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The Modifier Model of Autism and Social Development in Higher Functioning Children

Peter C. Mundy, **Heather A. Henderson**, **Anne Pradella Inge**, and **Drew C. Coman**
University of Miami, Department of Psychology, Marino Autism Research Institute

Abstract

The study of phenotypic variability in social impairments and comorbid emotional disorders in autism is important because it provides information on phenotypic differences that currently complicate diagnosis, research, and treatment of this disorder. Currently, though, relatively little is known about the processes that contribute to individual differences in social impairments and comorbidity in autism. In this paper, we present a model that suggests modifier processes (MPs), which are not necessarily specific to the syndrome refractor alter the expression of autism and contribute to fundamental behavioral and psychological differences in children diagnosed with this disorder. One MPs involves the somewhat surprising tendency of some children with higher functioning autism (HFA) to make attributions about other peoples thoughts, although they have social cognitive deficits Just as in other children, the attributions of children with HFA are linked to some of their behavioral problems Another MP involves the influence of differences in motivation associated with the behavioral activation and inhibition systems that can be assessed with measures of anterior EEG asymmetry. This dimension of motivation may be linked to how active but inappropriate and withdrawn children with HFA may appear. Third, differences in the self-monitoring of errors among children with HFA appear to be related to individual differences in IQ and social symptom severity in these children. The possible role of these MPs in diagnostic subgroups and differences in treatment responses among children with HFA are discussed. In addition, the role of MPs in understanding the effects associated with specific genetic functions in autism, such as those associated with the serotonin transporter gene (5-HTTLPR), is discussed. A conclusion of this paper is that the varied expression of autism may require that we understand how autism interacts with other non-syndrome-specific processes that are related to individual differences in all people.

DESCRIPTORS

phenotypic variability; comorbity; self-monitoring; motivation and attributional processes; autism

Children affected by autism and other pervasive developmental disorders (PDD) display significant individual differences in social behavior, development, and outcomes (Beglinger & Smith, 2001; Prior et al., 1998). These differences are very clear among older children with higher functioning autism (HFA) (Prior et al., 1998) and can be complicated by the presence of comorbid emotional disturbance, such as anxiety and depression (Kim, Szatmari, Bryson, Streiner, & Wilsonet, 2000). Understanding the nature of these differences is important for several reasons. The study of variability in social impairments and comorbidity in autism may assist in understanding phenotypic (i.e., visible) differences that currently complicate diagnosis, research, and treatment of this disorder (Beauchaine, 2003; Beglinger & Smith, 2001; Piven, 2002). Moreover, because the broader phenotype for autism may be marked by

Address all correspondence and reprint requests to Peter C. Mundy, Department of Psychology, University of Miami, PO Box 248185-0751 Coral Gables, FL 33124-0751. pmundy@miami.edu.

its association with depression- and anxiety-related disorders (Bolton et al., 1998; Piven. 2002; Piven et al., 1991), the study of the interplay between individual differences in comorbidity and social impairments in children with HFA may reveal fundamental features of the underlying pathophysiology of autism (Rutter, 1996). Finally, and perhaps most important, research on social impairments and comorbidity is essential to understanding the specific intervention needs of children with HFA (Bauminger, 2002; Rutter, 1996). Currently, though, relatively little theory or research has been specifically directed to identifying the sources of individual differences in social impairments and comorbidity among children with HFA. To address the need to explore this topic, we initiated a program of research in 1999 to examine the role of several behavioral processes in the prediction of variability in social impairments and comorbidity in children with HFA. For example, this program began with a study that indicated that some HFA children make attributions about others thoughts and behaviors, and this is related to the presence of comorbid symptoms of anxiety and externalizing behaviors. In the course of this program of research, we have begun to articulate and to test what may be a helpful model of developmental psychopathology in autism.

One common view is that phenotypic variability in autism is an outgrowth of multiple syndrome-specific etiological processes or initial causal processes (ICPs) that interact to contribute to differences in the final common expression of autism (see Figure 1). These ICPs likely involve multiple genetic, epigenetic, and neurodevelopmental factors (Dawson et al., 2002). So, for example, the ICPs could involve independent neurodevelopmental factors that affect impairments in face processing, imitation, representational thinking, attention control, and empathy in autism. All children with autism may have some level of deficit in these ICP domains, but they may experience different degrees of impairment across the core problem areas. The different combinations of more or less disturbance in the ICPs problem domains are thought to rise to significant developmental and behavior phenotypic variability among children with autism.

In addition, though, it is always important to keep in mind that although children with autism may be defined in terms of a common set of core problems, these children display a wide degree of inherent variability. When autism occurs it does so against the range of human individual differences we see in all children. The factors that give rise to the range of individual differences we see in all groups of people, such as temperamental inhibition or extraversion, may be regarded as potential modifier processes (MPs) that interact with autism and contribute to fundamental developmental, behavioral, and psychological differences in people affected by this syndrome. These MPs encompass both proximal and distal influences including socialization processes, cognitive style, temperament, and genes that on their own do not necessarily convey risk for autism but instead influence the behavioral phenotypic expression of this disorder (Bauminger, 2002; Meyer, Mundy, Vaughan Van Hecke, & Durocher, 2006; Mundy, 1995; Devlin et al., 2005). The effects of these types of modifiers are not specific to autism. Rather most, if not all forms of psychopathology, are influenced by processes that also give rise to the broad range of individual differences manifest in “typical” human development (e.g., see Beauchaine, 2003). Thus, the modifier model described is a generic set of processes in developmental disabilities. Nevertheless, it may be wise to adopt and adapt this model in work with children with autism to aid in understand puzzling differences in developmental course as well as intervention responsiveness that have been observed for children with this syndrome.

In this paper, we provide an introduction to the application of the modifier model to work with children with autism. Special emphasis is placed on research examining the roles of attribution processes, motivation, and self-monitoring in predicting variability in the course and expression of autism in children classified as HFA. Prior to providing the details of this

research, though, we present a brief outline to place the discussion of this research in the context of the literature on the intervention needs of children with autism.

Children With HFA and Intervention

Children with HFA display IQ and verbal scores above the range of mental retardation (e.g., IQ >70). The HFA designation is used in this report to refer to children with the diagnosis of autism, Asperger disorder, or both because the precision and validity of the criteria used to distinguish HFA from Asperger disorder in the current DSM and ICD nosologies is controversial (Gillberg, 1998; Macintosh & Dissanayake, 2004; Miller & Ozonoff, 2000; Volkmar & Klin, 2001). Recent prevalence estimates for all children with HFA range from 1 to 3 per 1000 (Engstrom, Ekstrom, & Emilsson, 2002; Fombonne, 2005) and as many as 50% of all children with autism are higher functioning (Honda, Shimizu, Misuni, Niimi, & Ahashi, 1996; Kielinen, Linna, & Moilanen, 2000). This rate of occurrence is significant and higher than previous estimates (Gillberg, 1998). Indeed, Fombonne (2005) recently reviewed 37 epidemiological studies of autism. Twenty-two of the studies included 10,000 or more participants and contained information on the prevalence of higher functioning children with autism and 12 of these had been conducted prior to 1998 and 10 had been conducted since 1998. Comparative data from pre- and post-1998 indicate that the average proportion of HFA classifications changed from 24.6% prior to 1998 to 43.9 % post-1998 (Fombonne, 2005) (see Figure 2). Such an increase likely reflects improved ascertainment of children with HFA (Wing & Potter, 2002), as well as several other factors such as improvements in early intervention with autism spectrum disorders (Smith, 1999), and some have suggested the effects of assortative mating (Baron-Cohen, Scott, Wheelwrite, Johnson, et al., 2006).

