Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder: Different Disorders, Overlapping Causes?

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Abstract

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) regularly co-occur with one another. This article considers why this is the case. Recent research, particularly twin studies, has questioned whether overlapping genetic and environmental influences cause ASD and ADHD. These studies have consistently reported that a considerable degree of the genetic influences on ASD and characteristic traits overlap with those on ADHD. The implications of these findings for molecular genetic research and for clinical practice are considered.

Introduction

When we think of autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), we may think of two fairly distinct groups of neurodevelopmental conditions. Children with ASD typically find social situations challenging, have difficulty communicating with others, exhibit striking interests in certain topics, and experience sensory atypicalities. Children with ADHD, on the other hand, are usually excessively hyperactive, behave in impulsive ways, or struggle to sustain their attention in certain tasks or settings. Indeed, in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1) the co-occurrence of these conditions was prohibited by exclusionary criteria; hyperactivity in children with ASD was seen as an 'associated feature' of ASD. However, these exclusionary rules did not seem to reflect clinical reality. Recent research has demonstrated that around 30-60% of individuals with ASD also qualify for a diagnosis of ADHD (2,3). The exclusionary rules have been removed from the fifth edition of the DSM (DSM-5) (4), meaning that individuals with either ASD or ADHD as their primary diagnosis can now be diagnosed with the other condition, if they fulfil the diagnostic criteria for it. The question now being asked by many researchers and clinicians is why do ASD and ADHD co-occur so frequently?

Overlapping Aetiology?

Some studies have explored whether ASD and ADHD could be characterised by similar brain-level differences using neuroimaging techniques, such as fMRI and electroencephalography. So far, studies have tended to produce mixed findings (reviewed at length by Rommelse et al. (5)), although this remains a fruitful research area. A frequently advocated explanation for comorbidity between two disorders is the notion that they may share aetiological risk factors (6). Could similar genetic and environmental influences cause both ASD and ADHD?

Behavioural genetic designs are well suited to investigate this possibility. Using family studies, higher rates of the disorder in relatives of individuals with the same disorder of interest indicate that it is familial. This design can be extended to examine shared familiality between two disorders; in relation to ASD and ADHD, one could explore the rates of ADHD in relatives of individuals with ASD, and vice versa, in comparison with control families. Such a method has seldom been deployed in relation to comorbidity between ASD and ADHD, with only one family study lending support to the notion of shared familiality between ASD and ADHD at the time of writing (7). However, it is noteworthy that families living in the same home share a certain proportion of their genes with one another and many aspects of their environment. Family studies are unable to tell us whether any shared familiality

between ASD and ADHD is due to overlapping genetic or environmental influences. To this end, the twin-study design has proven to be a valuable tool. This design capitalises on the differential genetic relatedness of monozygotic (MZ) twins, who share all of their segregating genes with one another, and dizygotic (DZ) twins, who share around half of their segregating genes with one another (just like a biological full sibling pair). The basic idea is that if MZ twins resemble each other to a greater extent than DZ twins on a behaviour of interest, then genetic factors are implicated in its aetiology. Complex statistical modelling can then be used to estimate the degree of genetic and environmental influences on a disorder or trait of interest, as shown in Figure 1a.

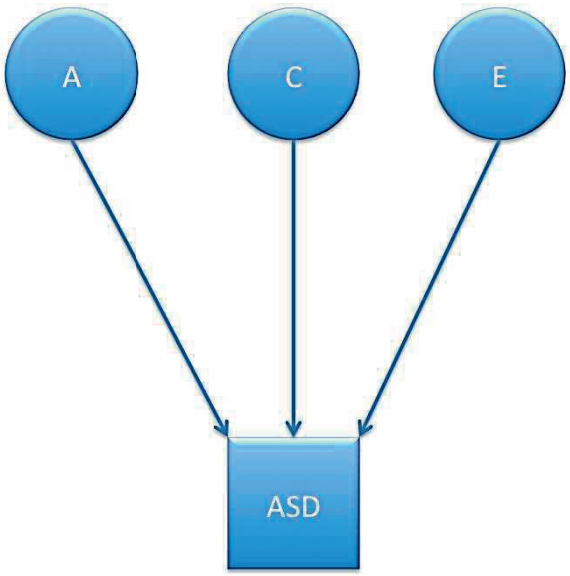
In twin studies of categorical diagnoses, it is possible to assess the rates of a disorder in the co-twins of individuals diagnosed with that disorder (known as concordance rates). If genetic factors influence the aetiology of a disorder, then MZ concordance rates should be higher than DZ concordance rates. This has been the case in twin studies of ASD and ADHD individually (reviewed by Ronald & Hoekstra (8) and Polderman & Posthuma (9)); indeed, twin studies have established that ASD and ADHD are amongst the most heritable of neurodevelopmental conditions.

