchetti & Sparrow, 1981). Finally, the person meets ADOS criteria for social but may or may not meet criteria for communication. PDD-NOS: by exclusion, all participants who did not fulfill criteria for the diagnoses of autism or AS, and did not receive a diagnosis of a ''non-PDD condition''. Non-PDD condition: participant does not meet criteria in the social domain of the ADI-R.

Safeguarding Procedures for Data Collection

A number of steps were taken to ensure the independence, reliability, and validity of the various data collection procedures:

Inclusion of Participants

Several procedures safeguarding the study from biased recruitment and cross-contamination among the key variables studied were taken. A package containing all of the clinical material available on a prospective participant (e.g., completed intake forms and inventories, past clinical reports) was reviewed by a research associate and all information regarding IQ and neuropsychological data or descriptions (except for Full Scale IQs), diagnosis of comorbid conditions, and family history data were blotted out. A different research associate, with clinical experience in the field of autism, then summarized this information in terms of ''caseness'' for participation in the study (i.e., the likelihood that the person had either HFA or AS). This person then presented this summary to a research team led by two of the investigators (AK and FV). A short videotape (lasting 5 min on average) of a parent interviewing the participant was also shown to the team, which included questions about school or work environment, friendships, descriptions of self, and leisure patterns. The team then rated the prospective participant on a scale of 1 to 5 on degree of ''caseness''. Given our objective to recruit prototypical cases, participants with the highest likelihood of having HFA or AS were invited to participate in the study.

Semi-Structured Interviews (ADI-R, ADOS, K-SADS, SCID)

The ADI-Rs were videotaped and the K-SADS or SCID interviews were audiotaped for subsequent rescoring and calculation of inter-rater reliability. These instruments were administered by trained research associates with demonstrated reliability with experienced trainers. Ten percent of ADI-R and K-SADS/SCID interviews were re-scored by another, equally experienced research associate. Agreement exceeded 90% in all cases. Both of these individuals were blind to diagnostic status of the probands and did not have direct contact with them. All of the ADOS interviews were conducted by one of the investigators (AK), whose reliability had been demonstrated several times with the authors of this instrument. This was this investigator's only role in data collection, remaining blind to the results of all of the other data collection procedures.

Intelligence Testing

The WISC-III or WAIS-III were administered by a postdoctoral psychologist blind to the diagnostic status of the participant and to results of the other data collection procedures.

Best-Estimate Procedures

Two senior diagnosticians (FV and DP) blind to participants' data or diagnostic status, and who had not had any direct contact with the participants, performed best-estimate diagnoses on the basis of the K-SADS/SCID forms (for comorbid symptomatology) and of the FHI (for presence of social or other psychiatric disorders in the family members of the probands). Both diagnosticians rated all forms. If an agreement of 90% or more was not obtained for a form, a consensual decision was made after face-to-face discussion (Leckman, Shotomskas, & Thompson, 1982).

RESULTS

Agreement Among the Three Diagnostic Schemes

Since different definitions of AS also impact on the definitions of Autism and PDD-NOS, case-assignments corresponding to these three

Table III. Case assignments according to the three diagnostic systems ($N = 65$)

	DSM-IV N (%)[a]	Speech delays N (%)	New system N (%)
Autism	33 (50.8%)	9 (13.8%)	18 (27.7%)
AS	16 (24.6%)	37 (56.7%)	25 (38.5%)
PDD-NOS	12 (18.4%)	15 (23.0%)	18 (27.7%)
Non-PDD[b]	4 (6.1%)	4 (6.1%)	4 (6.1%)
Total	65 (100%)	65 (100%)	65 (100%)

[a] Percent of the whole sample (i.e., $N = 65$) that received a given diagnosis in a given diagnostic system.
[b] The definition of "Non-PDD" was identical in the three systems.

categories according to the three diagnostic systems are provided on Table III. Four cases (6%) were defined as "non-PDD", and were, therefore, excluded from further analyses. There were major shifts in case assignment summaries by diagnostic category in the cases of autism, AS, and PDD-NOS. In the DSM-IV system, over 50% received a diagnosis of autism, and only 24% received a diagnosis of AS, whereas in the Speech Delays system, over 50% received a diagnosis of AS and only approximately 14% received a diagnosis of autism. In the New System, there were more individuals with AS than with autism (38% vs. approximately 28%).

Agreement among the three systems for diagnostic assignment to a given participant was 44%. Thus, 56% of individuals in this sample received at least two different diagnoses depending on the different diagnostic schemes. Agreement between the DSM-IV on the one hand, and the Speech Delays and New System on the other hand were 61% and 63%, respectively. Agreement between the Speech Delays and the New System was 61%.