Although an increasing number of children with HFA status may be among the best outcomes of national efforts to improve early identification and intervention for autism (Smith, 1999), the intervention needs of children with HFA remain considerable. These children exhibit chronic and robust deficits in social and communication skills, as well as problematic repetitive behaviors and overly focused or isolated areas of interest (Klin & Volkmar, 1997; Gillberg, 1998). Indeed, a recent study suggests that, presently, most children with HFA still require significant levels of family or community support when they reach adulthood (Engstrom et al., 2002). Their long-term outcomes, though, can be highly variable as some display improved social and communication skills, but others display a deterioration of these skills (Piven, Harper, Palmer, & Arndt, 1996). Moreover, variability in the social and emotional status of these children and their treatment is often complicated by symptoms of anxiety and other comorbid emotional or behavioral disorders (Ghaziuddin, Weidmer, & Ghaziuddin, 1998; Kim et al., 2000; Meyer et al., 2006; Soderstrom et al., 2002; Tonge, Bremerton, Gray, & Einfeld, 1999).

A small empirical literature has begun to emerge regarding intervention development for these children. Several recent studies have used group comparison designs to examine the effects of social stories, verbal, and nonverbal social skills training, interactions with typical peers, cognitive behavioral therapy (CBT), and computer face processing games as treatments for these children (Barnhill, Cook, Tebbenkamp, & Myles, 2002; Bauminger, 2002; Carter et al., 2004; Chiang, Lee, Frey, & McCormick, 2004; Nakabayashi & Matsumoto, 2003; Pakenham, Samios, & Sofronoff, 2005; Smith, Lovaas, & Lovaas, 2002; Solomon, Goodlin-Jones, & Anders, 2004; Sofronoff, Anthony, & Brown, 2004). Generally, these studies have reported positive but limited information on the outcomes of these interventions. For example, only two published studies have used the power of randomized control trials to provide methodologically rigorous tests of intervention effectiveness for children with HFA (Sofronoff et al., 2004; Solomon et al., 2004). Solomon et al. (2004) described a laboratory/clinic based intervention that had a positive impact on emotion recognition, analogue life problem solving, and

symptoms of depression in HIFA 8- to 12-year-olds. However, significant individual differences in treatment responsiveness were noted. Sofronoff et al. reported that a parent management-focused intervention led to parent reports of fewer and lower behavior problems in children with HFA as well as higher frequency positive social interactions in the home. Of course, these and all other intervention research with children with HFA are complicated by psychotropic medication(s) that primarily target the symptoms of anxiety, depression, or formal thought disorder (Martin et al., 1999).

The relative paucity of information on effective intervention methods for children with HFA has lead to the recognition that there is currently inadequate information to develop empirically based interventions that meet the specific needs of these children, leading to a marked discontinuity in the quantity and quality of care for older children with HFA (Bauminger, 2002; Kielinen et al., 2000; Rutter, 1996). To fill this gap in the intervention literature, at least four different strategies may be considered. One primary approach is to attempt to develop either behavioral or pharmacological interventions that target core features of the expression of autism in children with HFA. Another strategy is to modify and apply interventions that are specific to the amelioration of comorbid psychopathology (e.g., anxiety or depression) in these children. A third strategy, related to the first two, is to assume that combinations of treatment modalities will be effective for many children and to therefore explicitly examine the effects of combinations of treatments targeting core and comorbid symptoms and/or using both behavioral and pharmacological interventions.

A fourth less well-recognized strategy is to examine the non-syndrome-specific factors that naturally vary among all children, including children with HFA, and that influence the quality of life, course, symptom expression, social outcomes, and comorbidity in these children. The assumption here is that detailed information on individual differences in development and adaptation among children with HFA may highlight dimensions of behavior that are important and potentially malleable targets for intervention or reflect processes they may modify children's responsiveness to specific types of interventions. Unfortunately, few models of development in autism have been described to guide this type of research. Nevertheless, recent theory and research suggest that several core psychological processes may be especially important in this regard. One of these involves the capacity to make attributions about the behaviors of others (Meyer et al., 2006), another involves motivational tendencies associated with approach and withdrawal (Sutton et al., 2005), and a third involves the capacity to self-monitor goal-directed behavior (Henderson et al., 2006).

Attributions, Social Cognition, and Autism

As previously noted, children with HFA can be affected by comorbid emotional–behavioral disorders. However, little is known about the nature of comorbidity in these children. Comorbidity may be part of the clinical syndrome of autism and therefore related to core deficits, such as the social cognitive impairments that are often associated with autism. One notion here is that comorbidity in HFA may be related to self-awareness of their autism-related social limitations (Frith, 1996; Tatum, 2000). Indeed, some children with HFA have been reported to be very sensitive to teasing, peer rejection, and exclusion by others (Bauminger & Kasari, 2000; Bauminger, Shulman, & Agam, 2003), and they may be prone to negative self-evaluations in the face of information indicating that others regard them as less socially competent (Barnhill, 2001; Bauminger, Shulman, & Agam, 2004; Capps, Sigman, & Yirmiya, 1995). This suggests that social attribution processes may be related to differences in comorbidity among children with HFA.

This hypothesis may appear counterintuitive, though, in light of theory that suggests that a robust disturbance of social cognition and awareness of other people is an abiding characteristic

of all people affected by autism, regardless of IQ. However, it is important to keep in mind that the social-cognitive deficits associated with autism have been largely studied in terms of analogue problem solving tasks such as false belief paradigms. These analogue tasks do not test the tendency of children to try to think about other peoples thought in social situations they only test the accuracy of children's ability to accurately guess what a character in a picture, a story, or a video thinks or feels. It is also important to understand that children with HFA are not completely without social cognition. Rather they show a wide distribution of social cognitive skills but their distribution of skills is lower as a group than comparison children on social-cognitive measures. Moreover, just because they have difficulty with social cognition does not necessarily mean that they are uniformly less motivated to understand the thoughts of others (as in attributional thinking). Rather, some children with HFA may be just as motivated as their peers to think about the thoughts of others, but they may do so in a more error prone fashion.

To begin to examine some of these issues, Meyer et al. (2006) conducted a study with 31 children who had received the clinical diagnosis of Asperger disorder. These children ranged in age from 8 to 14 years and had an average verbal IQ of 109. A mixed comparison sample of children with typical development (TD subgroup $n = 16$) and learning disabilities (LD subgroup $n = 17$), who were matched to the HFA sample on age, gender, and IQ, also participated in this study. All the children with HFA scored above the criterion score of 13 for the High Functioning Autism Screening Questionnaire (ASSQ; Ehlers et al., 1999) and this instrument correctly identified 100% of the HFA versus TD samples, with one LD false-positive in comparison with the HFA group. As expected, the HFA sample significantly performed worse than the controls on a composite measure of social cognition that included first and second order false belief tasks (Ozonoff, Pennington, & Rogers, 1991; Perner, Frith, Leslie, & Leekam, 1989).

There were several interesting results in this study. Parent report on the Behavioral Assessment System for Children (BASC; Reynolds & Kamphaus, 1998) revealed the children with HFA differed from the TD and the LD children on a composite measure of symptoms of depression, aggression, atypicality, and anxiety. In addition, children with HFA reported more emotional symptoms on the child self-report version of the BASC relative to the control children. Specifically, the children with HFA appeared to be aware of their social difficulties and their impact on others in that they not only reported more social difficulties on the BASC Interpersonal Relations Scale but they also reported higher rates of *fear of negative evaluations by others* on the revised Social Anxiety Scale for Children (SASC-R; La Greca & Stone, 1993). Interestingly, the initial attempts to publish these data were met with reviewer skepticism regarding the reliability and validity of children with HFA's self-reports on measures relating to social awareness.

To address this issue, we ultimately gathered data that indicated that 18 children with HFA provided self-report with significant test–retest reliability on the BASC and the SASC-R measures across an 18-month interval, $r = .41$ to $.68$, $ps < .05$ (Meyer et al., 2006). Thus, these data suggested that (a) children with HFA present with mores symptoms of affective, anxiety, and externalizing disorders than controls, that (b) the children with HFA display stable individual differences in the self-report of these problems, and (c) that the children with HFA more frequently reported attributions involving fear of negative evaluations by others than did controls.

