Reviewer's report

Title: Identification of Distinct Network Topology and Resilience Features in Tuberous Sclerosis and Autism

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Reviewer: M Guye

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In this study, Peters and colleagues aimed at demonstrating specific features of whole brain functional networks in autism spectrum disorder (ASD) by using graph theoretical analysis of EEG functional connectivity. To demonstrate specificities of network topology in ASD, they measured several graph parameters in a group of non-syndromic ASD (ASD), a group of syndromic ASD (i.e. patients with tuberous sclerosis complex (TSC+ASD)), a group of TSC without ASD (TSC) and a control group. Interestingly, they found concordant features in patients with the TSC phenotype (i.e. TSC and TSC+ASD groups) and other features in patients with the ASD phenotype (i.e. ASD and TSC+ASD). Mean coherence, clustering coefficient, average path length, and global efficiency where significantly decreased in the TSC phenotype compared to others whereas long over short range connections ratios was significantly decreased and resilience was significantly higher in the ASD phenotype compared to others. The interpretation was that TSC phenotype is accompanied by structural alterations responsible for global decreased connectivity and major network topology alterations with both decreased segregation and integration, whereas ASD phenotype is related to a more specific alteration marked by an “increased local overconnection and decreased functional specialization”.

This is an interesting study showing the interest of graph theory applied to brain functional networks in order to better understand brain pathophysiology. The design is original. The results are clear and the interpretation interesting although easier in patients with the TSC than in patients with the ASD phenotype.

Major Compulsory 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 2000). 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.

- 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).

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.

3) EEG analysis
- What was the reference used?
- 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).
- 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.

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.

Minor Essential 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.

2) The heterogeneity of each entity, especially of TSC, should be better highlited. 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.

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

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.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests