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Neurodevelopmental disorders: a personal view

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Summary

Neurodevelopmental disorders such as Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD), although most commonly considered in childhood, can be life-long conditions. In this personal perspective that is shaped by clinical experience as well as 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, the importance of the social context and consider developmental change across the life-span. Finally we argue the importance of viewing neurodevelopmental disorders as traits but highlight that this is not the only approach to use. 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.

Search strategy and selection criteria

This article is a personal perspective 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 1st January 2010 to 31st March 2016 using the search terms "ADHD", "autism", "ASD", "communication", "language", "reading", "spelling", "tics" AND "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 1st January 2012 and 2016 and some older articles were also examined. Systematic reviews on ADHD and autism are published elsewhere.

Neurodevelopmental disorders are complex conditions that are far from straightforward to conceptualise. In this personal perspective article, we discuss some key issues for clinicians and scientists to consider. Our views have been shaped by clinical practice as well as by research and the intention of this article is to offer our perspective on neurodevelopmental disorders.

What we mean by neurodevelopmental disorder

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 aetiologically disparate; for example, rare genetic syndromes, cerebral palsy, congenital neural anomalies, schizophrenia, autism, attention deficit hyperactivity disorder (ADHD) and epilepsy. In our view, whilst it is important to recognise the importance of early and life-long developmental processes for health problems, an overly broad approach to grouping neurodevelopmental disorders becomes unhelpful[1,2].

In this article, we adopt the approach of DSM-5[3] that groups ADHD, Autism Spectrum Disorder (ASD), Intellectual Disability, Communication Disorders, Specific Learning Disorders and Motor Disorders (e.g. developmental co-ordination disorder and tic disorders) as "Neurodevelopmental Disorders" . Whilst 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 a variety of reasons[2].

Why group neurodevelopmental disorders?

What is the rationale for such a grouping?

One of the key defining characteristics of these neurodevelopmental disorders is that they typically onset in childhood, prior to puberty. They are also distinguished from many neuropsychiatric disorders in respect to their clinical course: despite being subject to maturational changes, neurodevelopmental disorders such as ADHD, ASD, intellectual disability, learning and communication disorders tend to show a steady course rather than the remitting and relapsing pattern that commonly characterises post-pubertal mood disorders and schizophrenia. These disorders are also characterised by prominent early-onset neurocognitive deficits and they more commonly affect males[5]. Although highly heritable[6], neurodevelopmental disorders are typically multi-factorial in origin; single major causes are rare (e.g. foetal 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 very 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, aetiology, treatment response and outcomes; ~~and~~ there is no specific clinical or biological characteristic that 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 elsewhere in DSM 5 (see elsewhere[2] for further discussion of these points).

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 expertise for children with these disorders crosses disciplines (e.g. child psychiatrist, psychologist, paediatrician, speech and language therapist, occupational therapist) as well as agencies (e.g. health and education) and 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-occuring reading disability is the domain of education services, motor co-ordination problems need to be assessed by an occupational therapist and language/social communications 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 organised around a single diagnosis (e.g. ADHD or ASD[7]) 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.

Why it is important to retain diagnostic distinctions

Although grouping is useful, it remains necessary to recognise important distinctions between different neurodevelopmental disorders. For example, the differential effects of medication highlight that despite overlaps, neurodevelopmental disorders are not biologically or clinically identical sets of problems. While stimulant medication[8] and atomoxetine[9] alleviate symptoms of ADHD and atypical antipsychotics can reduce severe tics[10], none of these medications impact on 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 patients themselves. Thus there is a clear indication to retain the practice of distinguishing these disorders as well as grouping them.

Neurodevelopmental disorders are more than their defining symptoms

Disaggregating individual clinical profiles

Historical tradition has influenced the defining features of many neurodevelopmental disorders and some of the decisions as to what to include 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 [11], 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 the example here, relevant, common ADHD profiles (see Figure 2~~1~~) 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[12,13]. Equally, emotional features involving mood lability and irritability used to be considered an integral aspect of ADHD[14] but would now be considered as part of a co-occurring disorder (e.g. anxiety, depression or oppositional defiant disorder). The overlap of ADHD with conduct problems is also prominent[15]. 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; the clinical implications of sub-threshold symptoms will be discussed later in this article.

