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The 'Fractionable Autism Triad': A Review of Evidence from Behavioural, Genetic, Cognitive and Neural Research

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Abstract Autism is diagnosed on the basis of a triad of impairments in social interaction, communication, and flexible imaginative functions (with restricted and repetitive behaviors and interests; RRBIs). There has been a strong presumption that these different features of the syndrome are strongly intertwined and proceed from a common cause at the genetic, cognitive and neural levels. In this review we examine evidence for an alternative approach, considering the triad as largely 'fractionable'. We present evidence from our own twin studies, and review relevant literature on autism and autistic-like traits in other groups. We suggest that largely independent genes may operate on social skills/impairments, communication abilities, and RRBIs, requiring a change in molecular-genetic research approaches. At the cognitive level, we suggest that satisfactory accounts exist for each of the triad domains, but no single unitary account can explain both social and nonsocial features of autism. We discuss the implications of the fractionable-triad approach for both diagnosis and future research directions.

Keywords Autism · Autism spectrum disorders · Cognitive theories · Fractionation · Twin studies

Autism is considered to be one of the most highly heritable of all psychiatric or developmental disorders, and yet the search for vulnerability genes for autism has proved disappointingly difficult. While heterogeneity of etiology (different cases have different causes) is no doubt a major stumbling block in this endeavor, we suggest that research has been hampered by an assumption that the different symptoms that define autism proceed from the same cause. Instead, in this paper, we suggest that social and nonsocial aspects of autism spectrum disorders (ASD) have distinct causes, at the genetic, cognitive, and neural levels. We review evidence relevant to the proposed 'fractionation' of the autistic triad of impairments: (1) research on the degree of clustering or fractionation of symptoms in population samples with and without autism; (2) factor-analytic studies exploring whether autism can be defined along a single dimension or requires a multidimensional space; (3) family and twin studies shedding light on the genetic structure of the triad; (4) relevant molecular genetic work; (5) cognitive accounts of autism, and the relationship between deficits in social cognition, executive function, and cognitive style; and, (6) neuroimaging work suggesting distinct neural substrates for these different cognitive functions. Implications of this approach for both diagnosis and research are discussed.

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Autism is Defined by Multiple Impairments

Since Kanner's first description of autism, the condition has been defined in terms of both social/communicative and nonsocial features. Indeed, for Kanner, the core of autism could be reduced to two facets, i.e., 'autistic aloneness' and 'insistence on sameness' (Kanner and Eisenberg 1956). Later work, notably that by Wing (see below) and Rutter (1978), led to diagnostic criteria structured around three core areas of deficit: social impairment, communication difficulties, and rigid and repetitive interests and activities. In current diagnostic systems (DSM-IV, APA, 2000; ICD-

10, WHO, 1992) impairments must be found in all three areas in order to make a diagnosis of autism. This triad definition prompted a search for the cause of autism, with an assumption that a single cause underlies all three areas of difficulty (albeit that this cause may be different in different individuals on the autism spectrum; etiological heterogeneity). By contrast, in this paper we will summarize evidence from the literature, and our own research, to suggest that the three diagnostic domains of the autistic triad are fractionable, with largely independent causes at the genetic, cognitive and neural levels.

The suggestion that the different symptoms that define ASD may have separable causes is not new. In a 1971 paper written with John Wing entitled 'Multiple impairments in early childhood autism', Lorna Wing (whose early writings on autism prefigure most important subsequent ideas) discussed the "*difficulty of explaining the whole syndrome on the basis of any single abnormality"* and suggested instead that autism represents *"a combination… of impairments…"*, explaining why "*isolated fragments of the full clinical picture frequently occur…".*

In 1989, both Robert Goodman and Dorothy Bishop discussed the idea that autism is the result of a collection of impairments. Goodman drew the interesting analogy with Wilson's disease, a syndrome of co-occurring but etiologically distinct medical problems. Bishop pointed out that "Virtually every symptom characteristic of autism can be observed in children who do not fit this diagnostic category", as documented in Rutter's (1966) early analysis of the Maudsley hospital records for 'psychotic and nonpsychotic children' over a 9-year period. Notwithstanding these early suggestions for fractionation, the prevailing view has been that research is well directed in searching for the susceptibility genes for autism, genes expected to contribute to variation in all three areas of the triad. To begin our review and discussion of our opposing, fractionable triad view, we summarize research to date regarding the structure of autistic symptoms and traits.

Structure of Autistic-like Behaviors within ASD and in the General Population

This section will focus on evidence from population research studies concerning whether the three aspects of the triad tend to cluster together in individuals. There are few studies, and the most important of which by Wing and Gould (1979), will be discussed in some detail. This study, collected from a psychiatric and 'mental retardation' register, investigated the prevalence of the triad of impairments and whether they tended to occur together, and was carried out on a clinical sample of children selected from an epidemiological study in Camberwell, London (Wing and Gould 1979). Of 914 children, 132 were selected because they showed at least one of the behaviors (severe impairments of social interaction, language abnormalities, repetitive stereotyped behaviors) or were severely intellectually impaired (so that they were in contact with any 'mental retardation' service, such as a mental handicap hospital). The authors assessed the children using the MRC Children's Handicaps, Behaviour, and Skills (HBS) structured schedule (Wing and Gould 1978), and observations and interviews with teachers, nurses, child care staff, and sometimes parents if the child lived at home.

Analyses were conducted in a clinical manner (they did not use factor analysis or cluster analysis) because the aim was to identify a system that discriminated among clinical groups by comparing groups of individuals under certain criteria. They divided their sample in two ways: presence or absence of any type of social impairment, and presence or absence of "social aloofness and indifference, especially to peers, and elaborate repetitive routines" present before age 5 years and lasting up to at least age 7 years (i.e., social impairments and RRBIs considered by Kanner to be fundamental to early childhood autism). Comparisons were made between those with and without any type of social impairment, and between those with and without the social abnormality meeting autism criteria. The authors reported evidence for a "marked tendency for these problems [social impairments, repetitive stereotyped behavior and absence or abnormalities of language and symbolic activities] to occur together". For example, of 74 children with any social impairment, 55% also had no symbolic activities, 55% had no speech, and 72% had only repetitive interest patterns—indicating a clustering of the triad. By comparison, the percentages for the sociable, mentally retarded children were 10%, 33%, and 7%, respectively.

Comparisons across groups formed on the basis of type of social impairment found social aloofness was most commonly associated with language impairments and RRBIs; 89% of the socially aloof had no speech and all (N=37) had no symbolic play and only repetitive interest patterns. Some children with 'passive interaction' and 'active but odd interaction' also showed language problems and RRBIs, but the overlap was not as high. They found 50% of the socially passive children and 65% of the socially odd children were not limited to repetitive interest patterns, and had constructive and repetitive interest patterns, and most (82–85%) did not show elaborate repetitive routines, that is, they had social impairments but fewer RRBIs. Also, 29–50% of the socially passive and socially odd children had no echolalia and a majority (65–94%) had speech, i.e., social impairments but fewer language problems. Four children showed repetitive interest patterns and were severely retarded, but had appropriate social interaction, i.e., RRBIs but no social impairments. In

short, some children showed social impairments (passive or odd interaction) but not RRBIs, and vice-versa.

