Author's response to reviews

**Title:** Hyperactivity Persists In Male and Female Adults with ADHD and Remains a Highly Discriminative Feature of the Disorder: A Case-Control Study

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Deesha Majithia, MSc  
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Dear Deesha,

Here is a revision of the manuscript “Hyperactivity Persists In Male and Female Adults with ADHD and Remains a Highly Discriminative Feature of the Disorder: A Case-Control Study”.

We have addressed in the revision all of the reviewer’s concerns and thank Professor Hughes for his insightful comments. We hope that the manuscript will now be acceptable for publication.

The following is a point-by-point response to the critique.

- **Q.** The Wender Utah Interview needs to be described and referenced and rationale for its choice. It is not as commonly used as other interviews (e.g., SCID).
- **A.** True - good pickup. The “Wender Utah Interview” is jargon we use in the lab. It is now correctly stated as the interview version of the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAAS) [1]. This was used to provide a series of adult ADHD-focused questions, as the SCID (Structured Clinical Interview for DSM-IV Disorders-I) does not assess for the presence of ADHD.

- **Q.** Tested twice per visit? Order of testing for the 4 attention tasks is randomized and important; but then two left out?
- **A.** Subjects were tested on all four tests in random order, though testing was spread out across two sessions. Taking more then two CPT-type tests in a single session would likely produce deteriorating results.

- **Q.** Please elaborate on the rationale for the choice of the No-4’s cognitive control test as opposed to the other Quotient tasks available? How do the different tasks differ from each other and how does it match up with Conner’s CPT-II? Was this an a priori decision? That isn’t clear. It also sounds like 3 types of tests were administered and No-4 chosen to compare to CPT-II. Why the other two test data aren’t presented is not elaborated upon. Should the statement where the decision to only compare the two is stated, be closer to the statistical analyses?
- **A.** Good point. We now describe the three different attention tasks with motion capture. These were the No-4’s cognitive control task, the Cued Response task and the Embedded Memory task. We indicated that
the No-4’s cognitive control task was selected for commercial development as its high target density
(90% targets) made it most suitable for analysis of fluctuations in attention state [2]. Results were not presented from the Cued Response and Embedded Memory task as motion measures were very similar between the three tests, and the Cued Response and Embedded Memory tasks were no better then the No-4’s task in discriminating subjects with ADHD from controls based on attention performance. Further, these two tasks were abandoned and are unavailable.

The statement regarding the decision to only compare the No-4’s and Conners CPT-II appears at the end of the protocol section shortly before the data analysis section. As this decision is now presented over two paragraphs (as oppose to a few sentences) it will be hard to miss.

Q. Does anything need to be said about foot movement measures since not used or valid apparently?

A. We don’t think that anything more needs to be stated. They were less valid then the leg measures (as the marker was more frequently obscured from camera view) but are highly correlated with the leg measures.

Q. Good definition of the various measures. But consider elaborating on derivation of “discriminative index” for Quotient, and “confidence index” for CPT-II and how they are, or are not related.

A. We now indicate that the Discriminative Index for Quotient was derived using logistic regression and the most important predictors were leg measures, head measures, attention shifts and errors of omission. We also indicate that the CPT-II Confidence Index was derived using discriminant analysis, and that the most important predictors were percent omissions, gender, age, beta, and reaction time across interstimulus interval.

Q. Data analysis: Is arguing, related to activity, that less significant or less able to discriminate, a variant of arguing to prove the “null hypothesis”?

A. No, we don’t believe so. The null hypothesis would be: r1 = r2. We are endeavoring to reject the null hypothesis by demonstrating that r1 < r2, or r1 > r2. However, we reordered the wording to state this in a more conventional way to avoid confusion ... “to test the hypothesis that attention measures were more significant and better able to discriminate between groups then objective measures of activity”.

Q. Statistics are well described and elaborated upon in text. I like the use of various models to describe the findings and believe that clearly strengthens the argument for importance of movement. Table 5 seems to be somewhat of an overkill, but I guess it sure addresses statistician’s concerned or who argue for certain models. They’re all there and basically support similar findings. Suspect some readers may be less familiar with the various Forest regressions or use of their statistical packages (documentation is good however). Might comment on that for the SAS/SPSS/S-Plus users; i.e., why it was chosen.

A. Thank you. We’ve now provided a conceptual description of random forests, neural network and support vector machines for reader unfamiliar with their use.

Q. Some might question why not test significance of age difference in demographics? Doesn’t matter to me - they’re close enough with SD reported. And inclusion as a covariate in the various models also supported that it was not a significant factor (important finding in itself).
A. Yes, now included.

Q. Is Figure 1 based on the best representative of an ADHD male and female and Control the best representative of a normal male and female? OR better, is it possible to create an overall composite? Some will always argue that the most representative was selected.

A. Good point. We’ve revised the figure to specifically select male and female ADHD and controls whose movement measures (microevents of head and shins) were closest to their respective group means.

Q. In Figure 2 it was hard (w/o color) to know with certainty which line went with which group – consider dotted, hashed, etc for black and white – might consider adding median cut-point.

A. Good point. Hopefully the Figure will be available in color. But for those who print it in black & white it has been modified to have dotted and hashed lines for clarity.

Q. Figure 3, not sure that all of the variables/measures are adequately defined anywhere. Or an explanation of why some repeat with this particular analysis (e.g., errors of commission, spatial complexity on mean decrease accuracy and mean decrease Gini)?

A. The mean decrease accuracy graph and mean decrease Gini graph represent two different ways of evaluating the importance of a variable as a predictor. Hence, all of the variables/measures were shown on the two graphs. This has now been clarified in the figure legend and better explained. All variables are mention on pages 18 and 19 of the manuscript, and descriptions provided for those that are likely to be less familiar. These are also the variables included in the Tables.

Q. Tables 1, 2 and 3 can be shortened with footnote of no significant effects of gender or age covariates using q-values and eliminating those columns of statistics. Likewise in text with a simple statement to the effect that age and gender were not significant covariates.

A. Tables were modified as suggested and statements about non-significance of age and gender effects added to text.

Q. Importance of Table 4? Please elaborate rationale and more written on significance of the findings.

A. Good point. We’ve added the following information.

Impairments in executive functions in adults with ADHD correlate with problems in occupational performance [3], and disturbances in executive function are considered by some investigators to be the underlying problem in ADHD, with inattention, hyperactivity and impulsivity as byproducts [4, 5]. If hyperactivity abates in adults with ADHD then objective measures of activity should correlate less strongly with executive function ratings then objective measures of inattention.

In short, the strong association between impairments in executive function and objective measures of activity is consistent with the hypothesis that these phenomena are neurobiologically interrelated.

Q. Discussion: Any comments about the impact of CPT ISI, position of stimulus, percent trials with
stimulus, and type of stimulus (figure vs. letter) on why this might make a difference in any of the results? Or is it safe to argue that this doesn’t matter given the activity findings. What about the neurobiology of figures vs. letters and how that might affect performance?

A. A paragraph was added discussing some of the differences between No-4’s and CPT-II, however in the end it is safe to argue that these differences do not matter much given the activity findings.

Q. Could they include a little more on the neurobiological basis of the activity from their earlier work that readers may not be familiar with or have access to?

A. This information is now provided and used to solidify the neurobiological associations between inhibitory motor control and executive functions. Thank you for the suggestion.

Sincerely yours,

References: