

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-specialisation. 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 (MS) or Parkinson's disease (PD), 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 MS and PD? 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 which 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 JL, 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 (AD), small vessel cerebrovascular disease, PD 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 JL, 2016).

In one community based study from the US, 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.*, 2008). Neuropsychiatric symptoms have both psychological and physical effects, with a significant part of caregivers' distress relating directly to them. Unsurprisingly, delusions and disruptive behaviors 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 AD, PD, 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, PSB 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 PD with pimavanserin, a drug that acts at the 5-HT_{2A} receptor (Cummings *et al.*, 2014), has been followed by a clinical trial using the drug in patients with AD 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-newsArticle&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.

Masud Husain
Oxford

References

Benito-León J, Cubo E, Coronell C, ANIMO Study Group. Impact of apathy on health-related quality of life in recently diagnosed Parkinson's disease: The ANIMO study. *Mov. Disord.* 2012; 27: 211–218.

Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised,

placebo-controlled phase 3 trial. *Lancet* 2014; 383: 533–540.

Hongisto K, Hallikainen I, Selander T, Törmälehto S, Väättäinen S, Martikainen J, et al. Quality of Life in relation to neuropsychiatric symptoms in Alzheimer's disease: 5-year prospective ALSOVA cohort study. *Int. J. Geriatr. Psychiatry* 2017.

Kozak MJ, Cuthbert BN. The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics. *Psychophysiology* 2016; 53: 286–97.

Landsall CJ, Coyle-Gilchrist IT, Jones PS, Rodriguez PV, Wilcox A, Wehmann E, et al. Apathy and impulsivity in frontotemporal lobar degeneration syndromes. *Brain* 2017; 140

Rocca P, Leotta D, Liffredo C, Mingrone C, Sigaud M, Capellero B, et al. Neuropsychiatric symptoms underlying caregiver stress and insight in Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 2010; 30: 57–63.

Rosen HJ, Allison SC, Schauer GF, Gorno-Tempini ML, Weiner MW, Miller BL. Neuroanatomical correlates of behavioural disorders in dementia. *Brain* 2005; 128: 2612–2625.

Schroeter ML, Vogt B, Frisch S, Becker G, Seese A, Barthel H, et al. Dissociating behavioral disorders in early dementia—An FDG-PET study. *Psychiatry Res. Neuroimaging* 2011; 194: 235–244.

Stanton BR, Leigh PN, Howard RJ, Barker GJ, Brown RG. Behavioural and emotional symptoms of apathy are associated with distinct patterns of brain atrophy in neurodegenerative disorders. *J. Neurol.* 2013; 260: 2481–2490.

Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int. J. Geriatr. Psychiatry* 2008; 23: 170–7.

Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr. Opin. Psychiatry* 2015; 28: 7–12.

Wint D, Cummings JL. Neuropsychiatric aspects of cognitive impairment. In: Husain M, Schott J, editor(s). *Oxford Textbook of Cognitive Neurology and Dementia*. Oxford: Oxford University Press; 2016. p. 197–208.