CHAPTER 1

Asperger Syndrome

An Overview

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Asperger syndrome (AS) is a serious and chronic neurodevelopmental disorder characterized by significant and severe social deficits along with restricted interests, as in autism, but, in contrast to autism, relatively and selectively preserved language and cognitive abilities. As presented in Table 1.1, formal diagnostic criteria for AS in the text revision of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Association, 2000) and the 10th edition of the *International Classification of Diseases* (ICD-10; World Health Organization, 1993; see Table 1.1) ruled out individuals who meet criteria for autistic disorder. The fifth and most recent edition of the DSM (DSM-5; American Psychiatric Association, 2013) eliminated AS as an official diagnosis, collapsing it into a presumably broader category of autism spectrum disorder (ASD). In the following chapters, discussion of AS refers to the disorder as defined by the most recent DSM-IV-TR and ICD-10 criteria. Clearly, the absence of an official diagnostic category does not render the information contained herein less relevant to the many individuals who have carried a diagnosis of AS, as well as to the many families, support groups, and advocacy organizations associated with AS.

TABLE 1.1. ICD-10 Research Diagnostic Guidelines for Asperger Syndrome

1. There is no clinically significant general delay in spoken or receptive language or cognitive development. Diagnosis requires that single words should have developed by 2 years of age or earlier and that communicative phrases be used by 3 years of age or earlier. Self-help skills, adaptive behavior, and curiosity about the environment during the first 3 years should be at a level consistent with normal intellectual development. However, motor milestones may be somewhat delayed and motor clumsiness is usual (although not a necessary diagnostic feature). Isolated special skills, often related to abnormal preoccupations, are common but are not required for the diagnosis.
2. There are qualitative abnormalities in reciprocal social interaction (criteria for autism).
3. The individual exhibits an unusual intense, circumscribed interest or restricted, repetitive, and stereotyped patterns of behavior interests and activities (criteria for autism; however, it would be less usual for these to include either motor mannerisms or preoccupations with part-objects or nonfunctional elements of play materials).
4. The disorder is not attributable to other varieties of pervasive developmental disorder; simple schizophrenia, schizotypal disorder, obsessive–compulsive disorder, anakastic personality disorder, reactive and disinhibited attachment disorders of childhood.

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Narrative text in both the DSM-IV-TR (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1993) noted that motor awkwardness and/or clumsiness are common and that, in contrast to autism, the restricted interests observed often take the form of unusual, intense, and highly circumscribed interest(s). Although not explicitly discussed, implication of diagnostic criteria was that generally the onset of AS (or at least its recognition) was usually after age 3. Before that, age problems in social interaction, communication, and responses to the environment must not be of the type seen in autism or must not be accompanied by the characteristic behavioral features of autism (see Kamp-Becker et al., 2010, for a recent study suggesting several areas of differences in the onset of the conditions).

Although described the year after autism (Kanner, 1943), the body of research on AS is much less extensive than that for autism; nevertheless, research has advanced markedly since official recognition (about 75 papers between 1944 and 1994, but over 1,800 papers from 1994 to 2010). During the 1970s and 1980s considerable progress occurred in the attempt to provide better definitions of autism, and it was on this body of work that DSM-IV-TR criteria rested. The official definition of autism was revised twice in the 14 years separating DSM-III (American Psychiatric Association, 1980) from DSM-IV (American Psychiatric Association, 1994), and even when it appeared in DSM-III for the first time, a considerable body of work on

diagnosis and definition of autism had accumulated. Its subsequent revision illustrates the importance of a deliberate, data-based approach to the problem. In this chapter we review the history of the diagnostic concept of AS; the rationale for, and limitations of, the extant diagnostic approaches; the validity of the concept; current controversies in diagnosis; with a final summary and recommendations for the future.

EVOLUTION OF THE CONCEPT: 1944–1994

The most recent definitions of AS evolved Asperger's original (1944) description of the condition he termed *autistic psychopathy* or *autistic personality disorder*.[1] This evolution has not been straightforward. As with autism, modifications in Asperger's description were proposed, initially by Wing (1981) and subsequently by many others (Klin & Volkmar, 2003; Klin, Pauls, Schultz, & Volkmar, 2005). Some of these changes moved the concept away from the one originally envisioned by Asperger, who regarded the condition as quite separate from autism and one that was, in many ways, more a personality than a developmental disorder (Asperger, 1979). Partly because of its ambiguous diagnostic status, markedly divergent views of the condition developed. Sometimes these alternative views are of only minimal interest from the perspective of nomenclature, but in other cases they are more critical. For example, the convention of viewing AS a synonymous term for adults with autism is of little interest, in that such a convention simply reifies an existing diagnostic concept around an important but nonessential characteristic (in this case, age). Similarly, the convention of equating AS with either pervasive developmental disorder not otherwise specified (PDD-NOS) or higher-functioning autism (HFA) has little importance from the point of view of nomenclature, since it simply substitutes one term for another (Volkmar & Tsatsanis, 2005). The much more critical question is whether AS differs in some important way or ways from autism, PDD-NOS, and other conditions in terms of its natural history, course and outcome, family history or genetic involvement, neuropsychological profiles, and important associated features, relative to implications for treatment and intervention, and so forth. These differences must be truly "external" ones, avoiding circularity of reasoning or of research strategy in that differences, if found, must reflect factors independent of original diagnostic assignment (Volkmar, Chawarska, Carter, & Lord, 2007; Rutter, 2011). Put another way, the issues are (1) whether AS can be separated from autism and other conditions in a reliable and empirical fashion, and, if so, (2) whether this discrimination has meaningful importance (e.g., for research or clinical work). Practical issues involved in diagnostic practice

[1]Note that, as is true of autism, it is likely that cases with what now would be viewed as AS were seen even before Aspeger's 1944 work; see Wolff (1996, 2004).

associated with AS have not yet fully benefited from recent improvements in diagnostic instrumentation seen in autism (see Campbell, James, & Vess, Chapter 2, this volume) although more rating scales are now available.

Finally, another set of complicating issues has arisen because several alternative concepts have been proposed that share at least some fundamental similarity with AS; semantic–pragmatic disorder, right-hemisphere learning disability, nonverbal learning disability, and schizoid disorder are some of these alternative concepts (Klin, McPartland, & Volkmar, 2005). All involve some degree of impairment in complex social skills. These concepts have their own histories of development and emerge from diverse disciplines. Before considering the uses and limitations of current official diagnostic approaches to AS, we therefore consider the various alternatives to definition of the condition that have arisen over the years, as well as the potential overlap between AS and these alternative diagnostic concepts. Given the centrality of Asperger's report, it is appropriate to begin with a discussion of his views of the concept before moving to alternative views and the centrally important role of Wing's (1981) paper in the evolution of the diagnostic concstruct.

ASPERGER'S REPORT: 1944

In 1944, Hans Asperger, a medical student, reported four cases (all boys) with marked difficulties in social interaction despite apparently adequate to excellent cognitive and verbal skills. In addition, these boys exhibited motor difficulties and unusual and intense circumscribed interests, and their fathers often exhibited similar problems. Asperger made the important point that these interests were so intense as to interfere with learning (i.e., were a source of impairment) and that family life often also centered around them.