This study's important purpose was to investigate the extent to which the behaviors described by Kanner clustered together in a clinical sample in a particular area, using a systematic and thorough approach. There was evidence for substantial clustering of social impairments, communication impairments, and RRBIs, particularly when social aloofness was the social impairment. However, the survey also clearly documented that some children had only certain aspects of the autism phenotype, and not others.

Interpretation of these findings nearly 30 years after this study is limited by changes in definition and criteria for ASDs. Their working definition for autism was quite narrow by current standards, and Wing has since suggested that there are no clear divisions between Kanner's autism and the other subgroups, and that these should all be considered within the concept of the triad of impairments (Wing 1981). The study was also limited by relatively small numbers of children, especially when divided into subgroups. In addition, and perhaps critically, the sample was selected from a psychiatric and mental retardation register and likely 'enriched' with children who had greater severity and comorbidity (Caron and Rutter 1991). It is likely that children at that time who were not severely mentally retarded but who showed one or more autistic-like features were in mainstream schools and not on the register, e.g., those now diagnosed as having high functioning autism, Asperger syndrome, or PDD-NOS. Furthermore, almost one-quarter of the 900 children originally screened had at least one of the problems assessed by the interview schedule (Wing et al. 1976). In most cases, it was decided that the problem was atypical for autism and the child was excluded. Although some of these children would now be diagnosed with an ASD, at that time impairments had to be more severe to reach diagnostic significance. These limitations suggest that it would be useful to explore this research question again in a representative population-based sample that includes children with ASDs.

More recently, population-based studies have mostly not been informative concerning the clustering of the triad. This is because the selection criteria have included meeting all (or sometimes two) of the three impairments (social impairments, communication impairments, and RRBIs) i.e., criteria for an ASD. These studies have focused on the diagnosed disorder, not on why and to what extent the triad of impairments cluster together. For example, in one epidemiological study, children were screened in a particular region and data were collected for all who showed any problems or delays in intellectual/academic development, speech/language, behavior/conduct, and social/interpersonal areas. Those individuals who showed impairments in at least two domains were selected, and then filtered down to children who met all autism criteria (Bryson et al. 1988). Unfortunately, the number of children showing impairments in only one domain was not reported, nor was the correlation between domains.

An epidemiological study of Asperger's syndrome in Sweden reported details about children who had some social impairments but no RRBIs (Ehlers and Gillberg 1993). The aim was to investigate AS prevalence, but their over-inclusive initial selection procedure meant that children were selected if they scored above a cut-off, which did not necessitate them scoring highly for all three impairments. Only five definitive Asperger cases were identified, but several additional children showed social impairments and no RRBI's. Interestingly no child had RRBI's without social impairments.

In our population-based studies, using data from over 3,000 twin pairs assessed between ages 7 and 9 years old, we have found modest-to-low correlations between autistic-like behavioral traits in the three core areas (Ronald et al. 2005, 2006a). Somewhat to our surprise, even social and communication impairments—which are often seen as almost indistinguishable in real life, and have been suggested to result from a single cognitive deficit (see below)—were only modestly related, with correlations in the range of 0.2 to 0.4. This relationship was no stronger than that between communicative difficulties and RRBI (correlations in the range of 0.3–0.4), while social impairments and RRBI were the least strongly linked (0.1–0.3). The modest correlations between the three areas of autistic-like traits held both across the general population and when only children with relatively extreme scores were considered (Ronald et al. 2006b). It therefore appears, that, in middle childhood at least, degree of social difficulty, communicative impairment, and rigid/repetitive behavior are only modestly related.

Indeed, within our large population-based sample, a considerable number of children showed isolated difficulties in only one area of the autistic triad, defined as scoring in the most severe 5% group from a general population sample. For example, 59% of children who showed social impairments showed *only* social impairments. Around 10% of all children showed only social impairment, only communicative difficulties, or only rigid and repetitive interests and behavior. We found that children who showed one impairment were at increased risk of showing a second or third autistic-like difficulty (see Table 1), but the risks were relatively low, emphasizing the separability of the three impairments. For example, only 32% of all children who showed social impairments also showed communication difficulties. Thus, although the three areas of autistic-like behavior and impairment occurred together at above-chance rates, as shown in Table 1, there was

Table 1 Co-occurrence of extreme autistic-like traits as defined by a 5% cut-off in the Twins Early Development Study, a general population sample, compared to rates expected by chance alone (from Ronald 2006)

	N (%)	% expected by chance
No high group	5944 (86.9%)	85.84%
High S Only	204 (3.0%)	4.51%
High C Only	210 (3.1%)	4.51%
High N Only	266 (3.9%)	4.51%
High S+C	44 (0.6%)	0.25%
High C+N	30 (0.4%)	0.25%
High S+N	61 (0.9%)	0.25%
High S+C+N	48 (0.7%)	0.0125%

Extreme impairments defined as a score in the top 5% of the distribution of the Chilhood Asperger Syndrome Test. No individual is a member of more than one group. Data from Ronald (2006) Unpublished thesis, University of London

S Social impairments, *C* communication impairments, *N* non-social behaviors

considerable evidence for fractionation of the three aspects of the triad as measured by the Childhood Asperger Syndrome Test (Scott et al. 2002).

Factor Analytic Studies of the Autistic Triad

A pertinent empirical question regarding the symptoms that characterize ASD is whether they constitute a single dimension/factor or multiple dimensions/factors. One way to explore this question is to conduct factor analyses on measures of autistic behaviors, and there have been at least 20 such studies to date. In a number of these (diagnosed samples) a large proportion of variance in autistic behaviours was explained by the unrotated first principal component (Constantino et al. 2004; Szatmari et al. 2002; Volkmar et al. 1988; Wadden et al. 1991). This provides evidence to suggest the triad of impairments constitutes one empirical factor, rather than consisting of multiple factors. However, it is notable that all of these studies used subscale scores, with the exception of the Constantino et al. (2004) study which used item scores. Unfortunately, not all studies reported the proportion of variance explained by the unrotated first principal component and so it is not possible to directly compare across studies using this index.

It is clear, however, that many factor analytic studies of diagnosed samples did not find evidence to suggest that autistic behaviors loaded on one single factor. Wadden et al. (1991), DiLalla and Rogers (1994), Berument et al. (1999), Stella et al. (1999), Miranda-Linne and Melin (2002), Tadevosyan-Leyfer et al. (2003), Lecavalier (2005), and van Lang et al. (2006) all reported three- to six-factor solutions, concluding that different autism behaviors separate out between factors. Two earlier small studies also found multiple factors that divided up social impairments and RRBIs: one found four categories from factor analysis of the Behavior Observation Scale for autism (Freeman et al. 1980) and the other found eight factors with eigenvalues above one, using the Autism Observation Schedule (AOS; Siegel et al. 1986).

The Bolton et al. (1994) factor analysis study of the Family History Schedule used a different approach, confirmatory factor analysis, and reached conclusions about the structure of autistic behaviors that fell somewhere between the other studies. Their hierarchical model included a single latent factor at the top of the hierarchy, and the subscales all had individual factors on the second level, and then items and smaller factors were on the third level of the conceptual model. This result falls between the results of all the other studies and suggests that there is a single latent 'autism' factor related to all triad impairments, but each domain also falls on its own factor.