IQ Profiles Across Autism, AS, and PDD-NOS as Assigned by the Three Diagnostic Schemes

IQ profiles, defined as Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), and Verbal IQ – Performance IQ (VIQ-PIQ), for the three diagnoses as assigned in the three diagnostic systems, as well as ANOVAs and Bonferroni post-hoc comparisons are provided in Table IV.

There were no significant differences for FSIQ, VIQ, and PIQ across diagnoses in the various diagnostic schemes. However, the VIQ – PIQ difference in two of the three diagnostic schemes (DSM-IV and New System) was. Post-hoc comparisons indicated significant differences between autism and AS. Differences between Autism and PDD-NOS bordered on significance, and there were no differences between AS and PDD-NOS.

Patterns of Comorbidity in Autism, AS, and PDD-NOS as Assigned by the three diagnostic schemes

K-SADS or SCID (Orvaschel & Puig-Antich, 1987; First, Spitzer, Gibbon, & Williams, 1996) forms were obtained on 47 of the 61 participants with a PDD diagnosis. The 14 participants that had to be excluded from this portion of analysis did not differ from the remainder of the sample on Age, FSIQ, VIQ, PIQ, or VIQ-PIQ. Of the various conditions included in the K-SADS or SCID, only six were observed in more than 10% of the entire sample ($N = 47$). These were OCD ($N = 11$ or 23.4%), ADHD ($N = 17$ or 36.2%), Depression ($N = 16$ or 34.0%), Social Phobia ($N = 11$ or 23.4%), Specific Phobia ($N = 14$ or 29.8%), and Generalized Anxiety ($N = 9$ or 19.1%). Eighteen Chi Square comparisons were carried out (rates of six comorbid conditions in autism, AS, and PDD-NOS × 3 diagnostic schemes). Given the number of comparisons, a difference in rates for a given comparison was considered significant only if $p \leq .01$.

Only two comparisons yielded significant differences, and both were within the New System. Individuals with PDD-NOS had more social phobia (53%) relative to both individuals with autism (7%) and AS (15%) ($X^2 = 9.573$, $p = .008$). Individuals with PDD-NOS also had more generalized anxiety (53%) relative to both individuals with autism (7%) and AS (10%) ($X^2 = 8.508$, $p = .010$). Given the relatively small number of cases, a $p \leq .05$ was applied to reveal trends in rates of comorbidity. In the DSM-IV system, ADHD was more prevalent in individuals with AS (58%) and PDD-NOS (50%) than those with autism (17%) ($X^2 = 7.060$, $p = .029$); and Social Phobia was more prevalent in PDD-NOS (50%) than in autism (13%) or AS (17%) ($X^2 = 6.416$, $p = .040$). None of the comparisons in the Speech Delays system approached significance. In the New System, two comparisons approached significance (in excess of the two comparisons that yielded significant results at $p \leq .01$). OCD was more prevalent in PDD-NOS (46%) relative to autism (7%) and AS (20%) ($X^2 = 5.948$, $p = .050$); and ADHD was more prevalent in PDD-NOS (61%) than in autism (14%) or AS (35%) ($X^2 = 6.540$, $p = .038$). In summary, the New System yielded more significant (and close to significant) comparisons of comorbid conditions across autism, AS, and PDD-NOS, although these

Table IV. IQ profiles for autism, AS, and PDD-NOS groups as assigned by the three diagnostic systems ($N = 61$)

	Autism ($N = 33$)	AS ($N = 16$)	PDD-NOS ($N = 12$)	Significance	Pairwise comparisons
DSM-IV					
FSIQ	98.2 (21.3)	98.63 (27.0)	97.7 (25.5)	NS	
VIQ	102.0 (21.7)	107.9 (27.0)	106.3 (26.8)	NS	
PIQ	94.1 (19.9)	84.8 (25.0)	88.2 (21.6)	NS	
VIQ-PIQ	7.5 (15.4)	23.0 (17.7)	17.6 (15.4)	$F = 4.55$, $df = 2,58$ $p = .015$	Autism/AS: $p = .026$ Autism/PDD: $p = .086$ AS/PDD: $p = 1.000$
	Autism ($N = 9$)	AS ($N = 37$)	PDD-NOS ($N = 15$)	Significance	Pairwise comparisons
Speech delays					
FSIQ	97.5 (18.9)	95.6 (24.6)	100.9 (24.7)	NS	
VIQ	100.3 (21.0)	103.0 (24.6)	109.2 (26.2)	NS	
PIQ	94.3 (14.2)	88.3 (23.5)	91.0 (21.4)	NS	
VIQ-PIQ	6.0 (13.9)	14.4 (17.6)	17.8 (16.1)	NS	
	Autism ($N = 18$)	AS ($N = 25$)	PDD-NOS ($N = 18$)	Significance	Pairwise comparisons
New system					
FSIQ	93.1 (23.7)	98.5 (22.5)	101.1 (26.4)	NS	
VIQ	95.9 (25.3)	107.0 (22.2)	109.4 (27.0)	NS	
PIQ	90.8 (20.0)	88.9 (22.1)	91.5 (22.9)	NS	
VIQ-PIQ	5.0 (14.9)	17.4 (17.6)	17.9 (14.1)	$F = 3.60$, $df = 2,58$ $p = .034$	Autism/AS: $p = .049$ Autism/PDD: $p = .083$ AS/PDD: $p = 1.000$

were primarily driven by the higher rates found in individuals with PDD-NOS, rather than by a direct comparison of the autism and AS groups.