At the time of Asperger's original (1944) work there was, of course, not the considerable interest in operational definitions that has characterized psychiatry so much since the 1970s (Klin, McPartland, et al., 2005; Spitzer, Endicott, & Robbins, 1978). As with Kanner (1943), Asperger provided a clinical account of what appeared to him to be a new syndrome. His description of this condition was inspired by his work with these boys, ages 6–11, who had marked problems in social interaction despite having what appeared to be good language and cognitive skills (see Frith, 1991, for an English translation). These four boys, however, were said to be representative of a much larger sample of children presenting with the profile described. In addition to the *problems in social interaction*, which Asperger emphasized by the use of the word *autism* in his original name for the condition (*Autistischen Psychopathen im Kindesalter*, or autistic personality disorders in childhood). He also noted other features that were commonly present. These included *egocentric preoccupations* with unusual

and circumscribed interests that were the focus of much of the child's life and which interfered with acquisition of skills in other areas; for example, the child might be fascinated with train schedules but be unable to plan or anticipate his own daily routine. Affectively, Asperger noted that these children had *difficulties in dealing with their feelings*, often tending to intellectualize them, and had poor empathy and difficulties in understanding social cues. In addition, Asperger mentioned that they had *motor vulnerabilities* and typically were awkward and clumsy, with odd posture and gait and generally poor awareness of the movement of the body in space; graphomotor skills were also poor and the ability to participate in group sports activities was compromised. In terms of language and communication skills, Asperger described these boys as like "little professors" who talked (often at great length) about the topic of their interest but who had *difficulties with nonverbal and pragmatic aspects of communication*, for example, in use of facial expressions and gestures, in modulation of their voice, and in responding appropriately to the nonverbal cues of their conversational partners. Behavioral difficulties included *noncompliance and negativism* often leading to aggression and other conduct problems. These difficulties stemmed from the marked egocentrism and highly circumscribed interests as well as from the poor social understanding and peer relations these children exhibited at school. Asperger's original paper also *emphasized familial factors*; that is, similar traits were seen in relatives, particularly fathers.

In terming this condition *autistic personality disorder*, Asperger (1944), like Kanner the year before (1943), used Bleuler's much earlier (1911) term *autism* in describing the marked social vulnerability. Bleuler's earlier term was created to capture "a loss of contact, a retirement into self and a disregard of the outside world" observed in schizophrenia (Asperger, 1979, p. 46). In his use of the term, Asperger was careful to contrast the condition he described from schizophrenia. Because of World War II, Asperger was unaware of Kanner's similar use of the term the year previously. Asperger's observation of similar traits in family members may also have led him to be more optimistic about ultimate outcome

ASPERGER'S DISORDER: 1944–1981

Originally published in German, Asperger's paper was the focus of relatively little interest in the English-speaking literature until Wing's seminal (1981) review a year following Asperger's death. The rather small body of work on AS prior to 1981 included discussion of AS as a personality, rather than as a developmental, disorder (van Krevelan, 1971, 1973; van Krevelen & Kuipers, 1962) and what are probably some of the first case reports of the condition in the English language literature, albeit by individuals unaware of Asperger's work (Robinson & Vitale, 1954).

In 1962, van Krevelen and Kuipers attempted to distinguish AS from Kanner's autism, suggesting that the latter was present from the first months of life, that language was absent or delayed, that there was a lack of interest in others, and that prognosis was poor. They contrasted this profile with the later onset/recognition of AS as well as the often precocious language development ("the child talked before he walked"); the one-sided, eccentric social style, which caused problems in social interaction despite social interest; and the apparently better prognosis. These views were elaborated by van Krevelen again in 1971 in an article in the first issue of the *Journal of Autism and Childhood Schizophrenia*, where he attempted to draw clear distinctions between autism and AS. Similar attempts had been made in the German literature, some of which were translated into English at around the same time (see Bolte & Bosch, 2004).

Despite van Krevelan's attempt to distinguish between the two conditions, considerable confusion arose about AS. This confusion stemmed from several sources. Firstly, it took several decades before investigators and clinicians were sure of the validity of autism, for example, apart from childhood schizophrenia, and indeed it was not until 1980 that autism was first officially recognized as a diagnosis. This naturally delayed evaluation of other, similar diagnostic concepts. Secondly, as research on autism was conducted in the 1950s and 1960s, it became clear that Kanner's original concept had to be modified; Kanner originally thought, for example, that autism was probably associated with normal intellectual levels, but it became apparent that many individuals with autism functioned in the intellectually disabled range.

Another source of confusion stemmed from the use of the same word, *autism*, by both Asperger and Kanner. This term reflected the core disability present in the children described in their accounts. In addition, both groups of patients had difficulties in the areas of affective reaction, nature and range of interests, and social use of language. The main differences in the two conditions appeared to be that in AS, early speech and formal language skills were acquired on time if not precociously, motor deficits were more common, and in contrast to autism, the apparent onset of the condition was after the first several years of life. In addition, all of the original cases described by Asperger had been boys, whereas Kanner had noted some girls with autism in his original report.

Other areas of divergence in the accounts included differences in speech and language skills, motor mannerisms, circumscribed interests, and ultimate outcome. Some of the differences in the original syndrome descriptions may relate to the nature of differences in the groups being reported; that is, whereas Kanner was describing more impaired and younger children, Asperger was describing older and apparently less severely impaired individuals. These differences contributed to the subsequent tendency to equate Kanner's syndrome with the "classically" lower-functioning autistic child and Asperger's description with the nonretarded and verbal child with

autism. It is important to note that Asperger himself emphasized the differences from autism once he became aware of the latter concept (Asperger, 1979), and indeed information on cases subsequently seen by him is consistent with this view (Hippler & Klicpera, 2003, 2005).

WING'S REVIEW: 1981

Wing's highly influential 1981 review brought Asperger's concept to the attention of a much larger audience. It provided a summary of Asperger's account, suggested some ways his description might be modified, emphasized the possible connection to autism, and provided a series of case reports. She suggested the term *Asperger's syndrome* for the condition. Her publication generated considerable interest and an expanding literature on the condition related both to a possible connection to autism, on the one hand (based on family history), and the possibility that AS was a possible transitional disorder with schizophrenia (see Klin, Volkmar, & Sparrow, 2000; Klin, McPartland, et al., 2005; Volkmar & Tsatsanis, 2005).

Wing's (1981) report of over 30 cases was important in that she was able to identify a group of individuals whose histories and clinical presentations were very similar to Asperger's account, as well as another group of cases in which the current clinical presentation was consistent but early history was not. In addition to summarizing Asperger's original work, Wing proposed some modifications of the concept based on her case series; these modifications were primarily related to the issue of early development and early clinical presentation. She suggested that difficulties might be apparent early in life (i.e., in the first 2 years) and might take the form of lack of interest in others, early language deficits, and imaginative play; also, her cases suggested that Asperger's speculation that these children talked before they walked was not always correct. Finally, she noted that sometimes the condition was apparently associated with mild mental retardation and could be seen in both males and females. Her use of the eponymous label *Asperger syndrome* avoided potential confusion in English regarding the use of the word *psychopathy* adopted by Asperger (who intended the term to suggest a personality).

Wing's (1981) description increased interest in this condition and prefigured much of the subsequent debate about boundaries, or lack thereof, with autism. She emphasized that despite her interest in Asperger's work, she fundamentally viewed the disorder as part of the autistic spectrum and was more concerned with broadening, rather than narrowing, Asperger's original concept. Not surprisingly, the modifications she proposed thus tended to blur the distinctions between AS and autism originally suggested by van Krevelen (1971). The latter had been reemphasized by Asperger himself just the year before (1979) when he noted areas of difference from autism (see also Hippler & Klicpera, 2003, for a review of cases seen by

Asperger over the years). These differences include the preserved language abilities as well as motor problems and the apparently later recognition of AS as well as differences in other clinical features (e.g., circumscribed interests).

ASPERGER SYNDROME: 1981–1994

Although not providing truly operational categorical diagnostic criteria, Wing's (1981) paper served as the basis for much subsequent work as authors attempted (with somewhat different areas of emphasis) to adapt her description into an operationalized definition. As a result of a series of approaches, all in some ways derivative of Wing (1981) but in other ways rather divergent, arose. Clearly for purposes of official systems such as DSM-IV and ICD-10, it clearly was important that AS differ from autism in some relevant and meaningful way or ways. Unfortunately, the lack of consistency in diagnostic approach complicated this discussion but did set the stage for possible inclusion of the concept in DSM-IV and ICD-10—that is, whether any substantive data on differences in clinical presentation course or treatment could be used to justify its inclusion (Szatmari, Bartolucci, & Bremner, 1989; Szatmari, Bremner, & Nagy, 1989; Tantam, 1988a, 1988b).

The DSM-IV field trial (Volkmar et al., 1994) primarily focused on autism, but as part of this work almost 50 cases of AS (based on clinician diagnosis) were submitted from sites around the world over the course of a year. This large sample of cases had some advantages in that comparisons could readily be made with relevant IQ-matched groups for which clinicians had diagnosed autism or PDD-NOS. Interesting significant differences were, in fact, observed both relative to HFA and PDD-NOS (different patterns of verbal–performance IQ in AS and greater frequency of circumscribed interests as well as greater social symptom severity than in PDD-NOS). And as result a tentative decision was made to include the condition in DSM as well as in ICD-10 (World Health Organization, 1993; Volkmar et al., 1994).

