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Autism Overflows: Increasing Prevalence and Proliferating Theories

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Abstract This selective review examines the lack of an explanation for the sharply increasing prevalence of autism, and the lack of any synthesis of the proliferating theories of autism. The most controversial and most widely disseminated notion for increasing prevalence is the measles–mumps–rubella/thimerosal vaccine theory. Less controversial causes that have been proposed include changes in autism diagnostic criteria, increasing services for autism, and growing awareness of the disorder. Regardless of its causes, the increasing prevalence of autism has put pressure on the field of autism research to generate productive and predictive theories of autism. However, the heterogeneity of brain deficits, impaired behaviors, and genetic variants in autism have challenged researchers and theorists, and despite 45 years of research, no standard causal synthesis has emerged. Research going forward should assume that autism is an aggregation of myriad independent disorders of impaired sociality, social cognition, communication, and motor and cognitive skills.

Keywords Autism · Brain · Prevalence · Theory · Thimerosal · Vaccine

Introduction

This selective review of the current state of research and theory in autism focuses on two questions facing the field. The first question is prevalence. In the past 20 years there has been an immense increase in the prevalence of autism and autistic spectrum disorders (ASD; Fombonne et al. 2006; Schechter and Grether 2008). Is this a true increase in cases? Many unique theories have been proposed as the cause of an actual increased incidence of autism, most importantly the vaccine theory (Young et al. 2008), but researchers in the field have reported countering data (Fombonne et al. 2006), and the starting point study for the vaccine theory in autism (Wakefield et al. 1998) has been shown to be based on a biased study sample and an unscientific agenda (Deer 2008). While it is possible and likely that the increasing prevalence is more apparent than real, as Wing and Potter (2002) have argued, nonetheless the prevalence of autism is increasing.

Whatever its causes, the increasing prevalence of autism/ASD has put pressure on the field of autism research to generate productive and predictive theories. Consequently, the second question of this review is whether brain-system theories of autism are progressive. The variability of autism has posed a great challenge for researchers and theorists. Lakatos (1970) argued that a progressive research program effectively explains variant data, generates new hypotheses, and confirms and expands the hard core of fundamental assumptions. However, the hard core assumptions of the field of autism are in conflict, pitting the assumption of autism as a scientific research entity against the assumption of immense variation within that entity. It is therefore more difficult for research and theory in autism to be additive and progressive, and often one theory simply replaces another, a problem Meehl (1990) called "ad hockery." Despite the overwhelming flood of causal theories for autism, the field has not made progress in creating a synthesized, standard predictive causal theory of autism, and it may well be time to abandon the effort to find a unifying causal deficit model for autism (Happé et al. 2006).

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Why Has the Prevalence of Autism Increased?

In the 12 years from 1995 to 2007, the prevalence of autism in children aged 3 to 5 years old receiving services from the California Department of Developmental Services increased each quarter, from 0.6 per 1,000 in 1995 to 4.1 per 1,000 in 2007 (Schechter and Grether 2008). In the 8 years from 1996 to 2004, the prevalence of Canadian British Columbia school-aged children diagnosed with autism increased from 1.2 per 1,000 to 4.3 per 1,000 (Coo et al. 2008). In the 11 years between 1987 and 1998, the prevalence of ASD in individuals born in the Montreal area of Canada increased at an estimated 10% per year from 4.6 per 1,000 to 10.8 per 1,000 (Fombonne et al. 2006). In the 9 years between 1994 and 2003, Shattuck (2006) reported that, excluding Massachusetts and Iowa, US states' prevalence of autism for children in special education increased from 0.6 per 1,000 to 3.1 per thousand.

In the brief two-year interval from 2000 to 2002, the Centers for Disease Control (CDC) US multisite study found no increase in the prevalence of autism spectrum disorders (ASD): in 2000, 6.7 per 1,000 children aged 8 were diagnosed with ASD (Developmental Disabilities Monitoring Network Surveillance Year Principal Investigators, Centers for Disease Control and Prevention, 2007a); in 2002, 6.6 per 1,000 were diagnosed with ASD (Developmental Disabilities Monitoring Network Surveillance Year Principal Investigators, Centers for Disease Control and Prevention, 2007b). The ASD prevalence rate was found to vary by state, with New Jersey reporting the highest prevalence in both 2000 (one per 100) and 2002 (1.06 per 100; Disabilities Monitoring Network Surveillance Year Principal Investigators, Centers for Disease Control and Prevention, 2007a, b). The CDC multisite study noted that the autism prevalence of 6.7 per 1,000 children was greater than had been previously found in many earlier studies, and a meta-analysis of earlier prevalence studies (Williams et al. 2006) found an earlier overall prevalence of 0.7 per 1,000 for autism and two per 1,000 for ASD.

It is not clear whether the staggering, apparent three- to ten-fold increase in prevalence of autism/ASD in the past 20 years represents a true increase in cases. Many unique theories have been proposed as the cause of an actual increase in autism prevalence. Four selected theories are briefly outlined here. One theory is Rogers' (2008) proposal that the increased prevalence of autism/ASD is likely to be the result of an increase in pregnant women taking folate supplements. This, Rogers argued, allowed increased fetal survival of infants with a genetic polymorphism that does not maintain normal folate levels which, in turn, resulted in an increase in children at risk for diminished methylation and consequently, abnormal neurodevelopment resulting in autism/ASD. Rogers (2008) noted that mutant forms of a gene for a folate-related enzyme, 5-methylenetetrahydrofolate reductase (MTHFR), have been found to occur in significantly higher frequency in ASD children.

A second theory is that of Theoharides et al. (2008) who hypothesized that the increasing prevalence of autism could be caused by the activation of pluripotent mast cells that then release key molecules that disrupt the gut–blood–brain barrier and lead to neurotoxic effects generating autism/ASD. Theoharides and colleagues (2008) proposed that non-allergic mast-cell activation releases mast-cell vasoactive, proinflammatory and neurotoxic mediators that, in turn, increase gut–blood-barrier permeability to intestinal toxic substances that then cross the blood–brain barrier and allow intestinal toxins to enter the brain.

A third theory is that of Waldman et al. (2006) who proposed that comparative data indicated that 17% of the increase in autism in California and Pennsylvania during the 1970s and 1980s was due to the growth of cable television. These authors argued that their findings are consistent with the hypothesis that watching an extensive amount of television might be a factor in the increase in autism.