Aggregation of Social and Other Psychiatric Symptoms in Family Members of Participants with Autism, AS, and PDD-NOS as Assigned by the Three Diagnostic Systems

Family History Interviews (FHI) as modified by Smalley and colleagues (1995) were obtained for relatives of 55 probands. The age and IQ profiles of the six probands for whom there were no family history data did not differ significantly from those of the remainder of the sample. Given the small number of siblings in these families, comparisons were limited to parents and grandparents. Five conditions were present at a rate of higher than 10% in the 220 parents and grandparents of probands according to results on the FHI: Depression, OCD, Generalized Anxiety, ''Broader Autism Phenotype'' (defined as symptoms in the social, communication, and behavior/interests cluster but of a possibly milder form than seen in probands), and Social Difficulties (an inclusive category denoting social difficulties of any kind). Fifty-five relatives (25%; 18% of males and 32% of females) met criteria for Depression; 28 relatives (13%; 17% of males and 8% of females) met criteria for OCD; 44 relatives (20%; 13% of males and 26% of females) met criteria for Anxiety; 26 (12%; 21% of males and 3% of females) met criteria for the Broader Autism Phenotype; and 67 (30%; 58% of males and 9% of females) met criteria for Social Difficulties. All of the male/female comparisons were significant at the $p < .05$ level, and two of them (Broader Phenotype and Social Difficulties) were significant at the $p < .01$ level, suggesting that future studies involving larger samples will benefit from separating genetic liabilities into male and female lines as these may contribute differently to specific phenotypes (see also Bolton *et al*., 1998; Murphy *et al*., 2000; Piven & Palmer, 1999).

Fifteen Chi-square comparisons were carried out (rates of five conditions in parents and grandparents of individuals with autism, AS, and PDD-NOS $\times$ 3 diagnostic schemes). Given the number of comparisons, a difference in rates for a given comparison was considered significant only if $p \leq .01$. At this level of significance, none of the comparisons were significant. To examine comparisons approaching significance, the threshold of $p \leq .05$ was used. For the DSM-IV system, Anxiety was the only condition for which there was differential aggregation in relatives of

probands with autism, AS, and PDD-NOS, revealing a continuum defined by lower percentage in autism (14%), larger in AS (24%), and larger still in PDD-NOS (31%) ($X^2 = 6.324$, $p = .042$). In the Speech Delays system, differential aggregation was obtained for Depression and Anxiety, with Depression singling out relatives of PDD-NOS probands (40%) (21% and 22%, respectively, in autism and AS) ($X^2 = 8.808$, $p = .015$), and Anxiety representing a continuum going from autism (lowest aggregation, 11%) to AS (21%) and then PDD-NOS (highest aggregation, 40%) ($X^2 = 8.468$, $p = .014$). In the New System, differential aggregation approaching significance was obtained for Anxiety (autism = 12%, AS = 18%, PDD-NOS = 31%) ($X^2 = 7.357$, $p = .025$), the Broader Autism Phenotype (autism = 5%, AS = 17%, PDD-NOS = 11%) ($X^2 = 5.685$, $p = .058$), and Social Difficulties (autism = 18%, AS = 35%, PDD-NOS = 36%) ($X^2 = 6.281$, $p = .043$). The distribution of Anxiety across the categories of autism, AS, and PDD-NOS in the New System mirrored the distribution of Anxiety in the other systems (with aggregation of symptomatology going from lowest in autism to highest in PDD-NOS). Only in the New System the comparisons for the Broader Autism Phenotype and of Social Difficulties were close to significance. Of interest also, only in the New System were rates of Broader Autism Phenotype and Social Difficulties in relatives of AS probands equal or greater than those of PDD-NOS; these rates were also considerably higher than in relatives of autism probands (close to double for Social Difficulties and over triple for the Broader Phenotype).

In summary, analyses of genetic liability in parents and grandparents yielded differential aggregation results in comparisons across relatives of probands with autism, AS, and PDD-NOS only at the $p \leq .05$. None of the comparisons was significant at the $p \leq .01$ level. Thus these results should be seen only as trends to be further explored in studies with greater statistical power. Nevertheless, in the area directly relevant to social disabilities (i.e., the "Broader Autism phenotype" and the more generally defined "Social Difficulties"), only the New System yielded results of interest. Comparisons in regard to Anxiety yielded differential aggregation in the three systems, whereas comparisons for Depression yielded differential aggregation in the Speech Delays system only. None of the OCD comparisons were significant. Of interest, genetic liability for Depression, OCD, and Anxiety was highest in relatives of PDD-NOS probands, whereas genetic liability for the Broader Autism Phenotype was highest in relatives of AS probands.

