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Annual Research Review: The transdiagnostic revolution in neurodevelopmental disorders

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Practitioners frequently use diagnostic criteria to identify children with neurodevelopmental disorders and to guide intervention decisions. These criteria also provide the organising framework for much of the research focussing on these disorders. Study design, recruitment, analysis and theory are largely built on the assumption that diagnostic criteria reflect an underlying reality. However, there is growing concern that this assumption may not be a valid and that an alternative transdiagnostic approach may better serve our understanding of this large heterogeneous population of young people. This review draws on important developments over the past decade that have set the stage for much-needed breakthroughs in understanding neurodevelopmental disorders. We evaluate contemporary approaches to study design and recruitment, review the use of data-driven methods to characterise cognition, behaviour and neurobiology, and consider what alternative transdiagnostic models could mean for children and families. This review concludes that an overreliance on ill-fitting diagnostic criteria is impeding progress towards identifying the barriers that children encounter, understanding underpinning mechanisms and finding the best route to supporting them. **Keywords:** Neurodevelopmental disorders; learning difficulties; working memory; ADHD; Autism; Developmental Language Disorder.

Introduction

Neurodevelopmental disorders (NDDs) affect children's cognition, academic attainment, behaviour, social interactions and lived experience. Up to 10% of children are identified as having one or more NDDs (e.g. NICE, 2019), and many more require support in or beyond school in these key areas of functioning (Department of Education, 2020). In this article, we consider how well current classifications of NDDs serve our understanding of this large and heterogeneous population of young people and review the conceptual, methodological and empirical developments that have set the stage for a radical rethink in both research and practice.

International diagnostic systems are widely used by clinicians to categorise difficulties, establish who receives additional support and inform intervention decisions. These systems provide the foundations for research too, framing conceptual thinking and guiding recruitment and analytic strategies. The most influential framework – the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) – includes specific disorders of learning and communication, autism spectrum disorder (hereafter autism), attention-deficit hyperactivity disorder (ADHD) and a range of other neurodevelopmental conditions.

This taxonomy has evolved in several respects over recent decades. Its most recent instantiation, the DSM-5, has relaxed some of the boundaries between disorders, diminished the emphasis on fixed inclusionary and exclusionary criteria, and increased acknowledgement of the variability within disorders. This is most notable in the case of autism, where a single broad category of NDD comprised of two variable domains of potential difficulty has replaced the three domains of difficulty – in social interaction, social use of language and symbolic play – that were previously required for a diagnosis (e.g. Volkmar & McPartland, 2014). The addition of new diagnostic options such as autism *with* intellectual disability or autism *with* language delay demonstrates the limits to which a categorical model can tolerate heterogeneity. Other diagnostic categories such as social (pragmatic) communication disorder have also been incorporated. In essence, the DSM-5 is a system used for assigning individuals to discrete diagnostic categories that appears to be straining at its limits.

Categorical diagnoses have long been adopted as 'ground truth' by many researchers. Study design, sampling approaches, analytic methods and theory are built on the premise that disorder categories reflect an underlying reality, shaping every aspect of the scientific architecture of NDDs. This status quo faces three fundamental problems. First, current taxonomies are not particularly effective in capturing the needs of the full population of children requiring additional support in the broad areas of learning, behaviour or social functioning. The application of arbitrary thresholds leads to the failure to identify individuals with milder difficulties that nonetheless impact significantly on their lived experience. This diagnostic problem is amplified by inequalities in access to both diagnoses and therapeutic support

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based on racial, ethnic and socioeconomic characteristics (e.g. Macdonald & Deacon, 2019; Mandell et al., 2009).

The second problem is that current diagnostic systems sit uneasily with the high levels of symptom variability within categories. Children with the same diagnostic label can vary widely in the scope, nature and impact of their symptoms (e.g. Kofler et al., 2019; Masi, DeMayo, Glozier, & Guastella, 2017). This makes diagnosis an unreliable guide to recruitment or intervention choice. The third problem is that current classification systems cannot easily accommodate the overlap across supposedly discrete disorders (Coghill & Sonuga-Barke, 2012). Allegiance to taxonomic systems has led many studies to the recruitment of highly selective samples based on either the presence or absence of a particular diagnosis, with known co-occurring disorders screened out at recruitment (e.g. Toplak, Jain, & Tannock, 2005; Willcutt et al., 2011). In reality, co-occurring diagnoses and difficulties are common: co-occurring learning difficulties are present in 44% of children with ADHD (Pastor & Reuben, 2008) and in 65%–85% of autistic children (Gillberg & Coleman, 2000), and ADHD and autism have co-occurrence rates ranging from 30%–70% (Joshi et al., 2017). The inevitable consequence of this third problem is that singular presentations of disorders dominate the research literature despite their relative rarity. In contrast, the majority of children at neurodevelopmental risk go unstudied, with more complex profiles or difficulties that fail to meet diagnostic thresholds relatively undocumented. The consequences of ill-fitting diagnostic frameworks are recapitulated for researchers and practitioners alike. Without robust and meaningful ways of capturing the complex array of characteristics of individual children in the population at large, progress towards understanding underpinning mechanisms and providing effective support for those in need is inevitably impeded. Moreover, we fail to build the evidence base that might challenge or improve upon current taxonomies.

The consequences of diagnostic systems that do not adequately capture the nature and range of individual difficulties are widely recognised in adult psychopathology (Cuthbert & Insel, 2013; Etkin & Cuthbert, 2014). Contemporary thinking here favours an alternative transdiagnostic approach that either softens adherence to the dominant diagnostic nosology or replaces it with a new framework characterising disorders in terms of dimensions rather than discrete categories (e.g. Dalgleish, Black, Johnston, & Bevan, 2020; Newby, McKinnon, Kuyken, Gilbody, & Dalgleish, 2015; Reininghaus et al., 2019; Sakiris & Berle, 2019; Titov et al., 2011). The dimensional systems neuroscience perspective developed by the NIMH Research Domains Framework (RDoC, Cuthbert & Insel, 2013) strongly endorses this approach.

The value of extending a transdiagnostic approach to NDDs has also been widely recognised (Sonuga-Barke & Coghill, 2014; Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016; Zhao & Castellanos, 2016). Transdiagnostic characteristics are more likely to reflect everyday life experiences and align with underlying mechanisms, neurobiology or potential interventions, than ill-fitting canonical diagnostic labels. For example, we have known for some time that genetic mechanisms associated with neurodevelopmental difficulties are far more likely to reflect transdiagnostic processes than to be disorder-specific (e.g. Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). However, this perspective has yet to transform the broader research field in which conventional small-scale group-based studies that investigate single disorders still dominate. This is unsurprising. Reconceptualising neurodevelopmental diversity requires a fundamental rethink of study design and scale, sampling frames and data analysis and interpretation. In this article, we review key elements of this debate, discuss new methods that test and challenge existing disorder classifications and highlight some of the hurdles and opportunities raised by a potential transdiagnostic revolution in NDDs.

What is a transdiagnostic study?

Transdiagnostic studies focus on characteristics and mechanisms that may not align with any conventional diagnostic category. Many different study designs have yielded transdiagnostic insights into NDDs. Figure 1 represents these designs as a spectrum ranging from studies that focus exclusively on standard diagnostically defined disorders through to data-driven discovery studies with no a priori clinical or subclinical selection criteria.

Recruitment by diagnosis

Case–control designs have been most widely used for studying NDDs. These compare a group of children meeting criteria for a standard NDD diagnosis, or a proxy or subclinical form of the criteria, with either another diagnostic group(s) or a typical group. Although commonly conceptualising NDDs as singular and distinct, such cross-syndrome studies have the potential offer key transdiagnostic insights when including multiple case groups (see Annaz & Karmiloff-Smith, 2005, for a review). For example, Steele, Scerif, Cornish, and Karmiloff-Smith (2013) compared children with Down's and William's Syndrome with the aim of identifying syndrome-specific characteristics. An important finding was that children's cognitive skills – their phonological awareness and letter knowledge – were excellent predictors of longitudinal growth in reading ability irrespective of the children's diagnostic status. Findings such as these provided the initial foundations for the current transdiagnostic impetus.