A fourth, and the single most widely-circulated theory of increasing incidence of autism, has been the vaccine hypothesis. This view has argued that new cases of autism/ASD resulted from the brain damage caused either by (1) the measles, mumps, rubella (MMR) vaccine itself, or by (2) thimerosal, an MMR vaccine stabilizer that is 50% ethylmercury (Tan and Parkin 2000). A study conducted by Young and colleagues (2008) was funded by the Autism Petitioners' Steering Committee of the no-fault National Vaccine Injury Compensation Program (NVICP). They reported significantly increased rates of autism, ASD, attention deficit disorder, attention deficit hyperactivity disorder, learning disorders, emotional disorders and tics associated with increased mercury exposure from thimerosal-containing childhood vaccines during the period from 1990 to 1996.

The Young et al. (2008) study was influenced by Wakefield et al. (1998), a study published 10 years earlier which reported finding autism in association with measles–mumps–rubella vaccination and bowel problems in seven of twelve children. Wakefield's paper was widely disseminated in a press release, video news release and a televised press conference which caused a firestorm of concern about childhood vaccinations that has resulted in decreasing immunization rates, increasing international public concern about autism, and self-recrimination in parents of autistic children and adults (Deer 2008).

The vast majority of research did not uphold Wakefield et al. 1998 findings. Hornig et al. (2008) were not able to replicate the Wakefield et al. (1998) data. Hornig and colleagues found no relationship between autism onset and time of measles-mumps-rubella vaccinations, and no differ-

ences between measles virus RNA in the ileum and cecum of autistic and typical children. An Institute of Medicine report (2004) concluded there was no causal link between the measles–mumps–rubella vaccine or thimerosal, and autism or autistic spectrum disorders (ASD). Honda et al. (2005) reported an increase in prevalence of ASD in a district of Yokohama city, Japan after the MMR vaccine had stopped being given to children. Fombonne and colleagues (2006) reported that during the 11-year interval of their study, the rate of ASD increased, while the rate of MMR vaccinations decreased in the same population. Fombonne et al. (2006) also reported that the prevalence rate of ASD was significantly higher in the thimerosal-free 1996–1998 birth cohort than in the thimerosal-exposed children in the 1987–1995 cohort. Schechter and Grether (2008) reported that the prevalence of autism in California increased *after* thimerosal was eliminated from vaccines. Commenting on Schechter and Grether's findings (2008), Fombonne (2008) linked the vaccine hypothesis to three other widely touted but ultimately failed hypotheses regarding autism: that "refrigerator" mothers caused the social aloofness of autism; that facilitated communication revealed hidden thoughts of individuals with autism; and, that secretin infusion reduced autistic symptoms.

Investigations uncovered that Wakefield et al. (1998) study did not have human subjects approval, and that study recruitment was biased because parents of ten of the twelve children were clients of Richard Barr, a British lawyer who had been attempting to sue the drug companies manufacturing MMR (Deer 2008). Barr had referred his clients to Wakefield because Wakefield had hypothesized a link between Crohn's disease (an inflammatory bowel condition) and the measles–mumps–rubella vaccine. Furthermore, before the study's publication Wakefield and the Royal Free Medical School had filed patent applications for a *single vaccine* against measles which could only succeed if standard MMR vaccines were discarded, and for a means of "completely curing" both inflammatory bowel disease and autism that depended on the personal bone marrow of one American, Hugh Fundenburg (Deer 2008). In addition to these science ethics failures, Wakefield accepted more than $780,000 from Barr who obtained this money from the United Kingdom's legal aid fund in his quest to sue drug companies, while Wakefield simultaneously founded *Immunospecifics Ltd*, a company intended to reap millions from the sale of "diagnostic kits" to be sold to worried parents (Deer 2008).

The greatest harm of Wakefield et al. (1998) tainted paper and its offspring articles and editorials is that the public worldwide has become wary of vaccines for their children. There have been serious outbreaks of measles in Britain, Switzerland, Israel and Italy because of parental fear of the vaccine, and in the first 7 months of 2008 there were more cases of measles in the US than in any comparable period since 1996, as increasing numbers of parents have refused to vaccinate their children, believing that vaccines cause autism (Harris 2008). J. B. Handley, the co-founder of Generation Rescue, a group that contends vaccines cause autism said "Most parents I know will take measles over autism" (Harris 2008, p. A16).

It is clear that television, internet, newspaper, and magazine reports of the vaccine's possible danger in causing autism has been effective in frightening many parents about vaccines, and it is probable that many parents have new concerns about signs of autism in their infants and young children as a result. It is not known, however, whether this elevated parental concern has been a factor in the increased prevalence of autism. If parental alarm regarding autism has lead to greater ascertainment, that would suggest an apparent but not real increase in incidence.

Along with heightened parental concern, changing diagnostic criteria have also been identified as a basis for the increased prevalence of autism/ASD. Williams and colleagues (2006) reported finding that autism prevalence was, in fact, influenced by the diagnostic criteria used, and Baker (2008) argued that the increase in prevalence of autism was "exactly what the mainline researchers expected" (2008, p. 249) because increased prevalence was "the logical consequence of their ongoing efforts to expand its definition and promote its recognition in developmental evaluation centers and the schools" (2008, p. 249). Working with Lorna Wing on the development of the changes in DSM (1980, 1987, 1991) criteria for autism and related disorders (Waterhouse et al. 1992), we had no expectation that the prevalence of autism/ASD would increase with the change from DSM-III (American Psychiatric Association 1980) to DSM-III-R (American Psychiatric Association 1987) criteria, nor did we believe that we were involved in efforts to expand the definition of autism or the autistic spectrum. Moreover, researchers have not welcomed the increasing prevalence of autism and ASD. Volkmar et al. (1997) argued that changes in the criteria from DSM-III to DSM-III-R broadened the concept of autism, contributing to an increase in prevalence over time, but that the changes from the DSM-III-R (1987) to the DSM-IV (American Psychiatric Association 1993,1994) criteria provided a welcome return to a more narrow definition of autism.

Despite the Volkmar et al. (1997) assertion that DSM-IV criteria had solved the problem of the increase in ASD diagnoses, Baird et al. (2006) claimed that DSM-IV (1994) (and ICD-10 (World Health Organization 1992)) diagnostic criteria for autism and ASD presented a problem precisely because the DSM-IV criteria description allowed such a broad scope in the interpretation of severity of symptoms that true prevalence could not be ascertained. Taking a more positive view of changes in diagnostic criteria, Kurita

(2006) proposed that improved ascertainment via changes in diagnostic criteria had led to the identification of a greater number of high functioning individuals with autism whose cases had been previously harder to detect.

