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Neurodevelopmental disorders: Cluster 2 of the proposed meta-structure for DSM-V and ICD-11

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Abstract

Background—DSM-IV and ICD-10 are atheoretical and largely descriptive. Although this achieves good reliability, the validity of diagnoses can be increased by an understanding of risk factors and other clinical features. In an effort to group mental disorders on this basis, five clusters have been proposed. We now consider the second cluster, namely neurodevelopmental disorders.

Method—We reviewed the literature in relation to 11 validating criteria proposed by a DSM-V Task Force Study Group.

Results—This cluster reflects disorders of neurodevelopment rather than a 'childhood' disorders cluster. It comprises disorders subcategorized in DSM-IV and ICD-10 as Mental Retardation; Learning, Motor, and Communication Disorders; and Pervasive Developmental Disorders. Although these disorders seem to be heterogeneous, they share similarities on some risk and clinical factors. There is evidence of a neurodevelopmental genetic phenotype, the disorders have an early emerging and continuing course, and all have salient cognitive symptoms. Within-cluster co-morbidity also supports grouping these disorders together. Other childhood disorders currently listed in DSM-IV share similarities with the Externalizing and Emotional clusters. These include Conduct Disorder, Attention Deficit Hyperactivity Disorder and Separation Anxiety Disorder. The Tic, Eating/Feeding and Elimination disorders, and Selective Mutisms were allocated to the 'Not Yet Assigned' group.

Conclusion—Neurodevelopmental disorders meet some of the salient criteria proposed by the American Psychiatric Association (APA) to suggest a classification cluster.

Keywords

Childhood; DSM-V; disorder; meta-structure; neurodevelopment

Introduction

In preparation for DSM-V and ICD-11 discussion has turned to the rationale for grouping disorders. The organization of the extant classifications is largely descriptive and atheoretical, but shared causes may permit some disorders to be grouped. A Study Group of the DSM-V Task Force considered whether DSM-V disorders could be organized in a way that would expressly recognize the possibility of shared features beyond symptomatic

expression. This raises questions regarding the level of specificity needed to justify grouping disorders.

This paper is one of a set of reviews (Andrews *et al.* 2009; Carpenter *et al.* 2009; Goldberg *et al.* 2009; Krueger & South, 2009; Sachdev *et al.* 2009) that present a case that DSM-IV and ICD-10 disorders can be organized by reference to a set of 'validating criteria' listed by the DSM-V Study Group. One core factor for organizing such groupings is to consider conditions that exhibit shared course or developmental profiles. The current review examines whether the disorders that are commonly associated with demonstrable deficits at birth or in early childhood form a cluster of disorders based on similar risk factors and clinical features. Neurodevelopmental disorders are thought to evolve through processes that alter trajectories in normal brain development. The review summarizes evidence for this view, but the manuscript is not designed to present a systematic review of the area.

Rutter *et al.* (2006) propose a grouping of neurodevelopmental disorders characterized by: 'a delay/deviance in maturationally influenced psychological features'; a persistent course that reflects a deviation in normal development; cognitive impairment; overlap in symptoms; strong genetic and environmental risks; and increased prevalence in males. The proposal from Rutter *et al.* shares many features with the current proposal, including the grouping of early manifesting conditions with strong genetic links and prominent cognitive symptoms. Differences with the Rutter *et al.* schema are described.

Method

This review considered whether some of the disorders currently included in the DSM-IV 'Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence' chapter and the ICD-10 'Mental Retardation', 'Disorders of Psychological Development' and 'Behavioural and Emotional Disorders with Onset Usually Occurring in Childhood and Adolescence' chapters could be considered as a potential cluster of 'Neurodevelopmental' disorders. We used 11 criteria developed by the aforementioned DSM-V Study Group (Hyman *et al.*, personal communication, 3 December 2007) that were based on the original Robins & Guze (1970) validating factors. These criteria are:

- (1) shared genetic risk factors;
- (2) familiarity;
- (3) shared specific environmental risk factors;
- (4) shared neural substrates;
- (5) shared biomarkers;
- (6) shared temperamental antecedents;
- (7) shared abnormalities of cognitive or emotional processing;
- (8) symptom similarity;
- (10) high rates of co-morbidity;
- (11) course of illness;
- (12) treatment response.