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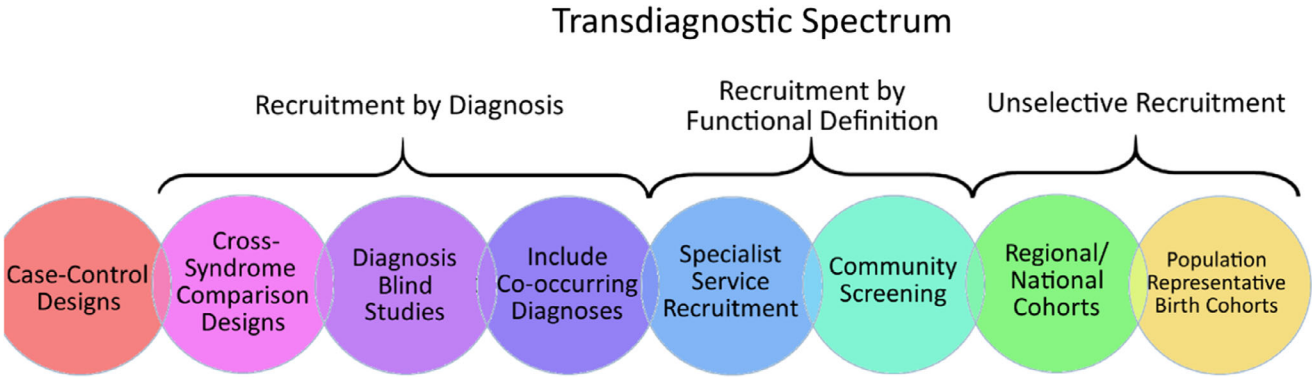

Figure 1 Transdiagnostic spectrum of study designs

Further insights can be provided by introducing more specific transdiagnostic design elements into study design. In diagnosis blind studies, formal diagnostic information that has formed the basis for recruitment is set aside for the purpose of analysis. For example, Kushki et al. (2019) recruited children with diagnoses of ADHD, autism or obsessive-compulsive disorder (OCD) in addition to a group of typically developing children. Combining the data from all participants enabled new data-driven groupings to be identified using hierarchical clustering. The groups differed in terms of cortical morphology, inattention and social skills, with little overlap observed between these groups and the children's diagnostic status. For example, multiple clusters were defined at least partly by elevated social communication and inattention difficulties, and children with any diagnosis could appear in these clusters.

Another way of incorporating transdiagnostic elements into a group design is to recruit additional groups of children who straddle conventional diagnostic boundaries. This approach can be useful for testing whether complex conditions are qualitatively distinct from the individual forms of the disorders or simply a sum of their parts. Findings from studies using these designs have largely favoured models of NDDs in which distinct phenotypic features conventionally considered to be characteristic of different disorders occur either in isolation or in combination in the individual (Bishop & Snowling, 2004; Kelly, Walker, & Norbury, 2013; Sokolova et al., 2017). For example, the Sokolova et al. study included autistic children, children with an ADHD diagnosis, and autistic children who experience high levels of inattention and hyperactivity. These studies have shown that the criterial ADHD symptoms of inattention and hyperactivity are highly common in a range of neurodevelopmentally at-risk populations including autism and reading disorders.

Functional recruitment

Although group-based designs can identify characteristics that cross-cut NDDs, their sampling practices reflect and reinforce conventional categorical classifications. Selecting participants who meet stringent criteria for a particular disorder inevitably exaggerates the distinctiveness of the diagnostic categories relative to the broader underlying neurodevelopmental population from which they are sampled. This approach also excludes children with difficulties that fall below diagnostic thresholds but are sufficiently great to require additional informal or formal in-school support (Landerl & Moll, 2010; Pastor & Reuben, 2008; see also http://embracingcomplexity.org.uk/). Failing to include the large mixed population of children who do not fit into conventional clinical criteria means we know little about them.

Relaxing recruitment criteria or adopting alternative ways to sample the broader population of individuals with neurodevelopmental difficulties provides a means of increasing the diversity and representativeness of the particular characteristics of interest. Some studies adopting this approach replace diagnostic criteria-based selection with sampling based on functionally defined needs, capturing many individuals who do not conform in either nature or severity to standard NDD criteria, as well as children who have existing diagnoses. An example is the Centre for Attention, Learning and Memory (CALM) project, which used a sampling frame designed to access a representative sample of the larger heterogeneous population of children at neurodevelopmental risk (Holmes, Bryant, & Gathercole, 2019). Recruitment was via referral by health and education practitioners of children experiencing significant difficulties in the areas of attention, learning or memory. Of the 800 school-aged children recruited, approximately a third had a diagnosis of ADHD, and smaller numbers had autism, other NDDs or mental health conditions. This cohort has already provided new insights into children with cognitive and learning-related difficulties. Using latent factor analysis, three broad dimensions of cognitive variability differentiated the sample – phonological processing abilities, executive skills and processing speed (Holmes et al., 2020). Of these,

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two dimensions were strongly associated with academic achievement: phonological processing skills in the case of reading and executive abilities for mathematics. An alternative method, using network analysis with community detection, applied to the CALM sample identified subgroups of children with different profiles of executive function, including conduct-like difficulties, elevated inattention and hyperactivity, and broader learning difficulties. Importantly, these data-driven subgroups were independent of their formal diagnostic status (Bathelt, Holmes, The CALM Team, & Astle, 2018).

Crutchley, Botting, and Conti-Ramsden (1997) also applied a functional approach to recruitment to establish a cohort of 242 children with language impairments attending speech and language units in England. These units provided specialist support for individuals with a wide range of primary language difficulties considered a barrier to successful mainstream education, with children attending based on need rather than strict inclusionary and exclusionary criteria. A striking finding was that 99% of the sample failed to meet the DSM IV (1994) criteria for what was then termed Specific Language Impairment (Conti-Ramsden & Botting, 1999). Data-driven cluster analysis identified six distinct subgroups with language difficulties with specific profiles spanning articulatory, phonological processing, syntactic and pragmatic difficulties (Conti-Ramsden, Crutchley, & Botting, 1997). Other influential approaches to investigating children at neurodevelopmental risk independent of diagnostic status have also been adopted. Longitudinal consortia such as British Autism Study of Infant Siblings (BASIS) and Study of Autism and ADHD Risk in Siblings (STAARS; Gui et al., 2020; Shephard et al., 2019) recruit siblings of individuals with known NDDs, such as ADHD and autism. These populations are known to have increased levels of clinical and subclinical features of the same disorders. This approach is particularly valuable in identifying neurocognitive precursors of difficulties manifested later in development. A further significant risk factor for neurodevelopmental difficulties is childhood deprivation and disadvantage (McLaughlin et al., 2011). Over-sampling of children from lower socioeconomic backgrounds, who are known to be at elevated risk, is a useful method of ensuring a diverse sample that minimises the bias towards affluent families evident in standard recruitment practices.

Unselective recruitment

At the extreme end of the transdiagnostic spectrum are large-scale studies in which recruitment is not tied any diagnostic or functional criteria. Recruitment is via other characteristics such as being a twin (e.g. Neuman et al., 2005) or living in a particular geographical region (e.g. Norbury et al., 2016). Some samples are established through stratified sampling. These studies provide the opportunity to identify children with neurodevelopmental characteristics of interest with reduced sampling biases, which increases representativeness relative to the designs already outlined. With sufficient depth of phenotyping, the sizes of these cohorts allow for the identification of children with features of interest, such as language-related or behavioural difficulties, on the basis of routinely collected data rather than diagnostic status (e.g. The Surrey Communication and Language in Education Study (SCALES), Norbury et al., 2016; Avon Longitudinal Study of Parents And Children (ALSPAC), Lawlor et al., 2019; The Colorado Learning Disabilities Research Center (CLDRC), Peterson et al., 2017; Twins Early Development Study (TEDS), Neuman et al., 2005). These studies can furnish invaluable population-level information regarding the prevalence, range, complexity and severity of neurodevelopmental difficulties in the population (e.g. Vamvakas, Norbury, Vitoratou, Gooch, & Pickles, 2019). Cohorts also provide the opportunity to use data-driven methods that test for more optimal classifications and to draw explicit comparisons with existing conceptualisations of NDDs.

The SCALES county-wide cohort of over 7,000 children starting school has provided new insights into the prevalence of language difficulties, as well as their phenotypic characteristics (Norbury et al., 2016). Approximately 10% of the children showed evidence of a language impairment, and of these, a quarter had existing medical diagnoses. The breadth of assessment provided important novel phenotypic insights into community language impairments. In particular, the severity of language difficulties was independent of variations in nonverbal IQ in the average to low average range, leading the authors to recommend that clinical support should not be restricted on the basis of IQ.