Unfortunately, the ambivalence over including this category was reflected in several last-minute changes in diagnostic approach, so that, in practice, the ICD-10 and DSM-IV definitions use age of onset as a primary differentiating feature and also give autism precedence (the "precedence rule"). As a result, many individuals who appear to have relatively prototypical forms of the condition are given an autism diagnosis instead (Volkmar, Klin, Schultz, Rubin, & Bronen, 2000; Volkmar & Klin, 2000). This approach reflects a concern that autism not be "overshadowed" by AS (the former being the much more well-known concept), an awareness that earlier diagnosis was more likely now than in the past (given greater parental

and professional sophistication), and some degree of skepticism about the validity of AS as a distinctive concept.

Very quickly the DSM-IV and ICD-10 approach was criticized widely, and even with the major changes in the text description that occurred in DSM-IV-TR (American Psychiatric Association, 2000) the approach continued to be criticized as overly narrow (Eisenmajer et al., 1996; Szatmari et al., 1995; Mayes, Calhoun, & Crites, 2001; Miller & Ozonoff, 1997). Table 1.2 summarizes key points of similarity and difference in these various diagnostic approaches.

ASPERGER SYNDROME POST-DSM-IV/ICD-10

Official recognition of AS clearly has stimulated a considerable body of research but, as noted previously, has not resolved some of the continued (and continuing) controversies to diagnosis. Clearly, comparisons across approaches are complex; Ghaziuddin, Ghaziuddin, and Tsai (1992) summarized some of these issues even before DSM-IV appeared. As a result of these issues and a lack of a generally agreed-upon diagnostic approach, several rather disparate approaches to diagnosis remain in common use and complicate interpretation of research findings.

The *spectrum approach* views AS as one manifestation of the broader spectrum of autism (e.g., Baron-Cohen, 2000a, 2000b; Constantino & Todd, 2003). The *speech-by-age-2 approach* focuses on the presence/absence of language delay in the first years of life; that is, in the absence of language and cognitive delay, AS becomes the default diagnosis (Gilchrist et al., 2001; Szatmari, Bartolucci, & Bremner, 1989). The *DSM-IV approach* represents a variation of the language delay approach (with the additional complexity of specifying the precedence of autism as a concept and specification of relatively normal early development). The *strict diagnostic approach*, likely more consistent with Asperger's original one, attempts to emphasize unique features of clinical presentation as well as history: for example, motor difficulties, circumscribed interests, and nature of early developmental processes (see Volkmar & Klin, 2000). This last approach emphasizes features more unique to AS, and in one study comparing these approaches, it was this last approach that was more likely to produce significant differences in IQ profiles, comorbidity of the proband, and family history of psychiatric symptom (Klin, Pauls, et al., 2005).

A growing body of literature on issues relevant to diagnosis/differential diagnosis of AS and HFA, although still relatively small, has now developed. In the following sections we summarize the limited available literature that directly assesses the impact of diagnostic approach as well as some of the relevant literature in specific areas: neuropsychology, psychiatric comorbidity, and family genetics. As will become apparent, the

TABLE 1.2. Comparison of Six Sets of Clinical Criteria Defining Asperger Syndrome

Clinical feature	Asperger (1944, 1979)	Wing (1981)	Gillberg & Gillberg (1989)	Tantam (1988a)	Szatmari, Brammers, et al. (1989)	DSM-IV (American Psychiatric Association, 1994)
Social impairment						
Poor nonverbal communication	Yes	Yes	Yes	Yes	Yes	Yes
Poor empathy	Yes	Yes	Yes	Yes	Yes	Yes
Failure to develop friendships	Yes	Yes	Yes	Yes	(implied)	Yes
Language/communication						
Poor prosody and pragmatics	Yes	Yes	Yes	Yes	Yes	Not stated
Idiosyncratic language	Yes	Yes	Not stated	Not stated	Yes	Not stated
Impoverished imaginative play	Yes	Yes	Not stated	Not stated	Not stated	Not stated
All-absorbing interest	Yes	Yes	Yes	Yes	Not stated	Of ten
Motor clumsiness	Yes	Yes	Yes	Yes	Not stated	Of ten
Onset (0–3 years)						
Speech delays/ deviance	No	May be present	May be present	Not stated	Not stated	No
Cognitive delays	No	May be present	Not stated	Not stated	Not stated	No
Motor delays	Yes	Sometimes	Not stated	Not stated	Not stated	May be present
Exclusion of autism	Yes (1979)	No	No	No	Yes	Yes
Mental retardation	No	May be present	Not stated	Not stated	Not stated	No

Note. From Klin, McPartland, and Volkmar (2005, p. 94). Copyright 2005 by John Wiley & Sons, Inc. Reprinted by permission.

available data vary quite dramatically across these three areas, and it is always important in interpreting this literature to be aware that fundamental differences in approaches to diagnosis may, of course, significantly impact the results obtained.

Direct Comparison of Diagnostic Approaches

Klin, Pauls, Schultz, and Volkmar (2005) directly compared three different approaches to the diagnosis of AS in 65 individuals with good cognitive skills but with severe social disability. In this study comparisons were made relative to IQ profiles, comorbid symptoms, and familial aggregation of social and other psychiatric symptoms. The three approaches compared were the DSM-IV criteria, the "absence-of-speech-delay" approach (presence of communicative speech by age 3; Szatmari et al., 2000), and a method more consistent with Asperger's (1944) approach (the "prototypic" approach). They noted the issues with DSM-IV but also emphasized the potential limitations of the speech-delay approach, in that it tended to minimize other features that might well contribute in important ways to the presentation of AS with what they suggested was considerable potential for increasing type II errors (i.e., of not finding differences that otherwise would be observed with a more specific approach). The prototypic approach was consistent with Asperger's report (see also Hippler & Klicpera, 2003; Volkmar & Klin, 2000). In this approach the features more unique to AS were emphasized (e.g., social interest but social insensitivity; language not just present but precocious, with the inclusion of one-sided verbosity as a necessary communication criterion; and factual, circumscribed interests that interfere with both general learning and with reciprocal social conversation). For the prototypic or strict diagnosis approach the DSM-IV precedence rule (autism being given precedence over AS) was reversed.

The Autism Diagnostic Interview—Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) were administered in all cases and used to operationalize the three diagnostic approaches (see Klin, Pauls, et al., 2005, for additional information). The 65 cases (61 male and 4 female) were evaluated using a standard set of assessments, including the ADI-R, ADOS, Wechsler IQ test, and structured psychiatric interviews. The mean IQ of the sample (primarily adolescents and young adults) was 98, but all had severe delays in social skills development; for example, standard scores on the socialization domain of the Vineland Adaptive Behavior Scales—Expanded Edition (Sparrow, Balla, & Cicchetti, 1984) were more than two *SD*s below the mean. In terms of psychological and psychiatric assessments, special care was taken to avoid bias by having evaluators blind to history and diagnosis. Best-estimate psychiatric diagnoses (for comorbidity and family psychiatric disorders) were completed by two senior clinicians not otherwise familiar with the cases.

In this study four individuals were excluded for having failed to meet a threshold for PDD. Of the remaining individuals there were major shifts in case assignment depending on which diagnostic system was used. Using the DSM-IV system, over 50% of cases had a diagnosis for autistic disorder and only 24% AS (with the remainder receiving a PDD-NOS diagnosis); with the speech-present approach the situation was essentially reversed, with 50% of cases receiving an AS diagnosis and only 14% a diagnosis of autistic disorder. With the presumably more prototypic approach, 38% of individuals met criteria for AS and 28% for autistic disorder. Over half of the sample (56%) was noted to have at least two different diagnoses using the three approaches. In the IQ data there were no overall differences for Full Scale, Verbal, or Performance IQ over the three systems, but the verbal–performance IQ difference that had previously been noted for AS was noted in individuals with this diagnosis in either the prototypic or DSM-IV approach. Differences in proband comorbidity were most robust with the prototypic approach. As expected, rates of anxiety and mood disorders were increased with some suggestion of differences across the various systems and categories. Interestingly, the prototypic approach to the diagnosis of AS was associated with higher rates of the broader autism phenotype in relatives of probands with a diagnosis of AS in that system.