The Constantino et al. (2004) study is one of the most recent studies, with one of the largest samples, and used a relatively new but influential measure, the Social Responsiveness Scale (SRS). The results provided evidence for a singular, continuously distributed underlying factor encompassing all the triad of impairments (Constantino et al. 2004). A single factor was also found using the ADI-R in this study, which contradicted other studies that have found multiple factors underlying this measure (Bolte and Poustka 2001; Tadevosyan-Leyfer et al. 2003).

A recent review restricted which factor analysis studies were included based on specific criteria, e.g. participants needed to be included across the autism spectrum, sample size had to be sufficient to justify the number of items entered into the analysis (Mandy and Skuse 2008). The authors concluded from a review of seven factor studies that met their criteria that all studies (but one) found evidence for multiple factors underlying autistic behaviors, and there was always a social impairment factor and a non-social factor. The exception was the Constantino et al. (2004) study. Mandy and Skuse (2008) suggested that the single factor structure reported by Constantino et al. (2004) may be explained by the fact that their sample mixed ASD and non-ASD groups, which might have had the effect that items discriminating ASD from non-ASD individuals masked the effect of differential item variance within ASD symptoms. Whether this is the case or not, it is important to acknowledge the different findings reported by Constantino and colleagues.

In summary, evidence is mixed concerning the factor structure of autistic behaviors from principal component factor analysis studies on clinical samples. One likely reason for different results is the different measures used, and particularly whether items or subscale scores were

factor analyzed. In addition, clinical samples varied in size and the type of children included (with autism, other ASDs, or non-PDD diagnoses).

An advantage of using clinical ASD samples to study the structure of autistic behaviors is that their 'face validity' in terms of how they relate to ASD, is not questioned. That is, if children have all received an ASD diagnosis from clinicians, then the relevance of findings from such samples to understanding autism is not questioned. In contrast, when studying general population samples, even with a reliable and valid measure of autistic behaviors, one question often raised is how the data actually relate to clinical ASD. Nevertheless, the restricted variance in narrowly defined clinical samples, as well as the circularity of investigating the relationship between the triad of impairments in a sample of individuals who, by definition, show all three difficulties, should also be noted as considerations. As Myhr (1998) pointed out when discussing DSM-IV PDD diagnoses: "The circularity involved in defining a sample and then finding differences in that sample which may be related to the definition of the sample has been an ongoing problem in this area". Even psychiatric patients with non-PDD diagnoses and PDD-NOS are likely to have greater comorbidity and severity than community samples (Gadow et al. 2005).

Four published studies have reported factor analyses on autistic-like behaviors in community samples. Community samples have several advantages, including more power from larger samples size, less sample bias from pre-selection, more variation in traits, and more representativeness. Most importantly, for study of the triad of impairments, the full spectrum of social impairments, communication impairments and RRBIs can be assessed, and how they relate to each other can be investigated in an unbiased sample. Individuals with zero, one, two, or three severe impairments can all be included, and how the impairments are correlated with each other can be measured.

The first study presented analyses on the SRS measure of autistic-like traits using data from a community sample of 287 children aged 4–14 years old (Constantino et al. 2000). Latent class analysis showed that classes differed in terms of severity of all items, not in terms of which items were and were not endorsed, the same conclusion reached with a clinical sample (Constantino et al. 2004). Confirmatory principal components factor analysis was carried out. Four factors were hypothesized to exist, each related to a different aspect of the social impairment domain, i.e., recognition of social cues, interpretation of social cues, response to social cues, and tendency to engage in social interaction, and each was represented by a minimum of eight SRS items. The four-factor model produced a first factor that explained 70% of the variance. When the number of factors was allowed to be free, a 12-factor solution resulted, again with a similarly large first factor. However, the authors noted that "given the high internal consistency of the measure, it is not particularly surprising that latent class analysis results were most consistent with a singular continuously distributed variable". The authors did not present the phenotypic correlations between behavior categories, which would be useful in considering their conclusions.

Second, the Autism Spectrum Quotient (AQ), a self-report measure to assess autistic spectrum traits in adults in the general population, was factor analyzed, using data from 201 undergraduates (mean age=20.9 years) (Austin 2005). The first unrotated principal component explained 14% of the variance. From oblique rotation, a three-factor solution was found, explaining 28% of the variance. The factors were labeled social skills, details/patterns, and communication/mindreading, reflecting the fact that the triad, as assessed in the AQ, split into three separate factors. Factor membership matched autism domains for nearly all items. The oblique rotation meant that the factors were allowed to correlate with each other and social skills, and communication/ mindreading correlated 0.2. Other inter-factor correlations were not reported. This study presents important new evidence that the triad behaviors fall into three empirical factors, when studied as traits in a community sample of young adults.

Two further studies addressed the AQ factor structure in community samples. Similar to the Austin (2005) AQ study, Hoekstra and colleagues (2008) collected adult self-report assessments on the AQ in Dutch adults, from 961 undergraduates and 302 parents of twins. In both samples it was found that a multiple factor model—either with two factors (one for social interaction and one for attention to detail), or a five-factor model, both fit significantly better than the one-factor solution. Between the two multiple factor models, the two-factor model was preferred for its slightly better fit and greater parsimony. The social interaction and attention to detail factors showed a modest correlation (r=0.19). Lastly, Auyeung et al. (2008) reported that factor analyses of parent ratings of 4–11 year old children from a population sample (N=1225) on the AQ-Child version led to a four-factor solution.

Finally, unpublished exploratory principal component factor analyses on the Childhood Asperger Syndrome Test (CAST) administered to over 3,000 8- and 9-year-old children from a community sample supported the multiple factor solution for autistic-like traits (Ronald 2006, unpublished thesis). For both the full and abbreviated CAST versions, exploratory principal component factor analyses led to between four and eight factors. Correlations between factors were all low to modest (the highest correlation was 0.35) and the first principal component never explained more than 14–22% of the variance. This pattern of results

applied for parent, teacher, and child self-report ratings of autistic-like traits.

The results from the SRS and AQ/CAST differ somewhat. With the SRS measure, Constantino et al. (2000) presented a large first factor with all the triad of impairments loading on it, whereas all three published studies of the AQ, and the unpublished CAST results, support multiple factor solutions. Samples characteristics differed. The Constantino et al. (2000) and Auyeung et al. (2008) studies had developmental samples, but with broad age ranges, whereas Austin (2005) and Hoekstra et al. (2008) studied young adults. In terms of sample size, the earlier two studies were somewhat disadvantaged compared to the more recent AQ and CAST studies, which included approximately 1,000 individuals or more.

