PERSPECTIVE

nature neuroscience

Time to give up on a single explanation for autism

Francesca Happé, Angelica Ronald & Robert Plomin

We argue that there will be no single (genetic or cognitive) cause for the diverse symptoms defining autism. We present recent evidence of behavioral fractionation of social impairment, communication difficulties and rigid and repetitive behaviors. Twin data suggest largely nonoverlapping genes acting on each of these traits. At the cognitive level, too, attempts at a single explanation for the symptoms of autism have failed. Implications for research and treatment are discussed.

Autism, and autism spectrum disorders (ASD), such as Asperger syndrome, are neurodevelopmental conditions diagnosed on the basis of a triad of behavioral impairments: impaired social interaction, impaired communication and restricted and repetitive interests and activities[1]. These core diagnostic features, which reflect Kanner's first reports of autism with an emphasis on "autistic aloneness" and "insistence on sameness", mark out a highly recognizable and yet richly heterogeneous group of children and adults[2]. Yet, despite half a century's research into ASD, there is little evidence regarding the unity of the three core areas of impairment. Indeed, an early epidemiological study[3], which set in place the notion of the triad of impairments, remains the only full examination of this issue; these authors found some evidence of clustering of the three impairments. The key importance of this issue is that researchers have, for the last half century and with only a few notable exceptions[4–6], been searching for the causes and cures for autism as a whole. Research on ASD at the behavioral, cognitive and genetic levels has proceeded on the assumption that the three impairments that define autism must be explained together. In this article, we question this basic assumption and present evidence at each of these levels that suggests the triad of impairments can be fractionated and should be studied separately.

Behavioral features of autism: integral or fractionable?

One of the challenges in establishing whether the triad of ASD features requires a unitary explanation or is, instead, fractionable, lies in the circularity of examining diagnosed populations. Because the diagnosis of autism (and even Asperger syndrome) requires impairments in each of the three key areas, examination of diagnosed populations cannot establish the potential fractionation of the triad. One way through this impasse is to explore the relationship between social, communicative and rigid/repetitive traits in the general population.

Francesca Happé, Angelica Ronald and Robert Plomin are at the Institute of Psychiatry, Kings College London, De Crispigny Park, London SE5 8AF, UK.
e-mail: spjgarr@iop.kcl.ac.uk

Published online 26 September 2006; doi: 10.1038/nn1770

Recent work suggests that autistic-like traits can be measured in the general population[7–9]. We can ask, for example, whether a child joins in playing games with other children easily, can keep a two-way conversation going or likes to do things over and over again in the same way all the time. The distribution of such traits supports a smooth continuum (at least at the behavioral level) between individuals meeting diagnostic criteria for ASD and individuals in the general population[10]. Importantly, there is no evidence of a bimodal distribution, or 'hump' at the extreme, separating clinical from nonclinical levels of difficulty[11]. We can therefore ask the question, do autistic-like social impairments, communication difficulties and rigid/repetitive behavior cluster strongly in the general population, suggesting the same underlying causes?

In our population-based studies, using data from over 3,000 twin pairs assessed between the ages of 7 and 9, we have found modest-to-low correlations between autistic-like behavioral traits in the three core areas[9]. 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[12], were only modestly related (with correlations (r) in the range of 0.2 to 0.4). This relationship was no stronger than that between communicative difficulties and rigid/repetitive behavior ($r = 0.3$–0.4), whereas social impairments and rigid/repetitive behaviors were the least strongly linked ($r = 0.1$–0.3). The modest correlations between the three areas of autistic-like traits were found both across the general population and when only children with relatively extreme scores were considered[13]. It thus appears that, in middle childhood at least, the degrees 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. 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, and these problems appeared to be at a level of severity comparable to that found in children with diagnosed ASD in our sample. We did find that children who showed one impairment were at increased risk of showing a second or third area of autistic-like difficulty, 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 did occur together at above-chance rates, there was considerable evidence for fractionation of the three aspects of the triad.

There is other evidence for the relative independence of the three core features of autism. Studies of the development of children with autism

suggest different developmental trajectories for different parts of the triad. Rigid and repetitive behavior and interests, for example, emerge later than social and communicative difficulties, are less good markers of autism in infancy, improve less from infancy to early childhood[14], are poorly predicted from early measures of imitation or language[15,16] and respond less well to some intervention programs[17]. There are some measures, however, most notably the Social Responsiveness Scale (SRS), which is heavily weighted toward the social domain, that do not show fractionation of the triad at the level of behavior[7,18]. It is unclear at this stage to what extent different findings are due to differences in measures. Unlike diagnostic tools, for which 'gold standard' measures exist that are used across studies, measures of autistic traits are still in development.