Similarly, Ghaziuddin (2005) examined family psychiatric history in nearly 60 subjects (diagnosed using DSM-IV). They noted that all subjects (mean age, 13 years) had normal IQ, significant social deficits, special interests, and pedantic speech, but no previous diagnosis of autism. Of the siblings of these individuals, four had AS (no cases of autism) and rates of AS were increased in other first-degree relatives. Both schizophrenia and depression were also more frequent than in the comparison group with HFA. Thus it appears that, perhaps not surprisingly, the stringency of diagnostic approach has major implications for research findings and that lack of consistency in diagnostic approach remains a major complication for interpretation of available research (Susan, Libby, Wing, Gould, & Gillberg, 2000).

NEUROPSYCHOLOGY

The area of neuropsychology has, without doubt, been one of the most productive in the literature on AS and its similarities and differences from autism and PDD-NOS. This issue is discussed in greater detail by Tsatsanis (Chapter 3, this volume). Differences in patterns of neuropsychological functioning are of considerable theoretical and practical interest. From the research side such differences can suggest potential differences in pathogenesis, mechanisms, or even relative to end phenotypes. Many of the topics that continue to be the focus of research were raised by Asperger in his original (1944) paper—for example, relatively preserved or advanced verbal

abilities, motor difficulties, clumsiness, and so forth. From the clinical side these issues may have particular importance for differences in intervention strategies. As has been discussed previously, the diversity in diagnostic practice and approach is a considerable complication in the comparison of research studies, as are other methodological issues (e.g., small sample size and lack of statistical power or diversity in ages of subjects studied). Accordingly, when relevant, the possible limitations of studies are noted.

Asperger's original report (1944) suggested some areas of variability in cognitive profile. In subsequent reviews of Asperger's cases (Hippler & Klickpera, 2003, 2005), differences in cognitive profiles were noted, with Verbal IQ preserved relative to performance or nonverbal abilities. A series of studies using more stringent diagnostic approaches has also demonstrated significant scatter in IQ test profiles—but a pattern of scatter rather different from that usually seen in autistic disorder, in which verbal, rather than nonverbal/perceptual, skills are preserved (e.g., Ehlers et al., 1997; Ghaziuddin, Mohammad, & Mountain-Kimchi, 2004; Koyama, Tomonori, Tachimori, Hisateru, Osada, et al., 2007; Lincoln, Courchesne, Allen, Hanson, & Ene, 1998; Ozonoff, South, & Miller, 2000). In addition, the specific pattern of assets and deficits has also been noted to be highly consistent with a nonverbal learning disability (NLD; Rourke, 1989), has been proposed to be characteristic of individuals with AS, and potentially could serve as a source of external validity for the syndrome (Klin et al., 1995; Klin & Volkmar, 1997).

The NLD subtype, which emerged from research on children with learning disabilities, represents a distinct profile of neuropsychological functioning characterized by better developed verbal skills, relative to visual, tactile, and complex motor skills, in addition to deficits in novel problem solving and concept formation. In Rourke's (1989) model, it is proposed that this pattern of neuropsychological assets and deficits eventuates in a specific pattern of strengths and weaknesses in academic (e.g., well-developed single-word reading and spelling relative to mechanical arithmetic) and social (e.g., overreliance on language to learn about themselves and the world and to navigate social situations, with less efficient use of nonverbal information) functioning. Individuals with NLD are increased at risk for internalizing disorders such as depression and anxiety. Clearly descriptive accounts of individuals with AS show considerable overlap with the clinical manifestations of the NLD syndrome.

In addition, an extensive investigation comparing the neuropsychological profiles of well-characterized individuals with AS or HFA offered strong support for a relationship between AS and NLD (Klin, Sparrow, et al., 1995). The sample in this study consisted of 19 individuals with HFA and 21 individuals with AS, diagnosed using stringent criteria modified from ICD-10 (World Health Organization, 1993). The neuropsychological records showed that a highly significant association between AS and NLD was obtained (n = 18) but not for autism (n = 1). Areas of deficit associated

with AS include problems with fine motor skills, visual–motor integration, visual–spatial perception, nonverbal concept formation, gross motor skills, and visual memory. Similarly the IQ profiles revealed a significant verbal–nonverbal split, with higher verbal than nonverbal skills; this pattern was not seen in the HFA group. Subsequent studies have both supported the association with NLD (Gunter, Ghaziuddin, & Ellis, 2002) and questioned it (Ambery, Russell, Perry, Morris, & Murphy, 2006), with other work focused more broadly on patterns of neuropsychological strength/weakness in ASD in general (see Tsatsanis, Chapter 3, this volume; Tager-Flusberg & Joseph, 2003; Noterdaeme, Wriedt, & Hohne, 2010). Differences in verbal fluency between the two conditions have been reported (Spek, Schatorjé, Scholte, & van Berckelaer-Onnes, 2009), although differences in diagnostic approach must be considered in evaluating these studies. Clearly, the study of distinctive cognitive profiles in AS, in particular, and in the broader autism spectrum group remains of much interest.

A smaller body of work on memory issues in AS suggests some differences relative to specific functions. For example, fact recall and semantic memory may be a strength, but aspects of spatial working memory (Morris et al., 1999) and visual memory (Ambery et al., 2006) may be impaired and impact on social processes. Similarly, difficulties may be observed in the range of abilities subsumed within the concept of *executive functions*: problem solving, forward planning, self-monitoring, set shifting, inhibition, organization, flexibility, and working memory (Bennetto, Pennington, & Rogers, 1996; Goldstein, Johnson, & Minshew, 2001; Minshew, Meyer, & Goldstein, 2002; Ozonoff, Strayer, McMahon, & Filloux, 1994; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006; Joseph, McGrath, & Tager-Flusberg, 2005). As with memory problems, these difficulties also can adversely impact social judgment and social decision making. Clearly, executive functioning difficulties are also seen in autism, although some suggestion of difference has been reported (e.g., Kleinhans, Akshoomoff, & Delis, 2005).

Motor and sensory issues have been the focus of some research resources. A range of problems, including in motor integration and broader relationships to sensory issues, have been noted as well (see Tsatsanis, Chapter 3, this volume). Consistent with Asperger's original report, persistent motor difficulties in AS samples (e.g., Ghaziuddin, Butler, Tsai, & Ghaziuddin, 1994; Manjiviona & Prior, 1995; Miyahara et al., 1997; Green et al., 2002) have been reported. Although suffering from various shortcomings, the earliest work in this area suggested significant impairment in motor skills in patients with AS, as compared to those with autism (e.g., Tantam, 1988a; Gillberg, 1989; Szatmari, Bartolucci, et al., 1989). Subsequent work has been better controlled and more equivocal in its findings, although again it suffers from the issues of diagnostic consistency (Ghaziuddin et al., 1994; Manjiviona & Prior, 1999; Ghaziuddin & Butler, 1998). A major issue in the interpretation of this literature has been a

general lack of attention to important changes in the nature of motor tasks; for example, over time social or imitation elements may be more central. An important and unresolved issue is the degree to which difficulties with organization and executive function impact motor difficulties (e.g., Rinehart et al., 2006). The severity of motor skills deficits has been noted to correlate with overall severity of AS (Hilton, Wente, LaVesser, Ito, Reed, et al., 2007).

Motor difficulties have both clinical and research implications. Difficulties in these areas present obstacles for information processing and pose challenges for learning, particularly when combined with strengths in other areas (e.g., verbal). The child may learn, over time, to develop compensatory abilities even when core difficulties remain. A further complication in interpreting results obtained.

Compared to autism, work in this area for AS is less extensive. Dunne and colleagues (Dunn, Myles, & Orr, 2002) reported difficulties relative to both under- and overresponsiveness on the Sensory Profile (Dunn, 1999). Other studies note differences in tactile sensitivity (Blakemore et al., 2006; Cascio et al., 2008). Similarly, studies of visual perception have noted differences relative to perceptual organization (Tsatsanis et al., in press). In individuals with AS, difficulties with organization and with seeing the "whole" image both impact on recall.

