Neurodevelopmental disorders

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Neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder, although most commonly considered in childhood, can be lifelong conditions. In this Personal View that is shaped by clinical experience and research, we adopt a conceptual approach. First, we discuss what disorders are neurodevelopmental and why such a grouping is useful. We conclude that both distinction and grouping are helpful and that it is important to take into account the strong overlap across neurodevelopmental disorders. Then we highlight some challenges in bridging research and clinical practice. We discuss the complexity of clinical phenotypes and the importance of the social context. We also argue the importance of viewing neurodevelopmental disorders as traits but highlight that this is not the only approach to use. Finally, we consider developmental change across the life-span. Overall, we argue strongly for a flexible approach in clinical practice that takes into consideration the high level of heterogeneity and overlap in neurodevelopmental disorders and for research to link more closely to what is observed in real-life practice.

Lancet Psychiatry 2017; 4: 339–46

Published Online December 12, 2015 http://dx.doi.org/10.1016/S2215-0366(16)30376-5

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Introduction

Neurodevelopmental disorders are complex conditions that are not straightforward to conceptualise. In this Personal View, we discuss some key issues for clinicians and scientists to consider. Our views have been shaped by clinical practice and research, and the intention of this article is to offer our perspective on neurodevelopmental disorders.

The term neurodevelopmental has been applied to a very broad group of disabilities involving some form of disruption to brain development. This definition groups together a very wide range of neurological and psychiatric problems that are clinically and causally disparate; for example, rare genetic syndromes, cerebral palsy, congenital neural anomalies, schizophrenia, autism, attention deficit hyperactivity disorder (ADHD), and epilepsy. In our view, although it is important to recognise the importance of early and lifelong developmental processes for health problems, an overly broad approach to grouping neurodevelopmental disorders becomes unhelpful.[1,2]

In this Personal View, we adopt the approach of DSM-5[3] that groups ADHD, autism spectrum disorder, intellectual disability, communication disorders, specific learning disorders, and motor disorders (eg, developmental coordination disorder and tic disorders) as neurodevelopmental disorders. Although we are not enthusiastic about all aspects of DSM-5, as discussed previously,[4] this approach to grouping neurodevelopmental disorders is a useful one for various reasons.[2]

Why group neurodevelopmental disorders?

One of the key defining characteristics of these neurodevelopmental disorders is that they typically onset in childhood, before puberty. They are also distinguished from many neuropsychiatric disorders by their clinical course: despite being subject to maturational changes, neurodevelopmental disorders such as ADHD, autism spectrum disorder, intellectual disability, and learning and communication disorders tend to show a steady course rather than the remitting and relapsing pattern that commonly characterises mood disorders and schizophrenia after puberty. These disorders are also characterised by prominent early onset neurocognitive deficits and they more commonly affect male individuals.[5] Although highly heritable,[6] neurodevelopmental disorders are typically multi-factorial in origin; single major causes are rare (eg, fetal alcohol syndrome, genetic syndromes) and such forms of disorder are classified elsewhere.[2] Finally, the level of overlap between these disorders and their constituent symptom dimensions is high. This further supports the rationale for considering them together. As is true of all classification systems and diagnostic groupings, neurodevelopmental disorders are highly heterogeneous in terms of their clinical characteristics, causes, treatment responses, and outcomes; there is no specific clinical or biological characteristic that

Key research questions

- Using longitudinal patient and population-based cohort designs, what potentially modifiable factors optimise neurodevelopmental outcomes? Test causal effects through different research approaches (eg, quasi-experimental and animal studies).
- How does multi-morbidity affect neurodevelopmental outcomes and the threshold for treatment (eg, longitudinal observational studies, treatment trials of complex disorders)?
- What is the natural history of neurodevelopmental disorders in the general population across ages (eg, via longitudinal population cohort designs)?
- How does social context (within and across countries) contribute to neurodevelopmental disorder associated impairments? For example, do longer-term outcomes (eg, employment, criminal behaviour) and impairments differ across time and populations? This could be achieved by investigating outcomes in low-income and middle-income countries versus high-income countries.
- Can we identify neurodevelopmental disorder subtypes that are clinically useful and that might transcend diagnostic boundaries and predict functional outcomes?

