Reviewer’s report

Title: Cortical Thickness in Youth with Major Depressive Disorder

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Reviewer: Kathryn R. Cullen

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This is a neuroimaging study that examined cortical thickness in adolescents with major depression. Overall it is well-written and the topic is important. However a couple of issues should be addressed before publication.

Major Compulsory Revisions

1. The introduction and discussion have neglected to include an important paper which serves as a point of reference for the findings:


Cortical thinning in persons at increased familial risk for major depression.


Source

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Abstract

   The brain disturbances that place a person at risk for developing depression are unknown. We imaged the brains of 131 individuals, ages 6 to 54 years, who were biological descendants (children or grandchildren) of individuals identified as having either moderate to severe, recurrent, and functionally debilitating depression or as having no lifetime history of depression. We compared cortical thickness across high- and low-risk groups, detecting large expanses of cortical thinning across the lateral surface of the right cerebral hemisphere in persons at high risk. Thinning correlated with measures of current symptom severity, inattention, and visual memory for social and emotional stimuli. Mediator analyses indicated that cortical thickness mediated the associations of familial risk with inattention, visual memory, and clinical symptoms. These findings suggest that cortical thinning in the right hemisphere produces disturbances in arousal, attention, and memory for social stimuli, which in turn may increase the risk of developing depressive illness.

   As noted above, this paper included children and adolescents and found cortical thinning in lateral to be associated with risk for depression, which is contrary to what is reported here. I would think that this paper should have contributed to a
hypothesis that authors would find cortical thinning in adolescents with MDD in lateral areas, and this discrepancy should be discussed. Of note, Peterson and colleagues did find increased thickness in the ACC in high-risk offspring which is consistent with the current findings.

2. In Methods, it's not clear exactly how they used the FreeSurfer program. FreeSurfer parcellates the brain into many many regions of interest and one can extract a cortical thickness value for each one. Did the authors compare groups across all ROIs, or just hypothesized ones? If only a few, please state more clearly which ones and why. Another FreeSurfer option is to use a program called qdec which compares thickness vortex-wise across the brain. Was this done, and the results happened to end up in medial frontal and ACC? If so this should be stated.

3. In the Statistical Analysis, there appears to be a partial sentence: In order to account for multiple comparisons, \( p < 0.01 \) [37]. Do authors mean to say that by setting the \( p \) threshold at 0.01 they accounted for multiple comparisons? This would be quite lenient given the number of regions possible in FreeSurfer.

Minor Essential Revisions

1. Since the groups only differed for the ACC on the left, please specify left ACC in the first paragraph of the introduction.

2. In the discussion, authors attempt to explain why they have found thicker cortexes in MDD. They claim that post-mortem investigations of neuronal and glial size and density support the results. In fact it appears the opposite, one would expect based on the post-mortem data that the cortex would be thicker.

Discretionary Revisions

1. Authors report correlations between thickness and other variables for depressed and not controls. It would be useful to know if thickness correlates with age in controls as well as depressed.

2. I appreciated the explanation of resolving the issue of thicker cortex in adolescents with MDD vs thinner in adults with MDD as perhaps to do with abnormal developmental trajectories. I think authors could expand that paragraph a bit to explain their theory further.

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

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