Genes 'for autism' or genes for independent traits?

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? Our research suggests that the answer is yes. Comparison of roughly 3,000 monozygotic and dizygotic twin pairs at ages 7 and 8 years (Twins Early Development Study Institute of Psychiatry) suggests that each aspect of the triad is highly heritable, both across the range of individual differences and at the extreme[9,13]. However, model-fitting analyses of cross-twin, cross-trait correlations suggest 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[9,19]. Thus, most of the genetic effects (at least in middle childhood) are specific, acting on just one part of the triad.

This new conclusion from two studies using a large normative twin sample fits with results from family studies of individuals with ASD. 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[20,21]. This suggests that the genes that contribute to autism segregate among relatives and have distinct influences on the different parts of the phenotype.

No single explanation at the neurocognitive level

In the name of parsimony, cognitive accounts have traditionally aimed to explain all three key features of autism. It is our belief, however, that the accumulating evidence of behavioral and genetic fractionation of the autistic triad is paralleled by a failure to find a single cognitive account for the three core features of autism. Indeed, we would argue that the evidence suggests we should abandon the attempt to find a single cognitive explanation, in favor of good accounts for each distinct aspect of the triad.

Current cognitive accounts of autism can be divided into those that posit a primary deficit in social cognition (theory of mind[12], emotion processing[22] or social orienting[23]) and those that posit a primary deficit in nonsocial or domain-general processing (executive dysfunction[24], enhanced processing of local features[25,26] or abnormal attentional processes[27]). To date, no primary deficit has been proposed that can plausibly account for the full triad of social, communicative and rigid/repetitive difficulties[28]. 'Social first' accounts easily explain why social and communicative difficulties might develop, but deriving rigid/repetitive behavior as a downstream effect has proved unsatisfactory. Repetitive behavior and interests do not appear to be simply a reaction to an incomprehensible social world; they occur in high-functioning individuals with ASD who have some social insight as well as in lower-functioning 'mind-blind' people with autism, and they serve self-stimulatory as well as calming functions[29].

Nonsocial or domain-general accounts of autism, on the other hand, struggle to explain why social insight and communication are so particularly impaired, often alongside average or high intelligence and good reasoning in nonsocial areas. A general appeal is often made to complexity, with the claim that social interactions are simply the hardest thing our brains have to process. But without a metric for complexity, this claim seems empty; after all, computers struggle to solve 3D segregation of objects in vision but need little processing power to multiply large numbers. By contrast, intellectually impaired children do not struggle to see in 3D, but may never master multiplication. The distinction is presumably that our brains evolved to solve some types of problems and not others; hence some tasks are 'easy' and some 'difficult' for a typically developed brain. Interpreting social stimuli may be one of the tasks for which our brains are adapted, thus complexity explanations of specific social impairments in autism seem unsatisfactory. Nor do the data, such as they are, suggest that the degree of cognitive impairment in, say, reading others' minds, is strongly related to the degree of detail-focus or repetitive behavior[30]. Instead, different cognitive accounts appear to explain the distinct features of autism well, and correlations can be found between specific test performance and symptom severity within each area of impairment[31,32].

Neuroimaging studies of autism also appear to offer support for the independence of the cognitive substrates for social, communicative and rigid/repetitive impairments. Imaging in healthy and ASD adult volunteers suggests that social cognition relies upon a specific network of brain regions, including the medial frontal cortex, temporoparietal junction, superior temporal sulcus and temporal poles[33]. Lack of preferential attention to speech in autism has been associated with specific abnormalities in encephalographic (EEG) studies[34], and lack of activation of superior temporal sulcus voice-selective regions in response to vocal sounds has been reported[35]. Rigid and repetitive behavior has been linked to caudate abnormality in ASD[36]. Future developmental neuroimaging will clearly be critically informative regarding the relative independence of brain substrates for key cognitive functions.

Implications

In light of the above research, we suggest 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. Clearly a question remains of why these three features co-occur at above-chance rates. At the genetic level, although the majority of genes appear to be symptom specific, there is evidence for a minority of overlapping genes between domains. At the cognitive level, impairments in more than one domain may interact; compensatory strategies may be reduced in the face of multiple impairments. Given the widespread comorbidity generally found in developmental psychopathology, what is most remarkable is the extent of fractionation among the three core aspects of autism.

