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REVIEW ARTICLE

Neurocognitive disorders: Cluster 1 of the proposed meta-structure for DSM-V and ICD-11

Paper 2 of 7 of the thematic section: 'A proposal for a meta-structure for DSM-V and ICD-11'

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Background. In an effort to group mental disorders on the basis of aetiology, five clusters have been proposed. In this paper, we consider the validity of the first cluster, neurocognitive disorders, within this proposal. These disorders are categorized as 'Dementia, Delirium, and Amnestic and Other Cognitive Disorders' in DSM-IV and 'Organic, including Symptomatic Mental Disorders' in ICD-10.

Method. We reviewed the literature in relation to 11 validating criteria proposed by a Study Group of the DSM-V Task Force as applied to the cluster of neurocognitive disorders.

Results. 'Neurocognitive' replaces the previous terms 'cognitive' and 'organic' used in DSM-IV and ICD-10 respectively as the descriptor for disorders in this cluster. Although cognitive/organic problems are present in other disorders, this cluster distinguishes itself by the demonstrable neural substrate abnormalities and the salience of cognitive symptoms and deficits. Shared biomarkers, co-morbidity and course offer less persuasive evidence for a valid cluster of neurocognitive disorders. The occurrence of these disorders subsequent to normal brain development sets this cluster apart from neurodevelopmental disorders. The aetiology of the disorders is varied, but the neurobiological underpinnings are better understood than for mental disorders in any other cluster.

Conclusions. Neurocognitive disorders meet some of the salient criteria proposed by the Study Group of the DSM-V Task Force to suggest a classification cluster. Further developments in the aetiopathogenesis of these disorders will enhance the clinical utility of this cluster.

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Introduction

As a classification of mental disorders, DSM-IV is descriptive and purportedly atheoretical. Although a descriptive approach improves reliability and communication between clinicians and researchers, the validity of a diagnosis is enhanced by known aetiology, which is most likely to predict treatment and prognosis. A future classification should therefore group disorders in clusters that reveal common aetiological factors. This paper is part of an attempt to achieve such a clustering for DSM-V and ICD-11 to provide a meta-structure for the classifications. It deals with the first of the five proposed clusters (Andrews *et al*. 2009*a*), that is the neurocognitive disorders.

The categorization of 'Cognitive' disorders in DSM-IV and ICD-10

The second chapter in DSM-IV is headed 'Delirium, Dementia and Amnestic and Other Cognitive Disorders' and these are also the section headings even though the 'Other Cognitive Disorders' section only lists one disorder, that is Cognitive Disorder Not Otherwise Specified (NOS), with examples of Mild Cognitive Disorder and Postconcussional Disorder within this. The corresponding chapter in ICD-10 is headed 'Organic, including Symptomatic Mental Disorders' and the section headings are: 'Dementia in Alzheimer's Disease; Vascular Dementia; Dementia in Other Diseases Classified Elsewhere (e.g. elsewhere in ICD-10); Unspecified Dementia; Organic Amnesic Syndrome, Not Induced by Alcohol and Other Psychoactive Substances; Delirium, Not Induced by Alcohol and Other Psychoactive Substances; Other Mental Disorders Due to Brain Damage and Dysfunction and to Physical Disease; and Personality and Behavioural Disorders Due to Brain Disease, Damage and Dysfunction'. The other 'organic' or 'symptomatic' mental disorders are included in two separate chapters of DSM-IV entitled 'Mental Disorders Due to a General Medical Condition' and 'Substance-related Disorders'.

Although DSM-IV is determinedly descriptive, it recognizes that, for this section, 'the etiology is either a general medical condition … or a substance' (APA,

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1994, p. 123). There is the clear and stated assumption in ICD-10 that all these disorders are due to brain disease or damage. Dysfunction is also mentioned but the text in the chapter makes it clear that the dysfunction referred to is related to disease or toxins affecting brain function. Thus, this group of disorders is defined as being due to an alteration in the neural substrate, often with the appreciation of distinct aetiology and pathogenetic mechanisms. With the rapid pace of advances in neuroscience, it can be argued that the neurocognitive disorders, more than any other in psychiatry, lend themselves to characterization by aetiology.

Method

Using the 11 criteria developed by a DSM-V Task Force Study Group (Hyman *et al*., personal communication, 3 December 2007), which were based on the original Robins & Guze (1970) criteria for the validity of a psychiatric diagnosis, we reviewed the literature pertaining to these disorders. The criteria are:

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

The first two authors of this paper (P.S. and G.A.) are members of the APA DSM-V Work Groups, but the Task Force did not officially appoint the authors to conduct this review. The authors considered the disorders in which neurocognitive dysfunction is the salient and defining feature. The literature was reviewed selectively for evidence to support or negate the validity of this cluster. This paper does not alter the definition of any DSM-IV or ICD-10 diagnosis, but simply specifies the relationships between the disorders in terms of shared antecedent factors, likely course and possible treatments.