DISCUSSION

This is the first study to examine concurrently the research implications of the utilization of three competing systems for the diagnosis of Asperger syndrome (AS). The diagnostic schemes were based on DSM-IV criteria (as operationalized through the ADI-R and ADOS), "Speech Delays" (whether or not a participant had delays in word acquisition by age 2 or of non-echolalic 2-word phrase speech by age 3), and a New System that examined onset criteria in more detail, reversed the DSM-IV "precedence" rule, and gave more prominence to symptoms thought to be prototypical of AS, such as verbosity and the presence of socially interfering circumscribed interests. Implications for research were studied in terms of potential validators external to diagnostic criteria, namely IQ profiles, comorbid symptomatology, and aggregation of social and other psychiatric symptoms in parents and grandparents of probands. Participants were cognitively high functioning individuals with a severe social disability.

Diagnostic assignment of autism, AS, and PDD-NOS varied greatly among the three systems. Consistent with reported concerns (Gillberg, 1998; Volkmar & Klin, 2000), the DSM-IV definition of AS seems overly narrow, with only a small proportion of cases receiving this diagnosis. In contrast, the Speech Delays definition of AS seems overly broad, assigning this diagnosis to a large a number of individuals who meet criteria for autism in the other two systems. The New System fell in between the two other systems in terms of number of AS case assignments. Consistent with previous reports (Ghaziuddin *et al.*, 1992a), agreement across the three systems and pairwise agreements for assignment of a diagnosis of autism, AS, or PDD-NOS to a given individual was poor. The concerning implication of this finding is that comparison across studies using different diagnostic systems for AS is virtually impossible. This finding highlights the need for validation studies across adopted diagnostic schemes towards the development of a consensual and well-validated definition of AS.

Comparison of FSIQ, VIQ, and PIQ profiles yielded no significant differences across diagnoses in the three diagnostic schemes. This finding is inconsistent with the notion that AS is simply "high IQ autism" (Miller & Ozonoff, 2000). Another notion surprisingly inconsistent with these findings is that the absence of early speech delays bias later IQ profiles towards a higher VIQ among individuals with higher functioning PDDs. In the comparison that

could more directly examine this issue, VIQ profiles for autism and AS in the Speech Delays system were fairly similar. In contrast, however, there was some suggestion in the same diagnostic system that the absence of early speech delays may bias IQ profiles towards a greater VIQ – PIQ differential, which is consistent with Rourke's (1989) developmental hypothesis of nonverbal learning disabilities (NLD) (Klin & Volkmar, 1996). In regards to the validation utility of IQ profiles, VIQ-PIQ differential was significant in autism – AS comparisons in the DSM-IV and in the New System, thus providing some support to the findings of our and other previous reports (Klin *et al*., 1995; Lincoln *et al*., 1995; 1998), but not in the Speech Delays system, thus accounting for the lack of this differential in studies adopting this nosologic scheme (Szatmari *et al*., 1995; 2000). Of importance, however, VIQ-PIQ differentials did not differentiate AS from PDD-NOS. Although our sample of individuals with PDD-NOS is unlikely to be representative of this population, our data suggest that this finding could indicate a line of vulnerability to socialization problems as predicted by Rourke (1989).

Comparisons based on patterns of comorbid symptoms were significant in the DSM-IV and the New System only. In DSM-IV, ADHD singled out autism (lower rates) from both AS and PDD-NOS (higher rates), whereas Social Phobia separated PDD-NOS (higher rates) from both autism and AS (lower rates). In the New System, four comparisons were significant, namely OCD, ADHD, Social Phobia, and Anxiety. In all of these significant comparisons, there was a continuum going from lowest rates in autism, to slightly higher rates in AS, to greatly elevated rates in PDD-NOS. Thus although comorbid symptomatology provided some validation support to the New System, and to a lesser extent to the DSM-IV, it worked primarily in the direction of separating AS from PDD-NOS. While the high rates of comorbid symptomatology in individuals with AS found in our sample are consistent with previous studies of AS patients (variably defined) (Ghaziuddin *et al*., 1992b; Kim *et al*., 2000; Green, Gilchrist, Burton, & Cox, 2000), we are not aware of another study that compared comorbid patterns across autism, AS, and PDD-NOS.