The implications of our argument are as follows. First, behaviorally it would seem useful to measure the three aspects of the triad separately, rather than rely on global ratings of autism severity, or ratings that focus exclusively on social functioning.

Secondly, molecular genetic studies, which have resulted in little by way of replicated linkage, should abandon the search for genes 'for autism' as a whole. Instead, we suggest approaches that will allow identification of genes contributing specifically to social, communicative or rigid/repetitive traits, as we believe that the majority of genes relevant to ASD will have symptom-specific action. Indeed, recent studies that have focused on subgroups within ASD, such as those showing

high levels of insistence on sameness[37] or those with delayed onset of phrase speech[38], have shown stronger linkage signals.

Heterogeneity within the autism spectrum is perhaps the biggest single obstacle to research at all levels[39]. A third implication is that heterogeneity in ASD, on our account, is not simply due to noise or the complex unfolding of development, but is an unavoidable consequence of variation along at least three largely independent (although of course interacting) dimensions of impairment.

Fourth, our argument and our findings within a large twin sample suggest that there may be many individuals with isolated impairments in one aspect of the triad, who do not meet diagnostic criteria for any recognized disorder, but show difficulties of comparable severity to those with autism. How we identify and meet the needs of these children and adults is a key challenge for the future.

Lastly, if different features of autism are caused by different genes, associated with different brain regions and related to different core cognitive impairments, it seems likely they will respond to different types of treatment. Abandoning the search for a single cause for a single entity of autism may also mean abandoning the search for a single 'cure' or intervention.

ACKNOWLEDGMENTS

We would like to thank all the families who participate in Twins Early Development Study, which is supported by Medical Research Centre grant G0500079 to R.P.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Published online at http://www.nature.com/natureneuroscience
Reprints and permissions information is available online at http://npg.nature.com/reprintsandpermissions/