The majority of population-level cohorts also yield longitudinal data, making it possible to identify the developmental changes in, and drivers of, neurodevelopmental outcomes. Longitudinal data from the SCALES project, for example, established that language abilities were highly stable over the first three years of school, with little evidence of language difficulties diminishing with time (Norbury et al., 2017). In a second example, using the TEDs longitudinal study of UK twins, Hayiou-Thomas, Smith-Woolley, and Dale (2021) identified 210 children at familial risk of language and literacy problems, and poor language, speech, emergent literacy and nonverbal skills at age four. They tracked the children longitudinally through successive waves to test which early characteristics were most strongly associated with language and reading abilities eight years later. Their data revealed that the number of preschool difficulties was a better prognostic indicator of later difficulties than overall severity of difficulties by contrasting cumulative risk with early severity models.

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Summary

It is evident that there is no single design template for an informative transdiagnostic study. The best designs are those best matched to the purpose of the research question, and even nonoptimal designs can generate unanticipated transdiagnostic insights. Comparisons of two or more groups of children with particular disorders are ideally suited to hypothesis-driven research of phenotypic characteristics that may extend across different disorders, especially if they incorporate groups of children who straddle conventional diagnostic boundaries. Setting aside the diagnostic information altogether can provide a direct way of challenging the validity of supposed boundaries within the dataset. However, these group designs inevitably exaggerate the distinctiveness of NDDs, excluding the large numbers of children in the community with mild but nonetheless significant areas of need. A fuller understanding that has the potential to challenge existing classification systems requires alternative sampling approaches that better represent the neurodevelopmental population at large.

New transdiagnostic approaches

Two main alternatives to standard group-based comparisons have become central to transdiagnostic research – dimensional and clustering methods. Both are distinct from the historical backdrop of univariate statistics that typically accompany the standard case–control design. While univariate approaches align well with categorical frameworks in which symptoms are considered to be either present or absent, these alternative methods are better suited to exploring the complex and heterogeneous nature of NDDs. Both use multivariate data reduction techniques with the potential to provide parsimonious models of large mixed samples. Dimensional methods use multiple measures to generate continuous scales corresponding to broad latent constructs, along which individuals can be located. Clustering methods use multiple measures to identity discrete subpopulations of individuals. Below, we discuss the conceptual underpinnings of the two approaches and some of the key insights they have generated so far.

Dimensions

The overlapping and inconsistent presentations of specific NDDs have led many to arrive at two main conclusions. The first is that neurodevelopment can be more usefully understood in terms of multiple continuous dimensions relating to cognition, behaviour, or neurobiology – with graduated levels ranging from typical through to atypical functioning. This is supported by continuities in the range of cognitive skills and behaviour both within community samples, across typically developing children, and in those with diagnoses. The second conclusion is that individuals may have elevated levels of difficulty across multiple dimensions, with the particular combination reflecting both the nature and complexity of their difficulties.

It may be tempting to think that a dimensional approach is simply rebranding existing NDDs as continuous scales: the ADHD scale, the autism scale and so on. This is not the case. A dimensional approach is novel in its focus on multiple overlapping continuities of characteristics rather than on singular, high level of classifications of canonical disorders. Dimensions reflect the shared variance across multiple measures that plausibly result from a common underlying latent construct, re-framing NDDs as a multidimensional space rather than a series of discrete, unrelated disorders. Dimensions are ideally identified through hypothesis-free data-driven analysis of broad sets of measures. This approach lends itself to broad assessment of characteristics found in children at neurodevelopmental risk, rather than one restricted to characteristics thought relevant to conventional disorder categories. A focus on dimensions of neurodevelopmental processes also favours a shift away from exclusive dependence on the selection of discrete groups defined by recognised disorders. It sits comfortably with the flexible recruitment strategies outlined in the previous section, designed to reflect the full constellation of characteristics relevant to key neurodevelopmental outcomes such as language abilities, academic learning, attentional control, social communication and lived experience. In these ways, dimensional approaches have the potential to transform not just research on the mechanisms of NDDs but also clinical and educational practice.

The identification of candidate neurodevelopmental dimensions is itself challenging, with many factors to take into account. One reason this is challenging is because there is a long-standing difficulty in establishing the appropriate level to conceptualise disorders that are primarily characterised by behaviour, psychology, cognition or psychopathology (e.g. Kendler, 2016; Zachar & Kendler, 2007). A reasonable starting point is evidence that a particular set of phenotypic characteristics are linked with multiple neurodevelopmental outcomes, such as children's language development, academic learning, social functioning and behavioural control. However, it is often the case that our understanding of the fundamental mechanisms underpinning these characteristics does not readily map onto broad continuous dimensions; instead, they may have either hierarchical or more complex structures. Consider the architecture of the cognitive system. Although the broad RDoC transdiagnostic framework specifies six cognitive constructs (attention, perception, working memory, declarative memory, language behaviour and cognitive control; Cuthbert

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& Insel, 2013), several of these have high degrees of overlap both in assessment methods and component processes. Moreover, the simplicity of high-level labels for the constructs is misleading, masking many of the functional distinctions established through experimental psychology and neuropsychology that have guided research and assessment of NDDs (e.g. Lezak, Howieson, Loring, & Fischer, 2004). For instance, executive functioning is often fractionated into separate components including attentional shifting and inhibitory control (Miyake & Friedman, 2012; Pennington & Ozonoff, 1996), working memory has been decomposed into distinct storage and executive components (Baddeley, Allen, & Hitch, 2011), and language consists of multiple functional elements that include vocabulary, word recognition, comprehension and pragmatic aspects of communication (Language & Reading Research Consortium, 2015). A similar case could be made for the other candidate dimensions.

If broad constructs such as these cannot be usefully conceptualised as dimensions, what level of description should be used? At the most granular level, dimensions have been represented as endophenotypes – measurable and highly specific aspects of behaviour that sit at an intermediate position between symptoms and their underpinning neurobiological mechanisms. An example is the proposal that reaction time variability in neurocognitive tasks (RTV) is an endophenotype for ADHD (Castellanos & Tannock, 2002; Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Tamm et al., 2012). Its reliability as a marker of ADHD is subject to debate, though, with meta-analytic data pointing to high levels of incidence extending to clinical control groups without ADHD (Kofler et al., 2013).

An alternative approach that has gained considerable traction in recent years is to use symptom-level data as a means of identifying dimensions that are neurodevelopmentally meaningful. Crucially, in this context 'symptom' is not necessarily constrained to a diagnostically defined characteristic, but in many cases reflects any measurable feature of a neurodevelopmental difficulty. By this approach, the data themselves define the dimensions, and while they can be tested against a priori theoretical assumptions, they are not constrained by them. Symptom dimensions identified in this way have drawn on statistical techniques ranging from analyses of covariance (Dolan & Lennox, 2013), regression-based analyses (Boxhoorn et al., 2018; Leno et al., 2018; Takeuchi et al., 2013), exploratory and confirmatory dimension reduction methods (Bloeman et al., 2018; Furlong et al., 2018; McGrath et al., 2016), latent class to latent trait models (Carragher et al., 2014) and taxometry (Marcus & Barry, 2011). Table 1 shows five possible broad transdiagnostic dimensions, derived from outcomes from a range of studies deploying different designs and methods. It should be noted that because the documented phenotypes of these disorders come from simple rather than complex (co-occurring) forms, this characterisation inevitably underestimates the population-level prevalence of these features. In the subsequent paragraphs, we briefly assess the available evidence for each of these putative dimensions in turn.

Hyperactivity/impulsivity and inattention are broad constellations of behaviour forming the primary basis for ADHD diagnoses. These are common characteristics of other neurodevelopmental populations too. High levels of hyperactive/impulsive behaviour are common in children with learning-related difficulties (Hawkins, Gathercole, Astle, The Calm, & Holmes, 2016); indeed, in some cases elevated inattention can be as common as in children with ADHD (Bathelt et al., 2018; Holmes et al., 2014; Willcutt, Pennington, Olson, & DeFries, 2007). In addition, both hyperactive / impulsive behaviours and inattention are common in autistic children (Arnett et al., 2018; van Steijn et al., 2012). Taxometry provides further evidence that both kinds of behaviour are distributed continuously across the population as a whole (Marcus & Barry, 2011). This statistical method tests whether data distributions are best characterised as continuous or categorical. For both hyperactivity/ impulsivity and inattention scores, findings from population samples and large samples of children with or without ADHD diagnoses have consistently favoured dimensional continuity, with little evidence for discrete difficulties tied to ADHD (Haslam et al., 2006; Hudziak, Achenbach, Althoff, & Pine, 2007; Marcus & Barry, 2011).

The pragmatic use of language is a further candidate for a dimension existing across multiple NDDs (Bishop & Norbury, 2002). Young autistic people show differences in these behaviours relative to nonautistic individuals, and these often occur in combination with restricted interests and repetitive behaviours, which may also have a dimensional basis (Lord et al., 2012). Social pragmatic difficulties are also characteristic of children with Social Pragmatic Communication Disorder (SPCD; Mandy, Wang, Lee, & Skuse, 2017; Norbury, 2014) and have been observed both in children with ADHD (van Steijn et al., 2012) and in those with learning-related problems (Mareva, the CALM Team, & Holmes, 2019; Hawkins et al., 2016; see to Rints, McAuley, & Nilsen, 2015).

There is emerging evidence that close links exist between social pragmatic communication skills and hyperactive behaviours. In a study of a mixed sample including children with learning-related cognitive difficulties as well as those with ADHD, Hawkins et al. reported high levels of co-occurrence between hyperactive behaviours and problems with the social pragmatic use of language (Hawkins et al., 2016). Using network analysis to track links between behaviours in this population in more detail, Mareva et al., 2019 discovered that the links between

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Table 1 Possible transdiagnostic dimensions and associated neurodevelopmental disorders

	Neurodevelopmental disorders					
Dimension	ADHD	Autism	Specific reading disorder (dyslexia)	Specific maths disorder (dyscalculia)	Developmental language disorder	Social pragmatic communication disorder
Hyperactivity and impulsivity	**	*				
Inattention	**		**	**	*	
Social communication	*	**				**
Executive functioning	**		*	*	*	
Phonological processing	*		**	*	**	

Developmental coordination disorder /dyspraxia is not included due to the paucity of studies reviewing its potential cognitive and behavioural dimensions.
*Moderate association, **Strong association.

hyperactivity and inappropriate initiation in communication were particularly strong. While clearly requiring further investigation, one possibility is that despite evidence for dimensionality, specific behaviours can act as conduits for transmission across dimensions, causing difficulties to cascade.

Phonological processing refers to the set of perceptual and cognitive skills involved in representing and manipulating the sound structure of language. It is assessed through tests of phonological awareness, rapid automated naming and verbal short-term memory. It too shows clear evidence for transdiagnostic dimensionality. A broad common dimension emerges because of close associations between phonological awareness and verbal measures of short-term and working memory (Gathercole, 2006; Melby-Lervåg, 2012). Difficulties in these skills are common symptoms of NDDs of reading and language (Bishop & Snowling, 2004; Elliott & Grigorenko, 2014; Hulme & Snowling, 2013). They are also present in many children with mathematical difficulties (Jordan, Wylie, & Mulhern, 2010; Peng, Congying, Beilei, & Sha, 2012; Swanson & Sachse-Lee, 2001) as well as in individuals diagnosed with ADHD (Holmes et al., 2014, 2020).

Executive function difficulties have long been considered a hallmark of ADHD (Barkley, 1997; Castellanos-Ryan et al., 2016; Pennington & Ozonoff, 1996) and also extend across a wide range of NDDs including reading difficulties (Wang & Gathercole, 2015), autism (Griffith, Pennington, Wehner, & Rogers, 1999) and communication impairments (Bishop & Norbury, 2005). Many studies have identified common executive function difficulties across pairs of disorders, such as ADHD and autism (Bloemen et al., 2018; Pennington & Ozonoff, 1996), and ADHD and learning-related difficulties (Holmes et al., 2014). However, while the consistency of executive function difficulties at what Pennington and Ozonoff term the molar level of analysis lack diagnostic specificity, differences in the specific nature of these difficulties within and across NDDs have also been reported (Boxhoorn et al., 2018; Carter-Leno et al., 2018; Holmes et al., 2014; Pennington & Ozonoff, 1996). There is considerable heterogeneity in the nature of executive function difficulties even for individuals with a common ADHD diagnosis. For example, Kofler et al. (2019), reported that although 89% of children with ADHD showed poor performance in at least one aspect of executive functioning (inhibitory control, set shifting and working memory), only a third of the sample had problems in two or more of these areas.

Why should the detailed nature of executive functions show this degree of variability both within ADHD and across NDDs? One possibility is that executive functioning represents a superordinate dimension of cognitive ability that is decomposable into correlated but distinct sub-dimensions, each associated with subtly different symptom constellations, such as set shifting and inhibitory control. Different executive function tasks have distinct as well as common sources of variance, in addition to the core aspect of cognitive control of interest, which further complicates things. Task designs vary widely in their nature and complexity, and behavioural responses include reaction times, span measures and accuracy measures. A second possibility that is not necessarily incompatible is that executive functions contribute to task performance differentially at different points on the ability spectrum or within different subgroups. For instance, a phonological detection task may not be designed as an executive function task, but for those with phonological difficulties this task may draw heavily on domain-general executive skills. All of these complicating factors combined mean that the failure to detect a single executive function dimension in latent factor analyses is unsurprising.

In summary, many of the phenotypic characteristics of common NDDs can be coherently characterised as regions of space governed by a relatively small set of underlying dimensions. Because these dimensions do not observe conventional diagnostic boundaries, this reconceptualisation has the clear

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potential to provide an effective guide to understanding, assessing and supporting children with NDDs, without recourse to conventional diagnostic systems that are often ill-suited to capturing the needs of the individual, not least because dimensions do away with arbitrary diagnostic thresholds. They also hold promise for researchers; any phenotypic measure that captures greater inter-subject variability, relative to coarse diagnostic classifications, will be more useful for establishing underlying mechanisms. A dimensional approach can also be far more informative about developmental change, relative to the presence or absence of a diagnosis. Multiple modelling techniques allow researchers to test whether and how relationships between dimensions change over developmental time. For example, the demonstration of mutualistic coupling between different cognitive skills over time, with one latent cognitive dimension positively influencing the future development of another, and vice versa (e.g. Kievit, Hofman, & Nation, 2019).

Dimensional approaches have limitations. Their data reduction methods lack experimental control and are largely unsuited for more precise, mechanistic understanding of neurodevelopmental processes. At the level of an individual study, dimensions must be understood in relative rather than absolute terms. Their heavy dependence on the measures and participants included in the analysis can make the labelling of any resulting dimensions difficult. Inconsistency in the labelling of these constructs across studies can itself make it hard to build consensus. Dimensions can be characterised at relatively broad levels as in the present section (e.g. phonological, inattention, pragmatic communication) or focussed on more narrowly defined constructs such as components of phonological processing (Ramus, Marshall, Rosen, & Van Der Lely, 2013). Both approaches are valuable, and the outcomes are in practice dictated by the available data; the range of variables included in the analysis governs the generality of the factors (dimensions). Data reduction methods identify the main axes of variation in selected measures for a particular sample, representing the largest amounts of the variance within the dataset. Unintended sources of common variance across measures (such as, e.g. whether the dependent variable is speed or accuracy, or the score a rating or frequency value) can influence the dimensions that emerge. This can lead to misinterpretation and low levels of generalisability. Likewise, the dimensional space will be heavily influenced by the quality of the measures included. Tasks or measures that most robustly capture individual differences will dominate the dimension reduction, especially if they are relatively coarse, whereas elegant experimental tasks not designed to be sensitive to individual differences may not be well-captured by any resulting dimensional space. The relationships between measures and latent dimensions can change with age – in essence, tasks can measure different constructs across development. This can be tested formally, but nonetheless can make comparisons of dimensions across ages difficult. Furthermore, dimensions that explain smaller amounts of variation within a dataset are lost in the course of latent variable analysis, meaning that potentially important sources of variation within the population can go undocumented. Relatedly, minority subpopulations, who are best characterised by different dimensions, can be obscured within the broader sample unless modelled separately. This is because a premise for most dimensional approaches is that there are no subpopulations.

Transdiagnostic clusters

The data reduction methods employed in dimensional studies are ideally suited to detect the broad latent constructs that characterise a sample. An alternative means of data reduction, clustering, offers a complementary approach designed to identify subgroups in the data. If a dimensional analysis identifies the broad multidimensional space that characterises the sample, clustering techniques allow for the optimal grouping of individuals within that space, based directly on particular characteristics in the data. They are applicable to a wide variety of different samples, ranging from diagnostically defined to large mixed populations of children. As with dimensional approaches, clustering techniques are best deployed in combination with sampling approaches that attempt to produce representative samples of the domains of interest. Clustering methods are widely used in other areas of science to test for the intersection between dimensions, or individual measures, within groups of individuals. In the context of transdiagnostic studies, they allow for the identification of constellations of cognitive, behavioural or neural features. The analyses then assign individuals to clusters characterised by particular profiles of scores across these features. In the scenario depicted in Figure 2, phenotyping data for a mixed sample of children has been scaled such that the multidimensional space can be characterised by two dimensions. A clustering analysis could then test how this space is occupied by participants. The identification of subgroups can also be achieved within some psychometric models, for example using factor mixture modelling (e.g. Lubke & Muthen, 2005; Zablotsky, Bramlett, Visser, Danielson, & Blumberg, 2018), but in the current section we focus primarily on findings from dedicated clustering algorithms.

Clustering approaches can be used to test the adequacy of standard classification of NDDs of the sample against known diagnostic status. Kushki et al. (2019) applied a clustering approach to phenotypic and cortical thickness data to identify

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subgroups within a sample of 226 children. Their sample included autistic children, those with ADHD or OCD diagnoses, as well as typically developing children. Cortical morphology data from 75 regions and data from inattention, obsessive-compulsive behaviour, social communication and general child behaviour questionnaires were subjected to a bagged multi-view clustering algorithm. The algorithm produced a hierarchical solution, with broad clusters that could be divided sequentially into more refined subtypes. Based upon the ratio of within-cluster homogeneity to between-cluster distinctiveness, Kushki et al. (2019) selected an optimal solution with ten clusters. Each cluster could be significantly distinguished from the others based on both the questionnaire and neural data. Children with each of the diagnoses were represented in every cluster; there was no significant alignment of diagnostic classification with the data-driven grouping. This led the authors to conclude that 'existing behaviourally defined diagnostic labels may not capture etiologically, biologically, and phenomenologically homogeneous groups'.

Recent uses of clustering as a data-driven means of distinguishing NDD phenotypes include simple k-means clustering (e.g. Astle, Bathelt, & Holmes, 2019), hierarchical and agglomerative clustering techniques (e.g. Bathelt, Vignoles, & Astle, 2021; Kernbach et al., 2018; Poletti, Carretta, Bonvicini, & Giorgi-Rossi, 2018; Siugzdaite, Bathelt, Holmes, & Astle, 2020), and community detection within networks (e.g. Bathelt et al., 2018). They are proving to be powerful tools to support systems neuroscience approaches to understanding NDDs, combining multiple sources of data across cognition and behaviour (e.g. Bathelt et al., 2018) and behaviour and neuroimaging (Bathelt, Johnson, Zhang, & Astle, 2019; Kernbach et al., 2018; Kushki et al., 2019).

The conclusions that can be drawn from clustering solutions depend on the types of samples to which they are applied. Data from diagnostically defined samples (e.g. Kushki et al., 2019) have the potential to challenge and redraw supposed boundaries between different constellations of difficulties. When combined with large-scale population-representative datasets, clustering methods have the potential to generate new insights about the relative prevalence and co-occurrence rates of different difficulties. Bathelt et al. (2021) subjected parental questionnaire data from a population-level birth cohort to hierarchical clustering to identify common behavioural problems when children were 10 and 16 years old. This enabled the mapping of longitudinal transitions between clusters, and the identification of factors predicting particular between-cluster transitions. While problems with hyperactivity/impulsivity, motor control, and conduct were prominent in childhood, adolescents' profiles were characterised by elevated problems with emotional control, anxiety, and inattention. Longitudinal transitions were associated with both socioeconomic status and cognitive performance in childhood. This data-driven approach allowed for developmental transitions in the frequency, presentation and co-occurrence of behavioural difficulties, and established key risk factors for specific transitions as children became adolescents (Bathelt et al., 2021). This example also highlights one final benefit of data-driven clustering: it allows for the manifestation of difficulties to change

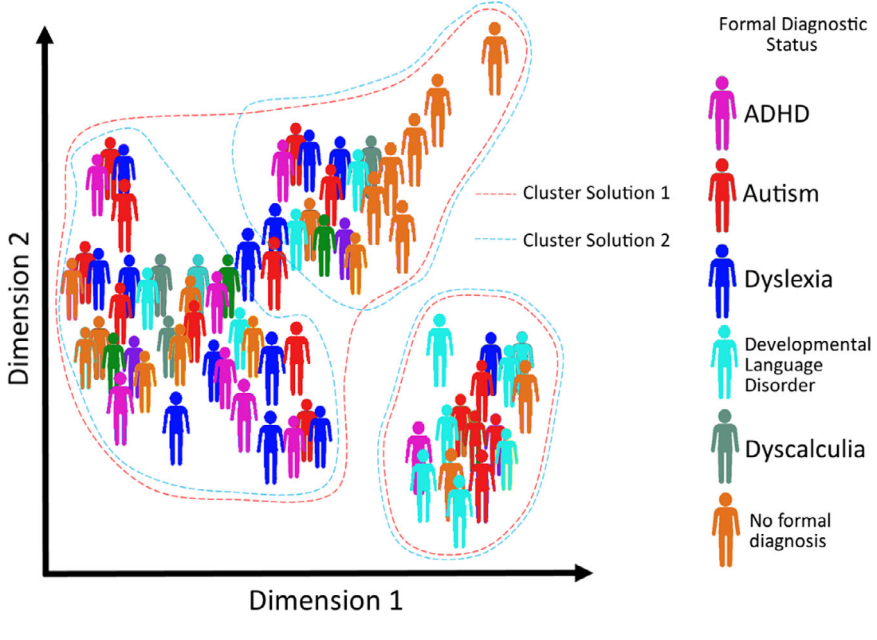

Figure 2 Alternative clustering solutions for a mixed sample

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across developmental time, in contrast to formal diagnostic criteria, which tend to be relatively static.

A common application of clustering has been to identify cognitive phenotypes in mixed populations. Archibald, Oram Cardy, Joanisse, and Ansari (2013) assessed learning and cognition in children from 34 schools in Ontario, as part of a population-representative study. Clustering identified six learning profiles, including children with low scores on either reading, maths or both reading and maths tests. Children with low language abilities showed difficulties in verbal short-term memory whereas those with lower reading and maths abilities had the poorest phonological awareness skills. There is also a small but growing set of studies that apply these methods to cognitive data from functionally defined samples, such as children who experience difficulties learning in the classroom (Astle et al., 2019; Poletti et al., 2018; Siugzdaite et al., 2020). These studies have identified a number of consistent cognitive phenotypes that include: (a) children with poor verbal skills including difficulties on tasks tapping vocabulary, phonological awareness, and letter-number sequencing; (b) children with poor executive skills, including spatial short-term and working memory; and (c) children with more widespread difficulties that span multiple domains. In each case, these groupings generalise to other data not introduced to the clustering algorithm. In other studies, clustering approaches have been applied to more focussed participant groups such as children with maths difficulties (Bartelet, Ansari, Vaessen, & Blomert, 2014) and those at risk of poor oral language and literacy outcomes (Cabell, Justice, Konold, & McGinty, 2011).

When applied to behavioural and clinical assessment data, clustering approaches have the potential to challenge clinical boundaries, because these are the data types that typically inform or reflect clinical decisions. Vargason, Frye, McGuinness, and Hahn (2019), for example, used data from national medical records to test for the co-occurrence between autism diagnoses and other clinically recognised conditions, including sleep, immune, seizure, psychiatric and developmental disorders. When combined with more fine-grained symptom-level data, clustering techniques can identify and refine behavioural subtypes of recognised NDDs (Lombardo et al., 2016). For instance, Stevens et al. (2019) identified five subgroups within a sample of children that all met the same autism criteria. The emergent clusters appeared to represent distinct profiles across different developmental domains, including language skills, social communication, executive functions, academic performance and play behaviours. Despite the shared diagnostic label, the clustering suggests there are multiple different groups of individuals, who may benefit from different types of support. Clustering within and across symptom-level data in samples of children with clinically recognised NDDs can also characterise heterogeneity in the co-occurrence patterns themselves. Cravedi et al. (2017) identified three different clusters of children with Tourette's syndrome, each characterised by a different profile of behavioural difficulties. Each cluster had different rates of co-occurrence with ADHD, attentional problems and learning difficulties. These data show that different clusters of Tourette's-related behaviours are associated with different behavioural profiles, and confer differential susceptibility for co-occurring difficulties, suggesting they might have different causes.