Scopus and Medline searches were conducted to identify English literature that considered each validator and each disorder. Comparisons between disorders are presented here to determine whether the 'neurodevelopmental' disorders share some common variance on all

or any of these criteria. The reader should note that it is a limitation of this review; that large data sets were rare and few studies compared the disorders with each other.

The proposed meta-structure presumes that there is greater within-cluster than between-cluster overlap of risk factors and clinical manifestations. Mental Retardation (MR), Pervasive Developmental Disorders (PDDs) and the Learning, Motor and Communication Disorders were found to share a number of similarities on the Study Group criteria. Of particular importance are their common genetic risks, cognitive processing deficits, early onset and persistent course. The co-occurrence of neurodevelopmental symptom domains also supports the grouping of these disorders. Disorders of childhood and adolescence that did not seem to overlap with the neurodevelopmental disorders in terms of these risks and manifestations were Conduct Disorder (CD), Attention Deficit Hyperactivity Disorder (ADHD), Selective Mutism, the Elimination Disorders, Tics, Eating/Feeding, and Separation Anxiety Disorders (SAD). CD shares the risks and symptomatic expression of the Externalizing disorders and is considered in the review by Krueger & South (2009).

ADHD exhibits some similarities with the Neurodevelopmental and Externalizing clusters but the weight of the evidence suggests a stronger relationship with the latter cluster. Early deviance in cognitive development and persistent failure in achieving maturational milestones are important facets of the Neurodevelopmental cluster. Although ADHD has been conceptualized in terms of selective attention processing, inhibitory and executive function deficits (Rutter *et al.* 2006), perturbations in these psychological abilities can be distinguished from the cognitive abnormalities associated with the Neurodevelopmental cluster (e.g. Willcutt *et al.* 2001). The course of the neurodevelopmental disorders is more stable than that of ADHD. In their meta-analysis Faraone *et al.* (2006) show that prevalence of ADHD declines with increasing age. Lara *et al.* (2009) using data from the World Health Organization World Mental Health Surveys report that 50% of childhood ADHD does not persist to adulthood, and persistence is predicted by disorder subtype, co-morbidity and parental mental illness, particularly paternal antisocial personality disorder. Nevertheless, such a rate of remission distinguishes ADHD from other disorders placed in this Neurodevelopmental cluster. Similar to other disorders included here, ADHD has an early symptom onset. Evidence also implicates both genetic and perinatal or early environmental factors in the condition, but there is limited evidence that ADHD and neurodevelopmental symptoms overlap genetically (e.g. language and social communicative deficits, restricted/repetitive behaviours and other cognitive impairments; Ronald *et al.* 2008). However, there are shared genetic risks between ADHD and antisocial conduct. Rutter *et al.*'s proposal acknowledges this but contrary to their conclusion this provides further justification in the current scheme for placement of ADHD outside of the Neurodevelopmental cluster and within the Externalizing cluster. The current proposal also emphasizes the overlap of ADHD and CD (e.g. Faraone *et al.* 2000; Thapar *et al.* 2001; Tuvblad *et al.* 2009), CD and other externalizing disorders including Antisocial Personality and the Substance-Use Disorders (e.g. Slutske *et al.* 1998; Kendler *et al.* 2003), and the shared familial risk of ADHD and the Substance-Use Disorders (e.g. Biederman *et al.* 2008) to justify the placement of ADHD outside the Neurodevelopmental cluster. All these disorders including ADHD are associated with genetically determined disinhibitory behaviours and temperaments (Nigg *et al.* 2002; Young *et al.* 2009; Krueger & South, 2009). None of these risks have been associated with the neurodevelopmental disorders.

There is some support for considering ADHD in this Neurodevelopmental cluster : cognitive deficits do occur in ADHD and they may reflect a deviance from normal development that would explain the persistence of ADHD in only some individuals. Nonetheless, the genetic overlap between ADHD and the externalizing disorders, its stable disinhibitory temperament and the remitting course of a substantial proportion of ADHD patients provide a more robust

justification to consider it as an externalizing rather than a neurodevelopmental disorder. More work, however, is needed to identify differences (between the ADHD subtypes) in terms of risks and clinical manifestations. Rasmussen *et al.* (2004) show that different ADHD subtypes cluster in families, and Lara *et al.* (2009) report that the different subtypes have different courses. Future investigations of subtype differences could delimit the aetiology of ADHD and other heterogeneous disorders and determine their placement in the meta-structure.