Diagnostic substitution has also been argued to be a source of an apparent but not real increase in the prevalence of autism/ASD. Shattuck (2006) noted that as autism prevalence increased in the US between 1994 and 2003, mental retardation declined by 2.8 per 1,000, and learning disabilities declined by 8.3 per 1,000. Coo and colleagues (2008) also reported that diagnostic substitution—e.g., changing a child's diagnosis from mental retardation to autism—explained one-third of the increased prevalence of school children diagnosed with autism. Conversely, Blaxill, a supporter of the vaccine theory, dismissed diagnostic criteria as a factor in prevalence, asserting that "Although both the nomenclature and the criteria set used to define autism have changed over the years, these changes are not so great as to prevent comparative analysis and do not explain major differences in reported prevalence over time" (2007, p. 549). Blaxill argued that lower prevalence rates in the past were, in part, the result of incomplete ascertainment of autism and ASD in young children, and Blaxill (2007) demanded that "increased rates of autism and related disorders be accepted as an urgent public health concern" (p. 549).

Determining the Factors Causing the Increasing Prevalence of Autism/ASD Will Not be Simple

Wing and Potter (2002) proposed that the majority, and perhaps all of the increase in prevalence of autism was apparent and not real, but resulted from changes in diagnostic criteria—including the spreading concept of ASD, growing awareness and knowledge among parents and professionals, and a rise in services for individuals with autism. Wing and Potter (2002) also concluded that increased prevalence could not be a result of MMR vaccine and thimerosal in the vaccine or any other environmental source theory because they lacked sufficient supporting evidence. The sociologist G. Eyal has proposed (personal communication, August 22, 2008) that autism prevalence grew in three stages: (1) in the 1970s individuals with mental retardation were deinstitutionalized thus increasing the prevalence of autism because many of these individuals fit the DSM-III R (1987) triad of diagnostic criteria for autism; (2) in the early 1990s autism was added to the Individuals with Disabilities in Education Act thus increasing the prevalence of autism because there now were concrete benefits to getting the diagnosis of autism; and, (3) from the 1990s to the present there has been increasing parent awareness and activism that has led to further increases in prevalence. For Eyal the epidemic of autism is the product of all the institutions that detect ASD, name forms of ASD, count ASD cases, and treat ASD cases (personal communication, August 22, 2008).

Whatever its source, the increasing prevalence of autism/ASD has put increasing pressure on researchers to solve the causal puzzle of what makes autism.

Are Theories of Autism Progressive?

Lakatos (1970) argued that experimental falsification of the null hypothesis was an insufficient test of a theory. Lakatos proposed that a field of research had to have a hard core metatheory of fundamental assumptions, and a protective outer belt of auxiliary assumptions that are the subject of active research. In his model the fundamental assumptions and the auxiliary assumptions together produce testable hypotheses that can provide confirmation and expansion of the hard core of fundamental assumptions. For Lakatos, in standard science programs most failed theories do not bring down, or even call into question the fundamental assumptions of the hard core. Because experimental hypotheses are formed from both the hard core and the auxiliary assumptions of the protective belt, researchers can easily reject the auxiliary assumptions in the protective belt, leaving the hard core of fundamental assumptions intact.

Lakatos argued that a theory should be judged on the basis of the progressivity or degeneracy of its auxiliary assumptions. For Lakatos, a progressive research program effectively explains anomalous data, generates new hypotheses, synthesizes findings additively, and confirms and expands the hard core of fundamental assumptions. However, when the protective belt of assumptions produces hypotheses and experiments that only serve to account for anomalies that would invalidate the hard core fundamental assumptions, a research program is in a state of degeneracy. Lakatos called non-progressive theories "ad hoc" and Meehl (1990) stated that, "As more and more 'ad hockery' piles up in the program, the psychological threshold (which will show individual differences from one scientist to another) for grave skepticism as to the hard core will be increasingly often passed, inducing an increasing number of able intellects to become suspicious about the hard core and to start thinking about a radically new theory" (p. 112).

An example of a progressive research program is molecular genetics. The hard core fundamental assumptions include basic concepts such as organic molecules, amino acids, DNA, RNA, polynucleotide structure, transcription, translation, genes, and gene regulation processes. One of many auxiliary assumptions is that there are only two processes that lead to novel traits. One process is gene duplication followed by divergence wherein one gene copy maintains its function and the other copy takes on a new expression pattern. The second process is co-option

wherein gene regulatory control increases in complexity, generating novel patterns of gene expression (Abzhanov 2008). If a third process was discovered, the assumption that there are only two processes would be negated, but no change would be imposed on the hard core of assumptions at the heart of the molecular genetics research program.

An example of a failing research program is transformational generative grammar. The hard core, fundamental assumptions are that grammar is the key element in human language (Chomsky 1965), and that grammar is the basis of language processes in the human brain (Hauser et al. 2002). However, research in linguistics, psychology and cognitive neuroscience has demonstrated that grammar does not have primacy in language structure or in brain processes (Lieberman 2005). As predicted by Lakatos's model, research now attempts to shore up the failing hard core assumption of the primacy of grammar (Tesar 2004), while at the same time many of those formerly working in this research program are now skeptical and launch attacks on the hard core assumptions (Pinker and Jackendoff 2005).

Lakatos Theory Applied to the Program of Autism Research

In Lakatosian terms, there are currently four hard core fundamental assumptions of the field of autism:

(1) That a developmental disorder called autism does exist as defined by the diagnostic criteria established in the DSM-IV TR (American Psychiatric Association 2000) and ICD-10 (1992);
(2) That there are variants of this core disorder that can be included, along with autism itself, in a larger entity called autistic spectrum disorders, whose variation can be accounted for by the inclusion of associated diagnostic groups (Asperger's, Retts, Childhood Disintegrative Disorder), also established in the DSM-IV TR (2000) and ICD-10 (1992);
(3) That there is wide variability in diagnostic traits and in associated impairments in individuals with autism and with other forms of ASD; and,
(4) That the majority of autism cases result from gene effects.