There are limitations to the current suite of clustering methods and the categorical allocations they provide. First, cluster assignment is always biased towards measures that explain the most variance in cluster assignment. When multiple different data-types are combined, clustering is unlikely to be driven equally by each. In the Kushki et al. (2019) study, for example, the clusters were distinguished primarily by the questionnaire data rather than the cortical morphology data. Secondly, most clustering algorithms are designed to find hard borders with clear space between putative subgroups. In reality, boundaries are likely to be fuzzy, as a consequence of both borderline cases and measurement noise. This makes it impossible to distinguish all members of genuine subgroups. Dalmaijer, Nord, and Astle (2020) have suggested that some of these limitations may be overcome by using other methods to identify groups within noisy datasets that contain multiple edge cases from different areas of science, such as c-means clustering (Bezdek, Ehrlich, & Full, 1984), co-clustering (Dhillon, Mallela, & Modha, 2003) or hierarchical density-based spatial clustering (McInnes, Healy, & Astels, 2017). In Figure 2, there are two potential clustering the solutions. The first assumes that there must be hard boundaries or 'clear water' between any subgroups, whereas the second assumes that subgroups with fuzzy boundaries are still meaningful. Finally, clustering techniques assume homogeneity within clusters. While clusters will by definition be more homogenous than the overall sample from which they arise, there may still be important variability which is lost.

Clustering is a highly flexible tool that is applicable to a wide variety of data types, from relatively coarse clinical record data, to fine-grained cognitive or behavioural symptom-level data. When applied to data from individuals with diagnosed NDDs, it can challenge existing boundaries, identify novel subtypes, and map co-occurrence patterns across disorders. When combined with functionally defined samples, clustering can map the heterogeneity of cognitive or behavioural profiles associated with an important outcome such as school performance. It can also be applied to large-scale representative samples for a more radical re-appraisal of how difficulties co-occur and change across development, and their relative prevalence in the wider population.

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To date, dimensional and clustering approaches have provided the main vehicles for advancing transdiagnostic understanding of NDDs, either by establishing continuous factors or alternative data-driven groupings. Dimensional approaches group variables to explain the variance within a neurodevelopmental sample. Clustering approaches group individuals to explain the profiles that exist within neurodevelopmental samples. At the outset, we outlined three core problems associated with the overreliance on the current diagnostic nosology – (a) arbitrary thresholds, and insensitivity to (b) within-category variability and (c) between-category overlap. Data-driven clusters or dimensions, when used appropriately, provide ways of addressing these limitations. For example, dimensions capture continuous gradations in performance without recourse to arbitrary thresholds, and multiple dimensions can combine to optimally capture variability without the need for categories. Clusters still apply boundaries, but they are not arbitrary. They can provide more optimal, data-driven ways of grouping individuals that may be more closely aligned with underpinning mechanisms and pathways to effective intervention. As highlighted above, both methods are able to capture developmental change, either as shifting relationships between dimensions (e.g. Kievit et al., 2019) or transitions in cluster membership (e.g. Bathelt et al., 2021). This is likely to be far more informative than a binary diagnostic label. As the field moves forward, further data-driven methods will be developed and applied to NDDs. Researchers are already using network-based approaches that focus on continuous measures without recourse to underlying latent dimensions (Borsboom, 2017; Mareva et al., 2019). These are distinctive in focussing on particular characteristics as meaningful integrated constituent parts of a disorder, rather than manifestations of underlying constructs that have distinct causal mechanisms. Over time, data-driven methods that sit conceptually somewhere between dimensional and clustering approaches may emerge. For example, artificial neural networks (ANN) are ideal for modelling complex datasets and have exceptional promise for understanding the complex patterns of distributions of neurodevelopmental characteristics. Because they adapt to fit the data, they have the potential to capture both continuities within the neurodevelopmental landscape alongside relative concentrations of profiles that, while meaningful, might not reach the conventional thresholds for hard cluster assignment (e.g. Siugzdaite et al., 2020).

Whatever analysis method is deployed – whether it be dimensions, clusters or something from the emerging array of alternatives – there is no substitute for quality cognitive and behavioural measures. All the methods we have described are data-driven, meaning that despite their apparent sophistication, they will be heavily influenced by the quality and sensitivity of the measures. For any of the analysis options to be informative, they need to be applied to appropriate data.

Transdiagnostic mechanisms

Both dimensional and clustering approaches provide means of putting aside diagnostic status whether known or unknown and seeking more parsimonious explanations of common and complex patterns of neurodevelopmental profiles. A transdiagnostic approach to neurodevelopment is more than alternative sampling frames and sophisticated analysis methods, valuable as they are. It reflects a deeper reconceptualisation of the nature of NDDs. Previous accounts of NDDs typically sought to postulate a common causal mechanism with the power to explain all observed profiles within a diagnostic boundary (Astle & Fletcher-Watson, 2020; Happe, Ronald, & Plomin, 2006; Pennington, 2006). The softening or removal of those categorical boundaries within a transdiagnostic framework calls into question this approach. How then does a transdiagnostic perspective within NDDs translate into underpinning mechanisms?

Cognitive and behavioural transdiagnostic mechanisms

Dimensions and clusters are ideal methods for phenotyping within transdiagnostic designs. However, multiple and different neurocognitive causes can drive variation in a dimension, or membership of a particular cluster. Particular phenotypes, whether conceived as dimensions or clusters, may be common because they are an emergent property of multiple converging pathways. In this way, many alternative configurations of underlying mechanisms might give rise to the same phenotype.

Consider phonological processing, one of the potential transdiagnostic dimensions highlighted in previous sections. Phonological processing skills are closely linked with early reading and language development (Brizzolara et al., 2011; Child, Cirino, Fletcher, Willcutt, & Fuchs, 2019; Holmes et al., 2020), and groups of children with phonological difficulties have emerged from data-driven clustering (Astle et al., 2019; Siugzdaite et al., 2020). However, it is unlikely that phonological dimensions or clusters are aetiologically homogenous. Some argue that phonological awareness is composed of different sub-processes (Melby-Lervåg, 2012). Supporting this, whether children can pronounce constituent phonemes of a word depends both on their phonemic (e.g. Bosse & Valdois, 2009) and rhyme awareness (e.g. De Cara & Goswami, 2003). Furthermore, many tasks that measure phonological awareness assess verbal short-term memory too (Gathercole, 2006). These potentially separable processes typically share variance, fit into cognitive models as good predictors

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of language development (Melby-Lervåg, 2012; Muter & Snowling, 1998) and provide the basic building blocks for reading acquisition (Bishop & Snowling, 2004). These multiple underlying cognitive processes could therefore also determine variance in a continuous phonological dimension or membership of a phonological difficulties cluster.

Causal heterogeneity becomes increasingly likely if dimensions or clusters reflect higher-order cognitive skills such as executive functioning. As noted previously, executive functioning is likely the most widely reported transdiagnostic dimension, cutting across a wide range of conditions including ADHD, Conduct Disorder, Oppositional Defiant Disorder, autism and children in the general population without diagnosed conditions (Abu-Akel et al., 2018; Bloemen et al., 2018; Dolan & Lennox, 2013; Halvorsen et al., 2019; Holmes et al., 2020; McGrath et al., 2016; Neely, Green, Sciberras, Hazell, & Anderson, 2016). Executive function difficulties likely arise through multiple constituent cognitive or behavioural processes and are therefore likely mechanistically diverse. This has two main consequences for a transdiagnostic perspective. First, as noted earlier, mechanistic diversity reduces the likelihood of deriving a single dimension or cluster for executive difficulties. Second, a wide variety of interacting mechanisms could give rise to executive difficulties. The more complex the cognitive or behavioural construct, the less likely it is that there is any simple mapping between an underlying mechanism and the surface-level presentation.