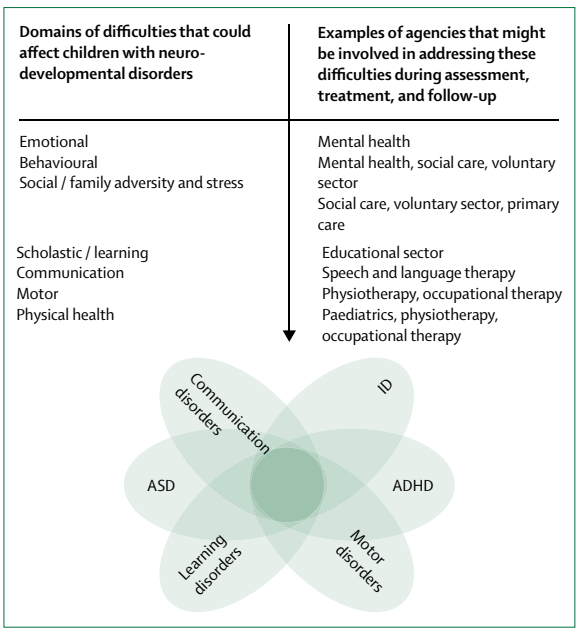

Figure 1: **Assessment and management of neurodevelopmental problems—the potential for fragmentation of services**
ID=intellectual disability. ASD=autism spectrum disorder. ADHD=attention deficit hyperactivity disorder.

clearly distinguishes this grouping from other neuropsychiatric disorders. For example, tic disorders do not tend to show a steady course and ADHD can remit in some. Schizophrenia and early onset conduct disorder are commonly characterised by early cognitive and developmental impairments but are grouped separately in DSM-5, which has been discussed elsewhere.[2]

Nevertheless, the early age of onset and high level of overlap means that grouping neurodevelopmental disorders in this way is also clinically useful. Assessment and treatment for children with these disorders requires specialists from a range of disciplines (eg, child psychiatrist, psychologist, paediatrician, speech and language therapist, and occupational therapist) and agencies (eg, health care and education), and treatment can be fragmented (figure 1). To provide one example, in the UK a child typically requires assessment for ADHD in a child mental health or paediatric service; co-occurring reading disability is the domain of education services, motor coordination problems need to be assessed by an occupational therapist, and language or social communication difficulties are the specialist domain of speech and language therapists. Many of these professionals are based in different services and local assessment and treatment provision are often organised around a single diagnosis (eg, ADHD[7] or autism spectrum disorder[8]) in a number of countries. If co-occurrence of neurodevelopmental disorders is the rule rather than the exception in clinical practice,[2] then grouping professional expertise, services and resources for children with these problems as part of a neurodevelopmental hub of expertise can help ensure assessment and intervention across all neurodevelopmental domains and explicitly recognise the overlaps. The same argument could apply to research that typically focuses on single diagnostic problems.

Why it is important to retain diagnostic distinctions

Although grouping of neurodevelopmental disorders is useful, it remains necessary to recognise important distinctions between the different subtypes. For example, the different effects of medication show that despite overlaps, neurodevelopmental disorders are not biologically or clinically identical sets of problems. Although stimulant medication[9] and atomoxetine[10] alleviate symptoms of ADHD and atypical antipsychotics can reduce severe tics,[11] none of these medications affect core features of the other neurodevelopmental disorders. Distinct diagnostic categories also provide a means for clinicians to readily communicate patients' difficulties with each other and with the patients themselves. Thus, there is a clear rationale to retain the practice of distinguishing these disorders as well as grouping them.

Are neurodevelopmental disorders more than their defining symptoms?

Tradition has influenced the defining features of many neurodevelopmental disorders and some of the decisions for inclusion might be considered arbitrary. Phenotypically, neurodevelopmental disorders are more than a defining set of symptoms and extend beyond the boundaries of a neurodevelopmental group. Indeed, Kanner, in his 1969 article on differential diagnosis,[12] highlighted the tendency to pigeonhole patients into a category rather than really understand them—"that children had not read the right books" when it came to diagnosis. If we take ADHD as an example, relevant, common ADHD profiles (figure 2) include not only its defining symptoms (hyperactive-impulsiveness, inattention) and features of other neurodevelopmental disorders but also additional cognitive deficits such as impaired working memory and planning.[13,14] Equally, emotional features including mood lability and irritability used to be considered an integral aspect of ADHD[15] but would now be considered as part of a co-occurring disorder (eg, anxiety, depression, or oppositional defiant disorder). The overlap of ADHD with conduct problems is also prominent.[16] Some of these symptom profiles will be recognised as an additional diagnosis. However, if symptoms do not achieve the threshold for a diagnosis, they will not be captured for the purpose of either research or clinical practice, yet will be an important source of heterogeneity; the clinical implications of sub-threshold symptoms will be discussed later in this Personal View.

The same tradition has influenced diagnostic exclusion criteria. For example, it has long been appreciated that the autistic spectrum includes children with intellectual disability, but in the case of ADHD, the absence of

intellectual disability was highlighted as important.[17] However, this assumption is now recognised to be invalid, and the practice of failing to diagnose ADHD in the presence of intellectual disabilityis starting to change.[18,19]

The finding that those exposed to early, severe privation display features of so-called quasi-autism[20] shows how disorders can present in an unusual fashion in an atypical social context. This highlights the importance of why assessments of phenomenology need to extend beyond core diagnostic criteria—and the constraints of a structured interview—and why assessing social risk matters. However, in clinical settings, assessments will typically extend beyond diagnostic items and most clinicians would accept the importance of assessing social context and taking into account an individual's current resources (eg, cognitive ability, quality of parenting, income) and demands (eg, classroom environment), and their level of functioning to devise a comprehensive management plan.

Gaps between research and clinical practice need to be bridged. Our view is that observation and clinical insights remain valuable for informing research questions. Also, research participants need to be characterised beyond a single core diagnosis; for example by assessing participants across dimensions of symptoms, functioning, and social factors beyond the primary diagnosis. A shared measurement toolkit used by different health-care professionals and researchers might be helpful in this context.

Why are profiles beyond core diagnostic features relevant?

First, for clinicians, different problem areas could require different evidence-based treatments that would not be captured by treatment guidelines for a single neurodevelopmental disorder; for example cognitive behavioural strategies for anxiety[21] and parenting interventions for behaviour problems.[22] Secondly, an individual's symptom profile across multiple dimensions can provide a useful prognostic index. Co-occurrence rates of problems and disorders are higher in clinics—so called Berkson's bias—which is unsurprising given that those with problems in multiple disorder domains are more severely impaired than those with problems in fewer domains.[23]

In addition to the selection of appropriate treatments, the outcomes must be considered. What sorts of co-occurring problems are associated with a poorer outcome? One possibility is that it is the consequence of the total burden of childhood problems regardless of the nature of psychopathology. Copeland and colleagues[24] addressed this using the Great Smoky Mountains longitudinal study. These investigators found that the cumulative childhood burden of psychopathology was the best predictor of adult health (eg, addictions, suicidality, serious physical illness), legal outcomes (eg, criminal act), financial problems (eg, unable to keep a job), and social outcomes (eg, no social support), even allowing for adult psychopathology and childhood psychosocial adversity. In a UK population-based study,[25] the total childhood burden of neurodevelopmental and conduct problems predicted a persistent ADHD symptom trajectory to adolescence.

