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Abstract

Background: Researchers have attempted to operationalise objective measures of cognitive fatigability in MS to overcome the perceived subjectivity of patient reported outcomes of fatigue (PROs). Measures of cognitive fatigability examine decrements in performance during sustained neurocognitive tasks.

Objective: This editorial briefly summarises available evidence for measures of cognitive fatigability in MS and considers their overall utility.

Results: ~~Findings~~ Studies suggest there may be a construct that is distinct from self-reported fatigue, reflecting a new potential intervention target. However, assessments vary and findings across and within measures are inconsistent. Few measures have been guided by a coherent theory, and those identified are likely to be influenced by other confounds, such as cognitive impairment caused more directly by disease processes, depression, and assessment biases.

Conclusions: Future research may benefit from (a) developing a guiding theory of cognitive fatigability, (b) examining ecological and construct validity of existing assessments, and (c) exploring whether the more promising cognitive fatigability measures are correlated with impaired functioning after accounting for possible confounds. Given the issues raised, we caution that our purposes as researchers may be better served by continuing our search for a more objective cognitive fatigability construct that runs in parallel with improving, rather than devaluing, current PROs.

Key words: Cognitive Fatigability, Fatigue, Multiple Sclerosis.

Introduction

A 2013 review on conceptualising fatigue in neurological conditions suggests separating perceptions of fatigue from the concept of fatigability[1]. Perceptions of fatigue in MS are measured by range of standardised patient reported outcomes (PROs) of the severity and/or impact of mental and/or physical fatigue[2-4]. Kluger et al argue that in contrast to these subjective reports, fatigability should be measured via objective indices and differentiates between motor fatigability, such as decline in peak forces after exercise, and cognitive fatigability[1]. Cognitive fatigability is defined as a "decline in processing speed, reaction time or accuracy over time after completing demanding cognitive tasks." (p.2).[5] In this personal viewpoint paper we present some of the challenges related to the measurement of cognitive fatigability specifically, and raise questions around their overall utility, ecological validity, and objectivity.

One of the key challenges is the inconsistency of operational definitions and measures applied across studies. To illustrate this, Table 1 summarises some of the measures and results from 21 studies that have been used to operationalise cognitive fatigability measures used in the context of MS[6-26]. Where relevant, the table differentiates between the demanding or continuous cognitive task and the measure of fatigability used alongside this task, but it is clear a wide range of methods and assessment have been used. We differentiate between the demanding or continuous cognitive task and the measure of fatigability used alongside this task. If we apply the definition of cognitive fatigability as a significant decline in processing speed, reaction time, or accuracy over time, after completing demanding cognitive tasks,[1, 5] oOf the 21 studies outlined in Table 1, 9 eleven show support for proposed measures of cognitive fatigability[6, 7, 11, 13, 15, 17, 20, 21, 23], indicated by an (*), next to the author's name, whilst 10 8 do not.[9, 12, 14, 16, 18, 19, 25, 26]

[Table 1 Here]

Challenges with existing measures

The principal challenge of most cognitive fatigability measures summarised in Table 1 appears to relate to paucity of theory. Some of the variability may be due to idiosyncratic definitions of fatigability. For example, Parmenter et al. ran a series of tasks with people with MS (pwMS) during periods of high, and relatively low, self-reported fatigue over two separate testing periods on different days [8]. There was no evidence of measuring fatigability before and after a demanding task. Other studies have used a similar approach[22, 24]. The theory and construct underpinning such methods is not clear. Indeed, only a handful Some of the studies in Table 1 refer to an *a priori* guiding theory, or pre-specified underlying mechanism(s), to understand the construct of cognitive fatigability construct[11, 13, 15, 17]. For instance A good example is, Sandry et al[15] where the authors set out to test cognitive load[16], cognitive domain[27], and temporal fatigue hypotheses[28]. More theoretically guided mechanistic work is needed to understand fatigability. whilst others tendednot to discuss theory If we fail to clearly conceptualise the construct we are trying to measure it becomes challenging to measure it accurately. The fact that some of the studies listed in Table 1 have used varied study designs and metrics that are inconsistent with existing operational definitions may be a symptom of this problem. For example, Parmenter et al tested pwMS during periods of high, and relatively low, self-reported fatigue over two separate testing periods on different days[8], and similar to other studies[22, 24], did not assess a decline in either information processing speed, reaction time or accuracy over time on *continuous performance* task, or probe task given *before and immediately after completing* a demanding cognitive task[1, 5], nor explicitly define how they operationalised cognitive fatigability[8, 24].

