Author's response to reviews

Title: White Matter Abnormalities in Adolescents with Generalized Anxiety Disorder: a Diffusion Tensor Imaging Study

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Author's response to reviews: see over
Dear editor,

Thank you for offering us the opportunity to revise our manuscript titled “White Matter Abnormalities in Adolescents with Generalized Anxiety Disorder: a Diffusion Tensor Imaging Study”, by Liao et al. for publication in *BMC Psychiatry*.

Generalized anxiety disorder (GAD) is a common anxiety disorder that usually begins in adolescence or early adulthood. GAD often increases the risk of other anxiety disorders and depressive disorder and causes significant distress or impairment in life. However, compared with other anxiety disorders, GAD is less studied, despite its high prevalence and clinical importance.

Previous neuroimaging studies have suggested an abnormal neural circuitry of emotion regulation including the amygdala and prefrontal cortex in both adult and adolescent GAD patients. Aberrant integrity of white matter in this neural circuitry has been verified in adult GAD patients. White matter abnormalities in adolescent GAD patients have not been detected. Twenty-five adolescents with GAD and 24 healthy controls underwent a diffusion tensor imaging scan. Fractional anisotropy (FA) was compared between groups using a voxel-wise Tract-Based Spatial Statistics (TBSS) analysis method. Compared with healthy controls, adolescents with GAD showed significantly reduced FA in right superior corona radiata, right uncinate fasciculus, and right inferior fronto-occipital fasciculus. The findings in the present study suggest a neural basis of emotion dysregulation in adolescent GAD patients.

We appreciated the excellent comments and suggestions from the editor and both reviewers regarding our manuscript. The language in this manuscript has been proofread by a professional copyediting company, Edaz. The point-by-point responses to the comments raised by the reviewers are listed in detail below. We have highlighted the major changes in the revised manuscript.

We hope that all these changes fulfill the requirements to make the manuscript acceptable for publication in *BMC Psychiatry*.

All authors state no financial conflict or other conflict of interest. We confirm that this material is not under consideration for publication elsewhere.

Thank you for your consideration.
Reply to reviewer Do Tromp
(http://www.biomedcentral.com/imedia/4896768181016874_comment.pdf):

Major Compulsory Revisions

Q1: The focus in the results section should really be put on the one effect in the left frontal white matter, as this is the only area that survives multiple comparison. The other results can be mentioned, but to a lesser extend and stating clearly that they do not survive multiple comparison, and as defined in the methods, should not be considered significant.

Reply: We would like to thank the reviewer for their helpful comments. We have changed the analysis method to TBSS as suggested by the other reviewer. This change can be seen in the paragraphs discussing “image data processing” and “statistical analysis”, as well as in the Results and Discussion sections.

Q2: Related to that, the paragraph in the discussion section should clearly state that the finding in the occipital lobe is not significant, and should not be over-interpreted.

Reply: We have removed the discussion about the finding in the occipital lobe.

Q3: It is noted that with respect to amygdala volume in GAD patients the results are different in a pediatric sample compared to adults, to prove this the authors supply reference 17 (De Bellis et al,2000), but that study actually shows the same effect as studies with an adult sample. The authors should double check that the references they supply concur with their arguments.

Reply: We thank the reviewer for pointing out this mistake. We were aware that the study by De Bellis et al. shows larger amygdala volume in adolescent samples; however, we wrongly described this evidence. We have changed this sentence to “Structural neuroimaging studies showed larger gray matter volumes in the amygdala in adult [15,16] and adolescent [17] GAD patients, whereas one study on adolescent GAD samples yielded decreased amygdala volumes [18].”

Minor Essential Revisions

Q4: The authors should consider naming the white matter regions in addition to the nearby grey matter regions.
Reply: We thank the reviewer for their insightful advice. In the revised manuscript we have changed the analysis method and named the white matter regions according the Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 white-matter atlas labels and the JHU white-matter tractography atlas.

Q5: A small number of language errors should be addressed. Considering having a native English speaker proofread the manuscript.

Reply: The revised manuscript has been proofread by a professional manuscript-editing company.

Discretionary Revisions

Q6: Please include a table or graph with means and effect sizes. Even though these effects are subtle they should be reported. This table should also include the MNI coordinates and significance levels for clarity.

Reply: We would like to thank the reviewer for their suggestion. In the revised manuscript, the results are different from the original manuscript because we used a new analysis method, TBSS. We have provided a table and a figure to present the results, Table 2 and Figure 1, in the revised manuscript.