Other evidence indicates that different symptom profiles show specificity in relation to the type of later psychopathology and functional outcome.[26,27] For example, in a Swedish study of multiple neurodevelopmental problems,[28] childhood ADHD predicted adolescent antisocial behaviour and impaired functioning independent of other neurodevelopmental problems. A systematic review[29] of longitudinal autism spectrum disorder studies has highlighted that child intellectual ability (measured by IQ) and early language ability appear to be the strongest predictors of outcome. The degree to which later functional and psychiatric outcomes of neurodevelopmental disorders are predicted by specific symptom profiles or the total burden of problems needs further investigation, as do the biological and social mechanisms that explain variation in outcomes. Longitudinal studies that span from childhood to adulthood are required to address such questions.

Multi-morbidity in clinical practice

The concept of multi-morbidity acknowledges the clinical importance of multiple problems in a single individual. Multi-morbidity is commonly defined as the presence of two or more chronic conditions in the same individual and is now a major concern in general medicine and primary care because of growing recognition that multimorbidity is common and has important clinical and service implications.[30]

For more on **Multi-morbidity** see https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0704

Fragmented service provision is one problem for patients with multi-morbidity. Clinical pathways that focus explicitly on the diagnostic process of one condition alone could be missing salient features of other disorders. Another is that assessment and treatment guidelines, including those relevant for ADHD and autism spectrum disorder,[7,8] typically focus on a single disorder, yet treatment needs and prognosis might be altered in the presence of other disorders.

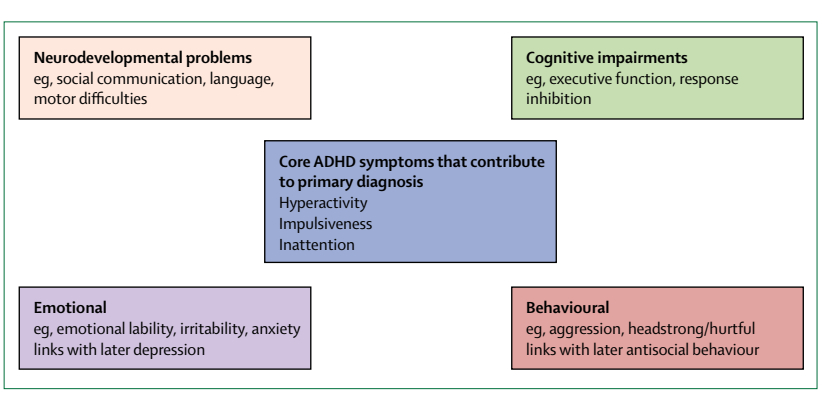

Figure 2: **Common clinical profiles associated with ADHD: where disaggregating a single diagnosis can be helpful**
The necessity of simultaneous interventions for the total profile of difficulties that accompany the primary diagnosis, even if these do not reach the required threshold for a so-called comorbid diagnosis, needs scientific assessment.

How might treatment be affected? First, the threshold for treating one condition might be altered by the presence of other conditions (eg, in the presence of certain conditions including renal disease and diabetes, the threshold for treating hypertension is lower).[31] Second, the effectiveness of a recommended treatment for the primary condition might be moderated by the presence of other conditions. This has not been widely investigated for child psychopathology although there are some exceptions.[21,32] For example, in the case of ADHD, behavioural interventions appear to be especially helpful for those with anxiety,[32] and although stimulants reduce ADHD symptoms in those with intellectual disability or autism spectrum disorder, medication is less well-tolerated in these groups of patients.[18,33] At present, we have limited evidence on how clinical management might be altered in the context of neurodevelopmental multi-morbidity; for example, should the threshold for providing intervention for communication impairments or autism spectrum disorder be lowered in the presence of ADHD? Typically, the diagnostic process is hierarchical and parsimonious and sometimes that is helpful because it simplifies the key issues and can help focus on the predominant features. However, it is being increasingly recognised that the use of a hierarchical approach and exclusion criteria can be problematic because important features beyond the diagnosis of primary interest might not be assessed and treated, or considered in research studies. For example, prior to DSM-5, ADHD could not be diagnosed in the presence of autism spectrum disorder.[34] This has meant that many research studies did not assess both phenotypes or excluded those with both conditions until this notion began to be challenged.[35] Future intervention and outcome research on individuals with multiple neurodevelopmental problems would be helpful in addressing this knowledge gap.

For more on the **Research Domain Criteria project** see http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml

Neurodevelopmental disorders conceptualised as traits

There is strong research evidence that favours the consideration of some neurodevelopmental disorders and diagnoses as lying at the extremes of dimensions.[14,36,37] For example, ADHD defined as a trait, typically using total symptom scores, behaves dimensionally in terms of its association with adverse outcomes[38]—there is no clearcut threshold beyond which adverse outcomes emerge. Also, the same genetic and early environmental risk factors that are associated with a diagnosis of ADHD or autism spectrum disorder predict trait levels in the general population.[39–43] However, categorical conceptualisation can be helpful for some purposes;[4] for example, when dichotomous and potentially risky clinical decisions, such as whether to prescribe medication to a child or not, have to be made.

Where does the cutoff point on a dimension lie?

This question is not straightforward to address because it depends on what the cutoff point is required for. In general for child psychopathology, sub-threshold diagnoses (insufficient symptoms to make a diagnosis but some evidence of impairment) are common, and are clinically important in terms of predicting poorer adult mental health and functional outcomes.[24] However, expanding diagnoses is unhelpful because there are potential social, psychological, and health risks,[44] as well as benefits of applying a diagnostic label and providing treatments. For example, NICE guidance for ADHD[7] applies a lower threshold for psychosocial intervention than for medication and recommends a step-wise treatment approach,[14] but that does not deal with the public health issue of sub-threshold cases of any neurodevelopmental disorder.

What is the dimension?

Another question is, how should one define the underlying dimension given that a diagnosis is more than just one trait? For example, ADHD symptom scores are highly correlated with many other traits, so a diagnosis of ADHD might not even be best conceptualised as lying at the extreme of a single measured ADHD trait (ie, total ADHD symptom count) but rather as being underpinned by multiple trait and disorder liabilities.[45,46]

Alternatives to a traditional categorical diagnostic approach are being considered in the context of research. The Research Domain Criteria (R-DoC) project is one such research framework proposed by the NIMH.[47] This project has been proposed as a means of investigating mental disorders by conceptualising them as dimensional constructs (eg, negative valence systems), which transcend diagnostic categories and integrate information across multiple measurement levels (eg, genes, molecules, cells, circuits, and self-reports). Although a dimensional framework is to be welcomed, and will be helpful for some types of research (eg, bridging basic science and human cognitive and imaging research),[48] as yet we do not have reliable methods for assessing many of the suggested R-DoC dimensions and we also do not know how they map onto complex, clinically relevant problems. It is important that this gap is spanned if research is going to inform clinical practice and clinical observations are to inform basic research.

Consideration of developmental change and a life-span approach

Symptom decline but persistence to adult life

Neurodevelopmental disorders are subject to maturational change.[2] Many child neurodevelopmental disorders typically improve with age and were previously considered to be childhood-limited problems. However, follow-up studies show that although outcomes are variable, for many individuals, neurodevelopmental problems and diagnosis persist into adult life.[1,29,49–52] Reported estimates of

diagnostic persistence rates vary widely and tend to be higher in patient samples than in population-based cohorts.[53] For example, if we take the example of ADHD, one meta-analysis[49] suggested a 15% ADHD diagnostic persistence rate to adult life. Autism spectrum disorder, language impairments,[54] and literacy-related difficulties[55] also commonly persist in many patients. Some core symptoms, for example ADHD-related hyperactive-impulsiveness[56] and autism spectrum disorder-related behaviours[29] decline considerably with age. In recognition of this finding, the required number of ADHD symptoms for a DSM-5 diagnosis of ADHD has been adjusted for adolescents and adults. However, there are few service provisions for neurodevelopmental disorders in adult life.[57,58]