Another major finding of the study of Meyer et al. (2006) was that, within the HFA sample, a composite score of social attributions was related to a composite parent report measures of comorbidity, $r\ (30) = .65$, as well as a composite of the child report measures of comorbidity, $r\ (30) = .54$. The composite social attribution measures included the Dodge (1993) social

attribution task (responses to video vignettes of brief ambiguous social interactions) and a paper and pencil attribution task (Why Do Kids Do Things; Crick & Dodge, 1996). On the former, the HFA sample significantly displayed more social information processing encoding errors versus the TD and LD subgroups, but no differences versus controls on the frequency of hostile social attributions on either the video or paper and pencil measure. In addition, the data revealed that measures of Theory of Mind (ToM), WISC-III Verbal Intelligence Quotient (VIQ), or Performance Intelligence Quotient (PIQ) were not related to either parent or child reports of comorbid symptomology. Furthermore, HFA participants who passed both ToM tasks ($n = 12$) were no different than those who passed fewer than two ToM tasks ($n = 19$) on the social attribution measures in this study.

Thus, these data indicated that as a group, the children with HFA reported displayed social-cognitive (ToM) deficits, but they also engaged in social attributions at a rate comparable to controls (Meyer et al., 2006). Their attributions may have been affected by social information processing errors. Nevertheless, their tendency to make negative attributions and their fear of negative evaluation by others were related to differences in comorbidity among these children. So although children with autism may have difficulty accurately appreciating the thoughts of others (social cognitive and social information processing deficits), they still generate representations of others' thoughts and intentions (attributions). Moreover, the latter may be especially important to consider in understanding and treating comorbid emotional disturbance in children with HFA. Along with the seminal observations of Barnhill (2001), these data suggest that children with HFA display differences in attribution processes and their awareness of problems in their social interactions. These differences may play a role in modifying the expression of autism in children with HFA and may be specifically related to relative risk for developing comorbid emotional disorders. The significant pattern of associations observed in this study also suggests that self-report data provides a valid source of stable individual differences regarding the social-emotional status of children with HFA.

Motivation, Behavioral Activation/Inhibition and Autism

In addition to social attribution processes, another psychological process that may modify the course and expression of autism involves motivational biases. Motivation biases may contribute to fundamental features of the syndrome and may be a pivotal issue for the design and implementation of successful interventions for children with autism (Koegel, Koegel, & McNerny, 2001; Koegel & Mentis, 1985). Basic research on motivation processes in autism, though, has been rare in part due to the difficulties in measurement. However, beyond autism, the study of individual differences associated with the behavioral activation system (BAS) and the behavioral inhibition system (BIS; Carver & White, 1994; Gray, 1994) have been useful in the research on individual differences in social and emotional responding.

The BIS refers to the aversive motivational system and is thought to regulate responses to signals of punishment, nonreward, and novelty. An individual bias toward BIS activation leads to a tendency to inhibit movement toward goals, to experience negative affective states such as fear and anxiety in response to novel cues, and to withdraw from novel situations and social interactions (Carver & White, 1994; Gray, 1994). Physiologically, the BIS is thought to involve the amygdala and a septohippocampal system with monoaminergic connections to the brainstem and the frontal lobes (Carver & White, 1994; Davidson, 2002). In contrast, the BAS refers to the appetitive motivational system that responds to signals of potential reward. The BAS functions to initiate movement toward goals, pleasurable experiences, or both. An approach bias contributes to the tendency to initiate goal-directed activities and interactions and to anticipate positive affective states when exposed to cues of potential reward (Gray, 1994), as well as anger/frustration when approach-related goals are blocked. Physiologically, BAS is thought to involve a dopaminergic system that involves components of the left middle-

superior frontal and precentral gyrus, the left inferior parietal lobe, as well as bilateral activation in the orbital frontal and anterior cingulate (AC) cortices (Pizzagalli, Sherwood, Henriques, & Davidson, 2005).

There are several reasons to consider differences in BIS/BAS activation in research on autism. One is that theory also suggests that BIS/BAS-related motivation might influence differences in social development in autism. Mundy (1995) observed that joint attention deficits in autism were more profound in the domain of initiating joint attention (IJA) bids than it was in the domain of responding to the joint attention bids of others (RJA). Data also indicated that IJA involved a positive affective component that was not apparent in RJA and that a specific impairment in sharing positive affect may be integral to disturbances in IJA among children with autism (Kasari, Sigman, Mundy, & Yirmiya, 1990; Mundy, Kasari, & Sigman, 1992).

These findings lead to the hypothesis that, aside from cognitive difficulties, the relative reduction in the frequency of initiated joint attention bids among children with autism may reflect the degree to which social approach (i.e., social orienting) was or was not rewarding for a given child. More specifically, Mundy (1995) suggested that a disturbance of neural systems that underpin approach behaviors related to the BAS may interfere with the typical tendency to engage in social approach behaviors in young children with autism and this contributes to joint attention disturbance and social impairments. This is consistent with the broader notion that a central focus of impairment in autism involves difficulties with the self-initiation of behaviors, perhaps due to motivational issues (Koegel, Carter, & Koegel, 2003). Moreover, recent observations suggest that young children with autism display distinct differences in social approach and avoidance tendencies that may be related to individual differences in responsiveness to specific intervention techniques (Sherer & Schreibman, 2005). Incorporating the notion of variation in social approach motivation into autism research may also help to explain the long standing observation of differences in behavior styles in autism, from active but odd approach-related behaviors to aloof or withdrawn behavior patterns (Wing & Gould, 1979).

A second line of reasoning that argues for BIS/BAS research on autism is that these dimensions of motivation have been associated with vulnerability for the development of mood and anxiety disorders, such as OCD (Coan & Allen, 2003; Davidson, 2002). Recall that the expression of autism may be complicated by individual differences in comorbid mood disorders as well as anxiety and OCD (Barnhill, 2001; Ghaziuddin et al., 1998; Meyer et al., 2006; Tonge et al., 1999). Moreover, the broader phenotype for autism may be marked by its association with familial vulnerability to these disorders (Bolton, Pickles, Murphy, & Rutter, 1998; Hollander, King, Delaney, Smith, & Silverman, 2003; Piven, 2002). Therefore, research on motivation tendencies associated with BIS and BAS may reasonably be expected to provide a new avenue of research on phenotypic variability in autism that is related to social development, presence of comorbid emotional disorders, and differences in intervention responsiveness.

One approach to assessing individual differences in BIS/BAS motivation tendencies is the measurement of resting EEG alpha asymmetry over the frontal cortex (Davidson, 2002). Anterior EEG asymmetry provides a stable indicator of trait-like patterns of brain activity associated with BAS/BIS or approach/withdrawal behaviors in adults (e.g., Pizzagalli et al., 2005; Sutton & Davidson, 1997), as well as in children, and even infants as young as 10 months of age (e.g., Baving, Laucht, & Schmidt, 2002; Fox, 1991; Fox et al., 2001). Individuals with greater relative left than right frontal activity display or self-report more activity, reward seeking, and approach behaviors as well as positive or anger affect. Alternatively, individuals with greater right frontal asymmetry display less activity and greater tendencies toward withdrawal, avoidance, as well as anxious dysphoric affect (Davidson, 2002; Pizzagalli et al., 2005; Sutton & Davidson, 1997).

These literatures lead to us to the conditional hypothesis that if approach/withdrawal motivational biases influence social and emotional development in autism, then anterior EEG asymmetry should be meaningfully related to social differences among children affected by this syndrome. Sutton et al. (2005) provided an initial test of this hypothesis that provided some supportive data. Parents reported fewer symptoms of social impairment for children with HFA with left versus right frontal EEG asymmetry. Data from that study also indicated that children with HFA with left frontal asymmetry displayed better cognitive flexibility but also reported more anxiety, social stress, and awareness of problems with their own social limitations than did other children with HFA (Sutton et al., 2005).