Comparisons based on rates of social and other psychiatric symptoms in parents and grandparents of probands revealed significant results for aggregation of Anxiety in all three systems, with lower rates for relatives of probands with autism and highest rates for relatives of probands with PDD NOS, with relatives of probands with AS falling somewhere between the two. Aggregation of Depression was found in the Speech Delays system only, with highest rates singling out relatives of probands with PDD-NOS. Only in the New System there was indication of differential aggregation of Broader Autism Phenotype and Social Difficulties. Of interest, the Broader Autism Phenotype rates were highest for relatives of probands with AS, followed by relatives of probands with PDD-NOS and lowest for relatives of probands with autism. While higher rates of anxiety and mood disorders have been reported in families of probands with autism relative to control populations (Bailey, Phillips, & Rutter, 1996; Piven *et al*., 1991; 1997), several studies have emphasized the greater importance of social deficits in the definition of genetic liability to autism and related disorders (Bailey *et al*., 1998; Piven *et al*., 1997; Rutter, 2000). This line of research adds value to the unique findings obtained with the use of the New System for the diagnosis of AS relative to the other two systems.

In summary, the results of this study indicate that research on AS is highly dependent on nosologic issues, and advancement in the field will require better operationalization of diagnostic schemes than were hitherto available. To some extent, the validity status of a diagnostic construct should be judged on its predictive power relative to variables of clinical or research interest (Szatmari, 2000). The New System proposed in this paper achieved on balance the greater separation between autism, AS, and PDD-NOS. AS could be differentiated from autism on IQ profiles (VIQ–PI differential favoring the former) and on the extent of genetic liability for the autism Broader Autism Phenotype and more generally defined Social Difficulties (higher in AS). AS could be differentiated from PDD-NOS on the basis of levels of comorbid symptomatology (higher in PDD-NOS) and of genetic liability for the Broader Autism Phenotype (higher in AS).

This preliminary study, however, has many limitations, including the relatively small number of participants (once the sample is broken into the various cells for statistical comparisons), the lack, as yet, of standardized instrumentation for data collection on important aspects of AS phenomenology, and the parental report nature of the measures of comorbidity and familial aggregation of psychiatric liabilities. Therefore, much research is needed to further substantiate the trend reported in this study, including the utility of the new diagnostic scheme for AS. Of importance will be the necessary refinement of

current diagnostic instruments such as the ADI-R and the ADOS to encompass diagnostic algorithms for AS. The availability of such instruments would greatly advance the field.

Though not the focus of this study, two sets of findings are of interest for future research. First, aggregation of psychiatric symptoms in fathers and grandfathers of probands followed a distinct gender difference in rates obtained. While Depression and Anxiety were more prevalent in females, OCD, and particularly the autism Broader Phenotype and Social Difficulties were much more prevalent in males than in females. In this context, given that the family data in this study were obtained through the family history method, there is a possibility that OCD symptoms may have been mixed somewhat with symptoms that could more adequately be characterized as obsessionalities and rigidities typical of the autism Broader Phenotype, thus gaining the direction of higher rates in males seen in the gender distribution of the Broader Phenotype. Collectively, these findings suggest the need to study genetic liability for autism and related conditions while considering the possibility that different liabilities may be gender specific. The second interesting set of findings concern the presence of much higher rates of comorbid symptoms in probands with PDD-NOS relative to those with autism and AS, combined with a possible NLD vulnerability in their IQ profile, and high rates of Anxiety and Social Difficulties in their parents and grandparents. These findings suggest the need to further clarify the extent to which individuals with this diagnosis share a core disability with autism (thus being, as it is often assumed, within the "autism spectrum"; Prior *et al.*, 1998), or present with qualitative discontinuities relative to autism that cannot be accounted for in terms of ability levels only. For example, the issue as to whether their social disability is primary to their condition, as in autism, or alternatively, it is the result of vulnerabilities in other areas such as neuropsychology, other psychiatric symptoms, and multiple and heterogeneous genetic liabilities, would require clarification.

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REFERENCES

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). (DSM-IV)Washington, DC: American Psychiatric Association.

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.), Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.

Asperger, H. (1944). Die 'Autistischen Psychopathen' im Kindesalter. *Archiv für Psychiatrie und Nervenkrankheiten*, *117*, 76–136.

Bailey, A., Palferman, S., Heavey, L., & Le Couteur, A. (1998). Autism: the phenotype in relatives. *Journal of Autism and Development Disorders*, *28*, 369–392.

Bailey, A., Phillips, W., & Rutter, M. (1996). Autism: towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *37*(1), 89–126.

Bolton, P.F., Pickles, A., Murphy, M., & Rutter, M. (1998). Autism, affective and other psychiatric disorders: patterns of familial aggregation. *Psychological Medicine*, *28*(2), 385–395.

Bosch, G. (1970). *Infantile autism*. New York, NY: Springer-Verlag.

Bowman, E.P. (1988). Asperger's syndrome and autism: the case for a connection. *British Journal of Psychiatry*, *152*, 377–382.

