Neuropsychiatric Symptoms of Major Neurocognitive Disorders as a Model for Understanding Neuroanatomic Dysfunction in Primary Psychiatric Disorders

Benalfew Legesse1*, Simon Ducharme2, Brent Forester1, Bruce H Price1 and James Ellison1

1McLean Hospital, Harvard Medical School, USA
2Department of Neurology, McLean Hospital, Harvard Medical School, USA

EDITORIAL

Advances in neuropsychiatry are increasing our understanding of brain-behavior relationships. With this knowledge, the classification of illnesses as psychiatric and neurologic appears increasingly outdated [1]. A basic tenet in neuropsychiatry is that brain disorders produce neurobehavioral symptoms by disrupting functional neural networks [2]. The specific network(s) affected and the pattern of progression determines the clinical syndrome that will be manifested. The various clinical syndromes of Alzheimer’s Disease (AD) illustrate this point. The typical mesial temporal effects of this disease are associated amnesia, often one of the earliest symptoms of AD [3]; however, a small number of people with AD pathology present with language deficits (progressive aphasia) [3], visual symptoms (Posterior Cortical Atrophy) [3], or frontal syndrome [4], representing varied consequences of a shared pathological process with clinical features that are determined by the cortical area initially affected.

In Major Neurocognitive Disorders (NCD), cognitive impairment has been considered the core, disease-defining feature [5]; however, associated non-cognitive neuropsychiatric symptoms such as apathy, agitation, depression, anxiety and psychosis are very frequent [2,6]. Neuropsychiatric symptoms of major NCD begin early in the disease process, often during the mild NCD stage [7]. These noncognitive symptoms do not always correlate with the severity of cognitive impairment [8]. Pathologic, structural and functional imaging studies suggest that these neuropsychiatric symptoms are not simply non-specific consequences of cognitive impairment; rather, they are correlated with specific regional brain abnormalities [9].

The neuropsychiatric symptoms of Major NCD overlap clinically with those of diseases classified primarily as psychiatric, although disease course, prognosis, treatment approach, and outcome often differ. Psychotic symptoms occur in 41% of patients with AD [10] and in an even higher percentage of patients with Lewy body pathology. Dysphoria, irritability and anxiety disorders are also common co-morbidities in Major NCDs [6]. Apathy is present in more than 70% of patients with AD [6]. The examples above are selected to demonstrate the relationships and are not intended to be comprehensive.

Not only the clinical manifestations, but also the neuroanatomical bases of symptoms common to neurobehavioral disturbances in Major NCD and primary psychiatric disorders are shared [11].

For example, delusions in schizophrenia and NCD both correlate with frontostriatal and temporal network dysfunction [9,12,13]. Volumetric and functional studies of the brains of people with auditory and visual hallucinations, whether diagnosed with schizophrenia or Major NCD, consistently associate these symptoms with alterations of function in relevant sensory and association regions [13-15]. Apathy syndromes, seen in primary psychotic and mood disorders and in Major NCD, have been shown to involve anterior cingulate gyrus, basal ganglia and other frontal regions regardless of the syndromal diagnosis [12]. Anxiety and depressive symptoms in Major NCD and primary psychiatric disorders, too, share similar neural substrates [12]. Finally, failure of theory of mind, lack of empathy, and poor impulse control seen in behavioral variant frontotemporal lobar degeneration shares symptoms and orbitofrontal and ventromedial frontal dysfunction with autistic syndromes [16].

Cognition, behavior and movement are dependent upon the activity of at least five frontosubcortical circuits: the motor, oculomotor, dorsolateral prefrontal, orbital frontal and anterior cingulate circuits [17]. These loops link the basal ganglia and different functional subdivisions of the prefrontal cortex into segregated but interconnected systems. Each circuit shares the same principal components and structures: frontal cortex, striatum, globus pallidus and substantia nigra, and thalamus.
While two of these circuits are primarily associated with motor and oculomotor functions, the other three are intimately involved in cognition and behavior [17].

Frontal-subcortical circuits provide the neurologic substrate for cognitive, behavioral and affective symptoms in patients with some Major Neurocognitive Disorders as well as other primary neuropsychiatric disorders such as Tourette’s syndrome, Huntington’s disease, obsessive-compulsive disorder, schizophrenia, and mood disorders [18]. The differential location and effects of neuronal degeneration on these pathways plays a key role in determining the clinical appearances of these disorders, in part based on the extent to which the five frontal-subcortical circuits are differentially affected [19].

Given the overlap of clinical symptoms seen in cognitive and behavioral disorders and the shared neural circuitry of these symptoms, the study of neurobehavioral symptoms in Major Neurocognitive Disorders offers an opportunity for increasing our understanding of the functional neuroanatomical abnormalities in primary psychiatric disorders. A disorder such as AD is a particularly attractive condition to investigate in this way, given our growing understanding of its neuropathology and our access to biomarkers such as amyloid imaging, features that are still lacking for most primary psychiatric disorders.

In addition to shared symptoms and neuroanatomic changes, shared genetic predispositions between some neurodegenerative disorders and primary psychiatric disorders have been proposed [20], which will provide additional avenues for further investigation of the link between primary psychiatric disorders and neurobehavioral disturbances of cognitive disorders. Carefully designed and well powered longitudinal studies looking at cognition, neurobehavioral symptoms and structural and functional imaging in patients with neuropsychiatric disorders will likely shed light on the neuroanatomic substrates of primary psychiatric syndromes.

REFERENCES