Author's response to reviews

Title: Brain Functional Networks in Syndromic and Non-syndromic Autism: a Graph Theoretical Study of EEG Connectivity

Authors:

Jurriaan M Peters (jurriaan.peters@childrens.harvard.edu)
Maxime Taquet (maxime@childrens.harvard.edu)
Clemente Vega (clemente.vega@childrens.harvard.edu)
Shafali S Jeste (sjeste@mednet.ucla.edu)
Iván Sánchez Fernández (ivan.fernandez@childrens.harvard.edu)
Jacqueline Tan (jacqueline.tan@childrens.harvard.edu)
Charles A Nelson III (charles.nelson@childrens.harvard.edu)
Mustafa Sahin (mustafa.sahin@childrens.harvard.edu)
Simon K Warfield (simon.warfield@childrens.harvard.edu)

Version: 5 Date: 2 January 2013

Author's response to reviews: see over
To the editor:

Dear Ms. Barnard, please find enclosed a revision of our manuscript entitled “Identification of Distinct Network Topology and Resilience Features in Tuberous Sclerosis and Autism”. In light of the reviewers' suggestion that we modify the title, we propose the new title “Brain Functional Networks in Syndromic and Non-syndromic Autism: a Graph Theoretical Study of EEG Connectivity”. We thank the reviewers for their insightful comments and have used their recommendations to significantly improve the manuscript. We believe that we have addressed all of the reviewers' comments.

In the previous version, we’ve failed to acknowledge the considerable scientific contribution of Dr. Clemente Vega, a staff pediatric neuropsychologist with the Division of Epilepsy, who has been instrumental in reviewing and analyzing the phenotypical data of the TSC patients. We would like to add him to the manuscript as an author.

We have added the information about ethical approval and parental consent to the Methods section of the manuscript, and confirmed that all authors approved the final version of the manuscript in the Authors' contributions section.

We’ve enclosed our copy of the revised manuscript using Microsoft Word “track changes” as suggested and for the convenience of the reviewers. As directed, we have also included at the end of this letter a detailed index of changes made to the manuscript in response to the reviews.

We thank you for your consideration of the revised manuscript.

Sincerely,

Jurriaan M. Peters and Maxime Taquet
Changes to the manuscript are grouped by reviewer. The original comment or request is listed in italics.

Changes Requested by the Editor

*Please add the information about ethical approval and parental consent to the Methods section of your manuscript*

- Methods, page 6: Edited the statement about institutional review board, as follows
  “Subject recruitment, data collection, retrieval and analysis were conducted with informed consent for the participation of children in the study by the parents when appropriate (e.g. waived for use of retrospective EEG data), using protocols approved by the Institutional Review Boards from Boston Children’s Hospital and the Semel Institute, University of California, Los Angeles.”

*Confirm whether all authors approved the final version of the manuscript in the Authors’ contributions section*

- Author contributions, page 25: Added the following sentence
  “All authors have approved the final version of the manuscript.”

Changes Requested by Reviewer 1

*In the introduction, explain the differences between functional MRI connectivity and functional EEG connectivity and how they can measure different aspects of physiology.*

- We thank the reviewer for this insightful comment and thank him for the opportunity to improve the manuscript. EEG and functional MRI (fMRI) both have their own strengths and weakness, and because of the vast amount of literature on fMRI connectivity we are glad to point out some of the strengths of EEG.
  Change in the manuscript: Introduction, page 3, added sentence and novel paragraph:
  “Functional connections form the building blocks of a functional network, and can be studied with neurophysiological techniques (e.g. electroencephalography, EEG) and by neuroimaging (e.g., functional MRI, fMRI).

  Compared to fMRI, EEG has reduced spatial resolution and localization is influenced by volume conduction. However, EEG has a better signal-to-noise ratio, and a substantially better temporal resolution. Moreover, EEG connectivity is directly related to neural activity, whereas fMRI is derived from the cerebral hemodynamic response to an increased metabolic demand[ref], with a lag of 1 to
2 seconds from the neuronal activation. Recently, intermittent motion of the head during fMRI acquisition was shown to generate an artifactual reduction in long range connectivity and increase in short range connectivity. This artifact may mask alterations in functional connectivity associated with autism, and complicate appropriate interpretation of functional connectivity MRI studies [ref]. The best way to compensate for this artifact after the acquisition is completed remains unclear and the acquisition of MRI scans of children with autism without motion is a challenging task. On the contrary, artifact assessment is part of routine EEG interpretation by the clinical neurophysiologist, and common post-processing techniques allow for motion rejection or correction.”