Defining the 'Neurocognitive Cluster' for DSM-V and ICD-11

Study Group criteria 4, 7 and 8 (neural substrate, cognitive abnormalities and symptom similarity) provide the strongest support for an organic or 'neurocognitive' cluster. Other criteria that provide some support are criteria 5, 9 and 10 (shared biomarkers, co-morbidity and course), and in the future, common treatments (criterion 11) may become available. In general, these disorders have a shared basis in neural substrate abnormalities with associated neurocognitive symptoms. The term 'shared' is used in the sense that a similar class of abnormalities underlie these disorders, but it does not mean that the same abnormality is present, as each disorder by definition will have a different set of abnormalities. Due to the underlying neural abnormalities, these disorders manifest abnormalities on neuroimaging or electrophysiology, and biochemical abnormalities may be present in some cases. Their course is generally predictable but may vary from recovery (e.g. delirium) to persistence (e.g. amnestic disorder) to progressive decline [e.g. Alzheimer's disease (AD)]. Co-morbidities often occur [e.g. delirium in a patient with dementia; vascular (VaD) and AD-type pathology in dementia] but this is not the binding characteristic of the cluster.

It is the *impression* of 'neurological disease' that sets the neurocognitive cluster apart from other clusters. The argument that they should be included in chapter VI (Diseases of the Nervous System) of the ICD is quite valid. We do not want to revisit the age-old debates on 'organic *versus* functional' or 'neurological *versus* mental' or 'primary *versus* secondary', and subscribe to the general neuroscientific premise that all mental disorders are brain disorders (Sachdev, 1996). The disorders in this cluster meet the standard of evidence of brain disease that a classically trained neurologist would expect. Yet they belong equally in chapter V (Mental and Behavioural Disorders) of ICD-10 because the substantive disturbance is mental and/or behavioural and psychiatry is often the first port of call for patients. So long as there are two distinct disciplines of psychiatry and neurology, these disorders will find themselves in two places at the same time.

The use of the term 'neurocognitive' is a slight departure from DSM-IV, which refers to these as 'cognitive' disorders. This is in recognition of the fact that disturbance of cognition is present in many mental disorders. An excellent example is schizophrenia, which encompasses disturbances in cognition, emotion and conation, with the former often being paramount. 'Neurocognitive' captures the concepts of cognitive disturbance as well as its neural substrate at the level described above; hence the exclusion of disorders such as schizophrenia from this cluster. The term 'cognitive' (Latin: *cognoscere*, 'to know') is generally used in a broad sense regarding the processes involved in information processing such as inference, learning, comprehension, decision making and planning. Cognitive deficits, for example, are common in

depression and some theories of depression argue that cognitive distortion may be a fundamental factor in the development of depression (Beck, 1975). Despite the cognitive features, and the success of cognitive behaviour therapy in many cases, mood disturbance remains the defining feature of depression, and cognitive distortion in the absence of mood change is not recognized as a depressive disorder. It can similarly be argued that, despite increasing focus on the cognitive deficits of schizophrenia and its neuropathological substrate, it is very likely that 'psychotic' symptoms rather than cognitive ones will remain the defining feature of schizophrenia. Disturbances of emotion and behaviour are commonly present in neurocognitive disturbances but these are not their defining features. Schizophrenia arguably lies more comfortably in the 'psychosis' cluster. Similar arguments can be presented for bipolar disorder, obsessive–compulsive disorder and other psychiatric disorders with cognitive symptoms.

A whole group of disorders that could have a valid claim to belong in this cluster is being excluded from this proposal; that is the neurodevelopmental disorders such as mental retardation, the pervasive developmental disorders and so forth. The latter group justifiably forms a distinct cluster (Andrews *et al*. 2009*b*). Although neurocognitive symptoms are shared by the two clusters, there is a clear demarcation in the developmental trajectory of the two clusters. Abnormalities of development and/or maturation of the brain characterize the neurodevelopmental cluster, such that the brain's 'normal' potential is never reached. In the neurocognitive disorders, however, normal brain development is the rule, albeit with some exceptions, and decline occurs from a previously normal base. The 'course of illness' (criterion 10) therefore differentiates neurodevelopmental from neurocognitive disorders. Neurodevelopmental disorders do not generally share co-morbidities (criterion 9) with the neurocognitive cluster, with some prominent exceptions such as high rates of AD in Down's syndrome (Holland *et al*. 2000; Tyrell *et al*. 2001; Coppus *et al*. 2006). If we use the crude test of a 'neurological disorder in the classic sense', many neurodevelopmental disorders do not meet the standard, although it does raise the issue of the crudity of such a test. There is of course a practical reason for the separation of these two clusters; they are diagnosed and treated by two distinct disciplines that warrant different pathways of training and differing sets of skills.

An important consideration is whether the 'Mental Disorders Due to a General Medical Condition Not Elsewhere Classified' or the 'secondary syndromes' of DSM-IV should be clustered with neurocognitive disorders. It is recognized that all psychiatric syndromes can be produced by neurological or other medical conditions in which 'organic' brain impairment can be demonstrated. Some of these disorders share neural substrates with neurocognitive syndromes. For instance, cerebrovascular disease may present primarily as a depressive disorder or a neurocognitive disorder, thereby arguing for shared aetiology (Alexopolous *et al*. 1997; Thomas *et al*. 2002), although the pathophysiological mechanisms will vary because different neural networks are involved to produce distinct deficits in different patients (Alexopoulos, 2003). We consider it more practical to cluster the 'secondary syndromes' with their primary counterparts. For example, depression secondary to cerebrovascular disease or Parkinson's disease (PD) or other medical conditions are best clustered with other emotional disorders. This is because the diagnostician consulting a patient with depression must consider the various medical conditions that may present with depression, and the therapeutic interventions for secondary depression are more akin to those for depression than for neurocognitive disorders. A similar argument holds for secondary psychosis or the other secondary syndromes.

Of interest, the criteria that bind the neurocognitive cluster together on one level (neural substrate and neurocognitive symptoms) also serve to differentiate these disorders on another level. For example, the specific abnormalities and neurocognitive profiles associated with AD, frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) draw obvious distinctions between the disorders. The aetiologies involved are multiple and varied, as is to be expected in a cluster, although some pathogenetic mechanisms may be shared, such as those of neurodegeneration in various dementias.

The composition of the cluster

This cluster comprises the disorders included under 'Delirium, Dementia and Amnestic and Other Cognitive Disorders' in DSM-IV and 'Organic, including Symptomatic Mental Disorders' in ICD-10. The broad conceptualization of these disorders has not changed greatly, except for the increasing realization that the diagnosis of dementia disregarded the fact that the disorder had usually been present for a long period prior to the categorical diagnosis, and that the pre-dementia stage had an impact on functioning and also offered an opportunity for intervention now and in the future (Sachdev, 2000). The considerable interest in mild cognitive impairment (MCI) attests to this (Petersen & Morris, 2005). It must also be mentioned that DSM-IV only had the category of 'Cognitive

Disorder NOS' in the 'Other Cognitive Disorders' section. It can be argued that this section should be populated with disorders of specific cognitive domains other than memory. The definition of dementia must be revisited, with the consideration that the requirement of memory impairment no longer be its necessary criterion if multiple other cognitive domains are affected. The boundaries between healthy ageing, MCI and dementia are the subject of much debate. The neurocognitive cluster, in particular dementia, encompasses several diseases that invite specific criteria of their own. There are associated symptoms and disorders such as agitation, psychosis and depression that must find an expression in the classification. In short, although the broad grouping of neurocognitive disorders may not invite much dispute, considerable refinement of criteria is necessary.

Applying the criteria recommended by the DSM-V Task Force Study Group to the neurocognitive disorders

Shared genetic and specific environmental risk factors

Specific genetic abnormalities have been identified as causative in a few neurocognitive disorders including early-onset AD and Huntington's disease (HD) (Huntington's Disease Collaborative Research Group, 1993; Strittmater & Roses, 1996; Tanzi *et al*. 1996; Ertekin-Taner, 2007). The majority of neurocognitive disorders have been found to be influenced by, rather than caused by, genetic risk factors. It is well established that the apolipoprotein E ε4 gene (*ApoE*4*) increases the risk of developing late-onset AD. *ApoE*4* has also been associated with developing VaD, DLB, Creutzfeldt–Jakob disease (CJD) and cognitive impairment following traumatic brain injury, although the reports for the disorders other than AD have been less consistent (Marin *et al*. 1998; van Everbrock *et al*. 2001; Nathoo *et al*. 2003; Pankratz *et al*. 2006; Ertekin-Taner, 2007). Furthermore, genetic abnormalities also influence the phenotypical expression of CJD (Parchi *et al*. 1996, 1999).