Q7: In the methods section also report the mean age of the sample within the text, not only in the table.

Reply: We thank the reviewer for their advice. We have now reported the mean age of the sample in the Results section of the revised manuscript.

Reply to reviewer Robert J Dawe
(http://www.biomedcentral.com/imedia/8995029691018068_comment.pdf)

Major Compulsory Revisions

Q1: The value of the manuscript hinges largely on the single figure, Figure 1, which shows the regions of significant or marginal FA differences between GAD subjects and normal controls. However, there are numerous problems with this figure and caption. First, it is probably too small. The regions of FA difference are visible only as white “blobs”. By increasing the figure size I would hope to see the variation in color within those blobs. This leads into the second point – I suspect the colorscales need to be rescaled. If all of the blobs are entirely white or nearly so, then the top end of the colorscale should be elevated in order to increase the dynamic range, thereby maximizing the amount of information conveyed by the figure. A third, smaller point – the axial sliced should be rotated ninety degrees counterclockwise. A fourth point – the caption includes figure subparts (i.e. (a), (b), and (c)), but there are no subpart labels within the figure itself.
Reply: We would thank you the reviewer for their comments. In the revised manuscript, the results are different from the original manuscript because we used a new analysis method, TBSS. These differences can be seen in the Results section.

Q2: TBSS, part of the FSL package, is becoming the standard method of analyzing DTI data in studies such as this one. The authors are familiar with FSL, as they used it to perform eddy current artifact correction and diffusion tensor fitting. Therefore, I’m not sure why they would not continue with the traditional pipeline, i.e. skeletonize the FA images using TBSS to ensure that misregistrations or differences in white matter tract size have not caused the observed FA differences. The authors themselves recognize that their approach has shortcomings (last sentence of discussion). It would be extremely easy and fast to perform the analysis again using TBSS, so I think the authors should do that or at least answer the question of why they did not use TBSS.

Reply: We initially performed the VBA analysis as usual in our institution. [Liao, Y., J. Tang, et al. (2010). "Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study." Brain 133(Pt 7): 2115-2122. Peng, H., H. Zheng, et al. (2012). "High-frequency rTMS treatment increases white matter FA in the left middle frontal gyrus in young patients with treatment-resistant depression." J Affect Disord 136(3): 249-257. ] However, we agree that TBSS has distinct advantages over VBA. Therefore, we have re-analyzed our data with TBSS as suggested by the reviewer in the revised manuscript. We have modified the “image data processing” and “statistical analysis” paragraphs, as well as the Results and Discussion sections accordingly.

Minor Essential Revisions

Q3: I gather that English is not the native language for any of the authors, and if this is true then they have done a remarkable job of preparing the manuscript for publication in English. Even so, there are some areas where the manuscript requires the attention of someone a bit more fluent in English. These areas are too numerous to mention, but here are some examples:

a. On page 4, the sentence, “Taken together, all the neuroimaging evidences have suggested an abnormality …” should be something more like, “Taken together, all the available neuroimaging evidence suggests an abnormality…”

b. On page 5, the sentence, “Then, 508 subjects whose SCARED scores …” is unintelligible.

c. On page 6, the sentence, “For each participant, the b0 images was normalized…,” should be, “For each participant, the b0 image was normalized …,” or, “For each participant, the b0 images were normalized …”

Reply: We thank the reviewer for their suggestion. The revised manuscript has been proofread by a professional manuscript-editing company.

a. On page 4, the sentence, “Taken together, all the neuroimaging evidences have suggested an
abnormality…” has been changed to “Taken together, all the available neuroimaging evidence suggests an abnormality…”

b. On page 5, the sentence, has been changed to “The SCARED is a reliable and valid screening tool for childhood anxiety disorder, with an optimal total cutoff point score of 25 to separate children with anxiety disorders from those without [27, 28]. Among 1885 subjects, 508 subjects’ SCARED scores were greater than 25, and the scores of the rest were lower than 25. Then, 673 subjects (508 SCARED scores ≥ 25; 165 SCARED scores < 25) were investigated by the same trained clinician and diagnosed using DSM-IV criteria and the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime (K-SADS-PL) version [29].”

c. On page 6, the sentence, “For each participant, the b0 images was normalized…” has been deleted, because the analysis method has been changed.

Q4: I emphasize that these are not the only areas that need attention with regards to grammar. The entire manuscript should be reviewed by a fluent, ideally native English speaker.

Reply: The revised manuscript has been proofread by a professional manuscript-editing company. We thank the reviewer for their valuable advice!