ARTICLE

The times they are a-changin'

Angelica Ronald, winner of the Spearman Medal 2012, looks at autism spectrum disorder and ADHD in the light of revisions to diagnostic procedures

Most of the time we think about clinical conditions, such as autism or ADHD or schizophrenia or depression, individually. Yet in reality it is extremely common for people to show more than one condition together. An example is autism and ADHD, which often occur together. The causes for this 'comorbidity' have been researched over the last five years, and some startling results are emerging.

questions

Can studying the overlap between autism and ADHD shed light on the causes of these individual conditions? Will it help us identify genetic and environmental risk factors?

Do children with both autism and ADHD represent a different category to children with either condition on its own?

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Many clinical and child psychologists will tell you that children with one behavioural condition often have others too. Known as comorbidity, this co-occurrence of conditions often applies to autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). The statistics are unequivocal: 30 per cent to 80 per cent of individuals with ASD also meet the criteria for ADHD, and 20 per cent to 50 per cent of individuals with ADHD also meet the criteria for an ASD (Rommelse et al., 2010).

Yet the last edition of the American Psychiatric Association's influential diagnostic code (the *Diagnostic and Statistical Manual of Mental Disorders*; DSM-IV) did not 'allow' for this co-occurrence. Even if individuals had both conditions, they did not receive both diagnoses, despite the consequences this might have in terms of treatment and education. The logic was that ASD includes ADHD – it was part of, or a result of, the ASD – and did not need to be considered separately.

However, as Bob Dylan likes to say, 'The times they are a-changin'.' The latest version of the DSM (known as DSM-5) *does* allow both ASD and ADHD to be diagnosed in the same individual. To many, this is an important change that will mean that the criteria reflect the 'natural' state of affairs. So, the statistics reveal considerable ASD–ADHD comorbidity, and the American Psychiatric Association is now acknowledging this. But what causes this high overlap? And what can it teach us about these conditions?

Shared genetic and environmental roots

Clinically, ASD and ADHD are conditions with many similar characteristics. Both are developmental conditions, meaning that they begin in childhood and often persist through life. Both conditions occur more frequently in males, often include problems with social functioning, and can occur in individuals with any level of IQ. Yet their behavioural characteristics are distinct. According to the DSM-5, ADHD is characterised by hyperactivity, impulsivity and inattention, whereas ASD is characterised by impairments in social communication and restricted, repetitive behaviours and interests.

We know from twin studies that ASD and ADHD are two of the most highly heritable behavioural conditions (Ronald & Hoekstra, 2011). But knowing that two conditions are highly heritable does not tell us why they co-occur. A specific type of analysis, known as multivariate twin model-fitting, is needed to assess the

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degree to which two conditions or sets of traits have the same genetic and environmental influences. What has become apparent in the last five years from converging findings from large twin studies, in Sweden, Australia, the US and the UK, is that ASD and ADHD share a considerable degree of genetic influence (Ronald, Edelson et al., 2010; Ronald et al., 2008; Taylor et al., 2013).

Such studies compared how alike one twin's level of autistic behaviours were with the other twin's level of ADHD behaviours. If the same genes cause both ASD and ADHD, it is expected that in identical twin pairs (who share all of their DNA code), the level of autistic behaviours in one twin and the level of ADHD symptoms in the other twin will be very similar, whereas less similarity between autistic and ADHD behaviours would be expected in fraternal twins because they do not share all their genes.

The results – which come from studies of both children and adults – show that a significant proportion of the genetic influences for ASD also influence ADHD. In twin studies, this is demonstrated from bivariate twin model-fitting. A useful statistic, called the genetic correlation, is derived from these models and demonstrates the extent to which genetic influences on one trait or disorder overlap with genetic influences on a second trait or disorder. Twin studies have consistently reported significant and modest-to-high genetic correlations in these studies. The findings are consistent whether categorical diagnoses or quantitative trait measures are used. This suggests that the link between ASD and ADHD is partly due to a common genetic pathway underlying both conditions. This has important implications for clinicians advising parents and prospective parents. Because ASD and ADHD, and their associated traits, share the same genetic influences, this means parents with a child or a partner with one of these conditions have an increased chance of either condition occurring in their future children.

The search for common genes underlying ASD and ADHD is currently conducted via a systematic approach called genome-wide association studies (GWAS; see, for example, Ronald, Butcher et al., 2010). In GWAS, hundreds of thousands, sometimes millions, of DNA variants are tested across the entire genome within a single experiment for association with a condition or trait of interest. Confirming the results from twin studies, the Psychiatric Genetics Consortium recently reported that ASD and ADHD share genetic influences based on a genome-wide analysis of tens of thousands of patients and healthy controls (Smoller et al., 2013).