Exposure to environmental pathogens has been linked to the neurocognitive disorders. Neurocognitive deficits have been associated with pesticide/fungicide and metal exposure, particularly lead (Schwartz *et al*. 1993; Hebert *et al*. 2000; Bleecker *et al*. 2005; Lanphear *et al*. 2005). Other neurotoxicant metals are mercury and arsenic, whereas some metals such as iron, zinc, copper and manganese can act as both nutrients and neurotoxicants (Wright & Baccarelli, 2007). To understand metal toxicity, it is important to identify the genes that regulate their metabolic enzymes. Recent evidence suggests that early life exposure to metals may produce epigenetic effects to influence adult disease phenotypes (Wright & Baccarelli, 2007). Much work has also been published on carbon monoxide and various solvents and neurotoxicology (Iregren, 2006).

Substance use has also been associated with the neurocognitive disorders. The example *par excellence* is alcohol abuse (Harper, 2007) but many other substances of misuse have been implicated. The relationship is best described with delirium, in which drugs such as anticholinergics have an aetiological role (Young & Inouye, 2007). Neurodegeneration has been associated with some drugs such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which has been linked with the development of PD (Langston *et al*. 1999).

Gene–environment interactions probably account for some of the aetiological factor variance in respect of the neurocognitive disorders (Caspi & Moffitt, 2006). Interactions have been described between *ApoE*4* and factors such as traumatic brain injury, diabetes and hypertension in the pathogenesis of AD (Li & Grupe, 2007; Van Den Heuvel *et al*. 2007). In addition to risk factors, protective factors for neurodegenerative disorders have been identified, in particular lifestyle factors such as nutrition and mental and physical activity, and these seem to interact with genetic factors (Valenzuela & Sachdev, 2006*a*).

In summary, several genetic and environmental risk factors have been identified for the neurocognitive disorders. These factors are diverse and do not, on the surface, provide a common thread to cluster the neurocognitive disorders together. However, on examining the intervening pathogenetic mechanisms that produce neuronal injury, dysfunction and loss, processes such as oxidation, mitochondrial injury, protein aggregation and apoptosis seem to be shared across some of the disorders (Halliwell, 2006). There are diverse genetic mechanisms underlying these processes that interact at the biomolecular level with non-genetic factors. Further developments in this knowledge base may well provide unifying mechanisms to explain the development of many of the disorders in this cluster.

It is also acknowledged that both genetic and environmental factors are important in the aetiology of most psychiatric disorders, although the pathophysiological mechanisms linking these factors are generally not well understood. Some data have been presented linking some genetic polymorphisms and vulnerability to stress for the aetiology of depression (Caspi *et al*. 2003), or childhood maltreatment and adult violence (Caspi *et al*. 2002), but this work remains at a very preliminary stage and is inadequate to underpin any attempts at classification.

Shared neural substrates

Neurocognitive disorders have demonstrable neural substrate abnormalities as their defining features, and these may be functional or structural brain abnormalities or both.

Structural abnormalities occur at both macroscopic (multicellular) and microscopic (cellular and subcellular) levels in most of the neurocognitive disorders. The dementias represent the best examples. Histopathological abnormalities characterize some of the dementias; for example, β-amyloid plaques and neurofibrillary tangles in AD; the pathological isoform of the prion protein in CJD; Pick bodies in some FTD cases; and Lewy bodies in DLB (Braak & Braak, 1991; Prusiner & DeArmond, 1994; Braak *et al*. 2004; Wiltfang *et al*. 2005). VaD is characterized by evidence of brain tissue loss due to infarction or subinfarction hypoxaemia due to large- and/or small-vessel disease (Hainfellner *et al*. 1998; Kalaria & Ballard, 1999; Armstrong *et al*. 2005). Neuronal loss is manifestly evident in the neocortices of patients with AD, FTD and DLB, and the basal ganglia in HD and DLB (Morrison & Hof, 1997; Schulz & Falkenburger, 2004; Thomas, 2006). In many cases of dementia, the neuropathological basis is an additive effect of multiple pathologies. Furthermore, neuronal loss in the anterior principal nucleus of the diencephalon is characteristic of Korsakoff's syndrome, a syndrome with amnesia and frontal-executive dysfunction (Harding *et al*. 2000; Kopelman, 2002). Although Korsakoff's disorder has its aetiology in thiamine deficiency in the setting of alcohol dependence, amnestic disorders may arise from multiple pathogens such as brain trauma, hypoxia and/or carbon monoxide poisoning. In all cases, however, there is demonstrable injury to the brain regions involved in memory processes. The same can be said for other focal neurocognitive syndromes manifesting with disturbances such as language (dysphasia) or complex motor function (dyspraxia). In these disorders, the severity of the neuropathology is generally related to the level of cognitive and emotional deficits and may be considered to be both necessary and sufficient in causation.