Change in predominant manifestation

Change does not simply involve a decline in core symptoms, since the predominant clinical manifestations are also subject to change and new co-occurring problems, such as substance misuse, can emerge.[59] For example, many patients who do not meet full diagnostic criteria for ADHD or autism spectrum disorder in adult life have sub-threshold persistence of core symptoms and a broader range of cognitive, psychiatric (eg, mood disorder or substance misuse), and functional impairments such as difficulties with employment or social relationships.[53,59,60] At present, there is very little known about potentially modifiable factors (eg, prenatal and early life environmental enrichment and social influences) that optimise neurodevelopmental outcomes and these factors are an important area for future research. Longitudinal observational designs will remain important but other methods will then be required to test causal hypotheses as discussed elsewhere.[61]

A life-course view

Until recently, adult symptoms of neurodevelopmental disorders were assumed by most clinicians to be a continuation from childhood-onset problems. An intriguing finding from the Dunedin longitudinal cohort study[53] challenges this assumption in relation to ADHD. Moffitt and colleagues[53] found that most cases of adult ADHD at age 38 years were not preceded by a childhood diagnosis. This finding has been replicated in two independent adolescent or young adult samples.[62,63] The later-onset ADHD symptoms were not entirely explained by concurrent or earlier comorbidities. This phenomenon cannot be explained satisfactorily by sub-threshold cases. The findings raise the question of what this adult ADHD phenotype is. Is it the manifestation of symptoms suppressed earlier in life because of early protective factors, or does it represent a different disorder altogether with a different pathogenesis, akin to juvenile-onset and maturity-onset diabetes? These findings have important implications for adult mental health services and for future research.[64] There is a need for detailed longitudinal characterisation of neurodevelopmental disorder phenotypes across ages in unselected populations to examine patterns of onset, desistence, and persistence across the lifespan. One challenge for such developmentally informative research is that both researchers and clinicians use different measures after age 16–18 years and informants typically change from parent reporting during childhood to self-reporting in adult life. One approach that might help bridge this gap between childhood and adult life is to encourage research investigations (and clinical services) that focus on transition ages (eg, ages 15–25 years).

How clinicians and researchers might proceed

Adopt a conceptual approach

Our main conclusion is that regardless of what framework is used for conceptualising neurodevelopmental or psychiatric disorders, there are problems if clinicians and researchers apply them rigidly without thought or critical reflection; for example by counting up items generated by a structured interview or generating a score (eg, ADI and ADOS generated diagnosis of autism spectrum disorder). Thresholds for defining disorders, ie, the number of required symptoms, are arbitrary. Failing to recognising comorbidities or symptoms beyond the primary diagnosis of interest is another risk. Historically, such an approach has caused problems (for example, comorbid ADHD and autism spectrum disorder being disallowed by DSM and ICD) for researchers and clinical practitioners. For example, a child might not meet the exact symptom cutoff for a diagnosis of ADHD but if they fall just below the diagnostic threshold and symptoms are interfering with function, then behavioural and social approaches typically used for ADHD might be helpful.

It is also important to adopt a developmental view across the life-span; this requires longitudinal research approaches that bridge child and adult life and a clinical perspective that goes beyond current presenting problems. The clinician is required to weigh up multiple factors when assessing patients, planning intervention, and predicting outcomes.[65] Individuals with the same diagnosis might require different types of intervention depending on co-occurring symptoms, age, social context.