Genetic Structure of the Autistic Triad

Family and Twin Studies of Autism

It was Rutter (1967) who noted that although sibling risk for autism was low in absolute terms, it was much higher than the population risk. This began the search for the causes of autism because it established that autism was familial. Twin studies have arguably made one of the largest contributions to our understanding of the causes of autism and autistic-like traits. All four of the original twin studies of autism reported consistent findings (Bailey et al. 1995; Folstein and Rutter 1977; Ritvo et al. 1985; Steffenburg et al. 1989). A large difference between monozygotic (MZ) and dizygotic (DZ) twins in their concordance for autism was reported in the first study, in a representative and valid sample of diagnosed individuals with autism ascertained through psychiatrists around Great Britain, and hospitals and the National Autistic Society (Folstein and Rutter 1977). Concordance rates were not explained by any biological hazards associated with the birth of these children, such as low birth weight, neonatal convulsions, or delayed second birth. This MZ–DZ difference in concordance suggested a major role for genes in the etiology of autism. Interestingly, within discordant pairs the autistic twin was usually worse off in terms of biological hazards surrounding the birth process. Across the four studies, concordance was estimated at 60% for MZ twins and 0–5% for DZ twins. That the MZ concordance was less than unity suggests there are also some nonshared environmental influences involved in the etiology of autism. Nonshared environmental influences are environmental influences that differentially affect children from the same family, and can include epigenetic processes, gene expression, de novo mutations, illnesses, intra- and extra-uterine environment, and measurement error.

In addition, the authors found that a less strict measure including some but not all of the features of autism—communication, linguistic, and/or social abnormalities (by definition, any individual with autism would be included in this broader category)—was even more heritable than autism i.e., a greater difference in MZ and DZ concordances. Folstein and Rutter (1977), Bailey et al (1995), and Le Couteur et al (1996) all showed that when defining individuals as probands in terms of just the social and communication abnormalities characteristic of autism, MZ concordance rates were higher than for autism (in the Steffenburg et al study, MZ concordances were equal for autism and the broader autism phenotype (BAP), both 91%). That is, the majority (90%) of the undiagnosed MZ co-twins in discordant pairs had social and/or cognitive-communication impairments, far fewer than the undiagnosed DZ cotwins (10%). Although these milder BAP impairments did not reach diagnostic cut-offs, they had major persistent impact on the individuals' lives continuing into adulthood: most did not have confiding relationships, did not live independently, and had employment difficulties (Le Couteur et al. 1996). This suggested that the strongest genetic liability is for the BAP (as defined here) and that the BAP is a qualitatively similar phenotype that has persistent effect on long-term outcome similar to autism. It was suggested that autism was one type of manifestation of this underlying genetic liability that is more heritable than autism itself.

These twin studies influenced molecular genetic research, of autism, which began in the early 80s. However, clinical twin samples have some disadvantages for assessing the BAP. First, all probands in an autism sample show all of the triad impairments, so it is not a representative sample for each impairment separately. This also means that samples are small. Second, in terms of the BAP, in order to look at the concordance of social impairments and communication impairments directly, it would be appropriate to start by screening for a representative sample of all twin pairs with at least one proband who meets the criteria for social impairments and communication impairments, rather than starting with autism probands. Third, BAP criteria in these twin studies was broad, with no one required common feature. Therefore, while it was innovative to consider the BAP as well as autism, an idea that has endured, cautious interpretation of these findings is needed. Nevertheless, these studies raised the important issue of whether symptoms that characterize part of the triad of impairments might occur on their own in milder forms than those demanded by diagnostic criteria, and whether milder forms might share the same genetic liability as autism.

Family studies have also explored the presence of the broader autism phenotype in relatives of individuals with autism. We have not covered in full the vast autism family

study literature here, but several well-conducted large studies using the Family History Schedule (FHS) have found consistently that relatives, including siblings and first- and second-degree relatives, show significantly higher rates of social impairments, communication impairments and non-social behaviors than control family relatives (Bolton et al. 1994; Pickles et al 2000; Piven et al. 1997; Szatmari et al. 2000). Moreover, often relatives showed just one or two of the autistic symptoms making up the triad, suggesting that the symptoms co-segregate in relatives. This pattern of familial inheritance would suggest that different causal influences affect the different autistic behaviors that form the triad.

Perhaps spurred on by these broader autism phenotype findings that questioned the strength of the relationship between the different autistic symptoms, a set of twin and family studies attempted to unravel the strength of the relationship between autistic symptoms using small selected samples where more than one child had autism in each family. The objective was to study whether related individuals varied less with each other (within-pair variability) than individuals unrelated to each other (i.e. between-pair variability). Comparing variability within and between concordant MZ twin pairs, for example, could help establish which phenotype aspects were familial. Two studies to date have examined intra- versus inter-MZ pair variability in autism. The first study had 16 twin pairs and found no evidence for greater within- than between-pair similarity for any component of the autism phenotype, using ADI scores and verbal and nonverbal IQ (Le Couteur et al. 1996). Their findings suggested that phenotypic variations, differences in the clinical manifestation of symptoms, are not an indication of genetic similarity, because MZ twins share most of their DNA code yet varied just as much within pairs as between pairs. However, a more recent but smaller study of similar design with 16 MZ twins and ADI subdomain and item scores contradicted the Le Couteur et al. study (Kolevzon et al. 2004). Kolevzon et al. (2004) reported significantly reduced within-family variance for all main ADI domains, suggesting these aspects of the autism phenotype do reflect genetic similarity. This study also did not find significant correlations between the social and communication domains or between the communication and RRBI domains. The only significant correlation was between the social and RRBI domains, and this was negative ($r=-0.53$). The authors suggested there was a lack of association between levels of the different symptom domains within families, and the different symptom domains should be considered as independent genetic traits.

In multiplex family studies it has been found that nonsocial repetitive behaviors are more similar within families than between families (Spiker et al. 1994). Other studies have found that IQ (Szatmari et al. 1996), nonverbal communication and verbal/nonverbal status (Goin-Kochel et al. 2008; MacLean et al. 1999), and delays in phrase speech (Silverman et al. 2002) are the most familial components. Social impairments have appeared to be familial in some studies (Szatmari et al. 1996) but not in others (e.g., Silverman et al. 2002). There also have been a substantial number of variables for which no family-basis was found. Finally, in a recent study, significant intra-class correlations (0.12–0.30) across siblings in multiplex families ($N=192$) were reported for five out of six factors that were derived from factor analysis of ADI-R items (Tadevosyan-Leyfer et al. 2003), suggesting familiality of these measures (language, compulsions, milestones, savant skills, and sensory aversions). Although the sib–sib correlation for the sixth factor, 'social intent', was not significant, it became significant when age was covaried.

These studies of intra-class correlations within diagnosed-related individuals (in either concordant MZ twins or multiplex siblings) are valuable but hindered by their small sample size and the restricted variance that individuals with autism are likely to show on the measures. There was no formal testing of models: the results are based on intraclass correlations which are likely to have large confidence intervals in small selected samples. Furthermore, these results did not provide specific estimates about the degree to which familiality in autistic behaviors is due to genetic or shared environmental influences. To formally test the degree to which different symptoms that characterize autism are due to genetic and environmental influences, structural equation model-fitting is required. The first twin study of MZ and DZ twins with PDD diagnoses (i.e. using broader criteria than for autism) has reported on the etiology of nonverbal communication and social interaction symptom domains as measured by the ADI subscales (Mazefsky et al. 2008). Both subscales were highly heritable: MZ polychoric correlations were 0.42–0.57, DZ: 0.01–0.12. There were significant nonadditive genetic influences and significant shared genetic influences across these two subscales. This study makes an important initial contribution to our understanding of the etiology of ASDs using a clinical sample, but was limited by low power in the analyses due to small sample size (94 MZ twins, 1,190 DZ twins and siblings) and it did not investigate the etiology of RRBIs. Also notable, the sample was not systematically obtained and therefore may reflect ascertainment biases.