How can this diversity be accommodated? Structural modelling of constituent processes incorporating hierarchical nesting of measures provides one way of identifying how varied pathways converge on a particular dimension (e.g. Fuhrmann, Simpson-Kent, Bathelt, & Kievit, 2020; Kievit et al., 2016), a property termed 'equifinality' (e.g. Simmons, Hilton, Jarrett, Tomeny, & White, 2019). Computational frameworks may also provide a means of handling complexity. Experimental analysis with bespoke paradigms that tease apart potentially separate processes could delineate underlying contributions to variability. Mathematical frameworks borrowed from computational psychiatry could then be applied to integrate trial-wise output from these bespoke paradigms, by parameterising fluctuations in underlying causal relationships (Adams, Huys, & Roiser, 2016; Huys, Maia, & Frank, 2016). To date, there have been very few attempts to use this approach to integrate across levels of explanation in NDDs. But as transdiagnostic datasets emerge, computational frameworks may provide a means of handling complexity. For instance, one computational model of autism incorporates physiological mechanisms, putatively reflecting noradrenergic signalling, alongside environmental stochasticity, within a hierarchical Bayesian framework (Lawson, Mathys, & Rees, 2017). This model parameterises relationships between different levels of explanation to track across trials and predict future behaviour. Computational frameworks may bring much-needed theoretical rigour to the field, including the ability to make and test novel quantitative predictions (Fried, 2020). One challenge they may be particularly useful for is 'multifinality' – the demonstration that a common single component might have a differential impact across individuals, depending upon the overall configuration of the system (Cicchetti & Rogosch, 1996). This is challenging to capture with any of the analysis tools we have mentioned so far, but computational models that simulate the mechanistic interactions between multiple component processes may be able to unpack why any particular component has a differential impact upon behaviour depending upon the wider configuration of processes.

Transdiagnostic brain mechanisms

As with cognition and behaviour, the hierarchical convergence of brain mechanisms is likely to be a recurrent theme in emerging transdiagnostic designs. A principal challenge for identifying transdiagnostic brain mechanisms is mapping between different levels of explanation, without losing complexity. How do multiple neurobiological processes converge on measurable cognitive/ behavioural dimensions or clusters? The risk is that in correlating voxel-wise brain activity with cognitive or behavioural dimensions we mask aetiological complexity with neural simplicity (see also Astle & Fletcher-Watson, 2020).

Variability in any cognitive or behavioural dimension is likely to be an emergent property of multiple converging structural or functional neural processes (e.g. Kievit et al., 2014; Siugzdaite et al., 2020). This is in keeping with developmental systems theory (e.g. Johnson, 2011), but difficult to capture with conventional mass-univariate statistics such as voxel-wise comparisons (e.g. Ducharme et al., 2012; Elton, Alcauter, & Gao, 2014; Gold et al., 2016). Contemporary structural modelling techniques such as hierarchical mimic modelling are currently being applied. Multiple neural effects (e.g. distinct individual differences in brain structure) and their association to intermediate cognitive processes (e.g. working memory, attentional control, inhibitory control) can be independently modelled using these methods, and in turn, these intermediate processes converge upon a higher-order cognitive dimension (e.g. executive function). As such, partially independent brain–behaviour relationships are modelled alongside their convergence with broader cognitive or behavioural dimensions (e.g. Fuhrmann et al., 2020; Simpson-Kent et al., 2020). Alternatively, machine learning allows researchers to integrate multiple convergent neural measures within rich phenotypic datasets (e.g. Alnaes et al., 2018;

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Siugzdaite et al., 2020) as well as polygenic information (Alnaes et al., 2018). However, caution is required when using complex multivariate techniques like machine learning as while capable of handling complexity, they are liable to overfitting. This can be mitigated through techniques such as within-sample hold-out cross-validation to test for generalisation, or regularisation approaches (Delgadillo, 2021). Out-of-sample generalisation is an even better solution, but with the scarcity of large transdiagnostic cohorts, it is rare yet possible.

Recent advances within systems neuroscience may prove particularly useful for establishing transdiagnostic brain mechanisms as in some cases the methods used incorporate hierarchical relationships by design. An already influential field is connectomics, the study of the functional (correlated activity) or structural (using measures such as fractional anisotropy, FA) connectivity between brain regions (e.g. Abbott et al., 2016; Hawkey, Tillman, Luby, & Barch, 2018). Once parcellated, the brain can be modelled as a system of integrated nodes, with structural or functional connections that vary in strength (Bullmore & Sporns, 2012). The resulting network, described in mathematical terms using graph theory, generates metrics that capture the importance of individual nodes within the network, the distance between nodes and the extent to which nodes share neighbours. Standard voxel-wise methods likely underestimate the contribution of the whole-brain network structure due to their reliance on spatially overlapping associations across individuals (Bathelt et al., 2018). In contrast, connectome characteristics capture effects that may be spatially variable across individuals, because they are hierarchical by design and can therefore be calculated at a nodal, regional or global level.

Within a transdiagnostic cohort, Bathelt et al. showed that the global organisation established using the FA connectome was far more sensitive to academic development than that identified using a voxel-wise FA skeleton (Tract-Based Spatial Statistics – TBSS). The reason is that FA differences must necessarily overlap across children to yield significant voxel-wise effects, whereas a connectome captures effects that have a consistent impact on organisation within different regions or globally, without the reliance on spatial overlap (see also Bathelt, Gathercole, Butterfield, & Astle, 2018, Bathelt, Scerif, Nobre, & Astle, 2019; Johnson et al., 2021). The application of connectomics in this space is in its relative infancy, and significant sensitivity challenges remain (Martino et al., 2014), but they do a good job of capturing hierarchical convergence. Indeed, certain characteristics of connectomes may come to represent particular transdiagnostic endophenotypes, because they capture the convergence of local neural effects by modelling their impact on regional or global organisation.

Transdiagnostic genetic mechanisms

Genetics and NDDs have an uneasy relationship, in part due to a history of underpowered single-gene case–control comparisons that were highly prone to type 1 errors (Bishop, 2009). This lack of power is especially common when neuroscience methods are included (Grabitz et al., 2018). The scale of a standard NDD study (e.g. $n < 500$) is simply not large enough to test for associations between individual genes and a particular phenotype, let alone discover novel variants. In reality, neurodevelopmental difficulties within the wider population are likely to be highly polygenic, with individual genes explaining tiny amounts of variance or being uninterpretable without information about other genes.

From this backdrop, multiple international consortia have formed to make possible genome-wide association studies (GWAS) of singular disorder categories in ADHD (Franke, Neale, & Faraone, 2009), language difficulties (Kornilov et al., 2016), autism (Glessner et al., 2009) and dyslexia (Gialluisi et al., 2019). These have the power to identify individual variants, which together have predictive power to distinguish cases from typically developing controls. Individual effects can be integrated by creating polygenic risk scores (PRS), which can be validated out-of-sample by testing whether they do indeed distinguish cases from controls in novel datasets. This is the point at which this approach can become transdiagnostic. PRS are less specific than previously thought, with large amounts of overlap across different NDDs and wider psychiatric and mental health conditions (e.g. Li, Franke, AriasVasquez, & Mota, 2021; Schork, 2018). These outcomes suggest that rather than detecting disorder-specific mechanisms, PRS measures identify genes underpinning variations in cellular and biological pathways that confer a set of broader, transdiagnostic vulnerabilities. Understanding the mapping between these pathways and wider neurodevelopmental cognitive and behavioural endophenotypes is challenging, with data at a sufficient scale only just emerging. Early findings suggest that PRS derived using single disorders are significantly associated with dimensions of both cognition and behaviour within the wider population. For example, ADHD PRS predict variability in inattention within the wider population (Groen-Blokhuis et al., 2014), PRS for autism and major depressive disorder predict performance on executive function tasks in nonautistic and nondepressed samples (Schork, 2018), and a schizophrenia PRS predicts a wide range of early cognitive and behavioural developmental skills in the areas of language, behaviour and social interactions. These transdiagnostic findings should come as no surprise. Long before PRS analyses became mainstream, pleiotropic effects (wherein a single gene is associated with multiple supposedly unrelated phenotypic traits)

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had been observed across multiple NDDs (e.g. Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Lam et al., 2019; Rommelse et al., 2011).

The second approach yielding transdiagnostic genetic insight is the study of NDDs of known genetic cause. The focus of this piece so far has been on the common NDDs for which the underlying causes are largely unknown. There is also a growing list of NDDs of known genetic cause. In addition to well-known disorders like William's, Down's and Fragile X syndrome, there is a growing list of rare disorders caused by single high-penetrance gene mutations picked up by routine genetic screening (Basel & McCarrier, 2017). Like other NDDs, there are a number of common symptoms that span disorders, including inattention and hyperactivity (Scerif & Baker, 2015), and social and communication difficulties (Baker et al., 2015). Where the causative gene has a known cellular or biological function, these NDDs can be grouped functionally. For example, genes associated with synaptic physiology can be contrasted with those associated with chromatin regulation across a range of neurodevelopmental dimensions. In one recent study, the functional role of the causative gene influenced some autism-relevant dimensions, like inflexibility, but not others (Brkic et al., 2020).