Wackermann (2006) noted that "Natural science searches for universal laws, so the notion of individuality does not play any role: the law of gravitation applies to all material bodies, without exceptions. However, in sciences studying human beings…our interest is an individual….We are thus facing a conflict between the aspiration to universality of science, and the uniqueness of individuals as objects of its study" (p. 422). In the program of research in autism there is an inherent conflict between the hard core assumption of autism as an entity in the universal scientific sense, and the hard core assumption that there is an immense amount of individual variation in the genes, developmental history, brain deficits, and behaviors of children and adults diagnosed with autism/ASD. Consequently, the resolution of this conflict requires experiments and theories (in the protective belt of auxiliary assumptions) to attempt to establish autism as a unitary entity while accounting for the immense amount of variation observed in autism.

Autism theorists have a difficult choice. They must either attempt the very difficult task of accounting for all the variation observed in autism, or must ignore some large portion of symptom variation, thereby threatening the fundamental assumption that autism exists as an entity, or must work to carve out subgroups within autism. Happé et al. (2006) said "Heterogeneity within the autism spectrum is perhaps the biggest single obstacle to research at all levels" (p. 1220), while Geschwind (2007) noted "This heterogeneity makes it difficult to conceive of models, whether cognitive, behavioral, or physiological, that capture common features of the autisms under one conceptual umbrella" (p. 949). Moreover, Nicolson and Szatmari (2003) asserted that autism appears to be so genetically heterogeneous that "each gene (or set of genes) may be a risk factor for a specific component of the autism phenotype" (p. 529).

Even more disheartening, theorists and researchers face an additional problem pointed out by Meehl (1990). Meehl noted that when a researcher inductively frames a study, for example, that if P—personality has five components, then Q—a significant percent of people tested will show evidence of five components, the research findings conclude that Q exists, therefore P is true. This is the fallacy of affirming the consequent: P then Q; Q; fallacy—*therefore P*. Even so, if repeated and related experimental findings support the existence of P, the formal logic fallacy is irrelevant.

However, if there are many competing theories or hypotheses that are not supported by repeated and related research findings, and by additive and synthesizable theory, the logical fallacy of affirming the consequent is a marker for Meehl's "ad hockery." Research in autism, like all other inductive definitional research, does implicitly commit the fallacy of affirming the consequent: if P-autism exists, then Q—there will be a significant group of individuals diagnosed with autism who have system X deficit; Q—these experimental findings demonstrate that a significant group of individuals with autism do have this system X deficit, therefore (fallacy) P—autism exists as an entity. Moreover, in the field of autism there have been and now are a plethora of competing theories that are infrequently additive or synthesizable.

Thus there are two questions for current theories of autism. How do current theories account for the wide range of

symptoms in autism/ASD? Do theorists work to synthesize their theories with the theories of others? Given that only a few of the many current theories can be considered here, answers to these questions will be provisional.

Brief Review of Selected Current Theories of Autism

Domes et al. (2007) found that typical individuals were significantly better at tests of interpreting the thoughts of others by looking at eyes in faces after being administered one nasal dose of oxytocin. The researchers argued that oxytocin might be the basis for being able to understand the minds of others, and thus play a role in the pathogenesis of autism. Domes et al. (2007) hypothesized that oxytocin's role in social comprehension could account for severe social impairment in autism, but did not claim any causality for the cognitive, motor, sensory, or other behavioral symptoms of autism. While this hypothesis is additive to work on oxytocin in autism (Green et al. 2001; Modahl et al. 1998), to studies of the oxytocin receptor gene in autism (Wu et al. 2005), and to the Theory of Mind theory of autism (Baron-Cohen et al. 1985), this hypothesis cannot be linked to or synthesized with many active theories of autism.

For example, Just et al. (2004) and Takarae et al. (2007) proposed that autism results from failed region to region brain connectivity wherein the brain's information integration circuitry is impaired by dysmaturation. Takarae et al. (2007) argued that their model explains *all* the variability in autism because the failure of integration would impair all higher cognitive processes, all sensorimotor control, and all social behaviors. However, there does not seem to be a clear way that the Domes et al. (2007) oxytocin theory could be integrated with the theory of integrative circuit dysmaturation, nor do Just et al. (2004) or Takarae et al. (2007) cite any data or theory on oxytocin in their theory construction.

The Just et al. (2004) autistic sample all had IQs of 80 or above. The Takarae et al. (2007) study sample all had IQs of 87 or above. Despite the dysmaturation theory's claim that it accounts for all autism variability, the theory can only apply to the 30% of individuals with autism who have such high IQs. Inability to generalize a theory to the whole population diagnosed with autism/ASD is a serious problem. Stanfield et al. (2008) conducted a meta-analysis of magnetic resonance imaging studies of regional brain size in autism. They concluded that total brain, cerebral hemispheres, cerebellum and caudate nucleus were increased in volume, but the corpus callosum area was reduced. They reported that diagnostic criteria was not a significant variable in their analyses, but they were concerned that so many of the studies in the meta-analysis included only individuals with autism who had IQs higher than 70, that their meta-analysis conclusions could not apply to the 70% majority of individuals with autism who have IQs that are 70 or lower.

Happé and Frith (2006) proposed the theory of weak coherence and strong local processing in autism. They argued that their theory of autism covered all the symptoms of autism with the exception of social cognition, stating that "Results to date suggest weak coherence is not reducible to executive dysfunction, and most studies suggest weak coherence is independent of deficits in social cognition" (2006, p. 21). Thus, because the Domes et al. (2007) hypothesis covers only social cognition, their theory regarding oxytocin is pre-empted from any synthesis with the Happé and Frith (2006) theory.

However the concept of weak coherence would seem to be consonant with the theory of Just et al. (2004) and Takarae et al. (2007). In fact, Happé and Frith (2006) cited Just et al. (2004) to propose that weak coherence may be the result of reduced brain interconnectivity. However, Takarae et al. (2007) did not mention weak coherence theory, and Just et al. (2004) denied consonance with weak coherence theory because, they argued, weak coherence theory lacked a plausible brain mechanism. Just et al. (2004) also claimed unreasonably that although findings of weak coherence-theory researchers Castelli et al. (2002) did demonstrate lower brain region intercorrelations for autistic participants, Castelli et al.'s findings could only be used to support the Just et al. (2004) underconnectivity theory. Just et al. (2004) asserted that Castelli et al. could not use their own findings to support their own theory because—Just et al. (2004) argued—weak coherence theory was based in a river analogy, and made fewer predictions than the underconnectivity theory.