The twin design can be readily extended to examine genetic overlap across two disorders by, for example, comparing the prevalence of ADHD across MZ and DZ co-twins of individuals with ASD. If ADHD is more prevalent in MZ co-twins of individuals with ASD than the DZ co-twins, then genetic influences on the association between ASD and ADHD are indicated. Statistical modelling can then more formally estimate the degree of aetiological overlap between two disorders, as shown in Figure 1b. Two studies of categorical ASD and ADHD have both confirmed that these groups of conditions are likely to share a considerable degree of genetic influences with one another, and a smaller proportion of their environmental influences (10,11).

An additional approach is to regard ASD and ADHD as the extremes of continuous distributions of subclinical, characteristic traits. Individually, traits of ASD and ADHD are strongly influenced by genetic factors (see (8) and (9)). The degree of genetic and environmental overlap between traits of ASD and ADHD can be estimated from the pattern of correlations between one twin's ASD trait score and their co-twin's ADHD trait score. If these correlations are higher in MZ than DZ twins, then genetic influences on the relationship between traits of ASD and ADHD are indicated. A number of recent cross-sectional twin studies have taken this approach and, with the possible exception of early childhood (12), twin studies have indicated that traits characteristic of ASD and ADHD share a considerable degree of genetic influences in middle childhood (11,13), early adolescence (14), early adulthood (15) and adulthood (13). Overlap in environmental risk factors between traits of ASD and ADHD appears to be low to moderate in the majority of these studies.

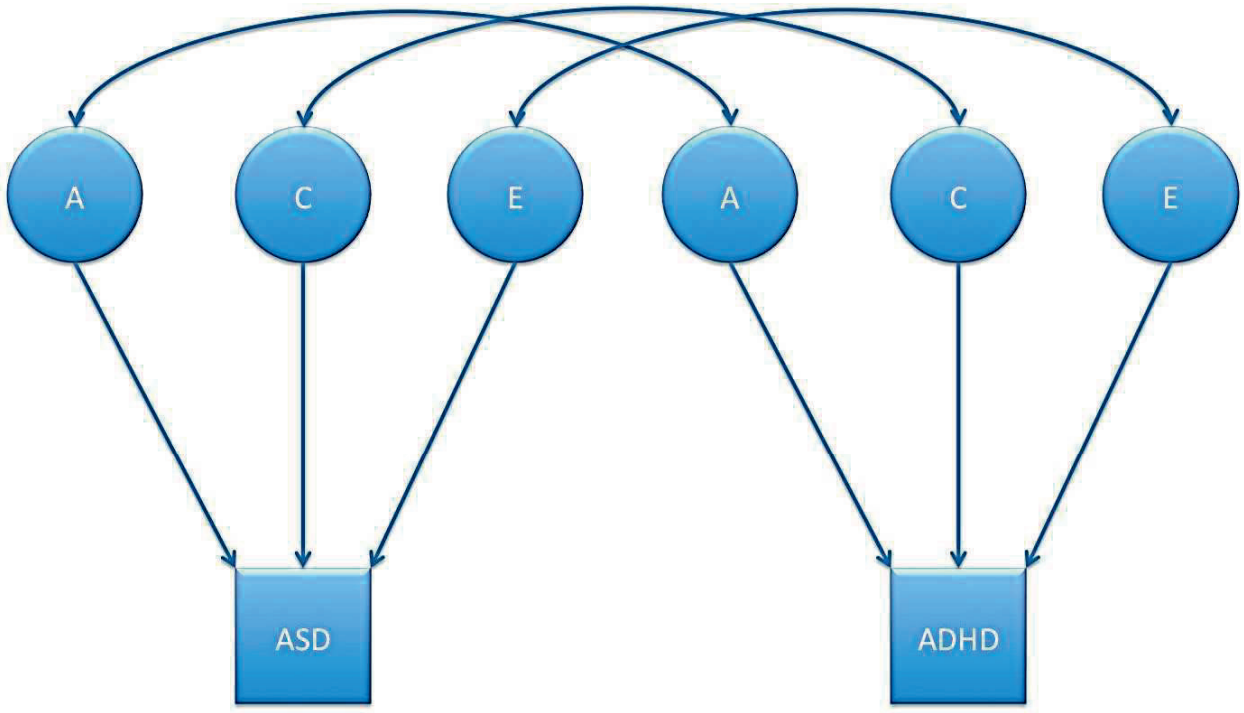
Figure 1 Path diagrams of a) a univariate twin model, and b) a bivariate twin model

a) A univariate twin model



The model formally estimates the degree of genetic influences on a disorder (represented by 'A'), and environmental influences (C and E). In this example, the influence of genetic and environmental factors on ASD is estimated.

b) A bivariate twin model



Both ASD and ADHD are again influenced by genetic (A) and environmental (C and E) influences in this diagram; the double-headed arrows that link A, C, and E for ASD and ADHD to one another represent the degree to which these aetiological influences overlap with one another.

What does all this mean?