It is also unclear how existing cognitive fatigability constructs relate to ~~existing~~ self-reported fatigue severity, and whether this is actually important. Collectively, ~~empirical~~ studies to date show marked inconsistency in this regard, where some show significant small to moderate associations with self-reported fatigue[11, 13, 14, 19, 20, 23, 24], and others demonstrate no, or inconsistent, relationships across different PROs or subscales[6, 7, 9, 15, 17, 21]. ~~In addition,~~ O~~o~~nly four studies have specifically assessed self-reported *cognitive* fatigue in conjunction with cognitive fatigability outcomes, which in the majority of cases show relatively strong positive associations when compared to more general measures of self-reported fatigue[6, 22, 23, 25]. The divergent correlational findings between measures of self-reported fatigue and cognitive fatigability across studies, and the differences between the magnitude of correlations between self-reported general and cognitive fatigue measures, have tended not to be explored further by most authors. Rather there appears to be a more implicit assumption that (a) the proposed cognitive fatigability construct is valid because it correlates with self-reported fatigue, or (b) no, or small, associations mean~~s~~ a distinct construct has been identified. This suggests there may be a potential disparity in how the cognitive fatigability construct is conceptualised by researchers, where such divergent, and potentially self-confirming, accounts of cognitive fatigability reflect a lack of theoretical clarity and guiding hypotheses stemming from these.

In addition, as limited attention has been paid to explaining potential mechanism(s) or factors, which may influence cognitive fatigability there is little guidance as to whether or how we might improve this outcome in the context of treatment trials. As far as we are aware, ~~Currently~~ no studies have examined whether cognitive fatigability~~, as measured in studies in Table 1,~~ in pwMS is amenable to change. Until we demonstrate that cognitive fatigability can be measured reliably, and modified to show clinically meaningful improvement, it may not be a useful outcome parameter for intervention research.

A second ~~related~~ problem ~~for all proposed measures of cognitive fatigability in Table 1 relates~~ is the ~~to their~~ ecological validity of measures. Self-reported fatigue is consistently related to poor quality of life, greater disability, and is the most cited reason pwMS stop work[29]. ~~-~~In contrast, few studies have explored the associations between cognitive fatigability measures and PROs assessing fatigue-related impact, and other domains such as physical or social functioning. Therefore, it is not yet clear whether a person's fatigability ~~impaired performance~~ on reaction time and demanding ~~accuracy~~ tasks directly translates to greater levels of fatigue-related disability when encountering everyday tasks.

When considering the multifaceted nature of fatigue, a third complex issue is the degree of potential confounding associated with cognitive fatigability measures. Specifically, few studies ~~listed in Table 1 attempted to~~ control for the influence of other potential~~ly~~ ~~overlapping~~ confounds in addition to neurological impairment~~processes~~, such as depression ~~, extent of neurological disability, and~~ or ~~testing-related~~ performance anxiety, making interpretation of findings challenging, and statements about "greater objectivity" of fatigability~~with neuropsychological~~ assessments somewhat less persuasive.

Disentangling secondary and primary fatigability may also be important. Kluger et al. ~~have termed,~~ defined "secondary" fatigue or fatigability~~, defined~~ as fatigue arising from "medications, chronic pain, physical deconditioning, anaemia, respiratory dysfunction, depression, and sleep disorders" (p.411[1]). Whilst ~~Apart from~~ seven studies in Table 1 [9, 11, 13, 14, 20, 23, 24]~~,~~ attempted to account for these factors most did not. ~~what Kluger et al. have termed, "secondary" fatigue or fatigability, defined as fatigue arising from "medications, chronic pain, physical deconditioning, anaemia, respiratory dysfunction, depression, and sleep disorders" (p.411[1]).~~ Distinguishing between primary and secondary fatigue may further inform the nature of the construct, development of theory and other potentially modifiable treatment targets that could lead to clinical improvement.

