EDITORIAL

Transdiagnostic neurology: neuropsychiatric symptoms in neurodegenerative diseases

The development of neurology over the last two decades has been characterized by a trend towards increasing hyper-specialization. Whereas many clinicians in the past felt comfortable dealing with the entire range of neurological disorders, this has now become extremely difficult—most might say, impossible—to achieve with the array of diagnostic and treatment options that have become established in many areas. For patients too, specialist clinics and expert advice have become crucial for their ongoing care. But it is also worth considering the possibility that hyper-specialism comes at a potential cost: loss of the ability to perceive, or even care about, the significance of common symptoms that cross conventional disease boundaries.

Even if there is awareness of ‘transdiagnostic symptoms’, it might be argued that these are not really worth worrying about too much because they don’t tell us anything fundamental about the disease process. Take depression or fatigue, two common and important symptoms that frequently occur in many neurological disorders. They are treated symptomatically and surely, many would argue, don’t tell us anything about the mechanisms underlying the diseases in which they occur. That might indeed be the case, although the fact that fatigue seems to occur more often in certain disorders, such as multiple sclerosis or Parkinson’s disease, raises the possibility that there might indeed be a biological basis to such symptoms, and that they are not merely a reactive, psychological response.

If that were to be the case, what would the common mechanism be that leads to fatigue across diverse diseases such as multiple sclerosis and Parkinson’s disease? Surely these disorders have very different underlying molecular pathologies, so there cannot be a common, mechanistic explanation across diseases? The answer though might not be at the level of molecular pathology. Both diseases are associated with disruption to brain systems and it is entirely possible that, regardless of the underlying pathology, the symptoms in any patient with either diagnosis arise because of the constellation of brain systems that are disrupted. Might there be common brain systems that are disrupted across diseases to lead to similar symptoms or phenotypes?

Intriguingly, very similar ideas have gained impetus in psychiatry where the attachment to diagnostic label is perhaps less strong, at least for some people. The lack of clearly established molecular signatures for the majority of psychiatric conditions means that there is growing concern that traditional disease categories might not capture underlying biology well. Frustrated with conventional diagnostic labels for psychiatric disorders, the National Institutes of Mental Health RDoC (Research Domain Criteria; www.nimh.nih.gov/research-priorities/rdoc/index.shtml) initiative seeks instead to describe brain functions and systems that are disrupted in any given patient (Kozak and Cuthbert, 2016). The ultimate aspiration might be to map disrupted brain function to specific brain circuits or networks, across conventional diagnostic boundaries. In turn, this might lead to treatments aimed at the disrupted function or network, regardless of the surface diagnostic label attached to a particular patient.

To make this more concrete, consider the negative symptoms that occur in some people with schizophrenia. Very similar symptoms of loss of motivation or anhedonia might occur in some individuals with major depressive disorder. Is it possible that both could be treated in the same manner? Perhaps, although it would be important first to ensure that seemingly similar symptoms of loss of motivation are actually manifestations of disruption to the same underlying brain system (Whitton et al., 2015).

Although these considerations are for brain disorders labelled ‘psychiatric’, there is no reason why the same logic would not obtain for diseases that fall under the care of neurologists. Just because we have better molecular or brain imaging markers for some ‘neurological’ disorders doesn’t mean we have an explanation for the varying constellation of symptoms associated with any one disease. Indeed, maybe these markers tempt us away from some important issues which, if addressed head on, might
actually make an important impact on the management of patients, across different brain diseases.

Take, for example, the case of neurodegenerative conditions. For many people, finding cures for these diseases means discovering treatments for the cognitive deficits associated with them: impairments in attention, memory, visuospatial ability, language and executive control. However, such a view risks ignoring the profound behavioural changes that often accompany and have such a major impact on quality of life in patients with these conditions (Wint and Cummings, 2016). A wide range of neuropsychiatric symptoms are now recognized to be associated with neurodegenerative disorders, with many patients suffering from more than one of these during the course of their illness.

The symptoms vary from agitation, irritability and impulsivity through to apathy and indifference, from depression to euphoria, from delusions and hallucinations to anxiety and sleep disturbance, from loss of empathy and socially inappropriate behaviour through to changes in eating behaviour and stereotyped behaviours such as pacing, wandering and rummaging. These neuropsychiatric changes cut across diseases. They occur frequently in Alzheimer’s disease, small vessel cerebrovascular disease, Parkinson’s disease and Lewy body disease, frontotemporal dementia (FTD) and a host of other conditions including Huntington’s disease, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) (Wint and Cummings, 2016).

In one community-based study from the USA, 97% of patients with dementia experienced at least one such symptom, with depression (77%), apathy (71%) and anxiety (62%) being most prevalent but disinhibition (31%) still occurring in a sizeable proportion (Steinberg et al., 2005). Neuropsychiatric symptoms have both psychological and physical effects, with a significant part of caregivers’ distress relating directly to them. Unsurprisingly, delusions and disruptive behaviours such as aggression appear to be the most burdensome to caregivers (Rocca et al., 2010). But even the less florid symptoms, such as apathy can impact profoundly upon people’s lives, across diseases (Benito-León et al., 2012; Hongisto et al., 2017).

Is it possible that disruption of common brain systems might lead to the same neuropsychiatric symptom across neurodegenerative diseases? The findings of several studies point to the possibility that this might be the case. For example, regions within medial frontal areas and basal ganglia have consistently been implicated across Alzheimer’s disease, Parkinson’s disease, FTD, PSP and CBS in patients with apathy (Rosen et al., 2005; Schroeter et al., 2011; Stanton et al., 2013). A report in this edition of Brain takes the transdiagnostic approach even further by examining both apathy and impulsivity in FTD, PSP and CBS (Landsall et al., 2017). The authors conclude that there might be common mechanisms underlying both these neuropsychiatric symptoms, across diagnoses.

Transdiagnostic approaches to neuropsychiatric symptoms might also have implications for therapy. Positive results for treatment of psychotic symptoms in Parkinson’s disease with pimavanserin, a drug that acts at the 5-HT2A receptor (Cummings et al., 2014), has been followed by a clinical trial using the drug in patients with Alzheimer’s disease who have psychosis. Preliminary results suggest that there were also positive effects in this group (http://ir.acadia-pharm.com/phoenix.zhtml?c=125180&p=irol-news Article&ID=2230818), although the data will need to be scrutinized carefully when fully published. Nevertheless, these findings point to the possibility that transdiagnostic approaches to neurological disorders might have an impact on our understanding both of the biology and the management of complex brain diseases.

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References
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