The same historical 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 (ID) was highlighted as important[16]. However, this assumption is now recognised to be invalid, and the practice of failing to diagnose ADHD in the presence of ID is starting to change[17,18].

The finding that those exposed to early, severe privation display features of "quasi-autism"[19] provides an illustrative case of how disorders may 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. However in clinical settings, assessments will typically extend beyond diagnostic items and most would accept the importance of assessing social context and taking into account an individual's current "resources" (e.g. cognitive ability, quality of parenting, income) and "demands" (e.g. classroom environment), as well as their level of functioning, in order to devise a comprehensive management plan.

~~How patterns of multiple symptom and contextual profiles are captured for research purposes is a relevant challenge if~~ Gaps between research and clinical practice need~~are~~ to be bridged. Our view is that observation and clinical insights remain valuable for informing research questions. Also, ~~and that~~ research participants need to be characterised beyond a single core diagnosis; for example by assessing participants across multiple dimensions of symptoms, functioning and social contexts, regardless of primary diagnosis. A shared

measurement tool kit used by different health-care professionals and researchers might be helpful here.

Why are profiles beyond core diagnostic features relevant?

Selecting appropriate treatments: First, for clinicians, different problem areas may require different sorts of evidence-based treatments that would not be captured by treatment guidelines for a single neurodevelopmental disorder; for example cognitive behavioural strategies (CBT) for anxiety[20] and parenting interventions for behaviour problems[21]. Secondly, an individual's symptom profile across multiple dimensions can provide a useful prognostic index. Co-occurrence rates of problems and disorders are elevated in clinics - so called Berkson's bias. This selection is unsurprising given that those with problems in multiple disorder domains are more severely impaired in terms of outcomes[22].

Predicting outcomes: What sorts of co-occurring problems index a poorer outcome? One possibility is that it is the consequence of the total burden of childhood problems regardless of the nature of psychopathology. ~~Recent work by~~ Copeland and colleagues [23] addresse~~d~~s this using the Great Smoky Mountains longitudinal study ~~of child psychopathology~~. These investigators found that the cumulative childhood burden of psychopathology was the best predictor of adult health (e.g. addictions, suicidality, serious physical illness), legal (e.g. criminal act), financial (e.g. unable to keep job) and social outcomes (e.g. no social support), even allowing for adult psychopathology and childhood psychosocial adversity. In a more recent UK population-based study, the total childhood burden of neurodevelopmental and conduct problems predicted a persistent ADHD symptom trajectory to adolescence. ~~The~~

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~~mechanisms by which cumulative childhood mental health burden leads to poor outcomes require investigation.~~

Other evidence highlights that different symptom profiles show specificity in relation to the *type* of later psychopathology and functional outcome[24,25]. For example, in a Swedish study of multiple neurodevelopmental problems[26] childhood ADHD predicted adolescent antisocial behaviour and impaired functioning independent of other neurodevelopmental problems. A systematic review of longitudinal ASD studies, highlighted that child IQ and early language ability appear to be the strongest predictors of ASD outcome[27]. The degree to which later functional and psychiatric outcomes of neurodevelopmental disorders are predicted by specific symptom profiles and/or the total burden of problems needs further investigation, as do the biological/social mechanisms that explain variation in outcomes. Longitudinal studies that span from childhood to adult-life are required to address such questions.

Multi-morbidity in clinical practice

The concept of multi-morbidity ~~in physical medicine~~ 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/primary care. That is because of growing recognition that multi-morbidity is common and has important clinical and service implications (Barnett et al, 2012) (https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0704).

Fragmented service provision is one problem for patients with multi-morbidity. Clinical pathways which focus explicitly on the diagnostic process of one condition alone may be

missing salient features of other disorders. Another is that assessment and treatment guidelines, including those relevant for ADHD and ASD[7,28] typically focus on a single disorder, yet treatment needs as well as prognosis might be altered in the presence of other disorders.