SAD shares the risks and clinical manifestations of the emotional disorders, in that there are genetic, environmental and temperamental factors that overlap with other childhood mood and anxiety disorders. SAD also increases the likelihood of anxiety disorders in later life and its course is less persistent than the typical neurodevelopmental disorder (e.g. Biederman *et al.* 1993; Pine *et al.* 1998; Feigon *et al.* 2001; Eley *et al.* 2008; Hirshfeld-Baker *et al.* 2008). For the Tic Disorders, there is not a strong case to include or exclude these disorders from the Neurodevelopmental cluster, although, again, as with ADHD and SAD the course of these conditions is different from the disorders included here. Tic Disorders have an early age of onset but they are typically transient, and although persistent cases do occur (Peterson *et al.* 2001) there are no delays in achieving developmental milestones. Similar concerns apply to the Elimination and the Eating/Feeding disorders, and the Selective Mutisms. These have been included in the 'Yet to be Assigned' group.

We now review the evidence that three sets of disorders (MR; PDDs; and the Learning, Motor and Communication disorders), now termed the neurodevelopmental disorders, could share validating factors that would support grouping them together in DSM-V and ICD-11.

Results

Shared genetic and familial risk factors

It is implicit from the early onset and marked deficits of the disorders considered for inclusion in this cluster that genetic factors could be salient in their development. The genetic determinants of syndromes that are not included in DSM-IV or ICD-10 but that are similar to the neurodevelopmental disorders, in terms of onset and marked and continuing deficits, support this presumption. For example, Down syndrome and Fragile X syndromes may be recognizable at birth and are associated with significant and continuing mental retardation, and result from trisomy 21 and X-chromosome abnormalities respectively.

Although several candidate chromosomal regions and genes have been proposed, genomic screens have not identified genes for any the neurodevelopmental disorders with the exception of the role of the *MECP2* gene in Rett's disorder (Amir *et al.* 1999. For reviews of possible loci see: *Communication Disorders*: Blood-stein & Ratner, 2008. *Learning Disorders*: Pennington & Olson, 2005. *PDDs*: Volkmar *et al.* 2005. The importance of genetic factors has nevertheless been confirmed in the Communication disorders (*Stuttering*: Andrews *et al.* 1991; Bloodstein & Ratner, 2008), Language Impairment (e.g. Expressive Language Disorder, Mixed Receptive-Expressive Language Disorder, Phonological Disorder: Plomin & Dale, 2001); the Learning disorders (Plomin & Kovas, 2005. *Reading Disorder*: DeFries & Alarcon, 1996; Pennington & Olson, 2005; Paracchini *et al.* 2007. *Mathematics Disorder*: Alarcon *et al.* 1997; Kovas *et al.* 2007), and most of the PDDs (*Autistic Disorder*: Folstein & Rutter, 1977; Steffenburg *et al.* 1989; Bolton *et al.* 1994; Bailey *et al.* 1995; Rutter, 2005. *Asperger's Disorder*: Volkmar *et al.* 1998; Ghaziuddin, 2005; Gillberg & Cederlund, 2005). The strength and scope of this evidence varies for each disorder; for example, most of the genetic research on language has focused on normal linguistic development whereas the genetics of language impairment has been largely

unexplored. There is scant genetic information about the written expression, motor and regressive neurodevelopmental disorders such as childhood disintegrative disorder (CDD).

A Neurodevelopmental 'cluster' presumes that there may be an overlap between the disorder-specific risks of these disorders that is not shared by disorders in other clusters; that is, the proposed clusters can be delimited by zones of relative rarity. In terms of this Work Group criterion, genomic screens have not identified 'neurodevelopmental' genes common to *all* these disorders. Nevertheless, familial studies which indicate the aggregation of related diseases, and thus it is presumed that disorders within clusters will co-aggregate, do support some common neurodevelopmental genetic risk. In one of the largest investigations into the risk factors of the PDDs, Lauritsen *et al.* (2005) in a Danish community family sample (total $n=943664$, autism $n=818$) show that the risk of Autism, Asperger's and other PDDs are increased in family members (siblings and parents) of autistic probands.