The known functional role of genes implicated in some NDDs, alongside their necessarily homogenous cause, means that these rare disorders provide a window into a set of molecular, cellular and biological pathways. When combined with broad phenotyping, this insight can inform transdiagnostic processes relevant to the broader population of young people at neurodevelopmental risk. In one example, rare genetically defined NDDs were combined with brain-wide gene expression data (Seidlitz et al., 2020). This study included genetic disorders caused by copy number variations (CNVs), including eight different NDDs: XXX, XXY, XYY, XXYY, Down syndrome, X-monosomy (Turner syndrome), del22q11.2 (Velocardiofacial syndrome) and del11p13 (Wilms Tumour–Aniridia syndrome). Structural neuroimaging could then be compared across the six CNV states represented by these disorders (+X, +Y, +21, −X, −22q11, −11p13). The cortical anatomy within each disorder was altered in a spatially specific way, depending upon the expression profile of the causative gene (see also Bathelt, Barnes, Raymond, Baker, & Astle, 2017). Despite the rarity of each group, this approach is revealing fundamental principles in how genetic variation can impact on specific circuits depending upon expression profile. This will likely be important for our understanding of the genetic underpinnings of the broader set of NDDs for which single genes are not implicated. It also reveals potential mechanisms of convergence, with apparently different underlying genetic causes converging at a neurobiological level if their expression is co-localised.

From the transdiagnostic concept to practice

The primary focus of this review is on the conceptual and methodological advances in research that are setting the stage for a radical reconsideration of NDDs. But it is also important to consider the practical consequence of this shift in thinking, and whether it makes any meaningful difference to young people with NDDs, their families and those who support them.

Accurate identification of individual needs

A diagnosis from a professional is a landmark moment for a family. Across health and education settings worldwide, this categorical benchmark has the potential to leverage funding and additional support. However, diagnostic status itself is a crude characterisation of a child's needs. The majority of transdiagnostic research has shown that formal diagnostic labels are relatively ineffective in predicting a child's cognitive or behavioural difficulties (e.g. Astle et al., 2019; Kushki et al., 2019), not least because of the large inequalities in who has access to the diagnostic process (e.g. Mandell et al., 2009). A singular diagnosis does not therefore provide practitioners or teachers with an accurate picture of the needs of the individual child.

There are several ways in which a transdiagnostic approach has the potential to improve this situation. Firstly, it encourages a broader assessment of cognition and behaviour. When assessment is structured around fixed diagnostic criteria designed to check for the presence of key symptoms, other potentially important characteristics can easily be missed. This can result in diagnostic overshadowing (e.g. Baraskewich & McMorris, 2019), with important characteristics overlooked in favour of those that would collectively confirm a particular diagnostic label. By softening adherence to these criteria and assessing areas of potential neurodevelopmental vulnerability within the broader population, a transdiagnostic approach provides the basis for a broader-based assessment of the potential needs of the child, irrespective of whether those align with a particular NDD diagnosis. This *child* – as opposed *diagnosis*-centred approach – directly informs the two core questions asked by practitioners: what are this child's strengths and difficulties, and how can we enable them to flourish?

A further benefit of a transdiagnostic framework is that its methods are likely more sensitive to subtle difficulties that may not meet a threshold for a diagnosis, but which are nonetheless impactful in everyday life. Whereas a fixed diagnostic framework typically dichotomises the presence or absence of a symptom, a dimensional approach allows for gradations in performance that will inevitably capture more subtle differences. This provides much richer information for the practitioner in understanding

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and supporting the child. It may also favour earlier intervention before functional outcomes compound to show sufficiently marked problems to meet diagnostic thresholds.

Finally, putting fixed diagnostic criteria aside opens the way for more dynamic characterisations of NDDs that allow for developmental change. Current classification systems like DSM are static, with little mention of the developmental context in which the difficulties occur. In contrast, data-driven clustering, for example, has demonstrated that constellations of difficulties, their neural underpinnings and their relative prevalence change qualitatively across childhood and adolescence (Bathelt et al., 2018, 2021). Understanding the changing manifestation of difficulties with development allows for better prognostication, and ultimately interventions that are proactive.

Transdiagnostic intervention?

The potential benefits of a transdiagnostic framework for the identification of child's needs have the potential to translate into intervention. The shift from a diagnosis-centred to a child-centred perspective means characteristics that are most impactful for the child become the focus for support and remediation, rather than characteristics that form a particular diagnostic category. As an example, an intervention for anxiety may not seem like an obvious priority for individuals with autism, because anxiety is not a diagnostic feature of the condition. However, 40% of autistic children have symptoms consistent with at least one anxiety disorder (van Steensel, Bögels, & Perrin, 2011), suggesting it should be a priority for intervention for these individuals. The broader assessment necessitated by transdiagnostic frameworks provides an important opportunity to identify children's strengths, which may be essential for effectively delivering an intervention. This is particularly so for problems of a cognitive origin (such as executive processes) that are largely resistant to modification through direct intervention (e.g. Shipstead, Redick, & Engle, 2012). This kind of compensatory approach designed to harness strengths to support areas of difficulty is already showing dividends through the provision of technological supports for autistic children (Grynszpan, Weiss, Perez-Diaz, & Gal, 2014; Kasari et al., 2014) and image-based rather than text-based learning materials for children with dyslexia (Mortimore & Dupree, 2008).

Inclusive classrooms

The classroom provides the frontline support for children with NDDs, with educational professionals shouldering the day-to-day responsibility for their positive development. Teachers may feel disempowered when a pupil receives a formal diagnosis (e.g. Sadler, 2005), as they are rarely given formal training in how to support children with NDDs. Diagnostic classifications may imply that clinical expertise is necessary to provide effective support, and access to more specialised resources are in short supply. This can result both in misconceptions about what teachers can expect (Kos, Richdale, & Hay, 2006; Sciutto, Terjesen, & Bender Frank, 2000) and a lack of confidence in how those children might be supported (Sadler, 2005).

In fact, though, children experiencing difficulties that affect learning, social integration and well-being have always been present in classrooms, and skilled teachers are well practised at tailoring classroom environments to help them flourish. If communicated and implemented well, a transdiagnostic approach has the potential to provide a much-needed framework to guide teachers in understanding the key needs of the individual pupil and finding the most effective support. This could be achieved through broad-based, light-touch systems of assessing individual needs to replace often-uninformative diagnostic labels assigned to only a minority of those who need support. Armed with the right transdiagnostic tools, school staff can gain vital systematic information about individual cognitive and behavioural needs. Regular monitoring and greater staff understanding of transdiagnostic abilities would also help identify relative strengths as well as difficulties, and age-sensitive characterisation. Such a systematic and broad-based approach may also be valuable in reducing inequalities in access to resources that distinguish children with a formal diagnosis of a NDD (often facilitated by parental lobbying and secured through private funding) from those without, who would be likely to gain equal benefit from the very same strategies and support (Elliott & Grigorenko, 2014).

Concluding remarks

Neurodevelopmental disorders are common and can have a lifelong impact on the lives of young people, their families and communities. They are also highly idiosyncratic, manifesting in a myriad of different forms ranging from disruptions limited to specific aspects of everyday functioning through to complex and pervasive difficulties. A guiding framework that can accommodate this degree of variability and complexity is vital for understanding the mechanisms that underpin NDDs, for identifying the particular needs of individuals and for guiding the support required to enable children to flourish. In this article, we argue that diagnostic taxonomies that classify individuals in terms of discrete categories are ill-suited to do this. Evidence-based transdiagnostic approaches provide compelling alternatives with the flexibility to capture the true heterogeneity of NDDs in the population at large.

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Key points

- Practitioners frequently use diagnostic criteria to identify children with neurodevelopmental disorders and to guide intervention decisions.
- These criteria shape research of neurodevelopmental disorders too – study design, recruitment, analysis and theory are largely built on the assumption that diagnostic criteria reflect an underlying reality.
- We evaluate contemporary approaches to study design and recruitment, review the use of data-driven methods to characterise cognition, behaviour and neurobiology, and consider what alternative transdiagnostic models could mean for children and families.
- An overreliance on ill-fitting diagnostic criteria is impeding progress towards identifying the barriers that children encounter, understanding underpinning mechanisms and finding the best route to supporting them.

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