~~A related problem is that most studies relied on global scores of cognitive impairment, e.g. the Paced Auditory Serial Addition Test three-second version (PASAT "3), which are traditionally designed to tap finer-grained neurocognitive problems, which again raises the question of how useful the terms we create are to describe fatigability specifically. For example, proponents of cognitive reserve theory, defined as both an active and passive process by which the brain actively attempts to cope with or compensate for pathology, might argue that cognitive fatigability merely reflects a person's attempt to attend to tasks more closely or slowly, and therefore expend more limited cognitive reserves far more quickly than individuals with less advanced disease or no pathology.~~

A fourth problem is that current empirical studies attempting to replicate findings across ~~identify~~ cognitive fatigability measures show mixed results. ~~constructs paint a mixed picture.~~ Neuropsychological assessments vary, and findings across[8, 16, 25] and within (e.g. PASAT[9, 18], SDMT[14], TOL[8]) measures appear to be somewhat inconsistent. Although we accept authors will invariably adopt different procedures and metrics, findings indicate that not all proposed cognitive fatigability measures have been replicated in other studies, and therefore conclusions in many cases are based on rather preliminary data, often with small to modest, and in one case uncontrolled[21], samples. For this reason, attempting to answer which is currently the best measure to use may be premature at this stage. However, some studies have made good efforts to minimise several sources of potential confounding where possible[14, 23, 24], or replicated findings with similar assessments, such as the Alertness subtest of the computerized Test

Battery for Attention Performance (TAP)[6, 23, 24], and different versions and scoring methods of the PASAT.[17, 19-21]

A final tangle in this seemingly Gordian tale relates to the practical difficulties of using what are potentially complex and lengthy procedures. Some are brief single-session assessments (e.g.[7]), whilst others can take up to up a month to assess (e.g.[9]), which renders the utility of the latter potentially limited in the context of time-pressured clinics and clinical trials.

Moving forward

Overall, cognitive fatigability may be a valuable construct to pursue, particularly if we wish to study the mechanisms associated with fatigue and cognition, and their interaction. Clearly there is a need to develop more theoretically grounded, valid, reliable and sensitive measures of cognitive fatigability for the purpose of clinical trials. However, at present it is unclear how much added value cognitive fatigability as a construct offers, in terms of enhancing our understanding of MS fatigue, when developing new treatments, or when evaluating the effectiveness of such treatments. For example, future research might well pave the way for novel remedial treatment components ~~based on improving cognitive reserve~~, which may enhance existing treatments for fatigue, such as energy conservation methods[30]; cognitive behavioural[31] or exercise therapy.[32]

Given the arguments presented, we will briefly outline what we perceive to be two important next steps in this area.

IIf we are to better understand the role of cognitive fatigability four key improvements could be addressed in future research. First, attempts should be made to In order to work more effectively and coherently towards this goal, future research into cognitive fatigability may initially benefit from (a) developinging a clear theory of fatigability, perhaps drawing on Kluger et al and Arafah et al's existing definitions, but also distinguishing between primary and secondary fatigue[1] and broader biopsychosocial models of MS fatigue (see e.g. [33])., which relates to the chosen measure. Second, more needs to be done to(b) eexamininge the ecological and construct validity of current measures which show best promise in this area existing assessments, including whether they generalise to people's experience of everyday cognitive demands. From the studies in Table 1, we suggest that the Alertness subtest of TAP and different versions and scoring methods of the PASAT may be most promising to explore. Third, , and (c) exploring explore whether the more promising cognitive fatigability measures are correlated with impaired functioning after accounting for possible confounds, and teasing tease out the extent to which these relationships overlap with existing PRO measures of cognitive fatigue severity and/or impact. In additionFinally, when designing new outcome assessments it would be helpful to consider the practical application of measures to ensure they have good utility in identifying clinically meaningful improvement, alongside PROs, in the context of sufficiently powered and theoretically-driven treatment trials.

It is also important to note, that whilst it may be helpful to further examine the role of cognitive fatigability, it should not be assumed these more objective measures are in some way superior to PROs in some dualistic "mind-body" explanation. Self-report instruments are a valid and important way of assessing people's perception of fatigue and its impact. It is important that we trust pwMS account of their experience and assume what they tell us is accurate. Given the issues raised,Therefore, we caution emphasise that our purposes as researchers may be better served by continuing our search for a more objective cognitive fatigability construct that runs in parallel with improving, rather than devaluing, current PROs.

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