How might treatment be affected? First, the threshold for treating one condition might be altered by the presence of other conditions (e.g. in the presence of certain conditions including renal disease and diabetes, the threshold for treating hypertension is lower)[29]. 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[20,30]. For example, in the case of ADHD, behavioural interventions appear to be especially helpful for those with anxiety[30] and although stimulants reduce ADHD symptoms in those with intellectual disability or ASD, medication is less well-tolerated [31,32]. 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 ASD 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 using 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 ASD[33]. 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[34]. Future intervention and outcome research on individuals with multiple neurodevelopmental problems would be helpful in addressing this knowledge gap.

Neurodevelopmental disorders conceptualised as traits

Evidence that neurodevelopmental disorders behave as traits

There is strong research evidence that favours considering some neurodevelopmental disorders/diagnoses as lying at the extremes of dimensions[13,35,36]. For example, ADHD defined as a trait, typically using total symptom scores, behaves dimensionally in terms of its relationship with adverse outcomes [37] - there is no clear-cut threshold beyond which adverse outcomes emerge. Also, the same genetic and early environmental risk factors that are associated with a diagnosis of ADHD or ASD predict trait levels in the general population [38–42]. 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 for a child or not, have to be made.

Where does the cut-point on a dimension lie?

This question is not straightforward to address because it depends on what the cut-point is required for. In general for child psychopathology, sub-threshold diagnoses (fewer symptoms but impairment) are common and are clinically important in terms of predicting

poorer adult mental health and function outcomes[23]. However expanding diagnoses is unhelpful because there are potential social, psychological and health risks [43] as well as benefits of applying a diagnostic label and providing treatments. For example, NICE guidance for ADHD[28] applies a lower threshold for psychosocial intervention than for medication and recommends a step-wise treatment approach[13] 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 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 (i.e. total ADHD symptom count) but rather as being underpinned by multiple trait as well as biological liabilities[44,45].

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 [46]. It has been proposed as a means of investigating mental disorders by conceptualising them as dimensional constructs (e.g. negative valence systems) (http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml) which transcend diagnostic categories and integrate information across multiple measurement levels (e.g. genes, molecules, cells, circuits as well as self-reports). Whilst a dimensional framework is to be welcomed, and will be helpful for some types of research e.g. bridging basic science and human cognitive and imaging research[47], as yet we do not have reliable methods for assessing many of the suggested R-doc dimensions and nor do we know how they map onto complex, clinically relevant problems. ~~There are some examples of~~

~~research that links biology to clinical phenomena; for example, longitudinal imaging studies suggest that ADHD persistence versus remission is associated with brain maturation[45].~~ It is important that this gap is spanned if research is going to inform clinical practice and clinical observations are to inform basic research. ~~One challenge will be to avoid an oversimplified view of psychopathology that fails to recognise the importance of social factors and developmental change.~~

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 previously were considered as childhood-limited problems. However, follow-up studies show that although outcomes are variable, for many individuals, neurodevelopmental problems/diagnosis do persist into adult life [1,48–52]. 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 suggested a 15% ADHD diagnostic persistence rate to adult life [48]. ASD, language impairments[54] and literacy-related[55] difficulties also commonly persist in many. Some core symptoms, for example ADHD-related hyperactive-impulsiveness[56], and ASD-related behaviours[27], decline considerably with age. In recognition of this the required number of ADHD symptoms for a DSM-5 diagnosis of ADHD has been adjusted for adolescents and adults. However service provision for neurodevelopmental disorders in adult life is limited[57,58].

Change in predominant manifestation

Change does not simply involve a decline in core symptoms as the predominant clinical manifestations are also subject to change and new co-occurring problems (e.g. substance misuse) can emerge [59]. For example, many who do not meet full diagnostic criteria for ADHD or ASD in adult life have sub-threshold persistence of core symptoms and a broader range of cognitive, psychiatric (e.g. mood disorder, 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 (e.g. prenatal and early life environmental enrichment, social influences) that optimise neurodevelopmental outcomes and this is an important area for future research. Longitudinal observational designs will remain important but other methods then are required to test causal hypotheses (as discussed extensively elsewhere[61]).

A life-course view

Until recently, it has been assumed that adult symptoms of neurodevelopmental disorders must be a continuation from childhood-onset problems. However an intriguing recent finding from the Dunedin longitudinal cohort group 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 now in two independent adolescent/young adult samples[62,63]. The problems were not entirely explained by concurrent or earlier comorbidities. The explanation of this phenomenon being explained by sub-threshold cases is also unsatisfactory. The findings raise the question of what this adult ADHD phenotype is. Is it the manifestation of symptoms suppressed earlier in life due to 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 as well as 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 life-span. 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- to self-reports 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 (e.g. ages 15 to 25 years).

Perspectives on 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 (e.g. ADI and ADOS generated diagnosis of ASD). Thresholds for defining disorders, that is the numbers 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 ASD being disallowed by DSM and ICD) for researchers and clinical practitioners. For example, a child might not meet the exact symptom cut-point for a diagnosis of ADHD but if they fall just below the diagnostic

threshold and symptoms are interfering with functioning-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 ~~regardless of age and~~; this requires longitudinal research approaches that bridge child and adult life- and a clinical perspective that goes beyond current presenting problems. ~~consider the history of the disorder in an individual patient and prognostic indicators with regards to future treatment planning and service provision across the life-span~~. The clinician is required to weigh up multiple factors when conducting assessments, planning intervention and predicting outcomes (see Leckman & Taylor for details of a "common-sense approach"). Individuals with the same diagnosis might require very different types of intervention depending on co-occuring symptoms, age (e.g. an adult vs. prepubertal child), social context (e.g. low income single parent with mental health problems and limited support at school vs. high income, strongly supportive extended family, private tutoring in addition to school).

Consider complexity vs. reductionism

We conclude that it is clinically helpful and scientifically justified to group neurodevelopmental disorders but necessary also to retain diagnostic distinctions. Of course, we recognised there is enormous heterogeneity in symptoms, outcome and treatment response across all neurodevelopmental and psychiatric disorders and there are no clear-cut boundaries between different disorders or between different groups of disorders. The strong overlap and a lack of clear-water between disorders does not mean it is necessarily helpful to completely dispense with diagnostic boundaries or groupings. Most clinicians will 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 to capture these complex phenotype patterns and associated subthreshold symptoms, and consider the social context and developmental factors in research as well as clinical practice. This is achievable and there are many examples of such research, some of which we have already discussed[23,65].

Complexity is the nature of clinical problems, so perhaps it is better to acknowledge this and attempt its capture if the gaps between neuroscience and mental health research as well as between 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[66], clinicians are being called upon to make decisions that affect resource allocation for a patient. It is not reasonable for services or agencies however to allocate intervention and support purely on the basis of a yes/no diagnosis, including ones made after lengthy, protracted and expensive assessments (e.g. educational support to be linked to a diagnosis of ASD). 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 significant 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 vs. splitting different forms of psychopathology as well as 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 (see Table 1~~2~~), rather than as fundamental truths; and not 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.

Declaration of interests by authors: We declare that we have no conflicts of interest"

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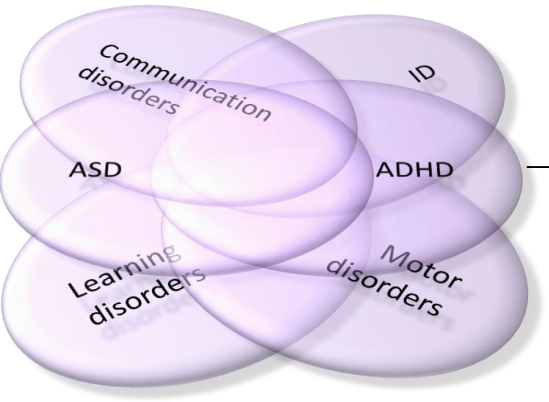
Table 1: Conceptualising neurodevelopmental disorders: a summary

• Group and distinguish neurodevelopmental disorders
• Disaggregate beyond core diagnostic symptoms
• Consider overall burden of psychopathology /multi-morbidity
• Social context (demands, resources and risks) is important
• Take into account developmental change across the life-span and maturational influences
• Traits and categorical diagnoses are useful
• Unhelpful to dispense with diagnosis or rigidly adhere to them



Presenting manifestation
Scholastic
Behavioural
Emotional
Social
Communication
Motor
Social/family adversity and stress
Physical health e.g. seizures