A broad phenotype that spans the neurodevelopmental disorders that increases the risk of language, social communicative deficits and restricted/repetitive behaviours (the 'autistic symptom triad') and other forms of cognitive impairment has also been identified. This dimensional model posits that Autism and Asperger's disorders fall at the 'severe' end of the genetic spectrum whereas disorders such as mild mental retardation occur at the 'mild' end of the spectrum. Subthreshold manifestations of all or some of the symptom triad can be inherited (e.g. *Twin studies*: Folstein & Rutter, 1977; Bailey *et al.* 1995; Le Couteur *et al.* 1996. *Family studies*: Bolton *et al.* 1994; Piven *et al.* 1997; Szatmari *et al.* 2000). Each symptom domain is moderately to highly heritable but it may be that independent genes are responsible for each symptom domain (Constantino & Todd, 2003; Ronald *et al.* 2005, 2006a, b; for a review see Happé & Ronald, 2008). The issue is not resolved.

Genetic data provide less support for the Neurodevelopmental cluster than for the Emotional and Externalizing clusters, where multivariate analyses of genetic-epidemiological data have identified 'internalizing/emotional' and 'externalizing' genetic liabilities that span most of those disorders (e.g. Kendler *et al.* 2003). Similar data are not available to conduct such analyses for all or even most of the neurodevelopmental disorders but there have been comparisons. Kovas *et al.* (2007) in the Twins Early Development study ($n=2596$) reported a substantial overlap in the genetic risks of reading and mathematical difficulties, as did Markowitz *et al.* (2005) in the Netherlands Twin Register ($n=1500$). Further bivariate and multivariate analyses of twin and family data may serve to identify other neurodevelopmental genetic commonalities and strengthen the justification for grouping these disorders.

In summary, disorder-specific genetic risks have been confirmed in all the neurodevelopmental disorders and there is evidence of a broad neurodevelopmental phenotype. Although these symptoms are heritable, it is unclear whether each symptom domain is caused by independent genes. The limited studies that assess the possible transdiagnostic genetic risk(s) of these disorders at the disorder rather than the symptom level means that the genetic and familial criteria provide weaker support for a Neurodevelopmental cluster than in the case of the Emotional and Externalizing clusters.

Environmental risk factors

Initial conceptualizations posited that deprived early environments caused these disorders. The growing amount of genetic data has meant that formative assumptions such as Kanner's 'refrigerator' mothers are now recognized as false (Kanner, 1943).

No environmental factors are necessary or sufficient causes of the neurodevelopmental disorders, even though several perinatal factors have been associated with some of the

disorders (e.g. *Autism*: Larsson *et al.* 2005). Other environmental risks have been identified in exceptional cases. For instance, toxic exposures to mercury and lead have been associated with isolated cases of autism and intellectual deficits respectively (e.g. Lanphear *et al.* 2005; DeSoto & Hitlan, 2007).

The utility of this criterion to define a cluster of neurodevelopmental disorders is restricted by the potential importance of perinatal risks that are difficult to define. The limited number of studies that examine environmental risks across disorders or symptom domains also restricts the importance of this criterion when defining a Neurodevelopmental cluster.

Shared neural substrates and biomarkers

Neurodevelopmental disorders are thought to evolve through aberrant processes not typically observed in any phase of normal brain development that alter trajectories in normal brain development (e.g. in *Autism*: Courchesne *et al.* 2001). It is likely that abnormal brain development is a product of gene and perinatal environment. This may explain the persistence of these disorders.

The precise pathophysiology of the neurodevelopmental disorders is unknown although deviations in cortical structures have been identified. The cortical profiles of the learning, communication and motor disorders are the least studied and therefore this review uses the PDDs as an example. In the PDDs, abnormalities in head size and cerebral volume occur. Macrocephaly (head circumference above the 97th percentile) is one of the most consistent physical findings in children with Autism (e.g. Lainhart *et al.* 1997; Stevenson *et al.* 1997) but at birth these children tend to have smaller heads than normally developing children, with some reports that a marked growth occurs between 6 and 12 months of age (Courchesne *et al.* 2003; Hazlett *et al.* 2005). Magnetic resonance imaging studies confirm this macrocephaly, showing that Autism is associated with abnormally large brain volumes, although the details differ between studies. A recent meta-analysis of 46 imaging studies found volume increases in total brain, cerebral hemispheres, cerebellum and caudate nucleus but a reduction in the corpus callosum (Stanfield *et al.* 2008). There is less evidence that macrocephaly is a defining feature of Asperger's disorder and there has been little investigation of this characteristic in CDD (Cederlund & Gillberg, 2004). In contrast to Autism, children with Rett's disorder are defined as having a normal head size prior to the onset of regressive symptoms (6–12 months of age; APA, 1994, p. 72, Criteria A and B). The cause(s) of these abnormalities are unclear.

