Author's response to reviews

Title: A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls A large case control study

Authors:

Frank H Duffy MD (fhd@sover.net)
Heidelise Als PhD (heidelise.als@childrens.harvard.edu)

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Author's response to reviews: see over
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RE: Manuscript 1580389126643948, Revision 2

Dear Lee,

We submit for your consideration our second revision of the manuscript entitled: *A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls - A large case control study*

We thank the Editor and the Reviewers for their second review of our manuscript and their additional insightful comments and criticisms. We attempt to answer these in the order they were raised. We believe that our revised manuscript is further improved given the additional thoughtful comments and criticisms offered.

Altered portions of the manuscript are highlighted in yellow.

**Reviewer 1**

We thank Reviewer 1 for the re-review of our revised manuscript and appreciate the Reviewer’s acceptance of the revisions we have made.

**Reviewer 2**

*Comment 1:* Reviewer 2 ‘…strongly suggest(s) that the authors stick to the technically accepted definitions of coherency and coherence rather than attempt to make their own definition of these important measures. First, COHERENCY is the ratio of the cross-spectrum to the square-root of the product of the two auto-spectra. It is a complex-valued quantity. Second, COHERENCE is the square modulus of coherency. It takes on a value between 0 and 1.’

*Reply to Comment 1:* We completely agree with Reviewer 2 and we accept his technical definitions which we have now incorporated in the Methods section, replacing our own.

*Comment 2:* Reviewer 2 states that the ‘…procedure for artifact rejection
remains unclear. … My own guess is this: (1.) First fit a linear regression model to each channel where the dependent variables are the EEG series and the independent variables are the different spectral components; (2.) Second extract the residuals which now represent the EEGs with artifacts removed and finally (3.) use these residuals in subsequent coherence analysis.’

**Reply to Comment 2:** The Reviewer is correct. We thank the Reviewer and have taken the liberty to use the Reviewer's specific comment in substitution of our earlier explanation in the Methods section with minor context related modification.

**Reviewer3:**

**Comment 1:** Reviewer 3 states that there are ‘... two major compulsory revisions remaining: 1. It is a substantial defect of the MS that the authors do not properly describe in their Discussion the most important results of the study for other researchers/clinicians. Precisely what are the most important ASD coherence characteristics in terms of increase/decrease in particular frequencies in particular regions?’

**Reply to Comment 1:** We have extended our findings with Reviewer 3’s comments in mind. For example from the Results section we report now in the Discussion section (1) that there was no obvious relationship between factor coherence electrode distance and/or involved spectral bands (Table 7); (2) that there was only a weak dominance of slow beta as the most involved spectral band and this is of uncertain significance; and (3) that no single lobe was more involved than any other. Moreover, we note now based on our results, that in agreement with many other studies, we identified a predominance of reduced coherence but also the presence of increased coherence. Other investigators have noted this as well and we reference the pertinent studies. We added, (1) that in contrast to others’ findings the coherence patterns we identified were sufficiently stable as to facilitate successful use in individual subject classification; and (2) that diagnostically useful individual factors showed loadings over a wide spectral range which to our knowledge has not been reported before. We speculated upon the clinical meaning of this latter finding. We report further (3) that the single most useful factor, namely factor #15, in ASD discrimination spatially appears to coincide with the left temporal Arcuate Fasciculus which has been speculated as abnormal in autism and recently shown to be so by MRI. We referenced the MRI study.

**Comment 2:** Reviewer 3 goes on to state that there is …‘2. … one further glaring problem remaining with this MS, concerning the authors’ reply to my previous comment:- (prior) Comment 3: ‘The findings of the study are related poorly to prior work cited in the Introduction. This needs to be discussed before the more speculative material.’ Essentially the authors ignore all previous coherence studies on ASD. While I appreciate their focus on methodology, their actual findings warrant publication here, not just methodology. What useful information can clinicians/researchers gain from this study NOW. Please list and discuss your most important ASD differences, then relate them to previous findings.’

**Reply to Comment 2:** We have modified and expanded the Discussion in keeping with Reviewer 3’s criticisms. We also now indicate the nearly universal finding of coherence change; furthermore we have referenced the publications that have preceded our studies in these discoveries. We have furthermore expanded the
discussion of our findings in order to amplify the clinical and research implications of our findings.

Additional more specific discussion of further detail (which we considered and from which we choose to refrain) in the ways in which our study differs from those of other authors, might have necessitated discussion on methodological or population differences and how they might have influenced results of some of the earlier studies: such as, among others, studies of adult populations, studies of high functioning ASD; the use of small group sizes; the absence of detailed artifact management; the use of sleep as a representative state; the potential dominance of muscle in gamma band EEG; the use of inappropriate statistics in the assessment of ASD-group vs. C-group coherence differences when large numbers of coherences/frequencies are analyzed; and the use of \textit{a priori} selected coherence pairs which may overlook unanticipated but important coherence associations and may limit generalizability of results, to name the most salient ones. It is our judgment that the population studied and methodology employed in our study and described in detail makes clear the differences and potential advantages over other approaches. We are hopeful that Reviewer 3 will agree with our decision and finds that our revised manuscript is now sufficiently responsive to his excellent points.

Again, we thank the Editor and the Reviewers for their additional insightful comments and criticisms and have taken great care to reply comprehensively. We have made the requested changes and consider the now substantially revised manuscript much improved on the basis of the reviewers and the editor’s comments. We trust that the revised manuscript now meets the Editor and Reviewers’ expectations.

In hope of a favorable review, we remain

Sincerely,

Frank H. Duffy, MD
and
Heidelise Als, PhD
The first place for children