1. *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, Washington, DC, 1994).
2. Kanner, L. Autistic disturbances of affective contact. *Nervous Child* **2**, 217–250 (1943).
3. Wing, L. & Gould, J. Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. *J. Autism Dev. Disord.* **9**, 11–29 (1979).
4. Goodman, R. Infantile autism: a syndrome of multiple primary deficits? *J. Autism Dev. Disord.* **19**, 409–424 (1989).
5. Bishop, D.V. Autism, Asperger's syndrome and semantic-pragmatic disorder: where are the boundaries? *Br. J. Disord. Commun.* **24**, 107–121 (1989).
6. Bishop, D.V. in *Autism: Neural Basis and Treatment Possibilities* 213–234 (Wiley, Chicester, 2003).
7. Constantino, J.N., Przybeck, T., Friesen, D. & Todd, R.D. Reciprocal social behavior in children with and without pervasive developmental disorders. *J. Dev. Behav. Pediatr.* **21**, 2–11 (2000).
8. Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J. & Clubley, E. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J. Autism Dev. Disord.* **31**, 5–17 (2001).
9. Ronald, A. *et al.* Genetic heterogeneity between the three components of the autism spectrum: a twin study. *J. Am. Acad. Child Adolesc. Psychiatry* **45**, 691–699 (2006).
10. Constantino, J.N. & Todd, R.D. Autistic traits in the general population: a twin study. *Arch. Gen. Psychiatry* **60**, 524–530 (2003).
11. Skuse, D.H., Mandy, W.P. & Scourfield, J. Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. *Br. J. Psychiatry* **187**, 568–572 (2005).
12. Baron-Cohen, S., Tager-Flusberg, H. & Cohen, D. *Understanding Other Minds: Perspectives from Autism and Developmental Cognitive Neuroscience* (Oxford Univ. Press, Oxford, 2000).
13. Ronald, A., Happé, F., Price, T.S., Baron-Cohen, S. & Plomin, R. Phenotypic and genetic overlap between autistic traits at the extremes of the general population. *J. Am. Acad. Child Adolesc. Psychiatry* (in press).
14. Charman, T. & Swettenham, J. Repetitive behaviors and social-communicative impairmanets in autism: implications for developmental theory and diagnosis. in *The Development of Autism: Perspectives from Theory and Research* (eds. Burack, J.A., Charman, T., Yirmiya, N. & Zelazo, P.R.) 325–345 (Lawrence Erlbaum, Hillsdale, New Jersey, 2001).
15. Charman, T. *et al.* Predicting language outcome in infants with autism and pervasive developmental disorder. *Int. J. Lang. Commun. Disord.* **38**, 265–285 (2003).
16. Lord, C. & Pickles, A. Language level and nonverbal social-communicative behaviors in autistic and language-delayed children. *J. Am. Acad. Child Adolesc. Psychiatry* **35**, 1542–1550 (1996).
17. Aldred, C., Green, J. & Adams, C. A new social communication intervention for children with autism: pilot randomised controlled treatment study suggesting effectiveness. *J. Child Psychol. Psychiatry* **45**, 1420–1430 (2004).
18. Constantino, J.N. *et al.* The factor structure of autistic traits. *J. Child Psychol. Psychiatry* **45**, 719–726 (2004).
19. Ronald, A., Happé, F. & Plomin, R. The genetic relationship between individual differences in social and nonsocial behaviours characteristic of autism. *Dev. Sci.* **8**, 444–458 (2005).
20. Pickles, A. *et al.* Variable expression of the autism broader phenotype: findings from extended pedigrees. *J. Child Psychol. Psychiatry* **41**, 491–502 (2000).
21. Piven, J., Palmer, P., Jacobi, D., Childress, D. & Arndt, S. Broader autism phenotype: evidence from a family history study of multiple-incidence autism families. *Am. J. Psychiatry* **154**, 185–190 (1997).
22. Moldin, S.O. & Rubenstein, J.L.R. *Understanding Autism: From Basic Neuroscience to Treatment* (Taylor & Francis, Boca Raton, Florida 2006).
23. Klin, A., Volkmar, F.R. & Sparrow, S.S. Autistic social dysfunction: some limitations of the theory of mind hypothesis. *J. Child Psychol. Psychiatry* **33**, 861–876 (1992).
24. Hill, E.L. Executive dysfunction in autism. *Trends Cogn. Sci.* **8**, 26–32 (2004).
25. Happé, F. & Frith, U. The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *J. Autism Dev. Disord.* **36**, 5–25 (2006).
26. Mottron, L., Dawson, M., Soulieres, I., Hubert, B. & Burack, J. Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J. Autism Dev. Disord.* **36**, 27–43 (2006).
27. Belmonte, M.K. & Yurgelun-Todd, D.A. Functional anatomy of impaired selective attention and compensatory processing in autism. *Brain Res. Cogn. Brain Res.* **17**, 651–664 (2003).
28. Happé, F. Cognition in autism: one deficit or many? *Novartis Found. Symp.* **251**, 198–207 (2003).
29. Turner, M. Annotation: repetitive behaviour in autism: a review of psychological research. *J. Child Psychol. Psychiatry* **40**, 839–849 (1999).
30. Pellicano, E., Maybery, M., Durkin, K. & Maley, A. Multiple cognitive capabilities/ deficits in children with an autism spectrum disorder: 'weak' central coherence and its relationship to theory of mind and executive control. *Dev. Psychopathol.* **18**, 77–98 (2006).
31. Lopez, B.R., Lincoln, A.J., Ozonoff, S. & Lai, Z. Examining the relationship between executive functions and restricted, repetitive symptoms of Autistic Disorder. *J. Autism Dev. Disord.* **35**, 445–460 (2005).
32. Briskman, J., Happé, F. & Frith, U. Exploring the cognitive phenotype of autism: weak "central coherence" in parents and siblings of children with autism: II. Real-life skills and preferences. *J. Child Psychol. Psychiatry* **42**, 309–316 (2001).
33. Amodio, D.M. & Frith, C.D. Meeting of minds: the medial frontal cortex and social cognition. *Nat. Rev. Neurosci.* **7**, 268–277 (2006).
34. Kuhl, P.K., Coffey-Corina, S., Padden, D. & Dawson, G. Links between social and linguistic processing of speech in preschool children with autism: behavioral and electrophysiological measures. *Dev. Sci.* **8**, F1–F12 (2005).
35. Gervais, H. *et al.* Abnormal cortical voice processing in autism. *Nat. Neurosci.* **7**, 801–802 (2004).
36. Sears, L.L. *et al.* An MRI study of the basal ganglia in autism. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **23**, 613–624 (1999).
37. Shao, Y. *et al.* Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes. *Am. J. Hum. Genet.* **72**, 539–548 (2003).
38. Buxbaum, J.D. *et al.* Evidence for a susceptibility gene for autism on chromosome 2 and for genetic heterogeneity. *Am. J. Hum. Genet.* **68**, 1514–1520 (2001).
39. Newschaffer, C.J., Fallin, D. & Lee, N.L. Heritable and nonheritable risk factors for autism spectrum disorders. *Epidemiol. Rev.* **24**, 137–153 (2002).