Issues of auditory processing suggest similar areas of difficulty in both children (Lepistö et al., 2006; Kujala et al., 2007) and fathers as well (Korpilahti et al., 2007). These difficulties may contribute to communication problems more generally.

Despite the limitations, the bulk of available evidence provides reasonably strong support for the notion that motor impairment is frequent in AS (and more frequent than in autism, although the evidence here is less strong). A major complication is the degree to which motor and sensory issues are (usually) intertwined with other developmental processes and the potentially very significant impact that social dysfunction may have on motor processes.

PSYCHIATRIC COMORBIDITIES

Issues of psychiatric comorbidity are complex (see Volkmar & Woolston, 1997; Rutter, 1997; Westphal, Kober, Voos, & Volkmar, Chapter 9, this volume). Comorbidities also appear to vary significantly over the course of development, with higher presenting complaints of attention and impulse problems in children but greater rates of mood difficulties and disorders in adolescents and adults. One reason, of course, for the greater interest in this topic is the substantially greater verbal abilities of individuals with AS, as compared with individuals who exhibit more classic cases of autism, wherein language problems limit the usefulness of many instruments.

Attentional problems have historically been one of the most frequent clinical complaints for children with AS, often as an initial presenting complaint, and have been the focus of some research (e.g., Hanson, 2003; Rinehart, Bradshaw, Brereton, & Tonge, 2001; Rinehart, Bradshaw, Moss, Brereton, & Tonge, 2001; Semrud-Clikeman, Walkowiak, Wilkinson, & Minne, 2010; Tani et al., 2006). These deficits can be expressed as isolated attentional problems, in the form of impulsivity, or as a combination of the two. In contrast to the typical child with attention-deficit/hyperactivity disorder (ADHD), individuals with AS may demonstrate excellent attention in some areas (e.g., in a focus on a topic of interest), but social and organizational difficulties contribute to difficulties with attention in other situations—a pattern rather different than seen in autism (see Rinehart et al., 2001). Paradoxically the "hyperfocus" on a topic of special interest can coexist with other types of attentional problems. The complex processes involved in attention to more complex tasks have been reviewed elsewhere (e.g., Townsend, Harris, & Courchesne, 1996; Wainwright-Sharp & Bryson, 1996; Hanson, 2003; Joshi et al., 2010), although the literature specific to AS is rather limited (see Pelphry et al., Chapter 13, this volume). The data are of interest in that they seem to suggest difficulties rather the opposite of those more typical in classical autism; that is, difficulties with sustained attention but not on shifting attention. The caveat is that the studies are few and constructs across studies not necessarily measured the same way; but this area is worthy of further and more systematic study. The ASD criteria published in DSM-5 permit concurrent diagnoses of ASD and ADHD, a change that will hopefully foster deeper understanding of the overlap between social and attentional difficulties in individuals with AS. As discussed by Westphal et al. (Chapter 9, this volume), attention difficulties are a frequent cause for pharmacological intervention.

In adolescents and adults, anxiety and depression are very frequent (Hanson, 2003; Humphrey, 2008; Kim, Szatmari, Bryson, Streiner, & Wilson, 2000). Anxiety may come from an appropriate awareness of the difficulties with social information processing, feelings of being overwhelmed by demands of typical peer interactions, and an awareness of the lack of understanding of the nuances of the social world. Depression may be viewed as a result of repeated failure experiences, over time, coupled with an awareness of social isolation and lack of interpersonal supports. Estimates of the rates of comorbid anxiety and/or depression in individuals with AS are high, with over 50% exhibiting one or more of these problems (Ellis, Ellis, Fraser, & Deb, 1994; Fujikawa, Kobayashi, Koga, & Murata, 1987; Ghaziuddin & Butler, 1998; Ghaziuddin, 2002; Ghaziuddin & Greden, 1998; Green, Gilchrist, Burton, & Cox, 2000; Howlin & Goode, 1998). On the other hand, individuals with HFA may also be at risk for these problems, and some reports find no differences between groups (e.g., Szatmari et al., 2000), although this may reflect the particular diagnostic approach used and the age of the sample. It has been our experience that

more able individuals with autism suffer less from depression and anxiety partly because of their lack of social interest and motivation, but this topic continues to merit study. In one report from our center, rates of these conditions in both probands and family members were higher in individuals with AS (Klin, Pauls, et al., 2005).

Other conditions have been described in association with AS (see Folstein, Chapter 14, this volume), although often this literature is based on case reports, which are then difficult to place in a broader context. Conditions observed have included Tourette syndrome (Kerbeshian & Burd, 1986; Littlejohns, Clarke, & Corbett, 1990; Marriage, Miles, Stokes, & Davey, 1993), obsessive–compulsive disorder (Fontenelle et al., 2004; Gallucci, Hackerman, & Schmidt, 2005; Kraemer, Delsignore, Gundelfinger, Schnyder, & Hepp, 2005; Ruta, Mugno, d'Arrigo, Vitiello, & Mazzone, 2010; Wendland et al., 2008) and gender identity disorder (Gallucci et al., 2005; Kraemer et al., 2005). Reported associations with psychotic conditions have included both major depression and bipolar disorder as well as schizophrenia (Stewart et al., 2006; Fontenelle et al., 2004; Duggal, 2003; Bejerot & Duvner, 1995; Gillberg, 1985; Wolff, 1998). Difficulties with diagnosis arise because of the social isolation of individuals with AS and their tendency to verbalize many of their thoughts (Ryan, 1992). One small study suggested differences in indices of thought disorder in AS versus in HFA (Ghaziuddin, Leininger, & Tsai, 1995). Some attention has focused on the association of schizophrenia with AS and suggested that AS might, in some sense, be a "bridging condition" (Wolff & McGuire, 1995). Some support for this possibility is noted in the literature (e.g., Nagy & Szatmari, 1986), although other studies fail to support it (Ghaziuddin et al., 1995). Family studies, although limited, do not seem to suggest higher rates of schizophrenia in family members; rather, mood and social problems appear more frequently (and are discussed subsequently).

Another line of work, again mostly limited to case reports, has noted conduct problems and violent behavior (e.g., Mawson, Grounds, & Tantam, 1985; Baron-Cohen, 1988; Hall & Bernal, 1995; Everall & LeCouteur, 1990; Scragg & Shah, 1994). In their review of the topic Ghaziuddin, Tsai, and Ghaziuddin (1991) found little support for this notion. Similar findings are noted by Hippler, Viding, Klicpera, and Happé (2010). In our experience it is much more likely that individuals with AS are victims and not victimizers; they are often teased and bullied (e.g., Sofronoff, Dark, & Stone, 2011), and their oddity and isolation make them frequent targets for others; this issue is addressed in greater detail by Woodbury-Smith, Chapter 12, this volume). Somewhat paradoxically, it is their tendency to rely rigidly on rules that may pose challenges for them (i.e., via failures to make appropriate exceptions and accommodations), and this can, at times, bring these individuals into conflict with school and legal authorities. With the onset of adolescence and increased sexual interest, lack of sophistication may lead them to make highly one-sided and inappropriate overtures

(e.g., verbal sexual requests). At times, an all-absorbing interest may even lead to legal difficulties.

The specificity of difficulties associated with AS, rather than with HFA, remains debated, but strong suggestion of differential patterns has emerged, and certainly better verbal skills would suggest important implications for treatments (see Volkmar, Klin, & McPartland, Chapter 5, this volume). Clearly, more systematic and comprehensive study is needed to understand both clinical service implications and, more broadly, potential implications for research conceptualizations.