Other neural and biomarker anomalies are evident. Electroencephalography abnormalities occur in some PDDs; for example in autism (Kagan-Kushnir *et al.* 2005; Coben *et al.* 2008) and in Rett's disorder (Kaufmann & Moser, 2000). Abnormalities of serotonin concentration and changes in cholinergic and GABAergic indices have also been associated with some of the neurodevelopmental disorders (Chugani *et al.* 1999; Bethea & Sikich, 2007) but these findings are far from specific, and none can be considered as either necessary or sufficient to cause the disorder or to provide a 'neurodevelopmental' physiological marker.

Although it is presumed that the abnormal developmental trajectory of these disorders are caused by some form of abnormal brain pathology, the identified abnormalities are seldom precisely defined, and to the extent that they have been examined across diagnoses, they seem to be non-specific.

Shared temperamental antecedents

Determining temperamental antecedents in young children affected by developmental disabilities is difficult. In cases where the individual is born with the disorder (MR, PDD) it is not possible to determine the pre-existing temperament. Unlike the Emotional and

Externalizing clusters, there is no evidence of a common temperament associated with the disorders considered for inclusion in the Neurodevelopmental cluster.

Symptom similarity and shared cognitive and emotional processing abnormalities

The neurodevelopmental disorders are similar in that they 'manifest... delay/deviance in maturationally influenced psychological features (i.e. the skills cannot develop unless the necessary neural structure is available)' (Rutter *et al.* 2006, p. 278). The disorders in this cluster therefore share the feature of 'impairment in development'. Moreover, compared to other conditions, such as ADHD, that also involve neurodevelopmental perturbations, the conditions included in the current cluster involve a more stable perturbation in development that persists in the majority of cases. The impairment(s), however, may be in one or several areas, and the pattern of impairment serves to specify the disorder. The developmental areas include deficits in cognition, social interaction, communication and normative behaviour. In the majority of cases, deviance rather than delay in reaching developmental milestones seems a more appropriate characterization, again differentiating the conditions in the current cluster from other so-called 'childhood' disorders. Given the integral nature of these domains to everyday life, some degree of functional impairment is also evident. Longitudinal studies show the persistence of the impairment into later life (Maughan & Hagell, 1996; Stothard *et al.* 1998; Howlin *et al.* 2000; Mawhood *et al.* 2000; Clegg *et al.* 2005).

Cognitive impairment is a key feature of the neurodevelopmental disorders. For most of the conditions included in the cluster, standardized tests exist for documenting the severity of the impairment. For example, cognitive impairment characterizes MR, learning, motor, and communication disorders, where standard measures exist for characterizing the impairment. The PDDs also involve cognitive impairment, although less standardized tests exist for identifying associated cognitive deficits in the PDDs than for other disorders included in this cluster. The nature of cognitive impairment varies among the disorders, ranging from deficits confined to specific core processes to more generalized problems. The notion of the presence of relatively 'preserved' capacities in the face of specific impairment is well established and even in disorders such as MR, where more pervasive deficit is expected, patterns of relative strengths and weaknesses are still evident (Sattler, 1992). With regard to MR, pervasive and significant deficit (>2 s.d.) in general intellectual functioning and significant limitations in adaptive functioning are expected and form part of the definition of the syndrome. With regard to the disorders that fall under the umbrella of PDD, at least half have intellectual impairment (Chakrabarti & Fombonne, 2001; Yeargin-Allsopp & Boyle, 2002). Autism is associated with more severe MR, whereas in Asperger's disorder, by definition, intellectual impairment is deemed to be not 'clinically significant', but deficits in domains other than intellectual functioning, particularly social communication, support the inclusion of Asperger's disorder here. For each of the PDDs, perturbations in social processing are detectable on standardized measures, such as the Autism Direct Observation Scale (ADOS, Lord *et al.* 1989). By contrast, the learning, motor and communication disorders are defined by more isolated deficits in the relevant domain(s), discordant with the individual's chronological age and measured intelligence.