In some neurocognitive disorders, structural abnormalities are not evident with extant clinical investigations, and functional disturbances are more easily demonstrable at the multicellular or network level. The best example of this is delirium, in which electrophysiological disturbances may be evident and are generally reversible (Cole, 2004). Structural abnormalities are not necessarily present in delirium although such abnormalities may increase the vulnerability to delirium (Inouye, 1999). Moreover, the functional abnormalities in delirium are often due to a secondary medical condition affecting the brain, and a primary neural substrate abnormality may not be the starting point. Delirium, however, belongs in this cluster because neurocognitive deficits are the defining features, and functional neural abnormalities are readily demonstrable in most cases.

The structural and/or functional brain abnormalities described above provide a unifying feature for neurocognitive disorders. There are situations in which such abnormalities are not manifestly evident, but there is reason to believe that this represents a limitation of the available or applicable technologies. For example, patients with clinically diagnosed mild delirium may have no neurological signs and the electroencephalogram (EEG) may be reported to be normal. In such cases, serial EEGs may be helpful in the diagnosis and will generally substantiate the neural state abnormality. In MCI, structural or functional brain abnormalities may be difficult to establish in an individual case and the only objective evidence may be on neuropsychological assessment. This situation is likely to change with the development of better biomarkers and more sensitive tests of brain dysfunction.

Neural substrates of the kind proposed for this cluster are not identifiable in other mental disorders. For instance, brain abnormalities have been demonstrated in schizophrenia, but they lack some important characteristics: they are neither necessary nor sufficient for a diagnosis of schizophrenia; there is no pathognomonic abnormality that is present in all patients with this disorder; and there is no concordance between demonstrated neural abnormalities and the identifying clinical features of schizophrenia (Harrison, 1999). Disorders in other clusters, with the exception of some disorders in the neurodevelopmental cluster, similarly fall short of meeting the standard of evidence in neural substrate abnormality proposed for this cluster.

Neurocognitive disorders are nevertheless commonly associated with non-cognitive features such as depression, psychosis, agitation and anxiety. For instance, psychosis has been reported in a median 41% of patients with AD (Ropacki & Jeste, 2005). This psychosis has a certain pattern; it is related to age, age of onset and stage of disease and typically lasts for a few months. The pattern suggests that psychosis may be an integral feature of the disease, and may be a consequence of the involvement of neuronal circuits that underlie the development of psychosis. However, psychosis is not the defining feature of the neurocognitive disorder, and its development may also be influenced by psychological factors. Similar arguments can be mounted for depression, agitation, and so on and so forth.

In summary, a neural state abnormality is the common and defining feature of this cluster as is implicit in the term 'neurocognitive'. If there is deficiency in the demonstration of such abnormality, it is likely to be remedied by advances in the sensitivity of the diagnostic techniques available.

Shared biomarkers

As neural substrate abnormality is the defining characteristic of this cluster, there is an expectation that surrogate biomarkers will be available. At one level, this is indeed the case. Used in the broader sense, a biomarker is an indicator of a biological state associated with a disease, as its signature or an endophenotype. In the narrower sense, it is a feature that can be used to measure the progress of the disease or the effects of treatment (Katz, 2004). Structural and functional brain imaging have offered much in terms of diagnostic tests and possible biomarkers. Brain atrophy is a feature of the dementias, and focal atrophy is also seen in amnestic and other focal neurocognitive syndromes, with the expectation that these change with the progression of the disease (Ashburner *et al*. 2003). In cases in which structural brain abnormality is not present, functional abnormalities seen on positron or single photon emission tomography or functional magnetic resonance imaging do relate to both the presence and the severity of the disorders (Zipursky *et al*. 2007). Neuroimaging biomarkers, however, remain limited. Although some imaging features, such as differential atrophy of the caudate nucleus in HD or the hippocampus in AD, may be of diagnostic value, no one biomarker can be a complete surrogate for the disorder (Chertkow & Black, 2007). Amyloid imaging with the carbon-11-labelled Pittsburgh compound B has recently been investigated as a biomarker of Alzheimer's disease, and although there is good correspondence between the signal on positron emission tomography and the amount of β-amyloid deposition (Klunk *et al*. 2004), many non-demented individuals also have a positive signal. This is in contrast with some medical disorders, such as diabetes mellitus, in which blood sugar level is a robust surrogate.