Courchesne and Pierce's (2005) theory of neuroinflammatory-impaired neurodevelopmental processes leading to an abnormally enlarged head was proposed to be the basis for *all* autism symptomatology, and included impaired long-distance connectivity as a feature of their model. Thus, Courchesne and Pierce's (2005) theory could, at least in part, be aligned with the Just et al. (2004) and Takarae et al. (2007) theory of underconnectivity and dysmaturation. But Courchesne and Pierce (2005) did not cite the Just et al. (2004), and Takarae et al. (2007) did not cite Courchesne and Pierce (2005). In fact, Takarae et al. (2007) noted that their model of dysmaturational integrative brain circuits would not be compatible with lobe specific pathology. Because Courchesne and Pierce (2005) argued that their model included serious impairment to the frontal lobes and cerebellum with relative sparing of the occipital lobes, Courchesne and Pierce's (2005) theory would thus be pre-empted from alignment with that of Takarae et al. (2007), despite the fact that both theories share the common

assumption of brain underconnectivity as causal to autism.

Kennedy and Courchesne (2008) proposed the theory of an impaired Task Negative Network (TNN) but spared Task Positive Network (TPN) as an explanation for *all* symptoms of autism. The TNN (also referred to as the default mode or the self-prospective system) includes medial prefrontal cortex, posterior cingulate/precuneus, and angular gyrus (Buckner and Vincent 2007). The TNN has been shown to be activated during social, emotional, and self-reflective tasks, including theory of mind, social perception, emotional processing, experience of joint attention, episodic memory, viewing personally familiar faces, and self and other person reflection (Fair et al. 2008). The TPN includes the pre-supplementary motor area, intraparietal sulcus, and superior precentral sulcus (Buckner and Vincent 2007). The TPN has been shown to be activated during externally-directed cognitively demanding tasks such as math calculations, sustained attention, and working memory (Fair et al. 2008).

Kennedy et al. (2006) and Kennedy and Courchesne (2008) found evidence for "disrupted intrinsic functional organization of the TNN in autistic patients but, at the same time and within the same patients, intact organization of the TPN" (2008 p. 1882). Kennedy and Courchesne (2008) stated that their theory applied to all autistic symptomatology for high-functioning individuals with autism, arguing that these individuals are over-interested in objects, rules, and regularities because the TPN is their cognitive strength and they are under-interested in, and unable to comprehend the many cues of social and emotional communication because of impaired TNN functioning.

Surprisingly neither Kennedy et al. (2006) nor Kennedy and Courchesne (2008) cited Courchesne and Pierce's (2005) theory that autism is caused by neuroinflammatory-impaired neurodevelopmental processes that increase head size. Neither Kennedy et al. (2006) nor Kennedy and Courchesne (2008) mentioned the cerebellum or fronto-cerebellar circuits or head size in autism. Courchesne and Pierce (2005) argued that frontal lobes, and cerebellum and fronto-cerebellar circuits were seriously impaired by widespread maldevelopment caused by aberrant neuroinflammatory response and neuroglial activation that likely disrupted "cell migration, axon targeting and elimination, apoptosis, neuronal differentiation, dendrite outgrowth and synaptogenesis, and minicolumn growth and functional differentiation" (2005, p. 167).

As none of the current models of the TNN include the cerebellum (Buckner and Vincent 2007; de Munck et al. 2008; Fair et al. 2008), it would be difficult to synthesize the Courchesne and Pierce (2005) model with the Kennedy and Courchesne (2008) model. Nonetheless it is surprising to find that a research group has proposed a theory that competes with their own prior theory without any consideration of, or reference to their own prior theory.

Rout and Dhossche (2008) hypothesized that "because Purkinje cells are involved in motor coordination, working memory and learning, loss of these cells are likely to cause symptoms defining behavioral parameters of ASD" (p. 218). They theorized that the timing and the type of maternal immune reactions to a fetus "may also determine the extent of Purkinje cell death and consequently the spectrum of the disorder" (2008, p. 219). Rout and Dhossche (2008) cited Courchesne (1997) to argue that atrophy of the cerebellar lobules was the most consistent neurological abnormality in autism, and that between 35 to 95% of Purkinje cells were lost in autism, but Rout and Dhossche (2008) did not tie their model to Courchesne and Pierce's (2005) theory.

How does the Rout and Dhossche (2008) model fit with the fronto-cerebellar deficit and severe malfunction of the cerebellum theorized by Courchesne and Pierce (2005) in their neuroinflammatory model? How does either model of cerebellar deficit fit with the absence of cerebellar involvement in the TNN (Buckner and Vincent 2007; de Munck et al. 2008; Fair et al. 2008)? How do the underconnectivity of Courchesne and Pierce's (2005) model, the Takarae et al. (2007) theory of underconnectivity, and the Happé and Frith (2006) weak coherence model fit with the failed TNN activation/normal TPN activation of Kennedy and Courchesne (2008) model? How does the Domes et al. (2007) oxytocin model fit with any of the other theories? Without theory synthesis these questions are left unanswered.

Wilson et al. (2007) reported abnormal left hemisphere production and maintenance of the gamma band of auditory magnetic steady-state responses in children and adolescents with autism. They suggested that the abnormality arises from an absence of local inhibitory interneurons. Wilson et al. (2007) tied their hypothesis to the under-connectivity theory of Just et al. (2004) because, they argued, "the key deficit in autism involves the coordination amongst processing centers distributed across the cortical landscape" (Wilson et al. 2007, p. 195).

Orekhova et al. (2007) also reported increased gamma band oscillations in individuals diagnosed with ASD, and the gamma band increase was inversely correlated with IQ. Geschwind (2007), commenting on this finding, noted that because IQ deficits are not diagnostic for ASD, and ASD overlaps mental retardation, increased resting high-frequency gamma band probably represents global brain dysfunction rather than a symptom of ASD. Geschwind's position counters the "hard core assumption" of the ASD diagnostic criteria: there is no exclusion for mental retardation.

Martineau et al. (2008) are among several groups of researchers who have proposed the defective mirror neuron system theory of autism. Martineau et al. (2008) reported

that during the study participants' observation of a human movement sequence, the hemispheric asymmetry index was higher than 1 for typical children and lower than 1 for ASD children for all EEG electrode sites, but the asymmetry index did not vary significantly during observation of non-human movement in either typical or ASD children. Dapretto et al. (2006) also reported that an fMRI study of high-functioning children with autism showed little or no mirror neuron activity in the inferior frontal gyrus. The researchers reported that inferior frontal gyrus activity was inversely related to social impairment severity, and proposed that an impaired mirror neuron system was the basis for autism social deficits. Despite the theory's claim, as noted before, the theory can only apply to the social deficits of the 30% of individuals with autism who have IQs 70 or higher.