Although the presence of aberrant development sets children with the neurodevelopmental disorders apart from the general population, this factor is not a point of absolute distinction from adults and children with disorders represented in other clusters. In fact, developmental delay and overt cognitive impairment are associated with multiple syndromes. Indeed, the disorders represented in the Neurocognitive cluster also have cognitive deficits as a key feature, as noted by Sachdev *et al.* (2009). A minor lowering (0.5 s.d.) of intellectual functioning is also associated with some externalizing disorders (Sattler, 1992; Sattler & Hoge, 2006; Krueger & South, 2009). In the neurodevelopmental disorders the cognitive symptoms arise early and persist as the defining feature of the syndromes. The

developmental impairments seem to have neural underpinnings. Cognitive deficits in the neurodevelopmental disorders are persistent, and this is supported by psychometric tests used to reliably track these deficits. In the future, the availability of such tests may allow characterization of the persistence of the core cognitive deficits in other clusters.

High rates of co-morbidity

Grouping the neurodevelopmental disorders presumes that within-cluster co-morbidity is higher than between-cluster co-morbidity. Few studies, however, have examined the differences between these disorders, and unlike analyses of the Emotional and Externalizing clusters there have been no analyses of within- *versus* between-cluster co-morbidity rates. Thus, for current purposes it is best to examine the co-morbidity of these disorders at the symptom level, and as noted in the last section, there is substantial overlap for all the neurodevelopmental disorders in terms of cognitive, social and communicative deficits, and particularly for intellectual impairment. Stuttering, for example, is associated with delays in the acquisition of language and with poor articulation independent of the stutter itself (Andrews & Harris, 1964), and MR occurs in most Autism cases (for reviews see Fombonne, 1999, 2003).

Co-morbidity is not exclusively limited to the disorders within the Neurodevelopmental cluster. MR (or intellectual impairment) is a key feature in the dementias of the Neurocognitive cluster (Sachdev *et al.* 2009), and emotional and externalizing symptoms may also co-occur with some of the neurodevelopmental disorders (e.g. Kim *et al.* 2000). Although the within-cluster co-morbidity between the neurodevelopmental disorders, particularly at the symptom level, supports grouping these disorders together, future analyses comparing co-morbidity rates across disorders and clusters may provide more robust support for this cluster.

Course of illness

The neurodevelopmental disorders have an early age of onset. Given the significant role of genetics in the development of all the neurodevelopmental disorders, it is presumed that these disorders are present from birth. For the PDDs, developmental problems may be recognized in the first year of life (Adrien *et al.* 1993; Osterling & Dawson, 1994; Baranek, 1999; Werner *et al.* 2000) although symptom severity and parental concern regarding their child's development can influence when the child receives a diagnosis (Stone *et al.* 1994; De Giacomo & Fombonne, 1998; Twyman *et al.* 2009). Autism diagnoses typically do not occur until 6 years of age (Howlin & Moore, 1997; Howlin & Asgharian, 1999) but Autism does tend to be diagnosed earlier than Asperger's disorder (mean age of Asperger's diagnosis is 11 years; Howlin & Asgharian, 1999). The onset of the early regressive symptoms in Rett's and CDD may mean that these conditions are diagnosed earlier than both Autism and Asperger's disorder. Some learning disorders and milder forms of MR may only be detected at a later age when academic testing occurs, typically in elementary school.

The course of the neurodevelopmental disorders is usually continuous, but some speech and motor disorders may be exceptions to this trend (*Communication disorders*: Stothard *et al.* 1998; Johnson *et al.* 1999; Kloth *et al.* 1999; Clegg *et al.* 2005; Bloodstein & Ratner, 2008. *Learning disorders*: Maughan & Hagell, 1996; Shaywitz *et al.* 1999; Mattison *et al.* 2002. *Motor Disorder*: Cantell *et al.* 1994, 2003; Sugden & Chambers, 2007. *PDDs*: Howlin *et al.* 2000, 2004; Mawhood *et al.* 2000; Cederlund *et al.* 2008). CDD and Rett's disorders by definition have a deteriorating course. Although the clinical profile in each neurodevelopmental disorder does change as the child matures, evidence of the underlying deficit typically persists. A persistent course, more than any other single characteristic, distinguishes the child-onset conditions included in this cluster from those included in other

clusters. In some cases where treatment is focused on function, a disorder may seem to remit. However, even here, treatments do not alter course *per se*; rather, they provide the individual with different skill sets, such as facilitating interpersonal and occupational skills for individuals with MR to compensate for a stable underlying deficit.