Cicchetti, D.V., & Sparrow, S.S. (1981). Development of criteria for establishing the Interrater reliability of specific items in a given inventory: applications to assessment of adaptive behavior. *American Journal of Mental Deficiency*, *86*, 127–137.

Clarke, D.J., LittleJohns, C.S., Corbett, J.A., & Joseph, S. (1989). Pervasive developmental disorders and psychoses in adult life. *British Journal of Psychiatry*, *155*, 692–669.

DeLong, G.R., & Dwyer, J.T. (1988). Correlation of family history with specific autistic subgroups: Asperger's syndrome and bipolar affective disease. *Journal of Autism Development Disorders*, *18*(4), 593–600.

Ehlers, S., Nyden, A., Gillberg, C., & Dahlgren Sandberg, A. (1997). Asperger syndrome, autism and attention disorders: a comparative study of the cognitive profiles of 120 children. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *38*(2), 207–217.

Eisenmajer, R., Prior, M., Leekam, S., Wing, L., Gould, J., Welham, M., & Ong, B. (1996). Comparison of clinical symptoms in autism and Asperger's disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *35*, 1523–1531.

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (1996). *Structured clinical interview for DSM-IV Axis I Disorders (Version 2.0)*. New York NY: Biomedical Research Department, New York State Psychiatric Institute.

Fletcher, J.M. (1985). External validation of learning disability typologies In P.B. Rourke (Ed.), *Neuropsychology of learning disabilities: essentials of subtype analysis*. (pp. 187–211). New York, NY: Guilford Press.

Folstein, S.E., & Santangelo, S.L. (2000). Does Asperger syndrome aggregate in families? In A. Klin, F.R. Volkmar, & S.S. Sparrow, (Eds.), *Asperger syndrome*. (pp. 159–171). New York, NY: Guilford Press.

Fombonne, E. (1999). The epidemiology of autism: a review. *Psychological Medicine*, *29*, 769–786.

Ghaziuddin, M., Tsai, L.Y., & Ghaziuddin, N. (1992a). Brief report: A comparison of the diagnostic criteria for Asperger Syndrome. *Journal of Autism Development Disorders*, *22*(4), 643–649.

Ghaziuddin, M., Tsai, L., & Ghaziuddin, N. (1992b). Comorbidity of autistic disorder in children and adolescents. *European Child & Adolescent Psychiatry*, *1*(4), 209–213.

Gilchrist, A., Green, J., Cox, A., Burton, D., Rutter, M., & Le Couteur, A. (2001). Development and current functioning in adolescents with Asperger syndrome: a comparative study. *Journal Child Psychology and Psychiatry and Ailied Disciplines*, *42*, 227–240.

Gillberg, C. (1998). Asperger syndrome and high-functioning autism. *British Journal of Psychiatry*, *172*, 200–209.

Gillberg, C., Gillberg, I.C., Rastam, M., & Wentz, E. (2001). The Asperger syndrome (and high-functioning autism) Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview. *Autism*, *5*, 57–66.

Gillberg, C., Gillberg, I.C., & Steffenburg, S. (1992). Siblings and parents of children with autism: A controlled population-based study. *Developmental Medicine and Child Neurology*, *34*, 389–398.

Green, J., Gilchrist, A., Burton, D., & Cox, A. (2000). Social and psychiatric functioning in adolescents with Asperger syndrome compared with conduct disorder. *Journal of Autism Development Disorders*, *30*, 279–293.

Gura, T. (1999). Gene defect linked to Rett syndrome. *Science*, *286*(5437), 27 .

Hippler, K., & Klicpera, C. (2003). A retrospective analysis of the clinical case records of 'autistic psychopaths' diagnosed by Hans Asperger and his team at the University Children's Hospital, Vienna. *Philosophical Transactions of the Royal Society of London*, *358*, 291–301.

Howlin, P. (2000). Outcome in adult life for more able individuals with autism or Asperger syndrome. *Autism*, *4*, 63–83.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*, 217–253 .

Kerbeshian, J., & Burd, L. (1986). Asperger's syndrome and Tourette syndrome: The case of the pinball wizard. *British Journal of Psychiatry*, *148*, 731–6.

Kim, J., Szatmari, P., Bryson, S., Streiner, D.L., & Wilson, F.J. (2000). The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. *Autism*, *4*, 117–132.

Klin, A., Carter, A., Volkmar, F.R., Cohen, D.J., Marans, W.D., & Sparrow, S.S. (1997). Assessment issues in children with autism In D.J. Cohen, & F.R. Volkmar (Eds.), *Handbook of Autism and Pervasive Developmental Disorders, (2nd ed.)*. (pp. 411–418). New York, NY: Wiley.