Other twin and family studies have directly assessed the etiology of autistic symptoms and employed formal model-fitting to derive specific estimates of the role of genes and environment, to answer the question: Is the behavioral or phenotypic separability of the triad of autistic-like traits mirrored at the genetic level; that is, are there separate genes contributing to social impairment, communicative difficulties, and rigid/repetitive behavior? This can be

assessed directly using multivariate twin model-fitting. Two of our studies obtained data on the autistic-like traits of over 3,000 MZ and DZ twin pairs at ages 7 and 8 years old in the Twins Early Development Study. We found that each aspect of the triad is highly heritable and shows modest nonshared environmental influence, both across the range of individual differences and at the extreme (Ronald et al. 2005, 2006a,b). However, multivariate model-fitting analyses of cross-twin cross-trait correlations suggested that more than half the genes that contribute to variation in, say, social (dis)ability are independent from those that contribute to variation in communicative skills or rigid/repetitive tendencies (Ronald et al. 2005, 2006a,b). Thus, most of the genetic effects, at least in middle childhood, are specific, acting on just one part of the triad.

A different kind of twin model-fitting analysis called Defries Fulker extremes analysis was employed on this sample to address the nature of the relationship between different autistic-like traits at the impaired extreme (using a 5% cut-off; Ronald et al. 2006b). Extreme autistic-like traits all showed high heritability and modest nonshared environmental influences. Genetic correlations, which were derived from the bivariate Defries Fulker extremes analysis, were again modest, ranging from 0.32 between social impairments and RRBIs, to 0.53 between social and communication impairments, and 0.57 between communication impairments and RRBIs. These results suggested that at the extreme end of the normal distribution, there were some genetic influences shared between the three different autistic traits but also evidence for genetic influences that were specific to each type of autistic behavior.

This new conclusion, from two large normative twin sample studies, fits with results from family studies of individuals with ASD. As described earlier, family and twin studies have shown that it is not only autism itself that is heritable, but that relatives show increased rates of the 'broader autism phenotype', which refers to subclinical manifestations of all or part of the triad of autistic features. Importantly, some relatives show only isolated traits, for example communication difficulties without social impairment or rigidity (e.g. Bolton et al. 1994; Pickles et al. 2000; Piven et al. 1997; Szatmari et al. 2000), suggesting that the genes that contribute to autism segregate among relatives and have distinct influences on the different parts of the phenotype.

One recent family study of multiplex ASD families has also addressed this question of the etiological relationship between the triad of impairments (Sung et al. 2005). This study used multivariate polygenic models with data from a sample of 201 nuclear families with at least two children with ASDs (average IQ of 80). They found low heritabilities (0.08–0.19) for language onset, social motivation, and range of interest/flexibility, and nonsignificant heritabilities for expressiveness and conversation skills. Genetic correlations between the traits were mainly not statistically significant, suggesting genetic heterogeneity. However, one high genetic correlation of 0.92 was found between social motivation and range of interest/flexibility. The authors reported that this was the first evidence from family data that the same genes influence these two autism components, an interesting finding requiring replication. The authors pointed out that the genetic variances and covariances were small, and the genetic correlations were quite unstable. It is surprising that the heritabilities were low for the five phenotypes, since autism is generally found to be highly heritable.

An advantage of results to date about the etiology of the autistic triad has been the use of both family and twin designs. Because any specific research design has assumptions and limitations that need to be taken into account, it is ideal to replicate findings across different research designs. In some respects the family study design might seem the more appealing of the two: families are easier to recruit than twins, and families seem more representative than twins. Yet, the family study design also presents substantial obstacles that the twin design can bypass. Family designs involve comparing degree of similarity between related individuals. This relatedness is usually assumed (rather than tested with DNA) and family designs are likely have a degree of error due to the fact that paternity is not always correct. However, both twins in a pair always share the same biological parents. Second, there are age differences between parents and offspring, and between siblings that must be taken into account in the choice of measures and the nature of the analyses with a family design. Age is always controlled for within a twin pair. Family designs usually require a control group for comparison to 'case' families: the twin design does not require a control group. This matching procedure can present difficulties because control groups do not usually control for all variables and different studies have used different types of control groups making direct comparisons complicated (Shaked and Yirmiya 2004). Family studies cannot partition variance into the degree to which it is due to genetic influences or shared environmental influences, but can only show the degree to which a trait or disorder is familial.

Therefore the twin design adds importantly to findings from family studies. The twin design has been critically assessed at length (e.g., Joseph 2002; Kamin and Goldberger 2002; Maccoby 2000; Martin et al. 1997; Rose, Lewontin, and Kamin 1984) and there are some limitations. Twins share their intrauterine environment but information on whether twins shared a placenta is usually unavailable, making it difficult to control for the degree to which twins shared the same intrauterine environment. Most twin models assume that there are no gene-environment interac-

tion effects, and they cannot estimate both shared environmental influences and nonadditive genetic influences in the same model. Recent findings suggest that there are small differences in copy-number variations between MZ twins. Although these are likely to only account for a small amount of variance, these differences need to be taken into account (Bruder et al. 2008).

Do the main assumptions of the twin design raise any particular issues for studying ASDs and autistic-like traits in twins? It has been debated whether autism occurs at a higher frequency in twins than in singletons (reviewed by Rutter 2005, see also Croen et al. 2002). A handful of autism studies have found that the rate of twins in their samples of affected sib pairs represent significant deviations from the expected proportion (e.g., Betancur et al. 2002; Greenberg et al. 2001). However, Visscher (2002) suggested that these data do not provide evidence that twinning increases the risk of autism and may instead reflect the ascertainment method used in these samples i.e., affected sib pairs (Visscher 2002). This is because an excess of MZ twin pairs, both with autism, would be expected in a sample of affected sib pairs given that genetic factors are causally implicated, but does not in itself suggest that being a twin confers risk. An excess of DZ twin pairs could be due to common environmental mechanisms, or due to the 'stoppage' phenomenon, where parents with one child with autism choose not to have more children (Visscher 2002). Other studies have presented evidence that being a twin does not confer a risk for autism (Hallmayer et al. 2002; Hultman et al. 2002). Therefore, there is mixed evidence on this issue with some strong arguments and data that support the suggestion that ASDs are not more common in twins.

Molecular Genetics of the Autistic Triad

Indirect evidence exists from linkage studies using diagnosed autism samples that different genetic regions may be associated with different domains within the autistic triad. For example, linkage signals have been shown to increase when families were selected based on particular nonsocial features such as having high scores on insistence on sameness (Shao et al. 2003), savant skills (Nurmi et al. 2003), high scores on the RRBI domain (Sutcliffe et al. 2005), severe compulsive behaviors and rigidity (McCauley et al. 2004), and repetitive behaviors (Alarcon et al. 2002). Similarly, linkage signals have been shown to increase when families with children with autism were selected based on particular language characteristics (Alarcon et al. 2002; Bradford et al. 2001; Buxbaum et al. 2001; Schellenberg et al. 2006; Shao et al. 2002) and nonverbal communication in autism (Chen et al. 2006). These studies provide suggestive evidence that different genetic loci may be associated with the different core behaviors that currently define the autism diagnosis (Szatmari 1999).