The results of the study of Sutton et al. (2005) were both consistent and inconsistent with theory in that left frontal anterior asymmetry was associated with better social skills but higher rates of anxiety in children with HFA. The latter finding may need to be interpreted in the context of a sample of children who by diagnostic definition have impaired social interactions. Thus, a motivation to approach and interact with others, coupled with a deficit in being able to do so, may result in heightened anxiety. However, the latter finding may have also be the result of the age range in the sample because previous research has indicated that the association between frontal asymmetry and social–emotional functioning may be different during adolescence than early childhood or in adults, especially for boys (Baving et al., 2002; Pradella et al., 2006). However, the Sutton et al. study had insufficient power to examine age-related effects. The study of Sutton et al. also did not include symptom assessments based on the current gold standard criteria for diagnosis, such as those derived from the Autism Diagnostic Interview (ADI; Lord et al., 1997), and did not include measures of all the emotional dimensions, such as anger expression, that may be related to approach versus withdrawal biases. Finally, the sample size in that initial study was quite small ($N = 23$) limiting the generalization of the findings to the larger population of children with HFA. Thus, there is a need to replicate and to extend the findings of the study of Sutton et al. (2005) before the putative relations of anterior EEG asymmetry and phenotypic variability may be considered to be a reliable phenomenon and significant in research on autism.

Burnette et al. (submitted) have provided this replication and extension in a study of an independent sample of 37 children with HFA and age-, gender-, and IQ-matched controls. EEG was recorded from left and right midfrontal (F3, F4), lateral frontal (F7, F8), central (C3, C4), and parietal (P3, P4) sites. Asymmetry scores were calculated for the four homologous electrode pairs (i.e., F3/F4, F7/F8, C3/C4, P3/P4) by subtracting the log-transformed alpha-band power density value for the left site from that for the right site (e.g., log F4–log F3). Positive asymmetry scores reflect relatively greater left-side activation. Similar to the our previous results Burnette et al. reported that within the HFA sample, greater left frontal asymmetry was associated with self-reports of greater awareness of their atypicality, more symptoms of OCD, greater social stress and fear of negative evaluation by others, and lower locus of control. However, in the study of Burnette et al., no relations between asymmetry and cognitive flexibility or other aspects of cognition were observed. This suggests that EEG asymmetry as measured in this study may be tapping into processes distinctively associated with motivation and social emotional development.

New findings in the study of Burnette et al. (submitted) included the observation that left frontal asymmetry was associated with a tendency for children with HFA to self-report more anger expression and that parents reported that their left frontal children with HFA displayed more symptoms of externalizing behavior disturbance (e.g., conduct disorder) than did right frontal children. Burnette et al. also reported two sets of findings that suggested that frontal asymmetry may be related to differences in the course of expression of autism in higher functioning children. First, although EEG asymmetry was again related to parent reports of social symptom presentation (i.e., less severe presentation in left frontal children), this effect was more

pronounced for younger children with HFA (8–11 years) than older children (12–16 years). Second, and perhaps most interesting, was the observation that greater left frontal asymmetry was associated with a later retrospective parent estimate of the age of symptom onset in their child (r = .61) as well as estimates of the "Age of 1st Concern" on the Autism Diagnostic Interview (see Figure 3).

The results of these two independent studies suggest that anterior EEG asymmetry may be an important marker of individual differences in the behavioral and the emotional status of children with HFA. In particular, children with HFA and left frontal asymmetry appear to be more inclined toward social approach and interaction, and this pattern of behavior may make their social symptom presentation less clear resulting in lower symptom reports in older children and later identification in young children. However, the social behaviors of approach-motivated children with autism may also lead to the experience of more social stress among these children. Specifically, our data suggest that children with HFA with greater left frontal asymmetry are more self-aware and have a more internal locus of control, which when combined with atypical social behaviors but high levels of social interest, may lead to more symptoms of social anxiety, social stress, acting out, and less overt satisfaction with interpersonal relations.

Our confidence in these conclusions is supported by preliminary analyses of data from our current NIMH project. Baseline data from 13 children with HFA indicated that greater left frontal and prefrontal asymmetries were associated with parent reports of fewer total social symptoms, less evidence of impaired self-awareness, and less evidence of impaired social cognition on the Social Responsiveness Scale (Constantino, 2004). Left frontal asymmetry was also associated with child self-reports of more symptoms of anxiety and hyperactivity and inattention on the BASC.

Self-Monitoring of Goal-Directed Behavior and Autism

A third potential modifying process we have been examining among children with HFA is the capacity to engage in self-monitoring. This refers to the ability to monitor one's own actions and progress toward a predefined goal and thus is essential for the successful execution of goal-directed behaviors. Specifically, when one is performing an action, an internally generated monitoring system compares a representation of the intended action with a representation of the ongoing action. If no discrepancy is detected current actions continue, but if a discrepancy is detected remedial actions are initiated (Bernstein, Scheffers, & Coles, 1995; Carver & Scheier, 1998; Coles, Scheffers, & Holroyd, 2001). This capacity for self-monitoring is part of the supervisory attention system (Norman & Shallice, 1986) and is supported by frontal–cortical networks including the prefrontal cortex, AC, supplemental motor area, striatum, and portions of the basal ganglia (Stuss, Shallice, Alexander, & Picton, 1995).

Impairments in self-monitoring are a hallmark of several developmental psychopathologies including attention deficit disorder, obsessive–compulsive disorder, schizophrenia, and autism (Hill, 2004; Nigg, 2000; Ozonoff & Jensen, 1999; Pennington & Ozonoff, 1996) and have long been emphasized in the pathogenesis of autism (Courchesne & Pierce, 2005; Dawson & McKissick, 1984; Frith & Frith, 1999; Russell, 1997). In particular, impaired self-monitoring has been linked to several symptom domains including perseverative responding, repetitive behaviors, poor imitation skills, and joint attention impairments (Hill, 2004; Mundy, 2003; Russell, 1997). Furthermore, the improvement of self-monitoring and associated self-management skills is an essential component of the efficacious treatment of many children with autism (Koegel, Koegel, Hurley, & Frea, 1992; Koegel, Koegel, & Parks, 1995). However, there are mixed findings from studies examining various aspects of response monitoring in autistic children. Several studies have documented deficits in specific aspects of response

monitoring including error correction and avoidance (Russell & Jarrold, 1998) and intention monitoring (Phillips, Baron-Cohen, & Rutter, 1998), but other studies have failed to document self-monitoring as a core deficit in autism (Russell & Hill, 2001). These discrepant findings may be due in part to the lack of consistency in both the definition and the assessment of response monitoring across studies (see Hill, 2004) and may also suggest that response-monitoring skills are better conceptualized as a modifier of symptom presentation among children with HFA rather than a syndrome-specific deficit. We have begun to examine these possibilities in studies utilizing an ERP measure of error monitoring.

EEG, the Anterior Cingulate, and Measuring Response Monitoring

The neuroanatomy of response monitoring has been explored using both EEG/ERP and imaging technologies. Recent research has uncovered specific electrophysiological markers of self-monitoring (Gehring, Goss, Coles, Meyer, & Donchin, 1993; Luu, Flaisch, & Tucker, 2000). When people make an error on a speeded reaction time task, there is a negative deflection in the ongoing EEG immediately following the response. This response-locked ERP is referred to as the error-related negativity or ERN (Gehring et al., 1993; Luu et al., 2000; Buch, Luu, & Posner, 2000). The amplitude of the ERN is associated with behavioral evidence of self-monitoring such as self-correction and slowing responses on trials after detection of ERN. Therefore, the ERN has been interpreted as a neurophysiological marker of error processing (Buch et al., 2000; Holroyd & Coles, 2002; Van-Veen & Carter, 2002). The ERN peaks within approximately 100 ms following the commission of an error. Thus, the ERN appears to reflect the extremely rapid, preattentive, or unconscious component of goal-related error monitoring.

The ERN is maximal at frontocentral midline scalp sites (Fz, FCz, and Cz) and source localization studies converge on the AC as the neural generator (Dehaene, Posner, & Tucker, 1994; Luu et al., 2000; Van-Veen & Carter, 2002). Several fMRI studies have localized error-related activity to the rostral anterior cingulate cortex (ACC; e.g., Kiehl, Liddle, & Hopfinger, 2000; Mathalon, Whitfield, & Ford, 2003); however, others have reported caudal rather than rostral ACC activity (e.g., Menon et al., 2001). It may be that caudal aspects of the ACC respond to the cognitive conflict that is inherent to error processing, whereas the rostral ACC may be selectively engaged by error processing (Mathalon et al., 2003). Neuroanatomically and functionally, the AC provides an interface between frontal action selection processes, limbic emotion or motivation processes, and motor output regulation (Holroyd & Coles, 2002).