Klin, A., Sparrow, S.S., Marans, W.D, Carter, A., & Volkmar, F.R. (2000). Assessment issues in children and adolescents with Asperger syndrome In A. Klin, F.R. Volkmar, & S.S. Sparrow (Eds.), *Asperger syndrome* (pp. 309–339). New York, NY: Guilford Press.

Klin, A., & Volkmar, F.R. (1996). The pervasive developmental disorders: Nosology and profiles of development In S. Luthar, J. Burack, D. Cicchetti, & J. Wiesz (Eds.), *Developmental Perspectives on Risk and Psychopathology* (pp. 208–226). New York, NY: Cambridge University Press.

Klin, A., & Volkmar, F.R. (1997). Asperger Syndrome In D.J. Cohen, & F.R. Volkmar (Eds.), *Handbook of Autism and Pervasive Developmental Disorders* (pp. 94–122). New York, NY: Wiley & Sons.

Klin, A., Volkmar, F.R., Sparrow, S.S., Cicchetti, D.V., & Rourke, B.P. (1995). Validity and neuropsychological characterization of Asperger syndrome. *Journal of Child Psychology Psychiatry and Allied Disciplines*, *36*, 1127–1140.

Klin, A., Volkmar, F.R., & Sparrow, S.S. (eds.) (2000). *Asperger syndrome*. New York, NY: Guilford Press.

Landa, R. (2000). Social language use in Asperger syndrome and high-functioning autism In A. Klin, F.R. Volkmar, & S.S. Sparrow (Eds.), *Asperger syndrome* (pp. 125–155). New York, NY: Guilford Press.

Leckman, J.F., Sholomskas, D., & Thompson, W.D. (1982). Best estimate of lifetime psychiatric diagnosis: A methodological study. *Archives of General Psychiatry*, *32*, 879–883.

Leekam, S., Libby, S., Wing, L., Gould, J., & Gillberg, C. (2000). Comparison of ICD-10 and Gillberg's criteria for Asperger syndrome. *Autism*, *4*, 11–28 .

Lincoln, A., Courchesne, E., Allen, M., Hanson, E., & Ene, M. (1998). Neurobiology of Asperger Syndrome: seven case studies and quantitative magnetic resonance imaging findings In E. Schopler, G. Mesibov, & L.J. Kunce (Eds.), *Asperger syndrome or High-Functioning Autism?* (pp. 145–166). New York: Plenum.

Lincoln, A.J., Allen, M., & Kilman, A. (1995). The assessment and interpretation of intellectual abilities in people with autism In E. Schopler, & G. Mesibov (Eds.), *Learning and Cognition in Autism* (pp. 89–117). New York, NY: Plenum.

Lord, C., Rutter, M. & DiLavore, P.(1996). Autism diagnostic observation schedule – Generic (ADOS-G). Unpublished manuscript. University of Chicago, Chicago, Illinois.

Lord, C., Rutter, M., & LeCouteur, A. (1994). Autism Diagnostic Interview–Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developed Disorders*, *24*, 659–685.

Mayes, S.D., Calhoun, S.L., & Crites, D.L. (2001). Does DSM-IV Asperger's disorder exist? *Journal Abnorm Child Psychology*, *29*, 263–271.

Miller, J.N., & Ozonoff, S. (1997). Did Asperger's cases have Asperger Disorder? *Journal of Child Psychology and Psychiatry*, *38*, 247–251.

Miller, J., & Ozonoff, S. (2000). The external validity of Asperger disorder: lack of evidence from the domain of neuropsychology. *Journal of Abnorm Psychology*, *109*, 227–238.

Murphy, M., Bolton, P.F., Pickles, A., Fombonne, E., Piven, J., & Rutter, M (2000). Personality traits of the relatives of autistic probands. *Psychological Medicine*, *30*, 1411–1424.

Orvaschel, H., & Puig-Antich, J. (1987). *Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)*. (4th ed). Pittsburgh, PA: Western Psychiatric Institute and Clinic.

Ozonoff, S. (2000). Neuropsychological function and the external validity of Asperger syndrome In A. Klin, F.R. Volkmar, & S.S. Sparrow (Eds.), *Asperger syndrome* (pp. 72–96). New York, NY: Guilford Press.

Ozonoff, S., Rogers, S., & Pennington, B. (1991). Asperger's syndrome: Evidence of an empirical distinction. *Journal of Child Psychology and Psychiatry*, *32*, 1107–1122.

Piven, J., Chase, G.A., Landa, R., Wzorek, M., Gayle, J., Cloud, D., & Folstein, S. (1991). Psychiatric disorders in the parents of autistic individuals. *Journal of American Academy Child and Adolescent Psychiatry*, *30*, 471–478.

Piven, J., & Palmer, P. (1999). Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families. *American Journal of Psychiatry*, *156*, 557–563.

Piven, J., Palmer, P., Jacobi, D., Childress, D., & Arndt, S. (1997). The broader autism phenotype: evidence from a family study of multiple-incidence autism families. *American Journal of Psychiatry*, *154*, 185–190.