Zhao et al. (2007) proposed a unified genetic theory of autism. Although they admitted they could not rule out environment factors, and did not consider the phenotypic features of autism, their theory nonetheless proposed a genetics-only basis for autism, which they asserted was justified by twin studies. Their model argued that there are two groups of families of individuals with autism. The first and smaller group is "autism in high risk families" wherein boys have an almost 50% risk of being diagnosed with autism. The second larger group is "low risk spontaneous mutation autism" wherein boys have a low risk of being diagnosed with autism. Zhao et al. (2007) theorized that these two groups were connected, claiming that the spontaneous mutation in the low risk families had "high penetrance in males and relatively poor penetrance in females; and high-risk families are from those offspring, most often females, who carry a new causative mutation but are unaffected" (p. 12831), while their boys face a 50% risk of being diagnosed with autism.

Although Zhao et al. (2007) proposed their model as the genetic template basis for *all* autism, they added that additional genetic factors must be involved in females with autism because of the high concordance of monozygotic female twin pairs, and that many different modifier genes were the cause the heterogeneous phenotypic expression of autism symptoms. They concluded that the halting effort to find causal mutations linked to autism would benefit from using their proposed core template because it would then be easier to find modifier genes.

Conversely, Grigorenko et al. (2008) hypothesized that functional polymorphisms in the promoter for macrophage migration inhibitory factor (MIF) made MIF a candidate gene for many ASD symptoms. They found an association between known functional polymorphisms of MIF and autism spectrum disorder-related behaviors. The researchers noted that plasma MIF concentrations correlated with the severity of ASD symptoms. It is not clear by what means the Grigorenko et al. (2008) model could be synthesized with the model of Zhao et al. (2007). Perhaps for Zhao et al. (2007) MIF would be considered as a modifier gene, but Grigorenko et al. (2008) identified MIF as a core source for ASD.

Three theories have proposed that the extensive variation in autism precludes the validity of any theory that attempts to explain all of autism. Folstein (2006) argued that current diagnostic criteria for autism/ASD broadened to include three distinct groups: (1) Kanner's autism; (2) Asperger Syndrome; and (3) a varied group including (a) phenylketonuria (PKU), tuberous sclerosis, neurofibromatosis, Fragile X, and Retts syndrome, (b) other genetic syndromes including those with dysmorphic features, with 15q11–12 maternal duplication, and with macrocephaly, and, (c) those whose development was compromised by infections such as congenital rubella, herpes encephalitis, and malaria encephalitis. Folstein proposed that autism included Kanner's autism and Asperger Syndrome, but not the third group. Folstein argued that the many disorders in the third group have nothing to do with autism and "need to be considered separately in studies of etiology and mechanism" (2006, p. 113). Folstein implicitly argued for a return to Kanner (1943) autism criteria noting that Kanner had identified a group of children who best fit with current genetic findings for autism, and that "36% of siblings of Kanner's cases had autism, severe social dysfunction (now called Asperger syndrome), or language/reading disorders" (Folstein 2006, p. 116). Folstein further noted that "The children Kanner diagnosed needed to "look" intelligent, to be alert and to show interest in things (although not people). He excluded children who had dysmorphic features or very low IQ" (2006, p. 116). Folstein reported that "although in DSM-IV, abnormal language development is the second of the three essential criteria; Kanner did not include structural language in his diagnosis because it is so variable in autism—some children he diagnosed had no speech at all and others achieved entirely normal grammar and syntax" (2006, p. 115). Folstein did not suggest which genes might underpin Kanner's autism and Asperger Syndrome.

Dawson (2008) outlined a model with three separate but intersecting disorders: autism, mental retardation, and language impairment. Dawson (2008) stated that "The response to intervention in autism spectrum disorder (ASD) is the predicted severity of ASD and presence/absence of two highly comorbid disorders: mental retardation and developmental language impairment" (p. 794). Dawson's model identifies one of the core diagnostic criteria for autism, language impairment, as "comorbid" with autism. This counters the hard core assumptions of DSM-IV TR (2000) autism criteria that communication and language impairment form one of the

required diagnostic features, and mental retardation is not an excluded condition.

Happé et al. (2006) argued that "it is time to give up on the search for a monolithic cause or explanation for the three core aspects of autism, at the genetic, neural and cognitive levels" (2006, p. 1219). They claimed that because more than half of the genes associated with each of the three diagnostic traits of autism/ASD—impaired social skills, impaired communication, and rigid and repetitive behavior—independently contribute to that trait alone, it would be more productive to study each of these three traits as a separate phenotype. Their research on 3,000 monozygotic and dizygotic neurotypical twin pairs at ages 7 and 8 years indicated that each of the three traits is highly heritable. Because the researchers proposed that molecular genetic studies stop conducting research looking for genes for autism as a whole, their theory directly counters the theories of both Zhao et al. (2007) and Grigorenko et al. (2008), as well as all "monolithic" theories of autism.

How Do Current Theories Account for the Variation in Autism/ASD?

As can be seen above in the brief theory review, autism theorists employ several strategies to account for the wide range of symptoms. These include excluding mental retardation as unrelated to autism, settling for an explanation of a subset of symptoms, attempting to explain all symptoms in one large-capacity theory, and splitting autism into phenotypic subgroups.

Excluding Mental Retardation from Autism

One strategy is to eliminate mental retardation as a component of autism by studying only individuals with higher IQs, or by defining mental retardation as an isolatable comorbidity (Dawson 2008). Researchers have excluded low IQ individuals with autism from their studies (Castelli et al. 2002; Dapretto et al. 2006; Just et al. 2004; Kennedy et al. 2006; Stanfield et al. 2008; Takarae et al. 2007), have negated findings in autism that are linked to IQ as outside the syndrome (Geschwind 2007), or have redefined autism as not including severe mental retardation (Dawson 2008; Folstein 2006).

Exclusion of mental retardation, however, is not part of the formal diagnostic criteria hard core assumptions about autism. Thus defining mental retardation as comorbid with autism (Dawson 2008), separate from autism (Folstein 2006; Geschwind 2007), or to be excluded from research and theory (Castelli et al. 2002; Dapretto et al. 2006; Just et al. 2004; Kennedy et al. 2006; Stanfield et al. 2008; Takarae et al. 2007), is a challenge to core diagnostic criteria.