The integral role of the AC in self-monitoring and guiding attention in relation to goal-directed actions suggests that it may be an especially important focus for research on autism. Attention regulation and motivation systems that prioritize social information processing in typical development may not be functioning properly in autism (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Klin, Warren, Schultz, & Volkmar, 2003; Mundy, 1995). Two research groups have also reviewed some of the behavioral and neuroscience literature relevant to this topic and have converged on the hypothesis that disturbances in functions of the AC, especially functions that serve to integrate attention to self and others, may contribute to the social orienting and related social cognitive deficits of children with autism (Frith & Frith, 2001; Mundy, 2003).

Consistent with these strands of theory symptoms that are often seen in children with autism, such as apathy, inattention, dysregulation of autonomic functions, variability in pain sensitivity, akinetic mutism, and emotional instability, are often manifest in individuals with AC impairments (Buch et al., 2000). Further, clinical and subclinical levels of negative affect and anxiety, including OCD, all of which can be present (or at least similar symptoms may be observed) in children with autism (Bolton et al., 1998; Piven, 2002), have been associated with exaggerated responses to errors both behaviorally and physiologically (Gehring, Himle, & Nisenson, 2000; Hajcak, McDonald, & Simons, 2004). Moreover, individual differences in the

amplitude of the ERN have been related to social interaction and withdrawal tendencies among typically developing children (Henderson, 2003).

Several imaging studies (Barnea-Goraly et al., 2004; Hall, Szectchman, & Hahmias, 2003; Levitt et al., 2003) as well as behavioral studies (Rinehart, Bradshaw, Brereton, & Tonge, 2002) suggest that autism may be associated with anomalous functioning of the AC. Moreover, two independent studies have observed that differences in metabolic activity in the AC are significantly related to variability in social symptom presentation among children with autism (Haznedar et al., 2000; Ohnishi et al., 2000). In interpreting these results, it is important to recognize that the central integrating role of the AC in attention and monitoring of goal-related behavior is such that AC-related behavioral deficits may emerge only in combination with, or as a modifier of disturbances in other related functional neural networks (Devinsky & Luciano, 1993). As such, the observations of Haznedar et al. (2000) and Ohnishi et al. (2000) raise the hypothesis that functions of the AC may be related to processes that modify the symptom presentation of children with autism an contribute to phenotypic variability in this disorder. In one of our recent studies we examined this hypothesis.

ERN and Autism

Henderson et al. (2006) recently examined the hypothesis that children with HFA would display differences form controls on behavioral and physiological (ERN) indices of self-monitoring and that these difference would relate to variability in symptom expression in autism. Forty-one children (24 HFA; 17 age-, gender-, and verbal IQ-matched controls) completed a psychophysiological assessment (EEG/ERP) in addition to a series of self-report and parent report measures of social/emotional functioning. EEG was recorded as children completed a modified version of the Eriksen Flanker task. In this task, children are required to indicate the direction of a central target in an array of five stimuli on compatible trials (< < < < < or > > > > >) or on incompatible trials (< < > < < or > > < > >), in which the target stimulus faces in the opposite direction from all other stimuli in the array. Correct performance required the child to press a button corresponding to the direction of the center arrowhead. The results indicated that ERNs were larger for error versus correct trials at the frontal and central sites but not at parietal sites for both diagnostic groups. Thus, there was evidence a frontal–central distribution of the ERN for both groups that was comparable to prior studies of other populations. However, a significant diagnostic group by verbal IQ interaction was observed because children with HFA with higher VIQs (> 103) had significantly larger ERNs compared to all other children. There was no group difference on ERN amplitude, though, for the lower verbal IQ groups (75–102) in this study.

To examine whether these physiological differences translated into differences in task performance, a comparable analysis was conducted with error rates as the dependent variables. An interaction between diagnostic groups revealed that only children with HFA with relatively lower VIQs differed from the control sample in total number of errors committed. The children with HFA with relatively high VIQs performed comparably to children in the control sample (Schwartz et al., 2005).

Correlation analyses indicated that parents reported that children with HFA with larger amplitude ERN had lower social impairment scores on the Social Communication Questionnaire (SCQ; see Figure 4). However, children with HFA with larger amplitude ERNs also reported a greater awareness of their social difficulties as reflected by higher self-reports on the social stress dimension of the BASC. Parents reported that children with HFA with larger amplitude ERNs displayed more internalizing symptoms on the BASC. Thus, ERN was associated with self- and parent report data on social/emotional functioning in children with HFA.

These data suggest that an electrophysiological index of response monitoring, the ERN, differed in amplitude based on children's diagnostic group and verbal IQ. Specifically, higher functioning children with autism who also were relatively high in their VIQ showed the highest amplitude ERNs. This makes considerable sense in the context of research and theory that suggests that ERN and error-monitoring facilities of the AC play an essential role in learning and cognitive development (Holroyd & Coles, 2002). Indeed, the results of the Henderson et al. (2006) raise the possibility that AC/ERN-related functions may contribute to phenotypic differences in IQ, such as the presence or absence of mental retardation among children with autism. Research on this issue is underway in studies that will explore ERN in both lower and higher functioning children with autism.

It was also interesting that the high amplitude ERNs in the children with HFA did not translate into superior behavioral performance on the flanker task. Rather high ERN children with HFA performed equally well compared to typically developing children in the control sample. Together these data suggest that heightened AC-related self-monitoring among the children with HFA may function in a compensatory fashion enabling some aspects of the behavioral performance of these children to approach the typical level of performance observed in a control sample. However, this compensatory function of AC-related self-monitoring may be a double-edged sword. It may contribute to a more typical pattern of behavior including less intense social symptom presentation. At the same time enhanced self-monitoring in children with HFA also appears to be associated with a greater interpersonal awareness and a heightened recognition of social interaction problems.

Of course, too much cannot be made of the data from this single study of a small sample of children. However, when combined with the previous observations of Haznedar et al. (2000) and Ohnishi et al. (2000), it may be useful to recognize that Henderson et al. (2006) is the third independent study to observe that functions of the AC are related to differences in social symptom presentation in autism. At a minimum, these data suggest that it is important to understand the nature of this linkage in phenotypic variability in autism. In this regard the results of Henderson et al. (2006) extend the previous observation by beginning describe the processes, such as self-monitoring, that may support this association. Indeed, similar observations regarding the cognitive control processes that relate to the role of the AC in symptom variability in children with HFA have been made in a recent fMRI study (Solomon, Ozonoff Ursu, Ravizza, Cummings, & Carter, 2007). Clearly, then, much more work is warranted to better understand the role of AC, cognitive control, and self-monitoring in the variable course and expression of autism.

Putting It All Together: Clinical Implications and Future Research

In the proceeding paragraphs, we have tried to use concrete empirical examples, primarily from our own work, to illustrate the modifier model of autism. This is not to say, though, that these are the only dimensions or variables that may play a modifying role in the development and expression of autism. Several other factors ranging from plasma oxytocin levels (Modahl et al., 1998), to autonomic responses and the vagal system (Althaus et al., 2004; Porges, 2003), as well as environmental and family factors (Greenberg, Seltzer, Hong, & Orsmond, 2006; Pakenham et al., 2005) may function as modifiers contributing to the wide range of phenotypic variability in social emotional development observed among children with autism. Indeed, in this paper we have not fully integrated our own work on attribution processes and family factors as modifiers of autism (Meyer et al., 2006; Zahka et al., 2007). Instead of an exhaustive review, this essay was developed simply to begin to acquaint the reader with the utility of expanding research on autism to include studies of the factors that may interact with syndrome-specific core elements the (i.e., the autism taxon) to better understand the nature of phenotypic variability in the presentation of the spectrum of autism-related disorders.