> "Traits related to both ASD and ADHD have been associated with prenatal maternal stress"

At this point you might be thinking, isn't it obvious that ASD and ADHD co-occur for genetic reasons – what else would explain such high overlap? However, an interesting counterexample is the relationship between ASD and anxiety, which also often co-occur. In fact a recent meta-analysis reported that up to 84 per cent of children with ASD experience impairing anxiety (White et al., 2009). However, similar twin model-fitting methods to those described above reveal that autistic traits and anxiety problems do not show a high degree of genetic overlap in childhood; instead, across childhood, the effect of having autistic traits appears to exacerbate children's anxiety problems (Hallett et al., 2010) – a form of 'phenotypic interaction'. For example, children who, as a result of their autism, have difficulties with social interactions may shy away from group situations and find it difficult to express themselves and get support. Having rigid routines can also create stress as children transition through school.

Now let's turn to the role of the environment in ASD and ADHD. Neither ASD nor ADHD is 100 per cent heritable, so this means part of the risk must come from the environment. Traits related to both ASD and ADHD have been associated with prenatal maternal stress (Ronald, Hickey & Whitehouse., 2011), and both conditions have been associated with pre-, peri- and postnatal complications (Kolevzon et al., 2007; Ronald, Happé et al., 2010; Thapar et al., 2013), suggesting there might be some overlapping environmental risk factors.

With any environmental risk factor, we also have to consider whether it operates independently of genetic effects. For example, a genetic problem that contributes to risk for ASD may also contribute to perinatal complications. If this is the case, trying to reduce the chance of perinatal complications will not reduce the risk of a child developing ASD. By contrast, if perinatal complications are themselves playing a part in increasing risk, then improving support during pregnancy, labour and neonatal care could reduce risk for ASD.

Interacting traits and symptoms

The individual symptoms of ADHD are thought to have considerable, although not complete, overlap in their genetic roots (McLoughlin et al., 2007). However, it appears that the core symptoms within ASD – impairments in social ability and communication and restricted repetitive behaviours and interests – are caused by largely distinct genetic and environmental causes (Dworzynski et al., 2009; Ronald et al., 2006; Ronald, Larsson et al., 2011). This led to the 'fractionable autism triad' hypothesis, which proposes that it may be most fruitful to aim to identify causes of individual symptoms within ASD rather than searching for a single unifying explanation (Happé et al., 2006).

It would seem sensible, therefore, to question which symptoms within ASD and ADHD most often co-occur, and what causes this co-occurrence at the level of specific symptoms. Relevant research is only just starting to emerge, but one recent

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study suggests autistic-like communication difficulties show a particularly high level of co-occurrence with traits of ADHD (Taylor et al., 2013).

Unfortunately, when studying the relationship between ASD and ADHD, researchers have been guilty of reporting mainly cross-sectional studies, despite the developmental nature of these conditions. Some rare, recent longitudinal research suggests that traits characteristic of ASD and ADHD influence one another across childhood from age 8 to 12, after controlling for shared genetic and environmental influences (Taylor et al., 2013). Another study has shown that the trajectories of autism-related social-communication impairments and ADHD traits are strongly linked across childhood from ages 4 to 17 (St Pourcain et al., 2011). Prospective longitudinal research on ASD and ADHD would be an excellent future research area for budding psychology students.

Looking ahead

Tempting as it may be, do not take all this evidence of ASD and ADHD overlap too far. There remains for the time-being good reason to consider ASD and ADHD as distinct conditions. While twin studies indicate that considerable genetic overlap exists, the same research also reveals genetic influences that are specific to ASD and ADHD individually. Some environmental risk factors appear also to be specific to each condition, such as maternal smoking during pregnancy (repeatedly shown to be a risk factor for ADHD, but not ASD, in offspring) and higher paternal age (a risk factor for ASD but not ADHD: Gabis et al., 2010). The core behavioural symptoms of the two conditions also remain distinct.

The good news is that changes to the DSM, allowing both ASD and ADHD to be diagnosed in the same individual, will provide researchers with a better ability to understand how these two disorders exist independently, comorbidly, and how they interact with one another. As neuroscience advances, we are also beginning to see how ASD and ADHD compare at the cognitive and brain level (Tye et al., 2013). For example, children with ASD have been shown to have differences in conflict monitoring and response preparation, whereas children with ADHD have difficulties with attentional orienting and inhibitory control. These characteristics were associated with different event-related potentials (ERPs) that index these cognitive processes (Tye et al., 2013). Children with both ASD and ADHD seemed to have an additive co-occurrence of both the condition-specific differences.

An emphasis on which particular symptoms are co-occurring within individuals, rather than just considering ASD and ADHD as single constructs, will also help to refine which treatments or interventions are most helpful for each individual.

Just as Bob Dylan sang, 'As the present now will later be past… For the times they are a-changin',' so we can hope that with more research, the relationship between ASD and ADHD will be better understood and lead to improved outcomes and treatment for individuals with these conditions.

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