In addition to neuroimaging, electrophysiology has offered the promise of biomarkers for neurocognitive disorders. Abnormalities of EEG are seen in most neurocognitive disorders, although these are most prominent in delirium. Although these are not generally specific to the disorder, some, such as CJD, can be recognized by characteristic sharp wave complexes on EEG (Wang *et al*. 2008). The use of quantified EEG, event-related potentials and sleep studies has further improved the potential for electrophysiological biomarkers. These biomarkers are also being developed for other psychiatric disorders such as depression, mania and schizophrenia, but their value in neurocognitive disorders is better recognized (Boutros & Struve, 2002).

Finally, genetic and biochemical biomarkers are increasingly showing promise for neurocognitive disorders. Disorders with Mendelian inheritance have clearly established genetic tests, with HD being the prime example of a single gene mutation with near-perfect concordance with clinical disease. Other disorders with trinucleotide repeat have been described (Gusella & MacDonald, 1996). AD has received the greatest attention, and reduced amyloid-β levels and increased phosphorylated tau protein levels in the cerebrospinal fluid (CSF) may be possible biomarkers (Wiltfang *et al*. 2005). However, the sensitivity and specificity of these biomarkers is still being examined. Similar abnormalities in the CSF have been reported in CJD (Otto *et al*. 1997, 2000), which has another protein that serves as a laboratory test (Green, 2002).

In summary, because of neural substrate impairment, there is considerable promise in the development of biomarkers for neurocognitive disorders. Although there are some shared biomarkers, especially for neuroimaging and neurophysiology, most biomarkers are likely to be specific for the disorder, which increases their clinical utility. The availability of biomarkers is likely to be an important feature of this cluster. However, biomarkers are unlikely to be exclusive to this cluster, and they may become available for other disorders, such as schizophrenia or bipolar disorder, that are not part of this cluster.

Shared temperamental antecedents

The only commonality between the neurocognitive disorders in respect of temperamental antecedents is that there is no common temperament associated with the neurocognitive disorders. The aetiologies of these disorders are such that they can occur in anyone regardless of their pre-existing personality or temperament. Pre-morbid personality or temperament may, however, influence the overall experience of the disorder and help or hinder rehabilitation or coping with the disease process.

High pre-morbid neuroticism may be related to the recognition of dementia (Lebert *et al*. 1995; Meins *et al*. 1998; Meins & Dammast, 2000). However, it is not known whether the observed pre-morbid personality profiles are true risk factors for dementia, lead to early symptoms being emphasized, or are early symptoms of dementia due to neurobiological changes (Meins & Dammast, 2000). The literature suggests that personality traits are more predictive of the behavioural and

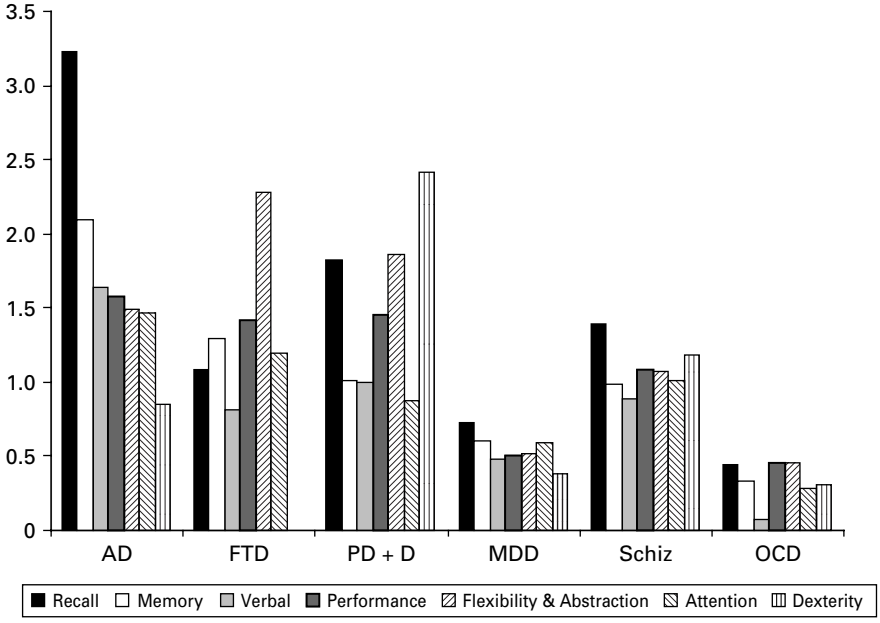

Fig. 1. Overall pattern of cognitive function by neuropsychological domain for some neurocognitive and other psychiatric disorders. The abscissa gives the mean effect size for each domain in the group, indicating impairment. AD, Alzheimer's disease; FTD, frontotemporal dementia; PD + D, Parkinson's disease with dementia; MDD, major depressive disorder; Schiz, schizophrenia; OCD, obsessive–compulsive disorder; Verbal, verbal intelligence; Performance, non-verbal intelligence (adapted from Zakzanis *et al*. 1999).

non-cognitive symptoms of dementia that occur as a result of the underlying disease process (Meins *et al*. 1998; Low *et al*. 2002). It must be recognized, however, that the prevailing theories on the pathogenesis of these disorders has made temperament an unappealing line of investigation, explaining the lack of empirical data on this question.