Could similar analysis techniques be applied to fMRI connectivity in the study of functional networks? The DTI references were helpful.

- Indeed, the graph analysis approach we describe for EEG, is not only also suitable for studying fMRI connectivity, but for bringing both fMRI and EEG into the same model. In the future, we plan to examine the role of connectivity models utilizing both DTI and fMRI data of TSC patients.

In the methods section, add information about what methods were used to control for multiple comparisons.

- The authors thank the reviewer for pointing this out, and providing the opportunity to clarify. We formulated the precise tests to examine prior to examining the data. We deliberately did not examine multiple other frequency bands, did not explore multiple individual possible electrode combinations (19x18 divided by 2 equals 171 possible combinations), or try other connectivity measures. Graph analysis has the advantage to avoid the many comparisons typically needed for group analyses at the connection level by generating a single scalar measure from the graph structure, rather than many individual measures between each electrode. In this manner, we have avoided multiplying the number of comparisons carried out. Further correction for the comparisons of the few graph measures used would require knowing the correlation between those measures, which is currently unknown.

In addition, each graph analysis provides a single comparison measure and so avoids the multiple comparisons typically needed for group analyses at the connection level (19 electrodes have 171 possible connections in each subject). A change in the level of significance to adjust for the use of the few graph measures we present, would require knowledge of the correlation between these measures.”
Were all of the results from the average of all of the electrode comparisons or was a comparison done at the level of individual electrode pairs?

- Thank you, this may have been unclear. None of the results are from comparison of individual electrode pairs. For the conventional analysis, for each individual, only 3 measures were calculated: Mean coherence, mean inter- over intrahemispheric coherence, and mean long- over short-range coherence. The same applies for graph analysis, for each individual we had only 3 measures (path length, clustering coefficient, global efficiency. (Note that Reviewer #2 has asked for additional analysis, see below.) Change in the manuscript: See prior change, above.

In the discussion section, explain if EEG frequency is important in the EEG connectivity analysis techniques.

- Thank you for pointing out this omission in the manuscript. The choice of frequency bands is highly relevant, as each band may reflect a different aspect of connectivity. We have considered analyzing the delta band (0-4 Hz), beta band (12-16 Hz) and gamma band oscillations, but (1) the EEG data may contain residual eyeblink and (slow) motion artifact after post-processing given the young, uncooperative clinical subjects. Also, (2) muscle activity is notoriously hard to remove and significantly interfered with the beta and gamma range activity. Technically, such an analysis is no challenge to execute but we would be reluctant to interpret the findings as meaningful. Change in the manuscript: Discussion, future directions, page 22, two new paragraphs

“Frequency bands clearly have different associations with different aspects of cognitive activity, with different roles in pathology and with different biophysical mechanisms, reviewed in [ref] and [ref]. Also, connectivity levels between regions are different for each frequency band [ref]. Some authors have proposed that long distance communication may be mainly reflected by synchronization in low frequency bands (alpha and theta range) while shorter distance local communication is supported by synchronization in beta and gamma frequency bands [ref]. As a result, it is imperative that any study should try to be as complete as possible in investigating connectivity in the different bands. However, to limit the number of comparisons, but more importantly because of potential muscle artifact (interference with beta and gamma bands) and potential residual motion artifact (interference with the delta band) in the EEG data of this challenging population, our study was restricted to the theta, upper and lower alpha bands.

Bands not studied include the delta band and the beta and gamma bands. Slower brain oscillations in the delta and sub-delta range appear to have a physiological role in sensory processing and cognition, even in the absence of environmental stimulation (e.g., the default mode network in resting EEG and fMRI studies) [ref]. In autistic patients, Coben and colleagues found the most significant coherence changes in autistic patients in the delta and theta bands.
compared to controls [ref]. Gamma frequency oscillatory activity has been implicated in local cognitive processes, and in the development of distributed cortical networks through both resting-state and task-related neural synchrony in this band [ref]. Unfortunately, while analysis of these bands would be no additional challenge to execute, with the current limitations of the clinically acquired data, findings would not be meaningful.”