SOCIAL FUNCTIONING

Over the past two decades research has increasingly focused on understanding the social difficulties associated with autism and AS. One major line of work has focused on difficulties in the ability to understand the mental life of others and their own subjectivity—what is usually termed *theory-of-mind* abilities (ToM; Baron-Cohen, 1989). The initial assumption was that a fundamental deficit in this area accounted for a major portion, if not all, of the individual's social disability. Although several lines of work have now questioned this view as overly simplistic, studies differentiating the performance of individuals with AS or HFA have been conducted and are of interest in clarifying the nature of the social disturbance seen in these conditions. For example, Ozonoff et al. (Ozonoff, Pennington, & Rogers, 1991; Ozonoff, Rogers, & Pennington, 1991) noted differences, with individuals with autism exhibiting significant impairment in relation to both AS and an age- and IQ-matched control groups. Similar results were noted by Bowler (1992) and Ziatas, Durkin, and Pratt (2003). Consistent with Asperger's (1944) original impression regarding the later ages of parental concern reported in AS, various studies have suggested that the social issues (e.g., problems in joint attention and play) are frequent early signs of autism in very young children (Baird et al., 2000), whereas parental concern arises later for individuals with AS (Klin, McPartland, et al., 2005).

Other work has suggested differences in the expression of ToM skills in the two conditions (Kaland et al., 2002). A difference was also observed in one positron emission tomography (PET) study using ToM tasks (Happé et al., 1996). No differences have also been reported, although issues of diagnostic assignment complicate interpretation of all these results (e.g., Dahlgren & Trillingsgaard, 1996). On balance, Frith (2004) concluded that the available data to that point suggested a milder degree of social impairment (at least, as expressed in ToM tasks) for individuals with AS, also noting that this finding might simply reflect higher verbal abilities.

Careful review of Asperger's original report emphasized the nature of adaptive ("real life") social difficulties. Van Krevelen (1971) emphasized this point in his description of the lack of empathy and intuitive

understanding and the difficulties in dealing with face-based social interaction. The tendency of individuals with AS to use words, logic, and thinking to negotiate the social world is encompassed in this view and offers an additional area of relevance both to differentiation from HFA and for purposes of intervention (see also Klin, Jones, Schultz, & Volkmar, 2003, who emphasize the importance of ecological context on results obtained). Tager-Flusberg, Joseph, and Folstein (2001) differentiated social perception for social reasoning and suggested that whereas in autism both are adversely impacted, in AS it is social perception, rather than cognition, that is primarily involved. As discussed below and elsewhere in this volume, this observation has important implications for intervention.

ONSET PATTERNS

In contrast to Kanner (who speculated that the condition he described was congenital), Asperger suggested that parents typically were not concerned for some years, although they had frequently reported an atypical pattern of early development characterized by precocious language skills and delayed motor abilities. This pattern was consistent with his description of parents frequently reporting that children with AS "talk before they walk," that words become an early and enduring "lifeline" for social connectedness, and of his eventual impression that the condition he described was, in some respects, more a personality trait than a developmental disorder. The observations of relatively more preserved patterns of verbal (as compared to nonverbal or performance) abilities are consistent with this description. On the other hand, it is possible that the delay in parental concern might reflect other factors: for example, the higher the cognitive potential, as a group, of the children with AS, the better the verbal skills (a frequently used proxy of overall ability that can mask areas of disability). Similarly, it might be that, to some extent, social interest is more preserved in AS and/or that it takes a different form than in autism.

Careful and meticulous history taking often does reveal some slightly unusual aspects of early development; for example, the child's speech may be precocious, but the "little professor" quality noted by Asperger may predominate with odd (for age) language use, pedantic speech quality, and so forth. Interestingly, parents do *not* typically report obvious signs of social disability (although these become much more obvious when children are required to interact with typical peers); attachment to family members seems unremarkable, and the level of social disability (at least at this age) appears to be more subtle usually than that typically seen in autism. Interactions with other children (peers or family members) may be more a source of early concern, in contrast to interactions with parents and older individuals who "scaffold" the child's social overtures and typically assume a less demanding social interactional pattern than peers. Accordingly, as

Asperger first suggested, it remains typical for parental concern to arise only as the child is routinely exposed to typical peers (e.g., in nursery and preschool settings) (see Klin, McPartland, et al., 2005).

The issue of onset in AS was considered in a recent study by Kamp-Becker and colleagues (2010), which considered early presentation of AS and ADHD (the latter condition also diagnosed later than autism and one frequently confused with AS in younger children). Parents of large groups of children with AS or ADHD were interviewed, and the authors reported that 10 features distinguished the groups, including problems in social development and communication, repetitive behaviors, and interests.

Clearly much more work in this area is needed, given our necessary reliance on parent report; that is, identification of younger children with AS would contribute significantly to formation of a research literature. The strong potential for children (of all types) to develop specific compensatory mechanisms and learn, at least eventually, to rely on areas of strength to cope with social disability also underscores the value of identifying the condition in younger children.

SPECIAL INTERESTS

In autism the issue of special interests has, in fact, tended to center in important ways on unusual *abilities*: on either peak skills (e.g., block design in IQ tests) or, in a small percentage of cases, on some isolated or "savant" ability (Hermelin, 2001). In Asperger's (1944) original description, he was careful to point out that the children he described had very significant and circumscribed *interests* that both interfered with their learning (e.g., of other skills) and also intruded on the family's life. From Asperger's description the interests of the children he described tended to center on amassing facts about some isolated area of interest, whereas the cases described by Kanner (1943) were more likely to have special abilities involving memory (e.g., for birthdays) or in terms of visual nonverbal abilities. As noted previously, Robinson and Vitale (1954) provided vivid descriptions of three children with unusual and all-encompassing interests that were very suggestive of Asperger's earlier work (of which Robinson and Vitale were unaware). In their report one child was focused on aspects of chemistry, another on astronomy, and a third on a transportation system. Kanner (1954) was the discussant of the paper and noted similarities and differences from the children he had described with autism (e.g., the interference of the behavior as was true of resistance to change behaviors in autism and significant social-communication problems, but also the context of more preserved social skills use of special interests to try to connect with others).

Given the early interest and Asperger's clear "demarcation" of this as an area of possible differentiation from autism, focused work on the topic has been remarkably limited. Baron-Cohen (1989) provided results

of a survey of a large group of children with ASD whose focus was obsessions (in some ways, different from special interests). They noted a high proportion of interest in fact-based knowledge in science and taxonomy. South, Ozonoff, and McMahon (2005) studied 40 higher-functioning individuals (with autism or AS) and reported interests in a range of topics that included science (space and physics), animals, video games, dinosaurs, and so forth. Interests were rather similar in both clinical samples. Klin, Danovitch, Merz, and Volkmar (2007) studied nearly 100 individuals with IQs in the normal range and a mix of diagnoses, using a special interest survey. The parent-completed ratings included descriptions of topic and degree of interference. Topics were grouped into eight overarching categories (facts and verbal memory, facts and visual memory, sensory behaviors, math, classification, dates/time, hoarding, and letters/numbers). Over 250 specific topics of interest were coded for the 96 individuals. Reliability of coding was high, using a chance-corrected statistic. Some developmental trends were noted, with shifts in interest over age (from preschool to school age). Interestingly, the degree of interference of these skills, as reported by parents, .correlated significantly in a negative direction with Vineland socialization scores for preschoolers and similarly in a negative direction with communication abilities in the school-age children. About two-thirds of the preschoolers and three-fourths of the school-age children had interests that centered around amassing facts, and it was noted that particularly when children were left to their own devices, they tended to gravitate to their special area of interest.

Other investigators have described the longitudinal course of special interests in AS. For example, Atwood (2003) noted that both the number and focus of the special interest shifts over time (with a shift sometimes being triggered by a specific event). Atwood also emphasized (as did Asperger) the degree to which the family may be forced to accommodate the child's special interest. This important point is very much in keeping with Asperger's original emphasis on how these interests potentially interfered with the child's learning and development as well as with family life. Accordingly, some intervention strategies focus on reducing or minimizing, to the extent possible, the degree to which these interests serve as a barrier to social interaction. On the other hand, sometimes these interests can be used productively, particularly if they have some potential social or ultimate vocational utility. Interests that are less highly unusual and idiosyncratic may also be easier topics of conversation and social interaction.

NEUROBIOLOGY AND GENETICS

Various lines of work have focused on neurobiological factors as possibly differentiating AS from HFA. As in other areas, the lack of consistency in diagnostic approach and small samples (particularly with neuroimaging

studies) pose major obstacles for interpretation. As with autism, early work (particularly case reports) suggested potential associations of AS with birth complications and various medical conditions (Miles & Capelle, 1987; Tantam, Evered, & Hersov, 1990; Ghaziuddin, Shakal, et al., 1995; Haglund & Kallen, 2011).