Numerous linkage studies have been conducted for diagnosed autism and nearly every chromosome has been implicated (see Abrahams and Geschwind 2008; Sykes and Lamb 2007; Yang and Gill 2007). For complex traits, linkage is limited to detecting large effects that may reflect a summary of effects over vast genetic distances. Allelic association is more powerful than linkage for detecting quantitative trait loci (QTLs) of small effect size (Risch 2000; Sham et al. 2000) and therefore has more potential for identifying causal variants associated with complex traits and disorders (Plomin et al. 2008).

Many candidate genes have been proposed for autism (see Abrahams and Geschwind 2008 for a recent review), and, like the linkage studies mentioned above, candidate gene studies have begun to explore the possibility of symptom-specific genetic effects in autism. A good example is the set of studies on the serotonin transporter gene and autism (*SLC6A4*). A recent study reported that subjects with the short version of the serotonin transporter gene promoter polymorphism (5-HTTLPR) (S/L or S/S genotypes) were rated as more severe on a social subdomain "failure to use nonverbal communication to regulate social interaction," whereas subjects with the long version (L/L genotype) were more severe on a nonsocial subdomain "stereotyped and repetitive motor mannerisms" and on an aggression measure (Brune et al. 2006). Increased severity on social/ communication domains in individuals with the short version was also found in an earlier study (Tordjman et al. 2001), and other variants within this gene have also been found to be specifically associated with increased severity on nonsocial domains (Mulder et al. 2005; Sutcliffe et al. 2005).

A problem with candidate gene studies is their nonsystematic nature. Genome-wide association studies, on the other hand, are highly systematic and are now feasible using new technology: SNP (single nucleotide polymorphism) microarrays (Hirschhorn and Daly 2005). To our knowledge, only one such study of autism has so far been published (Arking et al. 2008), a genome-wide, family-based association study of 72 multiplex families, but no genome-wide significant SNPs or haplotypes were identified.

Familial and Syndromic ASD

It is estimated that between 10–20% of ASD cases have known biological causes, referred to as syndromic autism. There are three main groups of causes in syndromic autism. The first is when individuals have known genetic conditions such as Fragile X or tuberous sclerosis. A

substantial proportion of individuals with these conditions show comorbid ASD: for example 25% of children with Fragile X also meet diagnosis for ASD. Second, some children with ASD have cytogenetic abnormalities. One of the most common types is a duplication on chromosome 15q11–13. Finally, de novo copy number variations have been reported in 2–10% of children with ASD. Interestingly, no one specifically-known biological cause appears to account for more than 1–2% of all ASD cases (see Abrahams and Geschwind 2008 for a review).

Syndromic cases can be contrasted to familial cases. The causes of familial ASD cases, which account for between 80–90% of all ASD cases, are unknown but thought to involve a complex interplay of multiple genetic and environmental factors. Familial ASD, as the name suggests, shows greater evidence for running in families than syndromic autism, which usually occurs in simplex families. It remains to be seen whether the phenotypic and genetic structure of the triad differs in syndromic versus familial cases of ASD.

Fractionation of Cognitive Substrates in ASD?

Wing and Gould's seminal report, and it's translation into diagnostic criteria defined along three dimensions in DSM-IV and ICD-10, presented a challenge to researchers to explain why deficits in social interaction, communication, and imagination/RRBIs should co-occur above chance. A desire for parsimony led researchers to seek a single explanation for all three areas of difficulty. We suggest, however, that the search for a parsimonious single-deficit account of the triad has been unsuccessful: at the cognitive level, as at the symptom/behavioral and genetic levels, autism may be characterized by fractionable impairments.

Explanatory Scope of Cognitive Accounts of ASD

In the 1980s, theories of autism were fundamentally changed with the discovery by Frith, Baron-Cohen and Leslie that children with autism failed simple tests of 'theory of mind', and were apparently unable to represent others' false beliefs, and mental states more widely. This specific deficit provides a good explanation for the pattern of social and communication difficulties in ASD—explaining why people with autism, for example, find lying inexplicable but show (mental age) appropriate patterns of attachment (see Baron-Cohen et al. 2000 for a fuller account of the theory-of-mind deficit explanation of autism). While there is continued debate as to whether theory of mind difficulties are primary, universal, or specific to ASD, the idea of mindblindness provides a good description and explanation for the day-to-day difficulties of those with ASD. It has prompted targeted interventions and educational approaches, early screening measures, and tasks amenable to neuroimaging methodologies.

While an inability to represent mental states can account for social, communication and imagination impairments (Wing's original triad), it cannot explain the non-social dimensions of ASD, such as restricted and repetitive behavior. The suggestion that RRBIs result from confusion and anxiety due to social incomprehension does not appear explanatory; RRBIs appear to be as pronounced and frequent in high functioning and more socially insightful individuals as in lower functioning individuals with ASD. In addition, repetitive behaviors have arousing as well as calming functions, and are often seen when an individual is left alone and unstimulated (see Turner 1999 for a review of repetitive behavior in ASD). This is not to say that social deficits do not, of course, play into the RRBIs. Lack of shared attention likely contributes to the unusual topics chosen for special interests but overall it has not proven possible, to date, to derive the full pattern of non-social deficits (and assets—see below) of ASD from a primary social deficit (see Happé 2000, 2001, 2003 for further discussion).

If 'social first' theories cannot explain the full triad of ASD symptoms, it is also true that 'non-social first' theories are similarly limited in their explanatory scope. Executive dysfunction was widely explored in the late 1980's and 1990's, with recognition that the perseveration, and planning and set-shifting difficulties seen in ASD resembled problems found in acquired frontal lesion patients. Several investigators suggested that frontal deficits might have cascading effects developmentally, sufficient to cause autistic social and communication impairments (for reviews see Hill 2004; Ozonoff et al. 2005; Russell 1997). These interesting accounts lost momentum due to the following factors. First, many executive functions (EF's) impaired in ASD are also impaired in other developmental disorders, such as ADHD, in which social and communication difficulties are *not* marked. While EF covers a multitude of specific skills, it remains unclear whether a specific profile of deficits distinguishes ASD and ADHD (Geurts et al. 2004; Happé et al. 2006; Johnson et al. 2007; Ozonoff and Jensen 1999). Second, evidence to date, although limited, suggests that very young children with ASD do not differ from ability-matched intellectually-disabled children in their EF performance (Griffith et al. 1999). In addition, individuals with ASD could be found who performed relatively well on, for example, theory of mind tests while performing very poorly on EF tests (Ozonoff et al. 1991). Lastly, robust evidence of problems in intention monitoring was not found by Russell and colleagues (e.g. Russell and Hill 2001), who had proposed this deficit as underlying, via

problems of agency, theory of mind impairment. Thus, executive dysfunction does not appear to account for the full triad of symptoms in autism, although it does show selective and specific relationships with restricted and repetitive behaviors, (Lopez et al. 2005).

