Author’s response to reviews

Title: Quantifying cognition at the bedside: A novel approach combining cognitive symptoms and signs in HIV

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Response to Reviewers

We have undertaken revisions to address the comments from Reviewer 2, which we detail point-by-point, below.

1. “Interventions may be more likely to succeed at earlier stages of [cognitive] impairment.” To better motivate the need for early screening and identification, please clarify which interventions, and provide citation

This sentence has been reworded, and references provided.

With regard to comment #1, the authors reword as follows: "there is an increasing focus on intervening at the first signs of decline". The authors state several times in this paragraph that identification of mild cognitive impairment in its earliest stages is a priority, that there is increasing focus on this, etc — but a statement about why this should be, and what the anticipated benefits to patients and clinicians might be, would go a long way in terms of motivating the paper.

A sentence has been added to make this point clearer.

3. The authors state that a "systems" approach to neuropsychological testing "may be less appropriate in HIV, where deficits likely arise from diffuse network degradation rather than the focal cortical or hippocampal degeneration seen in many primary neurological disorders." Most
neurodegenerative disorders are associated with disruptions in specific networks rather than focal degeneration (Seeley 2009, Neuron). Some degenerative disorders, including vascular dementia, chronic traumatic encephalopathy, and others, can show similar cognitive deficits to those described in HIV (attention, executive function, processing speed). The authors should clarify what makes HIV cognitive impairment special and why it is appropriate to measure cognitive function as a single construct in this disorder, as opposed to other disorders.

We did not mean to imply that HIV was “special” in this regard. We fully agree with the reviewer that there are many conditions that involve diffuse network degradation. We have reworded this paragraph to remove the unintended implication. The question of whether it is appropriate to measure cognition as a single construct is an empirical one that is addressed by this paper. It might also apply in other conditions, but this is beyond the scope of the current work.

With regard to comment #3, in their revision, the authors now state that deficits in HIV arise from diffuse network degeneration as opposed to the focal degeneration seen in Alzheimer's disease. Although early Alzheimer's disease may show the greatest structural atrophy in the hippocampi, as with other neurodegenerative disorders, it is associated with widespread disruptions at the network level as well. This statement should be reworded. It may be more fair to state simply that the pattern of deficits seen in HIV (attention, executive function, processing speed) is one that the authors hypothesize could be conceived of as a single construct, rather than trying to draw a distinction between "diffuse" network degeneration in HIV vs other disorders (particularly those, such as vascular dementia, CTE, etc that may present with similar deficits).

This study does not intend to make any claim about other ‘diffuse’ conditions. We included this introductory framework because we thought it would be interesting to clinicians, and make the Rasch analysis approach, which is novel and therefore often daunting to non-experts, more intuitive. We think it likely that all the conditions the reviewer mentions would be amenable to the same measurement approach, but this is obviously beyond the scope of the current study. We have removed the sentences that were troubling this reviewer.

10. The implications of a large percentage of participants meeting criteria for depression are very important here, especially as authors describe depression being a major confound for clinicians confronted with patients with mild cognitive complaints, and prior reports have shown that self-reported cognitive symptoms correlate highly with depressive symptoms and not as well with objective task measures (cited in Valcour 2011).

First, we clarify that only 37% of the sample met the cut-off for depression on the HADS or the BDI. We are able to confirm that those with and without depressive symptoms all fit the same Rasch model: that is, the presence of depressive symptoms did not exclude the person from being accurately measured on the items.

With regard to comment #10, the authors state "We are able to confirm that those with and without depressive symptoms all fit the same Rasch model." Would provide statistical evidence of this in the results section.
All participants, with a single exception, did fit the same Rasch model. This provides statistical evidence that the presence of depressive symptoms does not preclude measurement using the same hierarchy of items as is used to measure the non-depressed participants.

Though the caption explaining the abbreviations for the tests cited is helpful, Table 4 remains difficult to interpret. Recommend highlighting items from different groups in different colors or otherwise reworking.

The aim of Table 4 is to illustrate that self-reports are interspersed with performance-based items all along the hierarchy of cognitive ability. The specific performance-based items are by no mean a final set of items, and have been described in detail in another paper, which we cite. The caption gives an indication of the content of the items, many are well known to clinicians experience with bedside cognitive tests (for example, clock contour, serial 7s, fluency). The main point of this figure is to show that that some self-reported cognitive difficulties (in shaded boxes) relate in a predictable way to some performance-based items, which is the main finding of this study. This point has been made more explicit in the paper.

We hope that these additional changes will be to your satisfaction.