Changes Requested by Reviewer 2

Major revisions

1) Graph parameter selection
- I agree with the assertion made by the authors concerning the fact that “it is not yet established which measures are most appropriate for the analysis of brain networks”. Nevertheless, the choice of the three parameters used deserves more attention and questioning. The 2 classical measures introduced by Watts and Strogatz (i.e. clustering coefficient (C) and averaged path length (L)) are still used and clearly useful). Even if they are slightly different, two other measurements now widely used are considered to be representative of C and L: local efficiency and global efficiency. Local efficiency (#C) represents the segregation of the information and global efficiency (=1/L) represents the integration of the information (Rubinov & Sporns 2010). Therefore, it is unclear why global efficiency and not local efficiency was used in this study especially when abnormal segregation is postulated. In the same line, the modularity could also be measured and compared between groups.

- We agree with the reviewer on the fact that different graph measures could be used to characterize the same higher-level concept (e.g. integration, segregation, resilience). To characterize the small-worldness topology of networks, one needs to assess its integration and segregation. Integration is typically assessed by the characteristic path length or the global efficiency and segregation is usually assessed by the clustering coefficient or the local efficiency.

Proponents of the clustering coefficient argue for the intuition behind its formula (the probability to encounter triangles in the network), while proponents of the local efficiency argue for its unified physical meaning (as introduced by Latora and Marchiori, Physical Review Letters, 2001). In the latter paper, the clustering coefficient is shown to be a good approximation of the local efficiency. The two measures are closer for densely connected network, such as EEG-based coherence networks. In particular, a complete graph has both a clustering coefficient and a local efficiency equal to 1.

We agree that our choice of the clustering coefficient as a measure of segregation is in part arbitrary, as it was driven by its relative prevalence in the literature of weighted networks (see Barrat et al, 2004, Onnela et al, 2005, Saramaki et al, 2007).
For exploratory purposes we computed the local efficiency for the networks of all subjects in our population. We observed that the two measures were highly correlated ($\rho > 0.998$ for all three frequency bands). As a result, we found very similar group differences as with the clustering coefficient. Specifically, TSC is associated with a significantly lower local efficiency (ANCOVA: $p<0.005$), while no significant difference is associated with ASD.

As for the modularity measure, we agree that it can reveal other aspects of the functional networks, especially in fMRI-based network, cfr. the recent work by Rubinov and Sporns (Neuroimage, 2011). However, modularity is not a property of the network itself but a property of the network along with its partition in modules. When reported, the modularity is usually the maximum of the modularities over any possible partition of the network. This maximization was shown to be degenerated (see Good et al., Physical Review E, 2010). Besides this technical consideration, partitioning a network of 19 nodes into strictly defined modules does not seem relevant since it is likely that electrodes do not always match well defined functional regions (see Minor Revisions, question 3, below).

- Targeted attacks revealed significant higher resilience in patients with ASD (ASD and TSC + ASD). This is probably linked, as explained by the authors themselves, to different hub organizations. Thus, a more specific measure of hubs should be used and compared between groups to assess this hub organization (i.e. degree, centrality...). The adding value of these measurements is not trivial; it could add more confidence in the interpretation of the results especially for patients with ASD phenotype (ASD and TSC + ASD) (cf. point 2) below).

Thank you for suggesting further exploration of hub organization – it will indeed add confidence and facilitate interpretation of the higher resilience found. For each subject, we computed the degree of the first three hubs (ranked by degree) normalized by the sum of the degrees. ASD significantly decreases this normalized degree ($p<0.005$ for the first hub across all bands; $p<0.001$ for second hub across all bands except in the upper alpha band; $p<0.01$ for the third hub except in the upper alpha band). This supports the hypothesis that higher resilience is related to less specialized network, with main hubs that are less connected (suggesting decreased distinctiveness) in ASD.

Changes in manuscript:
- Results, page 16, resilience measures, 2nd paragraph, added:
  “As increased resilience could be related to an altered organization of hubs (highly connected nodes) in the network, we calculated the connection degree of the three highest connected nodes, compared to the sum of the degree of all nodes. In ASD, this normalized degree was significantly decreased across all bands ($p<0.005$ for the first hub; $p<0.001$ for second hub except in the upper alpha band; $p<0.01$ for the third hub except in the upper alpha band).”
- Discussion, page 21, 2nd paragraph, added sentence:
  “Our finding of a decreased level of connectivity of the main three hubs in the ASD population adds support to this interpretation.”
2) The authors hypothesized a “decreased long-range and increased short-range connectivity in ASD”. This is sustained by the decreased long over short range connections. However, one could expect an increased C and a decreased L associated with this feature which is not the case for ASD.

- This is a good question. The paper would indeed improve by anticipating this question as many readers may think the same: Why does the decreased long- over short-range connectivity not show up in the network analysis? The absence of a higher clustering coefficient for ASD despite the decrease in long-over-short range coherence tells us that nodes are spatially more clustered (conventional analysis) but not functionally more clustered (network analysis). This discrepancy is based on the conceptual difference between “physical distance” and “network distance”. The same applies for the path-length.

Change in manuscript: Discussion, page 19

“Also, the absence of a higher clustering coefficient and of a longer path length for ASD despite the decrease in long-over-short range coherence demonstrates that nodes are spatially more clustered (conventional analysis) but not functionally more clustered (network analysis). This distinction is due to the conceptual difference between “physical distance” and “network distance”.”

3) EEG analysis

- What was the reference used?

- Thank you, the choice of reference is important in connectivity analysis. Activity recorded at the reference electrode can influence the estimated correlations between EEG channels. While source or Laplacian derivations may diminish this influence, they can also obscure true long-range interactions (Nunez et al., 1997). Thus, like most authors, the average reference was used, and we mentioned it briefly in the section Methods, EEG recording and artifact rejection, page 7, second paragraph: “All raw data was imported, pruned, notch filtered at 60 Hz and an average reference was created using the BESA® Research 3.5 software package.”

Changes in manuscript: same page, same paragraph, added sentence to clarify: “The average reference was used for calculation of connectivity.”

- The authors should define the exact time window used for coherence analysis. This time window should be the same for all subjects or at least the same number of points should be considered (depending on both recording time and sampling rate).

- We agree that it would benefit the manuscript to report in greater detail on our coherence measure.

Changes in manuscript:

- Methods, EEG recording and artifact rejection, page 7: “After artifact removal, for each subject several segments of continuous EEG signal were available for analysis. While these segments varied in their
number and length, no group difference was observed in the mean, minimum and maximum length of these segments ($p > 0.15$ for both TSC and ASD conditions). The total duration of EEG data analyzed was higher in TSC subjects ($p < 0.01$) with an average time of 646 seconds compared to 439 seconds for non-TSC subjects. No difference related to ASD was observed in the total duration of EEG data analyzed. This difference in total length was accounted for in our definition of the connectivity measure.”

- **Methods, Mean Squared Coherence, page 8:**
  Paragraph name changed to “Connectivity Measure”, added paragraph “Combining the data from the different segments of continuous EEG recording by concatenation would span transitions which translate into artifactual high frequency content of the power spectrum. Thus, coherence was calculated for each segment individually. Our connectivity measure was obtained by computing the average of these coherences weighted by segment length. This method weighs longer segments more, and gives negligible weight to short segments. Specifically let $S_i(t)$ be the signal in the $i$-th segment, $L_i$ be its length, $N$ be the number of segments, $\text{Coh}(S,f)$ be the coherence of signal $S$ at frequency $f$ and $\Phi$ be the frequency band of interest, the connectivity measure reads

$$C = \sum_{i=1}^{N} \frac{L_i \text{Coh}(S_i,f)}{N} \Phi$$

- **The authors justified the choice of the theta, lower and upper alpha bands by the higher power density and SNR in these sub-bands found in the literature. However, why not using for example the delta band? Cohen and colleagues found the most significant coherence changes in autistic patients in the delta bands compared to controls (Cohen et al. Clin Neurophysiol 2008). Mathewson and colleagues found no significant difference of coherence at rest in the alpha band (Mathewson et al. Clin Neurophysiol 2012). I suggest that the authors do not limit their analysis to these 3 sub-bands.

- Thank you for allowing us to address that issue. We did not sufficiently justify our choice of the three bands (theta, lower and higher alpha), and the paper has benefited from explaining this further. At the suggestion of another reviewer, the relevance of the choice frequency bands in connectivity analysis is briefly addressed.
  Changes in manuscript: Discussion, future directions, page 22, two new paragraphs:
  “Frequency bands clearly have different associations with different aspects of cognitive activity, with different roles in pathology and with different biophysical mechanisms, reviewed in [ref] and [ref]. Also, connectivity levels between regions are different for each frequency band [ref]. Some authors have proposed that long distance communication may be mainly reflected by synchronization in low frequency bands (alpha and theta range) while shorter distance local communication is supported by synchronization in beta and gamma frequency bands [ref]. As a result, it is imperative that any study should try to be as complete
as possible in investigating connectivity in the different bands. However, to limit
the number of comparisons, but more importantly because of potential muscle
artifact (interference with beta and gamma bands) and potential residual motion
artifact (interference with the delta band) in the EEG data of this challenging
population, our study was restricted to the theta, upper and lower alpha bands.

Bands not studied include the delta band and the beta and gamma bands.
Slower brain oscillations in the delta and sub-delta range appear to have a
physiological role in sensory processing and cognition, even in the absence of
environmental stimulation (e.g., the default mode network in resting EEG and
fMRI studies)[ref]. In autistic patients, Coben and colleagues found the most
significant coherence changes in autistic patients in the delta and theta bands
compared to controls[ref]. Gamma frequency oscillatory activity has been
implicated in local cognitive processes, and in the development of distributed
cortical networks through both resting-state and task-related neural synchrony in
this band[ref]. Unfortunately, while analysis of these bands would be no
additional challenge to execute, with the current limitations of the clinically
acquired data, findings would not be meaningful."

- Thank you for pointing out the Mathewson reference – although it reports on
  adults we have included a sentence in the discussion (page 18)
  “Similar to our findings, Mathewson and colleagues found no significant
difference of coherence at rest in the alpha band in adults with autism compared
to controls [ref]”

4) Statistical age differences should be controlled between all the 4 groups used
for subsequent analyses and not only between all ASD subjects and controls and
between all TSC subjects and controls.

- We agree with the reviewer. Age differences were controlled for all four groups in
all subsequent analyses, through the incorporation of age as a covariate into the
ANCOVA model. The way the coefficients of the ANCOVA were defined (ASD
yes or no and TSC yes or no) the statistical analysis was not designed to detect
subgroup differences. However, we later performed a post-hoc subgroup analysis,
and thus should report on ages of subgroups as well.
- In our analyses, we performed post-hoc t-tests on the differences between the
subgroups. The contributions of TSC with and without ASD to the findings
related to TSC (mean coherence and graph measures) were not significantly
different. Similarly, the contributions of ASD with and without TSC to the
findings related to ASD (long- over short-range connectivity and resilience to
targeted attack) were not significantly different across all bands (except in the
theta band for 1 and 2 nodes removed, p = 0.02 and 0.04 respectively).
- The difference in sub-group age between idiopathic ASD and controls did not in
turn lead to the identification of a subgroup difference on these measures. There
were no differences in the findings between the groups and the subgroups on
these measures.
- Changes in manuscript:
  - Results, demographics, page 13 - added age comparisons between all subgroups:
“Age of TSC subjects with and without autism did not differ from controls (p = 0.48 and 0.16, respectively). No age difference was found between all ASD subjects and controls (p = 0.29), but there was a slight male predominance (p = 0.02). Non-syndromic ASD subjects were younger than controls (mean 4.1 years +/- 1.1 vs. 7.9 years +/- 5.6). Age differences were controlled for all four groups in all subsequent analyses, through the incorporation of age as a covariate into the ANCOVA model.”

- Results, subgroup analysis, page 16 – added a comment on this age difference: “The difference in sub-group age between idiopathic ASD and controls did not in turn lead to the identification of a subgroup difference on these measures. There were no differences in the findings between the groups and the subgroups on these measures.”

**Minor Revisions**

1) The issue of control selection from “patients” must be acknowledged in the discussion. For example patients with migraine may have slight modification of EEG rhythms.

   - Thank you for pointing that out. All control EEGs were formally interpreted as “normal for age” by a board certified clinical neurophysiologist, but still we have included various controls with a spectrum of neurological complaints. This is another aspect inherent to the retrospective nature of the study, and it is worth mentioning these limitations more.

   Changes in manuscript, Discussion, Future directions, page 23:
   “Finally, the heterogeneity of the study population should be emphasized. First, the use of clinical EEG data as controls could have introduced bias or variance from subtle EEG abnormalities that have escaped routine interpretation by the clinical neurophysiologist, and controls were recruited from a population with neurological complaints. Second, (…)”

2) The heterogeneity of each entity, especially of TSC, should be better highlighted. This might have an impact on the results. In addition, a possible effect of epilepsy on results could also be discussed. The prevalence of epilepsy in TSC is much higher in TSC than in ASD.

