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Editorial

Is there a cognitive signature for multiple sclerosis-related fatigue?

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There is a very large literature devoted to fatigue associated with multiple sclerosis (MS). This no doubt reflects the importance of the symptom, present in up to 80% of people with MS, two-thirds of whom rate it as one of their most troubling difficulties.[1,2] However, it is also likely that the size of the literature is an indication of uncertainty amongst clinicians and researchers as to a host of factors. These include the degree to which the symptom can stand alone and be measured objectively unencumbered by numerous potential confounders, the neural and biochemical abnormalities that give rise to the problem and, finally, and most importantly from a patient perspective, how best to treat it. Fatigue is not unique in this regard, but its prominent place amongst a list of equally complex abstract phenomena, like sadness, euphoria, irritability and pain, keeps it firmly in the cross hairs of researchers.

Wading through a weighty literature replete with so many competing theories and inconsistencies can by itself be a fatigue-inducing exercise, so it is invigorating to encounter a new idea that merits careful consideration. Hanken et al. propose that there is a particular cognitive signature for MS-related fatigue.[3] They have arrived at this conclusion by undertaking an extensive review of the MS cognition literature as it pertains to fatigue. This reportedly revealed an association between fatigue on the one hand and tests of alertness and vigilance on the other. Learning, memory, information processing speed, selective attention language and visuospatial processing, all affected to varying degrees in a substantial number of people with MS, showed no clear relationship with fatigue. Moreover, the authors reported finding an anatomical overlap between regions of brain atrophy (anterior cingulate, frontal and parietal cortex) in fatigued MS patients and the very same regions that activate on functional magnetic resonance imaging in healthy subjects performing tasks that probe alertness and vigilance. This, in turn, was cited as further evidence boosting the construct validity of their cognitive-fatigue hypothesis.

So far so good. But in arriving at this theory, the authors assume that fatigue is distinct from the lack of energy that characterizes the phenomenology of depression. It is not, however, clear how they disentangled this potential symptom overlap in their literature review. This is a thorny question because the phenomenology is key here and if there is no clear distinction made then the anatomical construct in particular breaks down. Of note is that fronto-parietal regions have been associated with MS-related depression too.[4]

The authors then speculate further by focusing on two neurotransmitters, noradrenaline and histamine, and suggest that inflammatory processes might lead to a down regulation of neurons releasing one or both of them, thereby inducing fatigue. However, there are no data to support such an opinion. The inflammatory hypothesis would imply that fatigue is only present, or more prominent, in relapsing-remitting (RRMS) as opposed to progressive MS. This is surely incorrect. Once more we circle back to depression, for if the neurotransmitter theory is to hold true, then what are we to make of a strong literature linking noradrenaline to depression, not just the fatigue associated with depression as the authors selectively highlight, but the core features of sadness, anhedonia, guilt, pessimism and so on. It also takes a stretch of the imagination to suppose that a multi-focal disease like MS selectively targets noradrenergic and histaminergic pathways only in a pervasive symptom like fatigue.

It is of course easy to criticize theories and hypotheses and when it comes to fatigue the complexity of the phenomenon almost invites it. There are many interesting and compelling aspects to the theory proposed here, but it is uneven with the strength of the cognitive-anatomical correlates undermined by looser and more speculative theorizing in relation to putative neurotransmitter abnormalities. Theoretical papers like these are nevertheless likely to stimulate a lively debate. which in itself can be useful, particularly given the importance of this topic. They also fulfill

another important task, providing the basis for further empirical inquiry in which the novelty of the ideas can be put to the test. The hypotheses set out here are all testable. Now for the data.

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