Whether mental retardation is part of autism, or part of any subphenotypic or subgenotypic subgroup of ASD requires empirical validation. For example, in a cluster analysis of a large group of ASD children (Fein et al. 1999) our research group did identify two distinct subgroups whose differentiation depended heavily on cognitive function level. Those in the higher functioning group showed a positive developmental trajectory, for example, moving from a Stanford–Binet Verbal Reasoning mean score of 80.73 to 84.43 between preschool and school age, whereas on the same measure, the lower functioning group scores dropped from a mean of 66.19 down to 50.94.

Gupta and Slate (2007) argued that that phenotypic overlap between mental retardation and autism was important. They noted that most genetic mutations found in relation to autism resulted in both cognitive *and* social impairments, while some genetic mutations could produce social impairment in one individual and cognitive impairment in another. Gupta and Slate (2007) theorized that it was probable that autism was caused by genes influencing "fundamental developmental processes in the central nervous system, such as synapse formation, synaptic plasticity, and axon pathfinding" (p. 433) which would generate a broad array of deficits including cognitive impairment combined with social impairment.

Unfortunately, when researchers have excluded mentally retarded individuals with autism from their studies (Castelli et al. 2002; Dapretto et al. 2006; Just et al. 2004; Kennedy et al. 2006; Stanfield et al. 2008; Takarae et al. 2007), they have excluded the opportunity to conduct an empirical test of their assumption that autism and mental retardation are two separate disorders.

Explaining a Subset of Diagnostic Symptoms

Another strategy is to limit theory coverage to social impairment, long considered the core deficit of autism (Dapretto et al. 2006; Domes et al. 2007; Martineau et al. 2008), or to claim that a theory covers all symptoms except social cognition (Happé and Frith 2006). However, as long as diagnostic criteria define autism by three core deficits, study designs must examine the social deficit along with the communication deficit and the rigid and repetitive behavior deficit. The social deficit cannot be proven to be true of all autism without knowledge of how that social impairment is bound to, or distinct from the remaining diagnostic features. First, as noted above, Gupta and Slate (2007) stated that the majority of genetic mutations associated with autism resulted in both cognitive *and* social impairments. Second, it is possible that a social deficit may be the product of a language deficit. For example, the Milligan et al. (2007) meta-analysis found a clear connection between language skills and theory of mind in typical

children. They reported that early language skills were a predictor of later skill on false-belief tasks. And Perner and Aichhorn (2008) observed that the association between Theory of Mind skill and activity in the temporoparietal junction may be a learned language and culture repository of skills that influence skill on false belief tasks.

Attempting to Explain All Symptoms in One Large-Capacity Theory

A third strategy is to attempt to explain all the diagnostic features of autism. The theories of Courchesne and Pierce (2005), Kennedy and Courchesne (2008), Rout and Dhossche (2008) and Takarae et al. (2007) all offer complete accounts of autism. Such all-encompassing theories of autism are hard to maintain because counter evidence is easy to come by, given the massive variation in all aspects of autism. Courchesne and Pierce (2005) and Rout and Dhossche (2008) theorized cerebellar deficit as a central source of autism, but, as noted above, the cerebellum is not involved in the TNN or TPN, so is Kennedy and Courchesne (2008) theory of failed TNN activation/normal TPN activation wrong? Or are the Courchesne and Pierce (2005) and Rout and Dhossche (2008) theories wrong? Or is there a possible synthesis as yet unknown?

Takarae et al. (2007) argued that the dysmaturation hypothesis explains *all* the variability in autism because the failure of integration would impair all higher cognition, sensorimotor control, and all social behaviors. However, their theory excluded data reported for lobe specific deficits, did not account for specific transmitter abnormalities, and could not fully explain the links between dysmaturation and cognitive function because Takarae et al. (2007) based their theory solely on high functioning individuals with autism, and thus have not explored the relationship between mental retardation and dysmaturation of the brain's integrative circuits.

Zhao et al. (2007) and Grigorenko et al. (2008) both proposed genetic models that might account for ASD. Their proposals represent two distinct types of genetic theorizing. While Grigorenko et al. (2008) argued that mutations in a single gene may account for all ASD symptoms, Zhao et al. (2007) proposed a template pattern of inheritance that needs to be filled in by a variety of spontaneous mutations, as well as specific modifier genes. Though both models hypothesize to account for the genetic basis of autism, no synthesis between these models is apparent.

In the interests of full disclosure, it should be noted that our research group (Waterhouse et al. 1996) theorized a complete model of autism. We proposed that that a set of four interacting brain deficits characterized autism: amygdala dysfunction, hippocampal dysfunction, oxytocin abnormalities, and aberrantly organized temporal and parietal association regions. We argued that these four dysfunctions could be present in varying degrees in each individual diagnosed with autism, thus giving rise to a wide range of symptom variation. Evidence supports the four dysfunctions (Amaral et al. 2008; Green et al. 2001; Modahl et al. 1998; Stanfield et al. 2008; Wilson et al. 2007), but autism includes more dysfunctions than we proposed, and the specific mechanisms we proposed were speculative. Our theory did not explain all the variation of autism then, nor does it now.

Splitting Autism into Subgroups

Happé et al. (2006), Folstein (2006), and Dawson (2008) presented three distinct models of dividing autism into subgroups. Happé et al. (2006) proposed the three diagnostic features of autism-impaired social skills, impaired communication, and rigid and repetitive behavior—as separate phenotypes. Folstein (2006) proposed that autism, as now diagnosed, included two true autism phenotypes, Kanner's autism and Asperger Syndrome, along with a large heterogeneous group of non-autistic individuals whose mental retardation was caused by specific genes or infectious diseases. Folstein proposed eliminating the heterogeneous group from studies of Kanner's autism and Asperger Syndrome. Dawson (2008) proposed three intersecting disorders: autism, mental retardation, and language impairment.

All three models were direct attacks on the hard core assumption of the DSM-IV-TR (2000) diagnosis of autism and other associated disorders. The Happé et al. (2006) position attacked the cohesiveness of the three diagnostic traits; the Folstein (2006) position attacked the extent of the ASD diagnosis by proposing that only Kanner's original diagnosis and Asperger Syndrome be included. The Dawson (2008) position attacked the inclusion of language disorders in the communication deficit of the diagnostic criteria, and explained mental retardation as a comorbidity.

For Lakatos and Meehl, a mounting numbers of direct attacks on the hard core assumptions of a research field combined with a plethora of unsynthesized theories are the signals of the beginning of a paradigm shift.