Agencies that might be involved in assessment, treatment and follow-up

Education Primary care Social care/voluntary sector

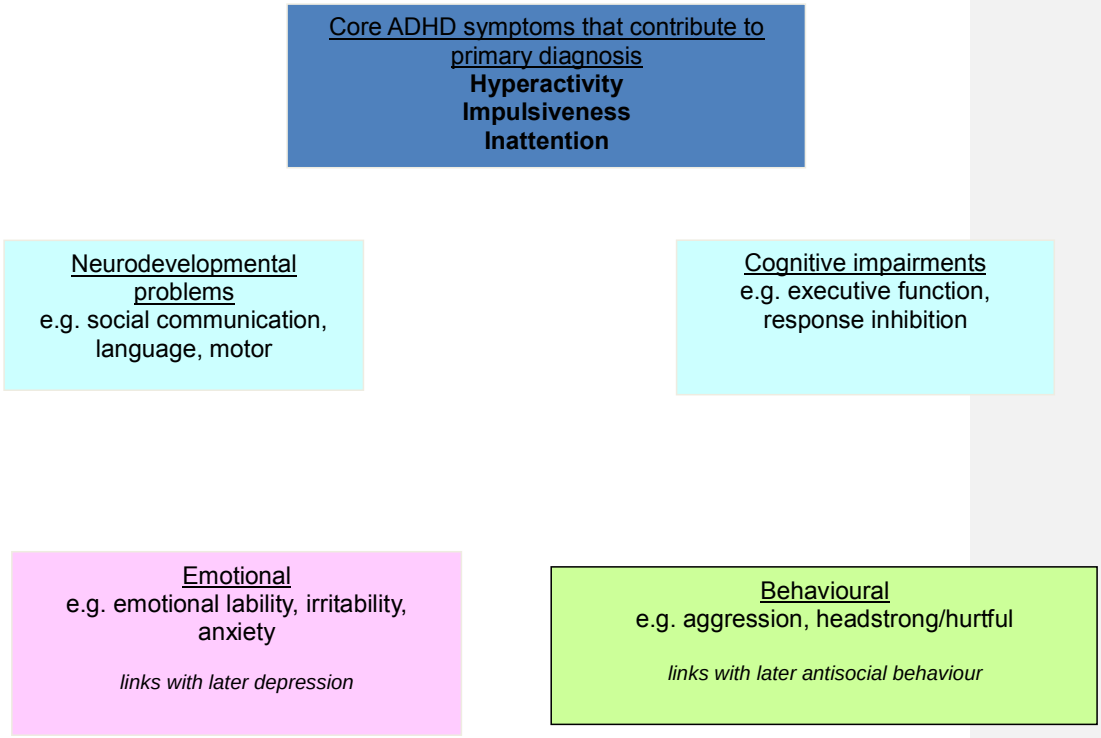
Speech and Language Therapy Occupational therapy, Physiotherapy

Mental Health Child Health

Figure 1. Assessment and management of neurodevelopmental problems: the potential for fragmentation of services

~~Figure 1~~

Common clinical profiles associated with ADHD: where disaggregating a single diagnosis can be helpful



~~Example 1: A child with ADHD and no other diagnosis could present with language and motor difficulties, executive dysfunction that further adversely impact on daily life and educational performance. The predominant concern of the family might be to do with severe, uncontrollable angry outbursts (irritability) that disrupt family relationships. All these domains are relevant for assessment and intervention.~~ The effectiveness 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 "comorbid diagnosis", needs scientific evaluation.

Five research questions

- Using longitudinal patient and population-based cohort designs, w~~W~~hat potentially modifiable factors optimise neurodevelopmental outcomes? Test causal effects through different research approaches (e.g. quasi-experimental and animal studies).
- How does multi-morbidity affect neurodevelopmental outcomes and the threshold for treatment (e.g. longitudinal observational studies, treatment trials of complex patients)?
- What is the natural history of neurodevelopmental disorders in the general population across ages (e.g. 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 and impairments differ across time and populations? This could be achieved by investigating outcomes in low and middle-income vs. high-income countries, for example.
- Can we identify neurodevelopmental disorder subtypes that are clinically useful and that might transcend diagnostic boundaries and ~~(e.g.~~ predict functional outcome~~s)~~?

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