Given possible differences in neuropsychological profiles, neuroimaging studies are of great interest—particularly given the apparent similarity of AS to the concept of "right-hemisphere syndrome" or "developmental disabilities of the right hemisphere" (Ellis et al., 1994; Gold & Faust, 2010; Gunter et al., 2002; Sandson, Manoach, Rentz, & Weintraub, 1994; Semrud-Clikeman & Hynd, 1990; Shields, 1991; Weintraub, Mesulam, & Kramer, 1981). In essence, this model suggests relative preservation of the left cerebral cortex (reflected in the many aspects of language preserved in AS but not in HFA), whereas right-hemisphere deficits would be reflected in social (pragmatic) and semantic problems and perhaps the NLD profile).

The available literature does suggest some areas of possible difference relative to cortical organization (Berthier, Starkstein, & Leiguarda, 1990), gray tissue abnormalities (McAlonan et al., 2008), limbic areas (McAlonan et al., 2002), and abnormalities in the temporal lobe (Jones & Kerwin, 1990). One recent meta-analysis (Yu, Cheung, Chua, & McAlonan, 2011) found significant differences, with reduced gray matter volume in the amygdala, hippocampal gyros, and prefrontal lobe. Semrud-Clikeman and Fine (2011) noted abnormalities in the occipital region, although others, such as, Via, Radua, Cardoner, Happé, and Mataix-Cols (2011), reported minimal differences. In contrast, Semrud-Clikeman and Fine (2011) noted that individuals with NLD and AS were more likely to exhibit specific abnormalities. Case reports from our center have included a father and son with AS (Volkmar et al., 1996) who exhibited right-hemisphere abnormalities and individual also with right-hemisphere abnormalities (Volkmar, et al., 2000; Korpilahti et al., 2007) and problems suggestive of NLD. Differences have also been found using proton magnetic resonance spectroscopy (see Murphy et al., 2002, 2006; Lotspeich et al., 2004; Berthier, Bayes, & Tolosa, 1993). White matter differences relative to normal controls and those with autism have been observed (Bloemen et al., 2010; McAlonan et al., 2008; McAlonan, Cheung, et al., 2009). Prefrontal cortex problems have also been noted in AS (Iwanami et al., 2011). One recent study suggested differences in cortical folding in the higher lobe as well as individuals with autism, but not AS, having higher folding levels (Jou, Minshew, Keshavan, & Hardan, 2010), although others (Williams, Goldstein, Kojkowski, & Minshew, 2008) did not notice this pattern (see also Hardan et al., 2008, on possible differences in other areas).

Given Asperger's (1944) initial observation of high rates of social disability in the fathers of the children in his cases, the issue of genetic mechanisms is of great interest, particularly since the recognition of the "broader

autism phenotype" in family members of children with autism only became apparent many years after Kanner's first description of autism. There have been reports of families with multiple children with AS or with a positive family history for the condition (Cederlund & Gillberg, 2004; Ghaziuddin et al., 1993; Gillberg, 1991). On the other hand, and starting with Wing's (1981) report, other investigators have suggested strong links between AS and autism (Folstein & Santangelo, 2000; see also Folstein, Chapter 14, this volume). Complexities around diagnosis complicate the interpretation of the limited work available. For example, DeLong and Dwyer (1988) reported high rates of AS in relatives of individuals with HFA as well as higher rates of bipolar disorder in family members of individuals with AS. Many case reports have emphasized the increased rate of social disabilities in first-degree relatives (Bowman, 1988; DeLong & Dwyer, 1988; Gillberg, Gillberg, & Steffenburg, 1992; Volkmar et al., 1996). In one study Klin, Pauls, and colleagues (2005) noted that about half of first-degree relatives of AS probands exhibited high rates of social vulnerability if a strict diagnostic approach to AS was used (further underscoring the importance of use and reporting of the diagnostic approach).

The observation that autism and AS might co-occur in the same family has been suggested to indicate that the two conditions are related. The complexity of autism genetics (Rutter, 2005) offers the possibility that with multiple genes involved in autism, some subset of genes might also be involved in AS (one of many possibilities), but this, of, does not necessarily imply that the two disorders are "the same" in a fundamental sense. The literature on the genetics of AS, per se, remains small (e.g., Anneren, Dahl, Uddenfeldt, & Janols, 1995; Saliba & Griffiths, 1990; Bartolucci & Szatmari, 1987; Tentler, Johannesson, Johansson, Rastam, Gillberg, et al., 2003) and the issue remains important, with recent work suggesting areas of similarity and difference (Sciutto & Cantwell, 2005).

COURSE AND OUTCOME

The relatively recent recognition of AS complicates, to some degree, interpretation of data on outcome. Howlin (2005) noted that early differences from HFA tend to diminish over time (interestingly, the same is true for autism, more broadly defined, and for severe language disorder). In some ways there is a general tendency toward improvement over time, although adolescence may provide special risks for teenagers with AS, given increased social and academic demands and looming challenges of work or college (Volkmar & Wiesner, 2009). There does appear to be increased risk for comorbid problems, particularly anxiety and depression. Neuromata vulnerabilities and organizational problems often appear to persist (see Murphy et al., 2006; Brown & Wolf, Chapter 11, this volume) also appear to persist.

For adults AS can present with sometimes subtle difficulties, especially in communication, social relationships and interests (see Powers & Loomis, Chapter 10, this volume), underscoring Asperger's original impression that the condition he described was more a personality style/pattern. It is frequently noted that either with help or on his or her own, the individual with AS may learn to use a host of compensatory strategies. For example, in one case seen in our clinic a child managed to markedly increase his nonverbal IQ by learning (on his own) to turn nonverbal problems into verbal ones (making Block Design on the IQ into a verbal problem of matrix algebra; Volkmar et al., 1996).

Studies of AS frequently suggest that, for many individuals, improvement over time is sufficiently great that, as adults, they no longer qualify for or need this diagnosis (i.e., they move past the boundary of disorder into the broader category of eccentricity in the normal population). This transition may happen in as many as 20%, or so, of individuals (Woodbury-Smith & Volkmar, 2009). As noted previously, there does appear to be increased risk for anxiety and depression, which can impact functional outcome (Woodbury-Smith & Volkmar, 2009; McPartland & Klin, 2006).

Although comparison to autism is complex, if one considers the entire range of autism, the outcome in AS is much better (Larsen & Mouridsen, 1997; Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008; Szatmari, 1991). The more complex and interesting question is the issue of outcome in AS as compared to the most cognitively able persons with autism.

Very long-term follow-up studies as well as cross-sectional studies of various age groups (with careful report of diagnostic approach used) would help to clarify these issues. Positive factors in AS include better preserved verbal abilities along with a strong desire for social contact. These factors are reflected in our observation that whereas we have rather rarely met a person with autism who is married, it is not uncommon to find individuals with AS who have done so (and, in fact, support books and resources for spouses are now available; Renty & Roeyers, 2007).

As a practical matter many adults with AS face various challenges in securing and maintaining employment. These challenges include persistent vulnerabilities in social abilities, pragmatic communication, and organization (Mawhood & Howlin, 1999). These challenges can take the form of poor adaptive skills, comorbid psychiatric conditions, and vocational issues and challenges—all of which require appropriate support. Supportive placements that maximize strengths and minimize social and neuropsychological challenges are important. Thus jobs involving less intensive social demands, less time pressure, and fewer organizational/executive skills and decisions are often better (Mawhood & Howlin, 1999; Muller, Schuler, Burton, & Yates, 2003). Computer-related occupations (with minimal direct interpersonal demands) may often be highly appropriate.