Prior, M., Eisenmajer, R., Leekam, S., Wing, L., Gould, J., Ong, B., & Dowe, D. (1998). Are there subgroups within the autistic spectrum? A cluster analysis of a group of children with

autistic spectrum disorders. *Journal of Child Psychology and Psychiatry*, *39*, 893–902.

Rourke, B. (1989). *Nonverbal learning disabilities: The syndrome and the model*. New York, NY: Guilford Press.

Rutter, M. (1999). The Emanuel Miller Memorial Lecture 1998. Autism: two-way interplay between research and clinical work. *Journal of Child Psychology and Psychiatry*, *40*, 169–188.

Rutter, M. (2000). Genetic studies of autism: from the 1970s into the millennium. *Journel of Child Psychology and Psychiatry*, *28*, 3–14.

Smalley, S.L., McCracken, J., & Tanguay, P. (1995). Autism, affective disorders and social phobia. *American Journal of Medical Genetics*, *60*, 19–26 .

Sparrow, S., Balla, D., & Cicchetti, D. (1984). *Vineland Adaptive Behavior Scales, Expanded Edition*. Circle Pines, MN: American Guidance Service .

Szatmari, P., Archer, L., Fisman, S., Streiner, D.L., & Wilson, F. (1995). Asperger's syndrome and autism: differences in behavior, cognition, and adaptive functioning. *Journal of American Academy Child and Adolescent Psychiatry*, *34*, 1662–1671.

Szatmari, P., Bryson, S.E., Streiner, D.L., Wilson, F., Archer, L., & Ryerse, C. (2000). Two-year outcome of preschool children with autism or Asperger's syndrome. *American Journal of Psychiatry*, *157*, 1980–1987.

Szatmary, P (2000). Perspectives on the classification of Asperger syndrome In A. Klin, F.R. Volkmar, & S.S. Sparrow (Eds.), *Asperger syndrome*. (pp. 403–417). New York: Guilford Press.

Tantam, D. (1988). Annotation: Asperger's syndrome. *Journal of Child Psychology and Psychiatry*, *29*, 245–255.

Thomsen, P.H. (1994). Obsessive-compulsive disorder in children and adolescents: A 6–22-year follow-up study: Clinical descriptions of the course and continuity of obsessive-compulsive symptomatology. *European Child Adolescent Psychiatry*, *3*, 82–96.

Towbin, K.E. (2003). Strategies for pharmacologic treatment of high functioning autism and Asperger syndrome. *Child and Adolescent Psychiatric Clinics of North America*, *12*, 23–45.

Van Krevelen, D.A. (1971). Early infantile autism and autistic psychopathy. *Journal of autism and Child Schizophrenia*, *1*(1), 82–86.

Volkmar, F.R., & Klin, A. (2000). Diagnostic issues in Asperger syndrome In A. Klin, F.R. Volkmar, & S.S. Sparrow (Eds.), *Asperger syndrome*. (pp. 25–71). New York, NY: Guilford Press .

Volkmar, F.R., Klin, A., & Cohen, D.J. (1997). Diagnosis and Classificiation of autism and related conditions: Consensus and Issues In D.J. Cohen, & F.R. Volkmar (Eds.), *Handbook of Autism and Pervasive Developmental Disorders* (pp. 5–40). New York, NY: Wiley.

Volkmar, F.R., Klin, A., & Pauls, D. (1998). Nosological and genetic aspects of Asperger Syndrome. *Journal of Autism Development Disorders*, *28*, 457–463 .

Volkmar, F.R., Klin, A., Siegel, B., Szatmari, P., Lord, C., Campbell, M., Freeman, B.J., Cicchetti, D.V., Rutter, M., Kline, W., Buitelaar, J., Hattab, Y., Fombonne, E., Fuentes, J., Werry, J., Stone, W., Kerbeshian, J., Hoshino, Y., Bregman, J., Loveland, K., Szymanski, L., & Towbin, K. (1994). DSM-IV Autism/Pervasive Developmental Disorder Field Trial. *American Journal of Psychiatry*, *151*, 1361–1367.

Wechsler, D. (1992). *Manual for the Wechsler Intelligence Scale for Children,* (3rd ed.). San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997). *Manual for the Wechsler Adult Intelligence Scale,* (3rd ed.). San Antonio: The Psychological Corporation.

Wing, L. (1981). Asperger's syndrome: a clinical account. *Psychological Medicine*, *11*, 115–129.

Wing, L. (1986). Clarification on Asperger's Syndrome (Letters to the Editor). *Journal of Autism Development Disorder*, *16*, 513–515.

World Health Organization (1992). *The ICD-10 Classification of Mental and Behavioral Disorders*. Geneva.: World Health Organization.