Treatment response

The main focus of treatment for the neurodevelopmental disorders is to reduce the maladaptive behaviours and increase functionality in the presence of the enduring deficit. Early and intense educative and behavioural treatments may increase skills and reduce maladaptive behaviours in some cases of PDDs (Sallows & Graupner, 2005; Remington *et al.* 2007), Developmental Motor (Pless & Carlsson, 2000), Communication (Bothe *et al.* 2006) and Learning disorders (Reynolds *et al.* 2003; Willner, 2005). However, few findings have been replicated in randomized controlled trials.

No pharmacotherapies reduce the core social and communicative deficits of autism or Asperger's disorder. These agents are used, however, to control co-morbid emotional and cognitive symptoms. For example, antipsychotics have been used to target co-morbid psychiatric symptoms and aggression in adults with MR (Williams *et al.* 2000). Cholinesterase inhibitors by contrast, may provide direct benefits for some cases of Autism (Chez *et al.* 2004).

In summary, treatment of the neurodevelopmental disorders is focused on improving functionality and therefore reflects the persisting nature of the disorders. There is a range of treatment options to manage the difficult and disruptive symptoms that accompany the neurodevelopmental disorders.

Discussion

MR, Learning, Motor, and Communication Disorders, and PDDs share some similar risk factors and clinical features. First, genetic influences play a relatively strong role in these disorders. Second, these are early-onset disorders characterized by abnormal neurodevelopmental processes, where children fail to progress in normal development. Third, the disorders exhibit a relatively continuous course, with few instances of complete remission, at least when compared to childhood-onset disorders included in other clusters. Thus, signs of these disorders will still be evident in adults. Finally, there is substantial co-occurrence of neurodevelopmental symptom domains within the cluster. These five features speak most directly to the DSM-V Task Force Study Group validating criteria 1, 2 (genetic and familial risk factors), 7 (cognitive processing), 8 (symptom similarity), 9 (co-morbidity), and 10 (course). The importance of these risk and clinical factors across the neurodevelopmental disorders supports their grouping in DSM-V and ICD-11.

The findings of this paper should be read with regard to two qualifications. First, the aim of this review and others within the proposed meta-structure was to determine whether similarities on some or all of the criteria proposed by the Task Force Study Group would support large groups of disorders, and that different combinations of the criteria would be important to the different clusters. The reviews thus focus most on disorder similarities and less attention is given to differences between clusters. The heterogeneity of the disorders considered for this cluster poses, to some degree, a second qualification to this review. The disparity between the clinical manifestations of the neurodevelopmental disorders suggests that they have different causes; and few causes are known. It is important for the reader to understand that this review does not purport to know the causes of these disorders, rather it claims that the disorders share similarities in terms of the DSM-V Work Group criteria.

Conclusions

The Neurodevelopmental cluster is largely characterized by the role of genetic factors; early age of onset; a continuing course; within-cluster co-morbidity; and the salience of cognitive symptoms. This profile is similar to the Neurocognitive cluster but the occurrence of these disorders during early development rather than after normal development differentiates the two clusters. Additional research is required, particularly with respect to the neural substrates and the biomarkers of the neurodevelopmental disorders, prior to making claims regarding possible commonalities between these two clusters. Disorders such as CD and ADHD, and SAD showed more similarity in risks, symptoms and course pattern to the Externalizing and Emotional clusters respectively, notwithstanding that the two latter disorders are not formally considered in those meta-structure reviews. Elimination, Eating/Feeding, and Tic disorders, and the Selective Mutisms have insufficient data to determine cluster membership and are included in the 'Yet to be Assigned' group. The overlap of the validating criteria of the neurodevelopmental disorders demonstrates that commonalities in both risk and clinical manifestations can be used to justify this group of disorders in DSM-V and ICD-11.

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