Author’s response to reviews

Title: Autism, Spectrum or Clusters? An EEG Coherence Study

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Dear Dr. Sicca

We thank you very much for your very thoughtful review of our recent submission that demonstrates the usefulness of EEG coherence factor based clusters in subjects on the autism spectrum. Per your suggestions the Discussion section has been augmented in two ways:

First, to more clearly elucidate the relevant domains that would be useful in establishing a future understanding of the cluster membership characteristics with references, including your very helpful points regarding presence or absence of epileptiform activity.

Second, to explain that our future plans include accessing new, suitable populations of ASD subjects with one or more of the desired evaluations or tests. As explained it would be a straightforward task (assuming these new populations have EEG data) to create on the new EEG data, coherence factors and discriminant rules based upon the current manuscript’s population EEG data. In this manner we would be in a position to establish relationships between external variables and EEG coherence data in ASD including differences between clusters C1 and C2.

We thank you for the time and effort you devoted to the review and we

Remain respectfully yours,

Frank H. Duffy, MD
Heidelise Als, PhD

18oct2018
Dear Dr Berchio

Thank you for your helpful review of our current manuscript that delineates two EEG coherence based clusters in ASD.

“…clarify Personality issues…” we have removed this unnecessary comment.

“…three dimensional space…” It referred to the three ‘automatic recognitions’ of Pruett and Povilelli. We have removed the above phrase as unnecessary and confusing.

“…list of discrete studies” We felt it was important to justify (1) that clusters could be found, (2) that methods varied considerably, and (3) results were based upon a mix of quantitative analysis and upon investigators’ conclusions. This sections “roughness” reflects the variegated approaches clinically utilized in autism to date.

We have also ADDED “goals” and “hypothesis” to the Introduction as suggested, removing them from Methods.

“…put less emphasis on the specific software…” Our personal experience with cluster analysis on clinical populations convinced us that at least 50% of findings in almost all studies have reflected investigators “personal views” and “oversight”. Over several years we have tried to develop an exploratory process that would exclude our own limiting assumptions (i.e., “what variable to use”, “how many clustering subgroupings should be created”, “what clustering method should be used”, and when done “which of the potential cluster configurations represented truth”). In our experience the NbClust program, developed without any professional connection to our group, very nicely provides methods to permit all the above parameters to proceed without need for extensive “expert input”. So, as can be seen in Methods and Results we entered all 40 factors as variables, asked for 1-15 clusters, we used both traditional clustering methods’, and we accepted the quantitative superiority of the two-cluster solution.

So we believe NbClust represents a major advance in the “objectification” of cluster analysis. This may not be widely appreciated but should be which is why the cluster methods and NbClust reference were prominent.

And as our coherence factors were also derived (see past articles) with similar “objectivity” we believe clustering findings are free of our own clinical biases.

“… goals and hypotheses to Introduction…” Done.

…”Wide range” 2-12” We had neglected to indicate that age was regressed from the original coherence variables prior to factor formation in the prior study. This was done in the prior ASD study and this fact has been added to Methods. “…CON is quite unusual.” Possibly so, however in all our past group studies Dr Als and has advised and we have used CON to stand for neurotypical controls. If readers look at our prior on-line relevant literature they will find CON, ASD, and ASP. So we would prefer to keep “CON” if we may.
“…what about ADI-R?” We have added this to correlative information as a typical assessment tool useful for correlative purposes.

…down-adjusted by software..” This is now referenced in Methods, referring to detailed explanations provided in our prior studies. Basically EEG sampling rate down adjustment was by multipoint interpolation. Spatial down adjustment (electrode reduction) utilized a very nice BESA™ option involving three dimensional interpolation based upon the high density electrode precisely known electrode positions (by photogramography) and classic electrode positions. Spline interpretation was used to drop from 128 to 24 electrodes. For the majority of subjects with just an initial set of 24 electrodes these were applied by very clinically experienced EEG technologists by head measurement techniques.

…Effects of residual eye blink and muscle artifact …” Again we have referenced descriptions of this approach as previously utilized and included the Semlitsch reference who was among the first to use the regression approach. So in summary for eye movement we used the BESA automatic eye movement removal software (now referenced in methods) and then the low, slow prefrontal activity remaining was removed by regression. Muscle was removed by visual inspection and low pass filtering, and finally by regression as described. We have included a reference to Semlitsch who we believe to be the first to reduce/remove artifact in EEG via regression.

“…how this cluster procedure … approaches current clinical debate…diagnosis in autism”.

We emphasize that EEG coherence data support the notion of sub-populations that may need differing educational management which is important information for the US educational system. Also research studies would need be aware of subgroups before study findings are generalized to the full ASD population. Also we add that clinical diagnosis should track DSM-5 recommendations and clinical diagnosis should be established by trained and experienced clinicians. The current role of EEG coherence factors data could serve as a helpful confirmatory test; we do not propose that EEG would in any way supersede current clinical tests in the hands of expert clinicians. Coherence factors and their derived ASD clusters should enhance sensitivity to the potential importance in the recognition of ASD subpopulations.

We have also explained the manner in which we plan to precede in order to establish correlations between and among clinical variables, coherence factors, and derived clusters in future studies.

Respectfully Yours,

Frank H. Duffy, MD
Heidelise Als, PhD