In this regard, several additional issues bear discussion. One issue concerns the degree to which phenotypic variability associated with measures of BAS-BIS motivation and rapid self-monitoring of goal-related errors rise to the level of information necessary for valid diagnostic subtyping among children with HFA. Previous attempts to identify diagnostic subgroups, especially to distinguish HFA from Asperger disorder, have been based on language, intellectual, or neuropsychological performance and have met with limited success (e.g., Beglinger & Smith, 2001; Fein et al., 1999; Gunter, Ghaziuddin, & Hadyn, 2002; Rinehart, Bradshaw, Brereton, & Tonge, 2002). Interestingly, though, theory has often emphasized that the distinction between HFA and Asperger disorder may involve differences in the functional status of the left and right frontal hemispheres (Rinehart et al., 2002).

Our data are consistent with this general notion of the importance of cortical asymmetry in differences in autism. However, the asymmetric systems and processes that we have focused on are associated with motivational processes. These we believe may be at least as important as asymmetries associated with cognitive or executive functions in distinguishing among children with HFA. Nevertheless, our data also suggest that non-hemisphere-specific executive, self-monitoring processes may also play an important role in differentiating children with HFA. These self-monitoring processes may even interact with hemisphere-specific motivation systems in the development of severity differences ASD symptoms. In a small sample of children, we have observed that parents reported more symptoms of social impairments for children with HFA who were classified as displaying both high versus low ERN and right versus left anterior asymmetry relative to all other HFA subgroups of children (see Figure 5). One interpretation of these data is that a behaviorally active approach style of interaction in combination with relatively strong self-monitoring contributes to a phenotypic presentation that may be furthest from the taxonomic prototype of autism. In this case, it would be likely that parent or professional reports of social symptom presentation would be affected by the interaction of a child's motivational biases and self-monitoring tendencies to a greater extent than with respect to either variable considered in isolation.

Thus, our data begin to suggest that motivation-associated measures of BEG anterior asymmetry and ERN measures of self-monitoring may tap into orthogonal processes that contribute to symptoms and perhaps diagnostic subgroups of children with HFA. A preliminary model of this differentiation of children with HFA is illustrated in Figure 5. Perhaps the first thing to notice in this model is that the subgroups of children with HFA are differentiated according to motivation factors that contribute to differences in active, approach-related behaviors versus inactive, withdrawal-related behaviors. This is very consistent with the social subtyping of ASD as active (but odd) versus passive (withdrawn) that was first described by Wing and Gould (1979). It may well be that measures of BAS and BIS tap into processes associated with Wing and Gould's initial clinical observations and that differences in activity level and approach behaviors may impact the early expression and identification of ASD in young children.

This model also illustrates the possible direct and indirect effects of self-monitoring. This may be related to learning and IQ differences among children with autism, as well as differences on self-awareness and the impact of self on others during social interactions (i.e., social relatedness). Approach motivation and self-monitoring, combined in the context of the autistic social impairments, may contribute to a higher frequency of somewhat more facile attempts at interaction with others. However, this combination may also engender ego dystonic reactions to failed social attempts and a relatively heightened self-awareness of the fundamentally different if not flawed nature of these interactions. This combination of motivation for higher frequency interactions but self-monitoring and self-awareness of social errors may contribute to heightened risk for the development of non-autism-specific social-emotional or social-behavioral disorders in a subgroup of children with HFA. This process description has much

in common with clinical and research descriptions of subgroups of children with HFA commonly referred to as Asperger disorder (e.g., Tatum, 2000). Alternatively, lower motivation for social interactions and less capacity for self-monitoring may contribute to a pattern of socially passive or aloof behavior with limit social insight that comes closer to the prototype of Kanner type autism in higher functioning children. The relations of this MP model to phenotypic characteristics and diagnostic subgrouping is illustrated in Figure 5.

Valid Diagnostic Subgroups

The validity of diagnostic subgrouping, though, is only apparent if the basis of the differentiation leads to clear implications about treatment, prognosis, and etiology. The degree to which the foregoing model meets these criteria is uncertain at this point; nevertheless, the model raises several hypotheses in this regard. Research has begun to examine the utility of cognitive behavior therapy for anxiety and a sense of negative self-evaluation, which may decrease the quality of life for many children with autism (Bauminger, 2002). Social skills groups and computer games on the other hand are viable platforms to enable children with HFA to learn and acquire more accurate social perceptions and engage in more flexible and adaptive social interactions with peers (Barnhill et al., 2002; Silver & Oakes, 2001). It is very likely, though, that children with HFA will display differential responsiveness to these and other intervention modalities. Phenotypic descriptions that assist in predicting and understanding differential responsiveness to interventions provide the type of information that is the sine qua non of diagnostic subgroup criteria. Measures of motivational bias and self-monitoring may provide this type of information.

A requisite first step of most cognitive–behavioral interventions (CBT), if not all behavioral interventions (Koegel et al., 1995), is for individuals to engage in some form of self-monitoring, such as monitoring of ideation, monitoring of emotions, or monitoring of behaviors. Thus, it seems eminently possible that variability in children with HFA's responsiveness to cognitive behavior therapies may be affected by, if not hinge upon their capacity for self-monitoring. Of course it is not clear if the self-monitoring function we assess with ERN is isomorphic with the self-monitoring functions involved in CBT. However, the empirical route to evaluating this possibility is relatively straightforward. If, as we suspect, ERN is related to CBT responsive in children with HFA, this will argue for its utility as a diagnostic subgroup marker.

Social skills groups may provide a useful platform for assessing and modifying the peer social interactive capacities of children with autism. Given the dynamics of this intervention modality, it is very likely that a child with a more active approach motivation may display more behaviors that may be more readily shaped through the use of positive reinforcement in the context of the social skills group. Of course self-monitoring may also affect the degree to which children may monitor and correct their errors in any learning situation including a social skills learning situation. Hence, children with HFA with approach motivation and better self-monitoring skills may be more responsive to typical social skills group interventions (cf. Koegel et al., 2001). Alternatively, if motivation and self-monitoring are linked to responsiveness to social skills interventions, this would also provide fundamental information about nonresponders and could contribute to a more informed approach to modifying interventions to meet the needs of the latter group of children.

In this regard, one approach may be to provide less active approach oriented children with more opportunities for treatment through computer based interactive social skill games. In this modality social approach, motivation may not be a factor in responsiveness. Reinforcement sensitivity associated with BAS/BIS may remain a factor of concern, but the ratio of reinforcements may be tightly controlled in this intervention context and manipulated to provide the best reward patter for different children. For example, BAS affected children may

be expected to maintain a high level of motivation and task engagement when receiving a moderate ratio of reward but BIS affected children may require a higher frequency and/or more varied pattern of reinforcement to maintain the same level of task motivation. Finally, self-monitoring would again likely play a role in social learning in this type of intervention paradigm. However, with a deeper understanding social interactive games may be constructed that include methods of fostering self-monitoring and these could be included to a greater or lesser extent based on the baseline levels of children's self-monitoring as they enter interventions.

Diagnostic Subgroups: Prognosis and Genetic Effects

The factors illustrated in the model in Figure 5 may also rise to the level of diagnostic subgroup markers if they contribute to an understanding or prognosis and etiology in autism. With regard to the former, one of the more intriguing observations to date is that motivations associated with anterior EEG asymmetry may be associated with the age that parents first notice problems in the early development of their children with HFA. As noted earlier, this may indicate that children with left frontal asymmetry display a more active and social approach style of behavior early on which makes their symptoms of autism less discernable. Of course, this presumes that EEG asymmetry data collected in childhood reflects a stable aspect of individual differences in temperament of children with HFA. Although there is some support for the longitudinal stability of behavioral tendencies associated with anterior EEG asymmetry in childhood, similar information is not yet available for children with autism. This issue may be particularly confounded if the child receives effective interventions that change the expression of the symptoms of autism. However, one advantage of BAS/BIS theory and anterior asymmetry EEG measurement methods is that they both appear to be applicable to children as young as 10 months of age (Fox, 1991). Thus, this issue is also open to empirical inquiry. Indeed, anterior EEG asymmetry measures may soon find their way into research on the infant siblings of children with autism to determine if this construct and measurement may assist in identifying children at risk for autism with latter onset of clear symptom expression and with a different prognosis vis-a-vis onset of comorbidity later in life.