Another account of ASD has focused on the non-social assets and uneven cognitive profile. Uta Frith's suggestion of weak central coherence in the late 1980's originally aimed to explain theory of mind impairments, suggested that social information processing places the greatest demands on contextual information gathering and integration of diverse information (Frith 1989). In later developments, Frith and Happé (1994; see also Happé and Frith 2006) suggested that weak coherence, or detail-focused processing, is largely independent from deficits in theory of mind—citing as evidence the fact that weak coherence was as pronounced in those passing theory of mind tasks as in those failing, and that the two facets of ASD could be found independently in the broader autism phenotype (see below). Thus, while a detail-focused processing bias likely interacts with social difficulties (e.g. featural face processing may make recognition of certain emotions hard; failure to integrate information in context will contribute to problems interpreting speaker's intent), the central coherence account specifically limits its explanatory scope to the non-social assets and deficits of ASD (Happé and Frith 2006). Other accounts focusing on perceptual-level abnormalities in ASD have been less explicit in their explanatory scope. Mottron's account of enhanced perceptual functioning (Mottron et al. 2006), and Plaisted's (2001) theory of reduced generalization and enhanced discrimination seem to have as their aim an explanation of the complete ASD symptom profile, although empirical links to social functioning have not been demonstrated.

Baron-Cohen's empathizing-systemizing account describes cognitive characteristics in a two-dimensional space: people with ASD, and to a lesser extent typical males, are characterized by good systemizing (understanding of closed systems) and poor empathizing (theory of mind, emotion recognition, etc.). The use of two dimensions plotted orthogonally in Baron-Cohen's diagrams (e.g. Goldenfeld et al. 2006) suggests that systemizing and empathizing are conceptualized as independent—in line with our suggestion of fractionable cognitive characteristics. However, the same group's work on possible biological foundations for poor empathising and good systemising appears to link these through the common influence of fetal testosterone: children exposed to higher fetal testosterone levels are reported to show poorer social and communication skills, alongside more narrow interests and better systemizing (e.g. Knickmeyer et al. 2005). The two dimensions, then, may be linked at the biological level, although it remains to be examined how tightly bound they are and to what degree systemizing and empathizing are independent aspects of ASD.

Neither executive dysfunction, detail-focus, nor hyper-systemizing would appear able to explain the social and communication sides of the triad. More generally, the very specific pattern of social and communicative difficulties seen in autism presents a major challenge to any 'domain-general' account of the disorder. Some (e.g. Minshew and Goldstein 1998) propose that social deficits result from non-social processing limitations because social processing is the most difficult thing we do. This argument, although intuitively appealing, requires a metric for processing difficulty (see Zelazo et al. 2001 for an attempt, and Perner et al. 1999 for critique). Without such a metric, our impressions of what is hard or easy have no empirical support: extracting 3-D object information from the visual array has proved extraordinarily difficult for computers, while complex mathematical calculation is easy; in intellectual disability, limited IQ does not affect the former but certainly limits the latter. Many domain-general accounts struggle to 'allow' the areas of average or above average performance seen routinely in ASD: people with autism who can recognize or generate prime numbers but not talk, make lightning calculations for dates but fail to understand social intent obvious to an ordinary 2-year-old, or, more mundanely, achieve very high IQ scores while being entirely oblivious to deception that an intellectually-disabled teenager would suspect.

In summary, we suggest that while satisfactory working theories exist for the various different aspects of autism, no one cognitive account to date can explain social, communication and non-social/RRBI patterns in ASD. The implication of our twin findings, indeed, would be that a unitary account is not needed and unlikely to be accurate. What evidence is there to date regarding the fractionation of performance in these different cognitive domains?

Patterns of Performance on Cognitive Tasks: Fractionation or Correlation?

If several cognitive deficits/styles are relevant to ASD, and underlie different symptom domains, we might expect to find fairly independent performance on experimental tasks designed to tap, for example, theory of mind, executive function and weak coherence. Is this the case? Below we briefly review evidence from research with individuals with ASD and with other groups in whom single deficits in one of these cognitive functions alone would provide further evidence of fractionation.

Interpreting correlations between aspects of ASD, either cognitive or behavioral, can be a 'glass half full–glass half empty' exercise: how large a correlation do we expect to

see if different tasks are in fact tapping a single underlying cognitive deficit? How small a correlation do we insist on to show fractionation/multiple cognitive deficits—given the pervasive effect of, for example, IQ or mental age, and the downstream effects of one impairment on learning skills in other areas? Similarly, demonstrating task success in one cognitive domain and task failure in another is only informative if the tasks chosen are somehow equated for difficulty (e.g., age of attainment in typical development). With these provisos in mind, the literature includes studies that examined performance across multiple cognitive domains in ASD. Executive dysfunction and theory of mind impairment have been shown to be dissociable in ASD (passing ToM tasks, failing EF tasks: Ozonoff et al. 1991), although Pellicano (2007) has reported a correlation between performance on the two types of measures, as well as contrasting unidirectional dissociation (good EF, poor ToM) in young children with ASD. Executive-function problems can be seen in the absence of theory of mind deficits in ADHD (e.g. Charman et al. 2001), and also in the broader autism phenotype (parents of children with autism; e.g. Hughes et al. 1997).

Theory of mind deficits also appear to be separable from weak coherence; typical Wechsler IQ profiles with peaks in block design, and poor integration of words in context in a homograph reading task, are seen regardless of whether participants with ASD pass or fail false belief tasks (Happé 1994, 1997; see also work by Jolliffe, e.g. Jolliffe and Baron-Cohen 2000). While Jarrold et al. (2000) have found inverse relations between measures favoring detail focus and those tapping social cognition in typical development and in ASD, a number of other studies suggest dissociability of theory of mind and coherence (Morgan et al. 2003; Pellicano et al. 2005, 2006). In the broader autism phenotype, self-rated social interests and skills were unrelated to self-rated detail-focus in control groups and only moderately related in a small group of parents of boys with ASD (Briskman et al. 2001). In the same group, self-report of detail-focus significantly predicted good performance on featural-processing tasks (Happé et al. 2001).

Lastly, executive dysfunction and weak coherence appear to be dissociable. Boys with ADHD show deficits in planning and response selection, but do not show detail-focused processing in either drawing or sentence completion tasks sensitive to weak coherence in ASD (Booth et al. 2003; Booth and Happé, submitted). Pellicano, who has done the most thorough work comparing patterns of performance across key cognitive domains in ASD, reported a relation between executive function and some tests aimed at tapping coherence in typically developing young children and those with ASD (Pellicano et al. 2005, 2006), although it was unclear whether the latter tasks confounded ability and style of processing. Interestingly, a recent study examining theory of mind, central coherence, and set-shifting (measured by ambiguous figure reversal) in a nonclinical sample, found each made an *independent* contribution to explaining variance in autistic-like traits (Best et al. 2008).

Fractionation of Key Neural Substrates?

If different aspects of the ASD triad are fractionable at the symptom level, genetic level, and have distinct cognitive underpinnings, do they also involve independent neural pathways? Neuroimaging studies of typically-developing volunteers give some indication of which pathways are involved in theory of mind, specific executive functions, and (to a lesser extent) detail-focused processing. For example, a large and growing body of research, using a wide array of tasks requiring attribution of mental states, suggests that theory of mind is associated with activation of medial prefrontal cortex, temporo-parietal junction, and amygdala complex (see Amodio and Frith 2006 for a comprehensive review). In ASD individuals these regions appear to be less active (e.g. Castelli et al. 2002), and structural abnormalities have been reported in medial prefrontal/paracingulate cortex (e.g. Abell et al. 1999). In addition, blood flow in these regions has been found to be significantly associated with social-communication symptoms but not with insistence on sameness (Ohnishi et al. 2000).