Shared cognitive and emotional processing abnormalities and symptom similarity

Deficits in cognitive processes and symptoms

Disorders in this cluster share the feature of impairment in one or more cognitive processes. Cognitive processes can variously be grouped, with one group of investigators categorizing them into seven domains: memory acquisition (or learning), delayed recall, verbal (or communication) skill, performance skill (motor), cognitive flexibility and abstraction, attention/concentration and manual dexterity (see Zakzanis *et al*. 1999). Others include language (which subsumes verbal skill), visuospatial ability and speed of information processing. The exact processes themselves are not necessarily 'shared' across the disorders of interest; rather, the presence of impairment is the common denominator. 'Impairment' associated with the disorders in this cluster is defined differently for each disorder, but typically involves a decline from previous functioning, or islands of deficit discordant with the individual's general intellectual functioning. Common across the disorders is the notion of the presence of relatively 'preserved' capacities in the face of specific impairment, or at least patterns of relative strengths and weaknesses.

Which domain is impaired, whether one or many domains are affected, the magnitude of the deficit(s), and whether the impairment is likely to be permanent, remitting or progressive differ between the disorders and can change with progressive disorders. In fact, cases of apparent cognitive impairment without known aetiology are often categorized or diagnosed on the basis of the pattern of their performance profile and its similarity to proforma profiles associated with certain disorders or aetiologies. For example, MCI characterized by disturbance in episodic memory, in particular impaired new learning, is often conceptualized as an early stage of AD even when other indicators of AD are not present. Other examples of disorder profiles and their expected trajectories over time are well documented in the literature and do not warrant detailed analysis in this article. For illustrative purposes, profiles from Zakzanis *et al*. (1999) are adapted in Fig. 1.

Although the presence of 'impairment' in one or more cognitive processes sets people with the aforementioned disorders apart from the general population, this factor is not a point of absolute distinction

from people with other mental disorders. In fact, cognitive impairment is associated with multiple disorders and also with other disorders of neurology not mentioned in DSM. For example, obsessive–compulsive disorder and major depressive disorder are associated with mildly impaired performance (<1 S.D. below mean) and schizophrenia with moderate impairment (1–2 S.D. below the mean) across many cognitive domains (see Zakzanis *et al*. 1999, Fig. 1). What distinguishes the neurocognitive disorders is that the neurocognitive deficits are both the presenting symptoms by the patient and the defining features by the physician, unlike obsessive–compulsive disorder, depression and schizophrenia. It cannot be assumed that the neural processes underlying the cognitive deficits are different for the disorders not included in the neurocognitive cluster. As an example, neuroimaging studies show that patients with bipolar disorder may have reduced prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (e.g. amygdala, anterior striatum and thalamus) (Strakowski *et al*. 2005). These abnormalities are considered to be responsible for the mood disturbance, but may also account for the cognitive symptoms seen in this disorder. Prefrontal modulation of subcortical structures is purportedly abnormal in some dementias such as HD and FTD, although the neural substrate in these is better defined than in bipolar disorder. It must therefore be concluded that it is the level and salience of neurocognitive impairment that sets this cluster apart, but the underlying neural processes may well overlap with disorders in other clusters.

Emotional processes

In addition to shared cognitive deficits, changes in emotional processing are commonly present in neurocognitive disorders. In the case where there has been some brain injury from any cause, characteristic behavioural/emotional patterns frequently follow. These emotional patterns result from disruption of neural processes that form the basis of emotional expression, in addition to reactions of the individual to injury and loss. Acute events can be responded to with fear, terror, perplexity and agitation, whereas chronic organicity may be associated with a range of emotion processes reflected by emotional dulling, depressed mood, apathy, hypersensitivity to personal interactions, heightened anxiety, or disinhibition coupled with diminution of anxiety. In adults these emotional symptoms reflect changes from pre-morbid functioning. However, these changes are not solely the product of neurological damage but also reflect complex relationships with pre-morbid factors and current demands (Lishman, 1998; Lezak *et al*. 2004; Lyketsos, 2006). Across the disorders proposed for the neurocognitive cluster, the commonality is the frequent co-occurrence of the emotional processing changes along with cognitive processing deficits, but within this group the actual emotional changes observed vary. Moreover, changes in emotions are not necessary for a disorder to belong in this cluster, and this cannot be considered as a binding feature for the cluster.