TREATMENT IMPLICATIONS

The issue of treatment implications of AS is discussed more extensively in the remainder of this volume. For purposes of this chapter our focus is specifically on the issues related to AS as a diagnostic concept apart from other disorders (see Volkmar et al., Chapter 5, this volume). As we have discussed elsewhere (Klin, Pauls, et al., 2005; Klin, McPartland, et al., 2005), treatment is essentially supportive and symptomatic, with some degree of overlap in treatment approaches relative to more able persons with autism but also with some important potential differences. The similarities include supporting social skill acquisition. Differences involve (1) different neuropsychological profiles (typically with much more preserved verbal skills in individuals with AS as compared to HFA) and (2) usually higher levels of social motivation in individuals with AS. Over the last several years the body of work in this area has increased dramatically with several hundred papers focusing on treatment issues. We emphasize that, in considering treatment options, it is also important to maintain an awareness of any comorbid conditions present and the possibility that these may be addressed through psychotherapy or medication (see Westphal et al., Chapter 9, this volume).

Pharmacological treatments can be used to address inattention, anxiety, or depression, although, to date, the core social disability has not been directly targeted (see Westphal et al., Chapter 9, this volume; Tsai, 2007, for reviews). Unfortunately, much of this literature has consisted of case reports or open clinical trails; double-blind studies focusing solely on the AS population are limited.

Psychological and educational interventions have been much more extensively discussed in the literature, with several books on the topic highlighting specific strategies (e.g., Ozonoff, Dawson, & McPartland, 2002; Atwood, 2003; Howlin, 1999; Myles, 2005; Chapters 5–8, this volume). As might be expected, interventions have typically focused on facilitating better verbal skills and particular areas of strength in AS, with an emphasis on developing and implementing compensatory strategies for weaknesses and providing environmental supports to maximize effective learning and functioning, with the important provision that all such supports be designed in the context of a comprehensive assessment (Klin et al., 2005). Typical supports include those involved in teaching basic social and communication skills, adaptive functioning, and (depending on what is developmentally appropriate) academic or vocational skills; as with autism, issues of generalization across settings are important (Lee & Park, 2007).

We have emphasized the importance of explicit teaching and rote learning, using a parts-to-whole verbal instruction approach (Klin, McPartland, et al., 2005). Motor (including graphomotor and visuomotor) deficits also require support via physical and occupational therapies and, where available, the use assistive technologies (e.g., using a laptop

to type assignments rather than writing, using electronic organizers). Occupational therapy that emphasizes the integration of activities with the learning of visual–spatial concepts and orientation, as well as body awareness, has been advocated. Similarly, an explicit focus on adaptive skills and generalization has been repeatedly emphasized as critical (Lee & Park, 2007). Unfortunately, the tendency of individuals with AS toward a rigid focus on familiarity and routine can pose challenges for generalization; on the other hand, these same tendencies can be used to encourage positive coping strategies.

Behavioral and emotional issues are frequently challenges to effective intervention and arise because social disability is associated with problems in regulation and self-awareness. The use of explicit problem-solving strategies such as rules/scripts/"self-talk" can be helpful. An increased body of work has focused on strategies dervived from cognitive-behavioral therapy (CBT; e.g., Wood, Drahota, Sze, Har, Chiu, et al., 2009; Cardaciotto & Herbert, 2004; Weiss & Lunsky, 2010; Farrugia & Hudson, 2006). Speech pathologists can also be helpful (both through direct intervention and consultation) in focusing on development of pragmatic skills. In general, the focus should be on explicit teaching/modeling/feedback of relevant tasks such as self-monitoring, topic management, turn taking, conversational rules, volume of speech, prosody, and so forth (Paul, Orlovski, Marcinko, & Volkmar, 2009; Shriberg et al., 2001; Weintraub et al., 1981; Paul, Landa, & Schoen, Chapter 4, and Rubin, Chapter 6, this volume).

Unfortunately, the social skills gap begins to increase more dramatically as individuals enter adolescence, often further exacerbating social isolation and leading to the potential for anxiety as well as the likelihood of bullying (Shtayermman, 2007; Carter, 2009; Dubin, 2007; McManus, 2008; Myles et al., Chapter 7, this volume). The latter problem increases dramatically in adolescence for many individuals, given their apparent good language skills, which can mislead both teachers and peers. Lack of appreciation of social nuance and difficulties in understanding humor and figurative language lead to further isolation, since the teenager with AS is frequently laughed at (for behaviors that others understandably see as humorous but are not usually meant to be); conversely, not being able to successfully use humor with peers (making what are meant to be jokes either about arcane topics of special interest or topics that usually would be considered too sensitive for discussion; see McCormick, 2001; Samson & Hegenloh, 2010) is equally stigmatizing.

Although evidence-based research is relatively limited, it does appear that a range of procedures can be used to teach social skills. These include direct work with a therapist, social skills groups, and peer modeling (see Paul, 2003). As with other areas (and in some ways even more so), the complexity of social interaction requires explicit teaching of rules (what can and can't be discussed and with whom), conversational and interactional

strategies, and so forth (Kaland, Mortensen, & Smith, 2011; Rubin & Lennon, 2004; Saulnier & Klin, 2007). The individual's often strong motivation to establish friendships and peer connections and the often strong verbal and rote-memory skills are important strengths than be used effectively in this process. The range of social skills teaching methods has also dramatically increased over the past decade and can be used for individuals of various ages (see Beaumont & Sofronoff, 2008; Macintosh & Dissanayake, 2006; Muller, 2010; Patrick, 2008). These groups may or may not involve typically developing peers and sometimes make excellent use of siblings as part of the group process. Psychotherapy (particularly if more conceptualized around a longer-term "life coaching" model) can be productive for this population as well (Munro, 2010; Mero, 2002; Volkmar, et al., 2011).

ASPERGER SYNDROME AND DSM-5

DSM-5, published in May 2013 (American Psychiatric Association, 2013), removed AS as a formal diagnosis. The decision to "drop" AS as a formal diagnosis has been the source of much controversy (see Volkmar & Reichow, in press). The broad conceptual focuses of DSM-5 likely impacted this decision by eliminating "subthreshold" categories, subtypes of PDDs used inconsistently by clinicians, alongside an emphasis on standardized diagnostic instruments for criteria. These problems were particularly relevant for AS, given the continued discussions of how best to "draw the line" separating the condition from HFA, the perception by many of AS as a specific personality style (as Asperger himself originally suggested; see also Rutter, 2011), and the relative dearth (not surprisingly, given the other controversies) of extensively developed diagnostic instruments demonstrating specificity for AS versus other forms of ASD (Taheri & Perry, 2012).

SUMMARY AND DIRECTIONS FOR THE FUTURE

The official recognition of AS as a diagnostic concept in 1994 markedly increased both scientific and public awareness of this condition (Wing, 2005). This increased awareness has resulted in a substantial and growing body of research and a similarly growing body of work focused on intervention strategies. This body of work also is a testament to an important clinical need.

In reviewing this work, it is clear that major differences in diagnostic approach have remained, reflecting both the DSM/ICD ambivalence about the category, but also, to some extent, the debate on validity of the concept apart from autism and the variability in its usage by clinicians (Lord et al., 2012). Both of these challenge have existed since Wing's (1981) seminal report. The decision to drop (rather than refine) the concept in DSM-5

will complicate research and clinical activities that could further clarify the validity and clinical utility of AS as an official diagnosis. The current state of research on the "validity" of AS as a distinct disorder might best be summarized as "inconclusive," leaving the door open to further research (Volkmar, 2010; see also Ghaziuddin, 2010, 2011; Rutter, 2011). The loss of the diagnostic term may, particularly in the United States, result in a loss of services for individuals residing in states that recognize AS as a handicapping condition. There will be a need to foster awareness of the DSM-5 stipulation that, for individuals previously meeting criteria for one of the PDDs as defined in DSM-IV, eligibility for services should continue even if they are now found not to meet the new set of DSM-5 criteria for ASD (American Psychiatric Association, 2013).

Given what increasingly appears to be the complexity of autism as a condition and the neural basis of social behavior, it seems likely that there may be many underlying paths of pathophysiology that result in it and in autistic-like conditions, so that perhaps the use of the term *autisms,* rather than ASD, might be more appropriate. Within the overarching category it seems likely that the identification of specific and more homogeneous subtypes could enhance both clinical work and research. There is some suggestion, from the data reviewed in this chapter, that a concept closer to that originally proposed by Hans Asperger may be most productive in this regard, but the issue remains an open one.

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