'Executive function' covers a multitude of higher-order cognitive processes, of which set-shifting and planning are perhaps the most reliably implicated in ASD (see Hill 2004 for review). In typically-developing volunteers, response selection is associated with a fronto-striatal network. In volunteers with ASD, Schmitz et al. (2006) reported increased activation of parietal lobes, compared with controls, during a switching task. Planning tasks, such as Tower of London, activate an extensive fronto-parieto-thalamic network in typically-developing adults (e.g. Wagner et al. 2006), while in ASD volunteers the same regions appear to be active but with reduced functional connectivity (Just et al. 2007).

Less work has been done on the neural substrates of weak coherence or detail-focused cognitive style. Neuroimaging work using tasks tapping detail focus, notably the embedded figures task, has suggested enhanced activation of early visual areas in ASD (Manjaly et al. 2007). Reduced global integrative processing and enhanced local-featural processing have been linked, theoretically, to recent findings of reduced functional connectivity, perhaps secondary to increased short-range and decreased long-range cortical projections (Belmonte et al. 2004; Rippon et al. 2007). Reduced functional connectivity, and the related notion of abnormal top-down modulation (C. Frith 2003), may be the

best candidate for a neural theory of ASD attempting to account for both social and non-social deficits.

Implications of the Fractionable Triad Approach

Implications for Diagnosis

The suggestion that the different aspects of the ASD triad have fractionable causes, at the genetic, neurological, and cognitive levels, is sometimes taken as an attack on the validity of the diagnosis of autism (see Mandy and Skuse 2008 for discussion). However, it is quite compatible to assert that ASD results when a number of independent impairments co-occur, and to assert that the resulting mix has a special quality, distinct prognosis and response to intervention, and is therefore worthy of a distinct diagnostic label. Similarly, when the cognitive characteristics of impaired theory of mind, executive dysfunction, and detail-focused bias co-occur (as they do above chance, see above), many possible compensatory mechanisms are stripped away and interactive effects occur. For example, a child who has difficulty tracking what a speaker intends (due to ToM impairment) may be unable to compensate by inferring from context (due to detail focus) what the speaker's message must mean. Thus the combination of triad impairments requires a special approach in terms of intervention and education.

While our position does not threaten the usefulness of the autism diagnosis, it may have implications in terms of current diagnostic categories. The DSM-V workgroups are considering as a cross-cutting theme whether a dimensional, as well as categorical, approach should be taken to diagnosis. The question arises whether one should conceptualize autism and related disorders as lying on one spectrum, or whether each individual should be mapped in a three dimensional space along three, perhaps orthogonal, dimensions: social interaction, communication, and RRBIs. Mapping individuals, or diagnostic subgroups, within a three dimension space would clarify, at least, the meaning of the currently vague 'PDD-NOS' label. In current DSM-IV criteria this can be applied to a child who shows all aspects of the triad but is sub-threshold for full diagnosis of autism, or to a child who shows only one aspect of the triad. This compounds problems of heterogeneity in ASD, and renders the 'PDD-NOS' label largely uninformative. This is no small problem given that PDD-NOS is estimated to be as common a diagnosis as autism and Asperger's disorder combined (Lauritsen, et al. 2004). Walker et al. (2004) reported that half of their group with PDD-NOS showed clinical-level social and communication impairments but failed to meet autism criteria for RRBIs. Such cases would surely be better labelled more specifically (see also Mandy and Skuse 2008), for example as 'partial triad' atypical autism cases.

Further study of those individuals receiving the PDD-NOS or 'atypical autism' label is warranted, as co-occurrence of triad symptoms can be tested without the circularity inherent in an autism sample, but at levels of clinical need that are rare in population samples alone. Our twin data suggest that significant numbers of children are rated by parents as showing just social, just communication, or just RRBI difficulties, sometimes at levels of severity comparable to those seen in diagnosed ASD. What, if any, diagnostic label do such children receive? Clearly, it will be vital to explore the nature of these children's difficulties in person and with cognitive assessments, in order to establish whether there are qualitative differences from ASD and what the clinical needs of such 'single deficit' children might be.

Implications for Future Research

Our twin studies suggest that, phenotypically and genetically, variation in social skill, communication competence, and restricted and repetitive behaviors and interests are considerably independent. One implication for research at the behavioral level is that care should be taken to assess each part of the triad separately, since global ratings of autism severity risk missing important information. The three aspects of the triad may even need to be fractionated further. For example, factor analytic studies have suggested that RRBIs split into at least two distinct types (broadly 'insistence on sameness' and repetitive sensory/motor behaviors), with different patterns of association and implications for prognosis (e.g. Szatmari et al. 2006). As Mandy and Skuse (2008) point out, it would be interesting to re-examine the twin data, specifically examining the relationship between 'insistence on sameness' and social and communication impairments. Within social impairment, too, there is clearly a range of potentially dissociable difficulties, only some of which are core to autism (e.g. Silani et al. 2008). Within weak coherence, a distinction has been drawn between reduced attention to/facility global processing, and enhanced attention to/facility for featural processing (Booth et al. 2003). It is a possibility worth testing, for example, that poor global processing *is* linked with executive dysfunction, while enhanced featural processing is not.

An important implication for theoretical accounts of ASD is that putative cognitive (and neural) underpinning(s) need not be *specific* to ASD—since it would be the combination of deficits that is unique to this disorder (see also Mandy and Skuse 2008). This may open the way to more research comparing different clinical groups, not only highlighting differences but also similarities in core deficits.

A major implication of our twin results is that molecular genetic studies looking for susceptibility genes for autism may have more success finding genes associated with specific behaviors within autism than with autism as a whole. Instead our approach would suggest genome-wide association studies of specific aspects of the ASD triad (e.g. social impairment-skill, or better still social insight as measured by cognitive tasks). In support of this proposal, recent studies taking narrowly-defined subgroups within ASD have had improved results (see above).

Of course, our studies provide only a starting point for investigation. In particular, it is notable that we do not have twin data on ASD-like traits before 7 years of age. How would the triad cohere in a younger sample? One might expect that different skills/impairments would become more inter-twined with age, as downstream effects take hold. However, it is also possible that initially monolithic functions become differentiated with age. Longitudinal studies of population samples are needed, beginning early in life. Such studies could also shed light on the trajectory of development in the three aspects of the triad. If these are fractionable, this might be indicated by rather different behavioral trajectories. Charman et al. (2005), for example, showed different rates of improvement in social interaction, (nonverbal) communication, and RRBIs in early childhood, and Sigman and colleagues have shown differential trajectories of improvement in language, social skills, and RRBIs in adolescence (Sigman and McGovern 2005; McGovern and Sigman 2005). Similarly, while response to type of treatment does not logically implicate type of cause, evidence of differential response to intervention would support a fractionable triad account.

Conclusions

We reviewed evidence for the proposal that autism represents a collection of fractionable characteristics and core cognitive impairments. While the three parts of the triad do co-occur above chance, they can be found in isolation, and some avenues of research may be best pursued within rather than across triad domains. While considerably more research is needed to decide whether the fractionable triad approach is correct and helpful, we believe that consideration of this approach generates new questions and research avenues of both theoretical and practical significance.

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