High rates of co-morbidity

Researchers have posited that a high rate of co-morbidity between like disorders may indicate a common underlying structure (Krueger, 1999; Krueger & Markon, 2006; Slade & Watson, 2006). There are no studies that have examined the co-morbidity between the neurocognitive disorders as a whole with the specific aim of extracting an underlying meta-structure. High rates of co-morbidity have been observed in some cases. Delirium commonly occurs in elderly patients with dementia in community and hospital samples, with prevalence estimates ranging from 20% to 90% (Fick *et al*. 2002; Leentjens & van der Mast, 2005). AD is often co-morbid with cerebrovascular disease in elderly individuals, and indeed dementia in the very old is usually due to the additive or interactive effects of multiple aetiologies (Ince, 2001).

In summary, there is a lack of empirical investigation of the co-morbidity of the neurocognitive disorders as a whole but the literature indicates high co-morbidity rates between some neurocognitive disorders.

Course of illness

The course of illness can be considered a unifying feature in that the onset is typically but not exclusively in late life. The course may vary, however, from recovery (e.g. delirium) to persistence (e.g. amnestic disorder) to progressive decline (e.g. AD).

The dementias typically have a late age of onset, with an exponential increase in incidence after the age of 65 years (Jorm *et al*. 1987). However, some dementias can develop in early or middle adulthood. The onset of delirium typically occurs in the elderly age bands ($\geqslant$65 years) with the highest prevalence of delirium being in populations aged >85 years. A higher risk of delirium has been linked with pre-existing dementia and is common in elderly medical in-patients (Burns *et al*. 2004; Siddiqi *et al*. 2006). The amnesias have a variable age of onset that is dependent on the underlying aetiology.

Most neurocognitive disorders are not reversible although partial recovery often occurs after acute brain injury. The exceptions are delirium (McCusker *et al*. 2003) and some transient amnesic disorders (Quinette *et al*. 2006). Prognosis for the neurocognitive disorders is poor, with the average duration of dementia from symptom onset to death being 8–10 years (Brookmeyer *et al*. 2002). This will greatly depend upon the type of dementia, but also varies with the stage of dementia and with individual factors such as brain reserve (Valenzuela & Sachdev, 2006*b*). Although delirium is considered transient, the predisposing vulnerability links it with poor hospital outcomes and a higher risk of death in elderly individuals (Inouye *et al*. 1998; Rockwood *et al*. 1999).

In summary, the course of the neurocognitive disorders is dependent on the type of disorder, the severity of impairment and co-occurrence of other physical health conditions. It cannot therefore be considered a unifying feature for this cluster.

Treatment response

As mentioned previously, the clinical course of neurocognitive disorders is variable, and at present the interventions available to significantly influence the course are limited. Delirium is an exception in which prompt intervention usually results in reversal of symptoms and recovery from the disorder. For the dementias, numerous treatments are being developed to reverse the symptoms and possibly influence the course of the disease. Cholinesterase inhibitors, specifically donepezil, rivastigmine and galantamine, have been proven to provide symptomatic relief in AD and DLB and possibly VaD, but there is no convincing evidence to suggest that they slow down the disease process (Hogan & Patterson, 2002; Erkinjuntti *et al*. 2004; Riepe *et al*. 2007). Most other extant treatments are for the behavioural and psychiatric symptoms, that is agitation, aggression, depression, anxiety, hallucinations and repetitive behaviours exhibited by patients. Cognitive and psychosocial interventions are important in the management of these disorders.

As far as the currently available treatments are concerned, it is neuropsychological rehabilitation and psychosocial interventions that are found to unify this cluster. It is possible that, in the future, treatments will be developed that target the pathomechanisms common to many of the disorders, such as oxidation, mitochondrial dysfunction, protein misfolding and aggregation and apoptosis, and these will provide unique unity to these disorders. Other promising treatments, such as those targeting the oligomers of β-amyloid in AD, will perhaps remain unique to certain disorders.

Conclusions

The disorders classified as the neurocognitive disorders meet some of the salient criteria proposed by the DSM-V Task Force Study Group to suggest a classification cluster. It is likely that continuing work on the pathogenetic mechanisms and the development of rational treatments will further enhance the features shared by these disorders and substantiate their natural grouping. It is proposed that these disorders be retained as a distinct cluster in DSM-V and ICD-11.

Declaration of Interest

None.

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