Do Theorists Align Their Theories with Other Theories or Do They Offer Competing Replacement Theories Suggesting Non-progressive "Ad Hockery"?

Clearly many theorists have worked to align their theories with prior theories and findings of others (Domes et al. 2007; Happé and Frith 2006; Rout and Dhossche 2008; Wilson et al. 2007). Just et al. (2004), however, argued that their theory of underconnectivity was not aligned with the

theory of weak coherence, going so far as to claim that although findings of Castelli et al. (2002) did provide evidence for weak coherence in autism, these findings could only support the Just et al. (2004) underconnectivity theory. For Lakatos and Meehl, this sort of arrogation of findings was competitive territoriality that was to be expected within large research programs and was not ad hockery.

Lakatos and Meehl defined ad hockery as replacing one theory with another, entirely different theory describing the same phenomenon, while *ignoring* the findings and theoretical concepts of the competing theory. Courchesne and Pierce (2005) argued that autism is caused by neuro-inflammatory-impaired neurodevelopmental processes that increase head size; Kennedy and Courchesne (2008) theorized that autism resulted from an impaired Task Negative Network (TNN) but spared Task Positive Network (TPN). Because the research group's 2008 theory ignores the 2005 theory, Lakatos and Meehl would call this ad hockery.

Even the limited range of theories reviewed here illustrates that there is a general pattern of ad hockery in the field of autism. It may be true that autism is caused by weak central coherence, failed theory of mind, dysmaturation of the brain's integrative circuits, fronto-cerebellar disorganization and cerebellar maldevelopment, loss of cerebellar Purkinje cells, an impaired Task Negative Network, and also caused by deficits in the mirror neuron system, by deficits in maternal immune reactivity to fetuses, by neuroinflammation from other sources, by oxytocin abnormalities, by abnormal amygdala function, by abnormal hippocampal function, by abnormal left hemisphere gamma activity, and by mutations in the MIF gene, all based in a two-stage inheritance pattern along with modifier genes.

Each theory is supported by data, but it is implausible that any single individual diagnosed with autism would have all of the brain and genetic deficits currently hypothesized. The variation in autism and the selective targets of individual studies make it, in fact, impossible.

The field is now cluttered with unsynthesized ad hoc theories. New ad hoc theories are continuously forming on the basis of new findings in psychology (Theory of Mind), genetics (MIF) and neuroscience (mirror neuron system, default mode, amygdala function). New theories are also formed on small data sets or even on the basis of single cases. For example, Bonneh et al. (2008) reported a case study of a boy with autism who experiences a hierarchy of cross-modal extinction, in which auditory information extinguishes visual and tactile processing. While it is possible that this boy's dysfunction would fit our research group's theory of "canalesthesia" in autism (Waterhouse et al. 1996), it is more likely that this autistic boy's deficit is not explainable by any existing theory. Bonneh et al. (2008) also think this autistic boy's deficit is not explainable by any existing theory because they proposed their own new ad hoc theory of autism based on the impairments of this child alone. They argued that autism results from mono-channel of winner-takes-all perceptual processing in which a stronger perceptual representation extinguishes weaker representations.

Forty-five years of autism research has not produced a reasonable or progressing standard causal theory of autism. The myriad of competing theories of autism, while supported by evidence are, nonetheless, ad hockery. As Happé et al. (2006) title proclaimed "It is time to start giving up on a single explanation for autism" (p. 1218).

Conclusion: The Center Will Not Hold

Rather than continue to construct theories that try to explain all the variation in autism, there should be a paradigm shift accepting that all the phenotypic and genotypic variation in autism cannot be encompassed by any single theory. De facto, if autism is caused by such a myriad of neural and other systemic deficits in development, there must be phenotypic and genotypic subgroups that have not yet been discovered. Amaral et al. (2008) called for studies of "larger populations of better-phenotyped individuals" (p. 142). However, better subphenotyping and better subgenotyping is most likely to discover a multitude of small subpopulations, and the mechanisms underlying each genotype/phenotype subpopulation of autism may be complex. For example, Kelley et al. (2008) argued that individuals who are diagnosed with autism and also have fragile X (FX) have reduced cAMP signaling. They propose that this indicates that autism in FX "is unique, whereas a normal to high cAMP level would indicate that autism may be a compensatory process to increase cAMP levels" (2008, p. 8).

Judging from many specific findings like those of Kelley et al. (2008) and the review conclusions of Amaral et al. (2008), Nicolson and Szatmari (2003), and Stanfield et al. (2008), it is improbable that two or three phenotypes (Folstein, 2006; Happé et al. 2006) will be sufficient to accommodate the collocation of deficits now included in autism and ASD. This leaves the field in a definitional quandary: If there is no autism, how can populations with the current diagnostic deficits be defined?

The social explosion of awareness of autism and the increasing prevalence of autism create a strong social force against disbanding the diagnostic category. However, public pressure increases the need to generate productive and predictive models, and this cannot be done while research and theory remain focused on explaining autism as a monolith.

Competent human social interaction and flexible behavior in changing contexts are skills that are likely to depend on nearly all the brain systems we possess (Fair et al. 2008; Milligan et al. 2007; Ochsner 2008; Waterhouse et al. 1996). Consequently it is not reasonable to assume that in the future a brain deficit will be found to provide a unifying causal explanation for autism. Of the 20,500 human genes (Clamp et al. 2007), 4,636 have been shown to be expressed in the brain (Wang et al. 2007), and Khaitovich, Enard, Lachmann, and Pääbo (2006) reported that although gene expression varies little from region to region of the brain, nonetheless "The only genome-wide feature specific to humans so far detected is the acceleration of evolution of genes expressed in the brain" (p. 700). Given the thousands of brain-expressed genes and genes for brain development that influence aspects of social interaction skill and flexible behavior in changing contexts, and given findings to date for the genetic basis of autism (Grigorenko et al. 2008; Morrow et al. 2008; Zhao et al. 2007), it is not reasonable to assume that in the future a gene or set of genes will be found to provide a unifying causal explanation for autism.

Autism research should start over with a new hard core assumption that autism consists of more subphenotypes and subgenotypes than we have yet been able to hypothesize. We could begin with a provisional list of as many deficits as have been discovered in association with autism. Work could then proceed, via non-statistical analysis of complete genotype and phenotype studies of individual variation, to form groups. Exploring individual variation patterns while resisting the pressure to identify every study finding as "the cause of autism" might help move the field toward a progressive and productive splintering of the monolith.

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