One thing we know is that the search for specific genes underlying ASD and ADHD individually has proven to be difficult, with many null results. However, as molecular genetic studies increase in size and power, and begin more reliably to pinpoint genes associated with risk for ASD or ADHD, then we can, according to the twin studies mentioned here, expect there to be a considerable degree of overlap. For example, two recent publications by the Cross Disorder Group of the Psychiatric Genomics Consortium (16, 17), notable for reporting on very large samples, indicated that calcium-signalling genes were linked with both ASD and ADHD (and, intriguingly, major depression, schizophrenia, and bipolar disorder). As more large studies, such as these, emerge, we should expect findings regarding genes associated with ASD and ADHD to converge still further.

What does this mean for clinical practice? As we mentioned in the introduction, ASD and ADHD are two different groups of disorders; yet they do not appear quite so dissimilar at the genetic level. As a consequence of their genetic overlap, one would expect a large proportion of individuals with ASD as their primary diagnosis also to qualify for a diagnosis of ADHD and vice versa. Furthermore, if one child in a family has ASD, on average there will be a higher chance that their future siblings could develop not only ASD but also ADHD. Such predictions can be informative for genetic counselling services.

Concluding Remarks

ASD and ADHD might be different groups of disorders but behavioural genetic evidence suggests that the genes that cause ASD overlap with those that cause ADHD. As we learn more about the genetics of ASD, it is likely that we shall discover more about the genetics of ADHD (16, 17).

GP comment.

What have I learned from this paper?

There is a large overlap between autism and ADHD. It would be easy to miss ADHD in someone with autism because the diagnosis of autism may "overshadow" other issues. Furthermore, there is a chance that family members of a person with autism spectrum disorder might have ADHD and vice versa. GPs need to be aware of the possibility that both these diagnoses might need to be managed, not only in the same individual but also in different members of the same family.

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed.). Washington, DC, American Psychiatric Association, 1994
2. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 2008; 47: 921-929
3. de Bruin EI, Ferdinand RF, Meester s, de Nijs PFA, Verheij F. High rates of psychiatric co-morbidity in PDD-NOS. J Autism Dev Disord 2007; 37: 877-886
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th ed.). Washington, DC, American Psychiatric Association, 2013
5. Rommelse NNJ, Geurts HM, Franke B, Buitelaar JK, Hartman CA. A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. Neuroscience Biobehav Rev 2011; 35: 1363-1396
6. Caron C, Rutter M. Comorbidity in child psychopathology: Concepts, issues and research strategies. J Child Psychol Psychiatry 1991; 32: 1063-1080
7. Mulligan A, Anney RJL, O'Regan M, Chen W, Butler L, Fitzgerald M, Buitelaar J, Steinhausen H-C, Rothenberger A, Minderaa R, Nijmeijer J, Hoekstra PJ, Oades RD, Roeyers H, Buschgens C, Christiansen H, Franke B, Gabriels I, Hartman C, Kuntsi J, Marco R, Meidad S, Mueller U, Psychogiou L, Rommelse N, Thompson M, Uebel H, Banaschewski T, Ebstein R, Eisenberg J, Manor I, Miranda A, Mulas F, Sergeant J, Sonuga-Barke E, Asherson P, Faraone SV, Gill M. Autism symptoms in attention-deficit/hyperactivity disorder: A familial trait which correlates with conduct, oppositional defiant, language and motor disorders. J Autism Dev Disord 2009; 39: 197-209
8. Ronald A, Hoekstra RA. Autism spectrum disorders and autistic traits: A decade of new twin studies. Am J Med Genet Part B 2011; 156: 255-274
9. Posthuma D, Polderman TJC. What have we learned from recent twin studies about the etiology of neurodevelopmental disorders? Current Opinion in Neurology 2013 (online publication)
10. Lichtenstein P, Carlström E, Råstam M, Gillberg C, Anckarsäter H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. Am J Psychiatry 2010; 167: 1357-1363
11. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. J Child Psychol Psychiatry 2008; 49: 535-542

12. Ronald A, Edelson LR, Asherson P, Saudino KJ. Exploring the relationship between autistic-like and ADHD behaviors in early childhood: Findings from a community twin study of 2-year-olds. J Abnorm Child Psychol 2010; 38: 185-196
13. Lundström S, Chang Z, Kerekes N, Gumpert CH, Råstam M, Gillberg C, Lichtenstein P, Anckarsäter H. Autistic-like traits and their association with mental health problems in two nationwide twin cohorts of children and adults. Psychol Med 2011; 41: 2423-2433
14. Taylor MJ, Charman T, Robinson EB, Plomin R, Happé F, Asherson P, Ronald A. Developmental associations between traits of autism spectrum disorder and attention deficit hyperactivity disorder: A genetically informative, longitudinal twin study. Psychol Med 2013; 43: 1735-1746
15. Reiersen AM, Constantino JN, Grimmer M, Martin NG, Todd RD. Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. Twin Res Hum Genet 2008; 11: 579-585
16. Cross Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. Lancet 2013; 381: 1371-1379
17. Cross Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nature Genetics 2013; 45: 984-994