Consider complexity versus reductionism

We conclude that it is clinically helpful and scientifically justified to group neurodevelopmental disorders but also necessary to retain diagnostic distinctions. Of course, we recognise there is enormous heterogeneity in symptoms, outcome, and treatment response across all neurodevelopmental and psychiatric disorders and there are no clearcut boundaries between different disorders or between different groups of disorders. The strong overlap and lack of distinction between disorders does not mean it is necessarily helpful to completely dispense with diagnostic boundaries or groupings. Most clinicians will

Panel: Conceptualising neurodevelopmental disorders: a summary

- Group and distinguish neurodevelopmental disorders
- Disaggregate beyond core diagnostic symptoms
- Consider overall burden of psychopathology and multi-morbidity
- Consider importance of social context (demands, resources, and risks)
- Take into account developmental change across the lifespan and maturational influences
- Note that traits and categorical diagnoses are both useful
- Note that it is unhelpful to dispense with diagnoses or rigidly adhere to them

Search strategy and selection criteria

This article is a Personal View and not a review; the authors identified papers according to their relevance to the conceptual issues being discussed. Papers published were first identified by searches of PubMed from Jan 1, 2010 to March 31, 2016 using the search terms "ADHD", "autism", "ASD", "communication", "language", "reading", "spelling", "tics", "child", "adult", "longitudinal", "comorbidity", "multimorbidity", "genetic", "prenatal", "aetiology". Only articles published in English were included. Reviews on neurodevelopmental disorders, book chapters, and NICE guidelines published between Jan 1, 2012 and March 31, 2016 and some older articles were also examined. Systematic reviews on ADHD and autism are published elsewhere.

recognise that neurodevelopmental disorders are more than a set of diagnostic criteria, and that multiple impairments or multi-morbidity are the rule rather than exception. However, research funders, service funding and planning, local assessment policies, and national guidelines are not necessarily as flexible. Interventions are not identical for different types of problems, so it is important that research captures these complex phenotype patterns and associated subthreshold symptoms, and considers the social context and developmental factors that are important in both research and clinical practice. This is achievable, and there are many examples of such research, some of which we have already discussed.[24,66]

Complexity is the nature of clinical problems, so perhaps it is better to acknowledge this complexity and incorporate this into research designs if the gaps between neuroscience, mental health research, and real-life clinical practice are ever to be bridged. Clinicians need to apply clinical judgement as well as evidence and guidelines, and researchers need to engage directly with clinicians so that research is clinically meaningful.

A neurodevelopmental disorder diagnosis is inadequate as a means of rationing

In our view, as patient expectations grow and resources diminish,[67] clinicians are being called on to make decisions that affect resource allocation for a patient. It is not reasonable for services or agencies to allocate intervention and support purely on the basis of a yes or no diagnosis, including ones made after lengthy, protracted, and expensive assessments (eg, educational support to be linked to a diagnosis of autism spectrum disorder). That is because an individual's needs are not best captured by diagnosis alone. Systematic and validated methods for assessing the needs of children and adults with neurodevelopmental disorders beyond diagnosis are needed to avoid those with subthreshold symptomatology but substantial impairment missing out on vital service provision.

So do we dispense with diagnosis? We think not. There are long-standing arguments in psychiatry disputing the validity and value of diagnosis and on lumping together versus splitting different forms of psychopathology in addition to concerns and apologies about relying on reported symptoms. This is not helpful for practitioners and patients.

For current purposes they are reasonably reliable, useful for communication and attempting to standardise treatment approaches, provided they are used sensibly as a framework (panel), rather than as fundamental truths; and they should not be used as the sole means of determining patient care. For researchers, it is premature, in our view, to dispense with diagnoses, but equally we need to empirically and critically assess the value of alternatives.

Contributors
AT and MC undertook the literature search. AT drafted the initial manuscript with MR. AT, MC, and MR contributed to revisions and the final submitted draft.

Declaration of interests
We declare no competing interests.

Acknowledgments
The authors' research is funded by the MRC, ESRC, and Wellcome Trust. We are grateful to Lucy Riglin, Stephan Collishaw and Kate Langley for their helpful comments on an earlier version of this manuscript.

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