   - We agree that the manuscript would improve if we mention this limitation. In the study we use binary variables (autism yes/no and TSC yes/no), which do not reflect the wide range of autism spectrum disorders, nor the phenotypic variability in TSC. In prospective studies this can attempted to be addressed. The same applies for cognitive and epilepsy variables, although severe epilepsy, cognitive impairment and autism tend to travel together in TSC (see van Eeghen et al., 2012). We also agree that the effects of epilepsy on networks should be discussed.

   Changes in the manuscript: Discussion, future directions, page 23, new paragraph:
   “Finally, the heterogeneity of the study population should be emphasized. First, the use of clinical EEG data as controls could have introduced bias or variance from subtle EEG abnormalities that have escaped routine interpretation by the clinical neurophysiologist, and controls were recruited from a population with neurological complaints. Second, autism is a spectrum disorder with a wide range of severity, not well reflected by a binary variable (presence or absence of
ASD). In future studies continuous variables could be used, such as the calibrated severity score of the Autism Diagnostic Observation Schedule [ref], or the Social Responsiveness Score (SRS), which was recently used in another cross-disorder approach of autism [ref]. Third, patients with TSC have wide variability in their phenotypical presentation. We did not incorporate anti-epileptic or psychoactive medication, and epilepsy-severity variables into the model, while in TSC up to 90% experiences seizures in their lifetime [ref]. With this high co-occurrence of epilepsy, cognitive impairment and autism in TSC [ref], it is possible that differences found may represent more global neurocognitive and behavioral dysfunction in TSC [ref] – although in our patients we did not find an association between severe cognitive impairment and autism. While EEG segments with epileptic discharges were excluded from analysis, it remains possible epilepsy impacted the network analysis, in particular of the TSC population. However, interictal functional networks of patients with epilepsy are characterized by increased connectivity (especially in the theta band) and topological changes including increased regularity and hub-like organization [4 refs] – which we did not find."

3) Network analysis from EEG electrodes faces the issue of the node definition as electrodes do not always match well defined functional regions.

- The authors agree on this point. It is briefly mentioned in the Discussion, Future Directions, page 21, first sentence: “Nodes should best represent brain regions with coherent patterns of extrinsic anatomical or functional connections which is problematic with EEG [ref].

We will clarify it with an additional comment. Changes in the manuscript: the Discussion, Future Directions, page 21

“Nodes should best represent brain regions with coherent patterns of extrinsic anatomical or functional connections which is problematic with EEG [ref]. Specifically, node definition with only 19 electrodes is problematic as the locations do not match well defined functional regions. Higher density EEG with 128 or 256 channels in an experimental setting can overcome this problem in part, although inherent to the technique only superficial aspects of the brain network can be modeled.”

In addition, the reproducibility of electrode position relative to functional areas is difficult to assess especially when different numbers of channels are recorded like it is the case in this study. This point should be discussed

- Thank you for pointing this out. It is true that the 10-20 international system of electrode placement produces fairly reliable reproducible scalp positions within one patient, but not necessarily across patients and over time with growth and maturation of skull and underlying structures. Throughout the manuscript, we avoided assumptions about geographic changes relating to underlying anatomical structures (e.g. frontotemporal connectivity), with the exception of inter- and intrahemispheric coherence measures. Rather, we focused on network properties.

Changes in the manuscript: Discussion, future directions, page 21

“In addition, electrode positions relative to underlying anatomical structures and functional areas are subject to variability, to changes related to growth and maturation and to methods of electrode placement used (e.g. high density electrode cap or net). Thus, the level of anatomic accuracy of current study does
not allow for examining in detail the relation between functional and structural connectivity.”

**Discretionary Revisions**

*The title is surprising. The purpose is unclear. For the usual reader, the fact that different patterns exist between STC and ASD is evident. The fact that topological features of both phenotypes are typical even when the 2 phenotypes are mixed could appear in the title and benefit to the impact of the paper.*

- Thank you for pointing that out. Prior to submission, we have had several discussions in our group about what findings should be represented in the title. We agree that the title now lacks clarity. Mentioning all four subgroups (with mixing of the phenotypes) and the consistent findings in conventional coherence, topological and resilience measures would make the title long, complex and uninviting to the reader. We propose the following title:

*Brain Functional Networks in Syndromic and Non-syndromic Autism: a Graph Theoretical Study of EEG Connectivity*