Finally, with regard to etiology, evidence suggests that autism may be largely gene dependent (e.g., Dawson et al., 2002). Therefore, to more completely understand the modifiers of development in higher functioning children with autism (HFA) it is essential to consider the potential role of genetic factors. One related area of research has focused on the polymorphism of promoter region of the 5-HT transported gene (5-HTTLPR, locus SLCGA4) because of its associations with platelet hyperserotonemia in autism, individual differences in the behavioral expression of autism and differences in stress sensitivity and anxiety in the family members of children with autism (Tordjman et al., 2001). A recent report from the NIH Collaborative Programs of Excellence in Autism (CPEA) has explicitly called for research designed to "resolve the impact of variation in alleles of the serotonin transporter gene (SLCGA4) on liability to autism or phenotypic variation in autism may be a key to our understanding of this syndrome" (Devlin et al., 2005, p. 1114). Devlin et al. (2005) and Tordjam et al. (2001) have suggested that 5-HTTLPR polymorphism itself does not covey risk for autism but instead influences the behavioral phenotypic expression of this disorder. That is, 5-HTTLPR may not be a gene associated with susceptibility per se but rather with processes that modify the expression of autism.

5-HTTLPR is especially of interest to us because it has been associated with a predisposition to anxiety and negative emotionality in adults (Munafo et al., 2003; Hariri et al., 2005) as well as in children (Fox et al., 2005). Thus, this polymorphism may be expected to relate to variability in BIS/BAS bias and its influence on developmental differences in children with HFA. In addition, the 5-HTTLPR polymorphism has been associated with differences in ERN

and AC functions related to error monitoring and behavior regulation (Fallgatter et al., 2004). Indeed, research has linked this polymorphism to functional differences in the AC and interconnectivity between the AC, the amygdala, and the ventromedial prefrontal cortex (Hariri et al., 2005; Heinz et al., 2005; Pezawas et al., 2005).

These studies are noteworthy and relevant to our own program of research for three reasons: (1) we have observed that BIS/BAS-related anterior EEG asymmetry as well as ERN amplitude in children with HFA are related to differences in social–emotional and cognitive development, presumably through processes associated with differences in appetitive motivation, error monitoring, and self-regulation (Henderson et al., 2006; Sutton et al., 2005); and (2) neural circuits involving AC, amygdala, and ventromedial frontal cortex have been described as integral to variability in the social phenotype of children with autism (Dawson et al., 2002; Mundy, 2003). It follows then that if research can substantiate a functional relations between 5-HTTLPR and variability in the expression of autism mediated by BAS/BIS-related motivation and ERN self-monitoring, these observations would also support the use of the latter as a marker of valid diagnostic subtyping in children with HFA.

With these hypotheses in hand our program of research is ready to begin to evaluate if EEG asymmetry measures of motivation and ERN measures of self-monitoring contribute to diagnostic subgroup differentiation in children with HFA. Only time will tell if these processes and their associated measures rise to this level of utility in research and intervention with higher functioning children affected by autism.

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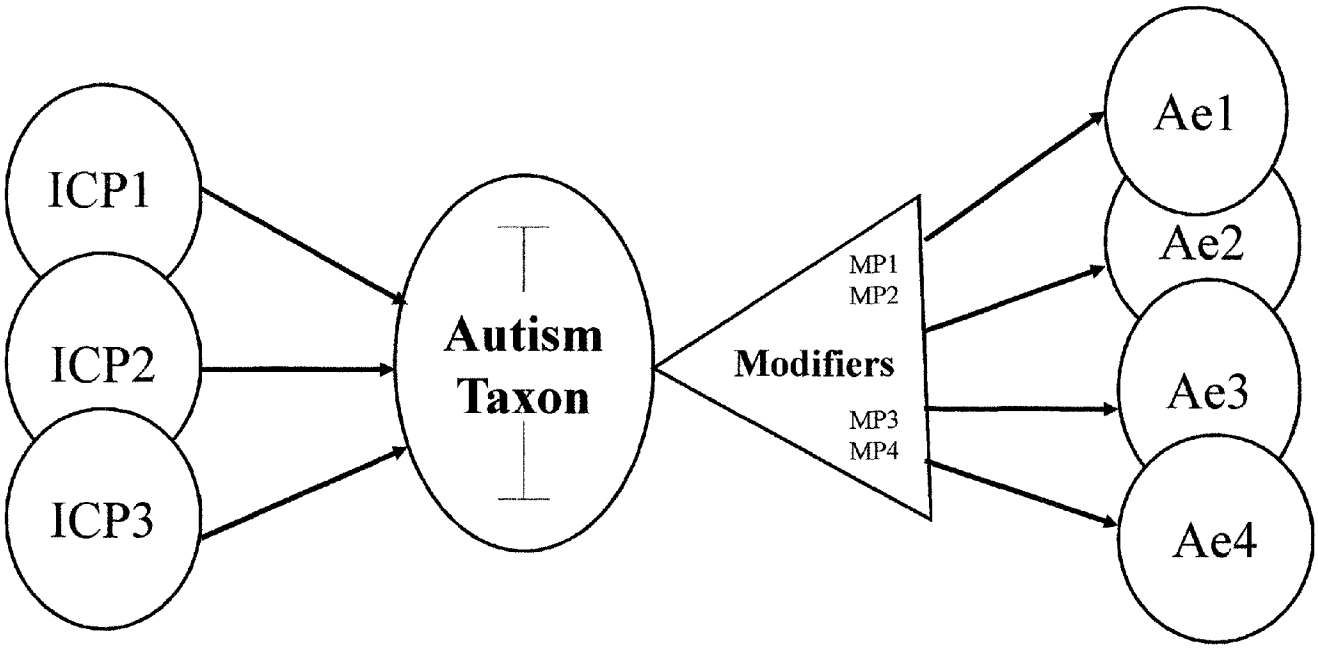

Figure 1.
Phenotypic variability in autism arises from two sources: syndrome-specific initial causal processes (ICP) and non-syndrome-specific modifier processes (MP). Variability in the disruptions of multiple genetic and neurodevelopmental ICPs contributes to initial individual differences in the early postnatal expression of autism. Subsequently, the core pathology (taxon) is refracted into multiple forms of expression of autism (Ae1, Ae2, etc.) in interaction with non-syndrome-specific biological and environmental MPs (e.g., activation–inhibition and self-monitoring tendencies).

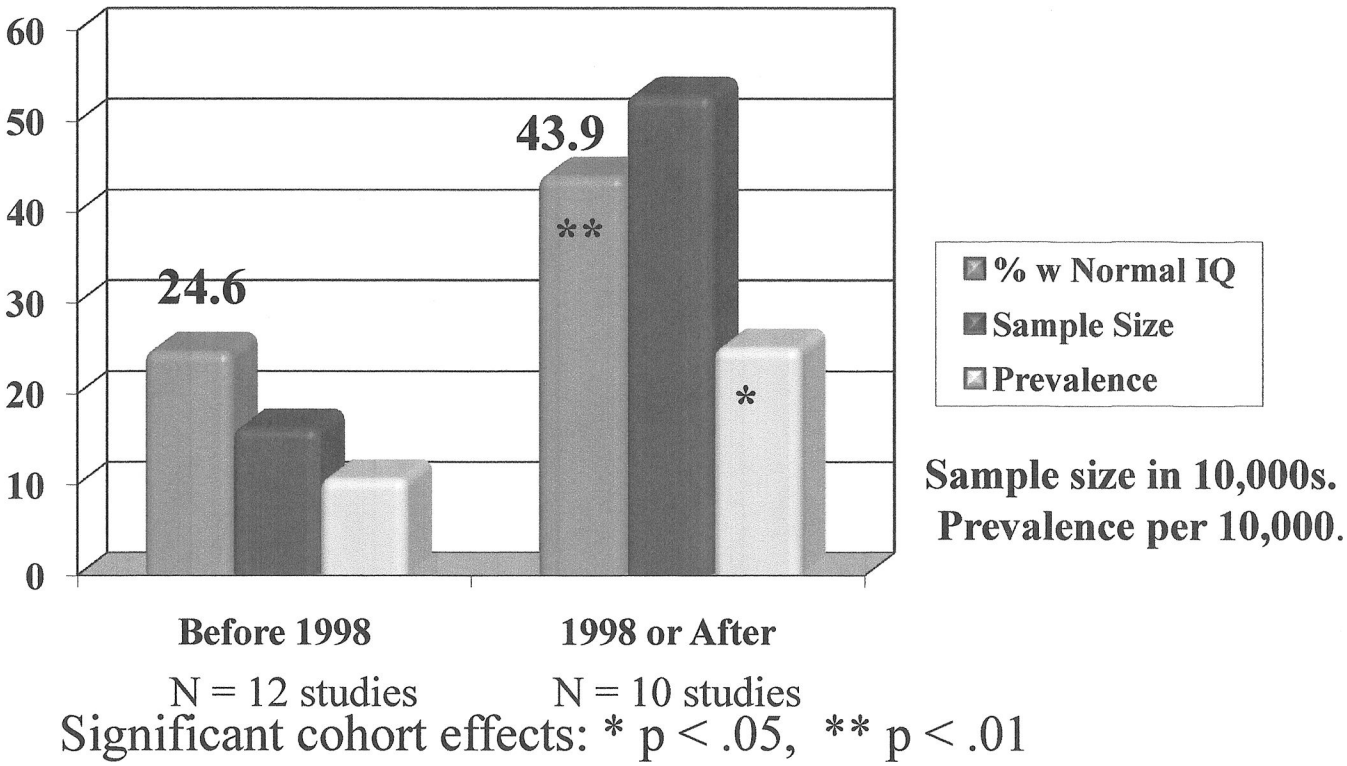

Figure 2.
Estimate of increase in HFA prevalence based on data from 22 of 37 studies in described by Fombonne's (2005) description of changes in the epidemiology of autism.

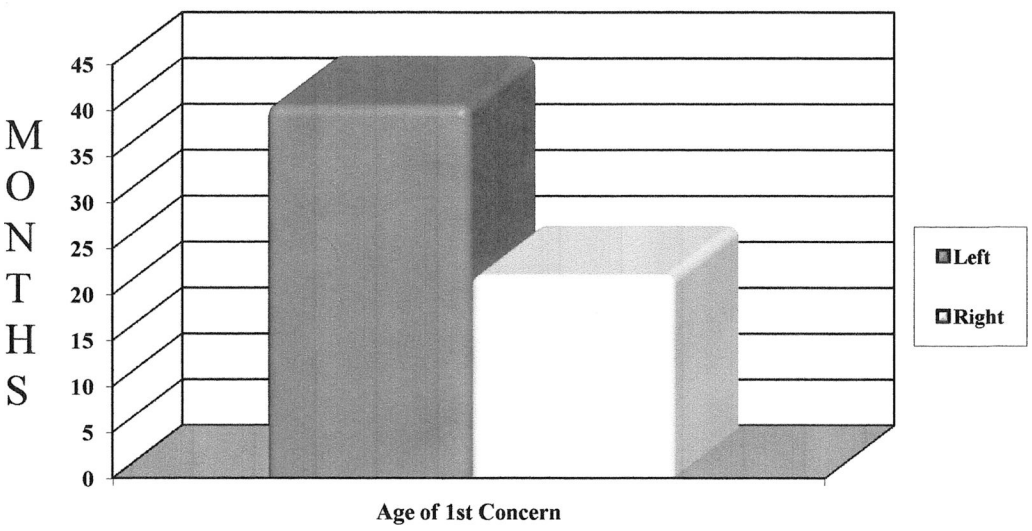

Figure 3.
The relation between EEG asymmetry and ADI "age of 1st concern."

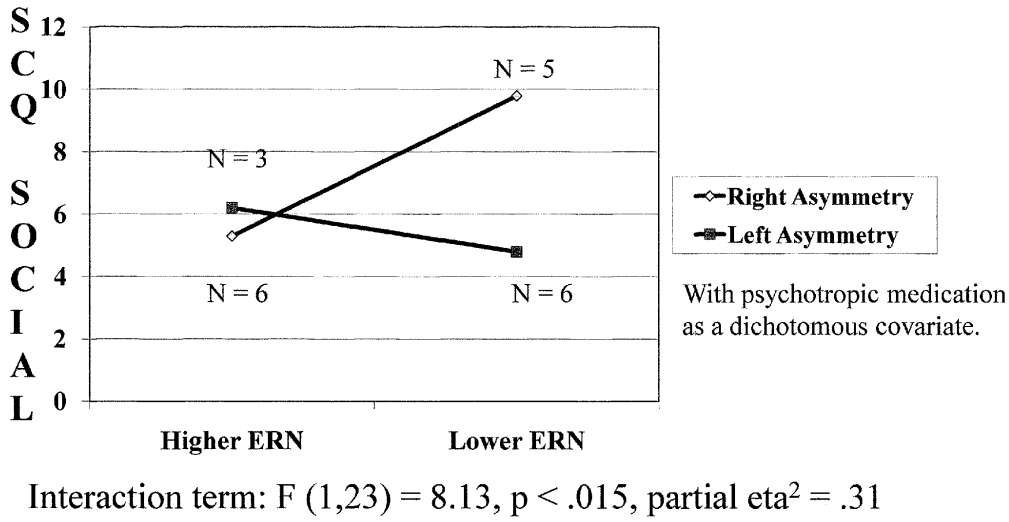

Figure 4.
Graphic representation of the conditional effects of ERN and EEG asymmetry on social symptoms in a small sample of children with HFA.

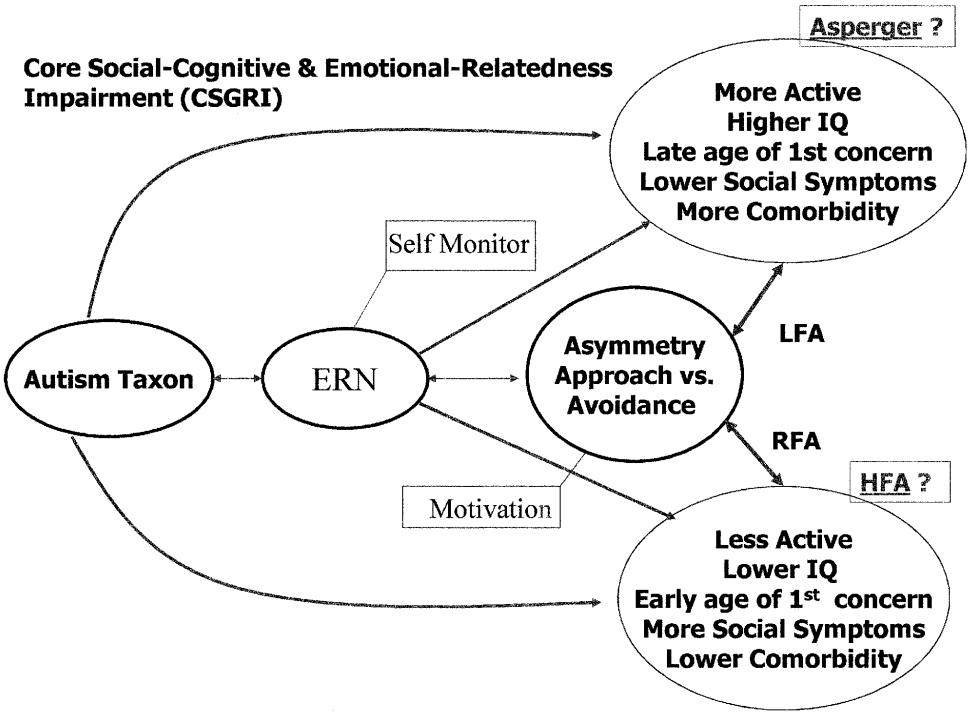

Figure 5.
Illustration of a modifier model of autism and the possible contribution of motivation and self-monitoring processes to diagnostic subgroups of Children with HFA.