



Is autism one or multiple disorders?

We need to reconceptualise autism, not only for research, but also for clinical practice

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doi: 10.5694/mja12.11667

From the earliest description of autism in 1943 to the present day, there has been a widely held view that the behavioural anomalies associated with the disorder occur more often together than would be expected by chance, and therefore there will be a single causal pathway that explains the non-random co-occurrence of these symptoms.¹ The phenotypic variability of autism has proved to be a major stumbling block for aetiological research. The heterogeneity spans the entire range of intelligence quotients (IQs) and language abilities, as well as other behavioural, communicative and social functions. While any psychiatric condition is likely to incorporate a degree of heterogeneity, the variability in the nature and severity of behaviours observed in autism is thought to exceed that of other disorders.^{1,2} The variety of presentations of people with autism is described in the Box.

Major advances in aetiological research have been made over this period; most notably, the discovery from twin

studies of greater concordance for autism among monozygotic (70%–90%) compared with dizygotic (0–10%) twin pairs, providing clear evidence that the disorder is, at least in part, genetic in origin.³ However, after seven decades of intense investigation, the research community is yet to identify proximal (neurobiological) or distal (genetic and environmental) causes that lead to the full constellation of behaviours seen in all individuals with an autism diagnosis.

Variable presentations of people with autism	
Feature	Range of presentations
Communication	Non-verbal to fluent verbal language
Eye contact	Poor to excellent
Repetitive behaviours	Low frequency/intensity to very high frequency/intensity
Motor skills	Poor to excellent
Intelligence quotient	Very low to very high
Sleep	No difficulty to significant difficulty

One response by researchers to this failure to explain behavioural variability has been to seek out biological subgroups within the broader population of people with autism. However, these studies have generally underperformed, with only weak evidence that subgroups formed around IQ, age at first word or verbal ability yield a more genetically homogenous population. A second response, which has been gaining increasing momentum, has been to reconsider our understanding of what “autism” is. In particular, there has been a proposal to move away from conceptualising autism as a unitary disorder with a large spectrum, to viewing it as a syndrome of multiple and separate disorders⁴ — in essence, re-examining “autism” as “the autisms”.

An instructive example here is cerebral palsy. In the mid 19th century, cerebral palsy was thought to be a unitary disorder caused by anoxia secondary to trauma occurring during labour and delivery. However, the variability in the nature of impairment between individuals with cerebral palsy, spanning varying degrees of motor, intellectual and sensory difficulties, led researchers to hypothesise that there may be many causal pathways, with only a minor proportion of cases being a direct result of perinatal hypoxia. Other identified causes include a range of genetic syndromes, neuronal migration disorders, complications of preterm birth, infections and inflammation in utero, and postneonatal causes such as bacterial meningitis.⁵ Contemporary international agreements for diagnosis therefore emphasise that cerebral palsy is an umbrella term covering a wide range of syndromes that arise secondary to a variety of brain lesions or anomalies occurring early in development.⁶

Current evidence suggests that autism may also best be conceptualised as an umbrella term for a collection of behavioural disorders resulting from a range of causal pathways. It has been estimated that autism has a known genetic aetiology in 10%–15% of diagnosed individuals, but the loci and nature of these lesions vary, from known syndromes to observable cytogenetic lesions and rare de-novo mutations (eg, copy number variations).⁷ Among the remaining cases of autism, no single genetic risk variant has been found to occur in more than 1% of individuals.⁷ Similarly, environmental risk factors identified through epidemiological studies — such as in-utero exposure to selective serotonin reuptake inhibitors⁸ and traffic pollution⁹ — differ considerably in the hypothesised biological paths to disorder, and as yet, no known environmental exposure is deterministic of autism.

Given that diagnosis is currently based on behaviour, the question of whether autism is one or multiple disorders is ultimately one about the neurobiological causes of these behaviours. It remains to be determined whether:

- genetic and environmental risk factors “fan in” on a common neurobiological substrate, such as the posterior superior temporal sulcus, that has the capability of underpinning the considerable behavioural heterogeneity in autism (one disorder); or
- a combination of genetic and environmental risk factors affect different brain regions and functions, which in turn prescribes the behavioural profile of each individual (multiple disorders).

A key research aim will be to investigate the correspondence (if any) between known genetic/environmental risk factors and neurobiological risk factors for autistic behaviours, using increasingly sophisticated environmental monitoring, genetic sequencing, and neuroimaging techniques.

Elucidating the underlying nature of the disorder(s) is a crucial step towards tailoring intervention to the biological and cognitive makeup of each individual. A recent study in the United States has provided clear evidence that intense and sustained behavioural therapy based on applied behavioural analysis principles can alter the neurological responses of children with autism to social stimuli, such as faces.¹⁰

For the future, we can certainly hold the hope that these treatment effects would be even more pronounced once therapy is targeted to the neural substrates subserving autistic behaviours. However, to get to this point, the question that research must answer is whether these neuropathways are the same for every individual who receives a diagnosis of autism.

Acknowledgements: Andrew Whitehouse is funded by a National Health and Medical Research Council Fellowship (1004065).

Competing interests: No relevant disclosures.

Provenance: Not commissioned; externally peer reviewed.

- 1 Boucher J. Redefining the concept of autism as a unitary disorder: multiple causal deficits of a single kind? In: Fein DA, editor. *The neuropsychology of autism*. New York: Oxford University Press, 2011: 469–482.
- 2 Waterhouse L. *Rethinking autism: variation and complexity*. London: Academic Press, 2013.
- 3 Rutter M. Genetic studies of autism: from the 1970s into the millennium. *J Abnorm Child Psychol* 2000; 28: 3–14.
- 4 Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Curr Opin Neurobiol* 2007; 17: 103–111.
- 5 McIntyre S, Taitz D, Keogh J, et al. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. *Dev Med Child Neurol* 2012; Nov 26. [Epub ahead of print.] doi: 10.1111/dmnc.12017.
- 6 Badawi N, Watson L, Petterson B, et al. What constitutes cerebral palsy? *Dev Med Child Neurol* 1998; 40: 520–527.
- 7 Abrahams BS, Geschwind DH. Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet* 2008; 9: 341–355.
- 8 Croen LA, Grether JK, Yoshida CK, et al. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry* 2011; 68: 1104–1112.
- 9 Volk HE, Lurmann F, Penfold B, et al. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry* 2013; 70: 71–77.
- 10 Dawson G, Jones EJ, Merkle K, et al. Early behavioral intervention is associated with normalized brain activity in young children with autism. *J Am Acad Child Adolesc Psychiatry* 2012; 51: 1150–1159. □