Reviewer's report

Title: Test-Retest Variability of High Resolution Positron Emission Tomography (PET) Imaging of Cortical Serotonin (5HT2A) Receptors in Older, Healthy Adults

Version: 2 Date: 30 October 2008

Reviewer: James Holden

Reviewer's report:

Major compulsory revisions:

Page 5: Methods: Were the subjects screened for handedness? If so, that should be reported here. If not, a brief discussion point should be included citing this as a potential confound (see below).

Page 8: The repeatability coefficient (RC) should be defined at first mention. In addition to the computation method already present (but in the wrong place), the interpretation in terms of confidence intervals should be included, and both be given a reference citation.

Then RM% can be dealt with. The choice of the name RM should be explained, and if it is not original with this paper, a citation is needed. It should not be called a coefficient of variation, or even related to a coefficient of variation, as this term is universally accepted to mean the standard deviation of something divided by the mean of the same thing. This object expresses twice the standard deviation of the difference between two things divided by the mean of those things, not the mean of the difference. The desire to scale the differences by the magnitude of the things that are differing would be understandable, but the RC is not a difference, but the variability of a difference. This needs interpretation and clarification in both the Methods and Discussion sections. One simple solution would be to delete all reference to RM% as it adds very little meaningful information. Another might be to scale the standard deviation by the mean of the absolute difference.

Page 8: The comment about intersubject differences in fND is unjustified and unnecessary. This paper has only one point (at present), that the same measurement performed twice gives the same result. The data have nothing to say about what determined that result. If the revision includes commentary about age dependence, that would be the time to say that the changes in BPND are interpreted as changes in Bmax, if the assumption is made (about which the current data say nothing) that fND is the same at all ages.

Page 9: The result of excluding two subjects from the analysis of the anterior cingulate cortex is hard to follow. Presumably the pairs of end points given are for the left and right sides, but this needs to be said explicitly. Also it was the change in the ICC that was not statistically significant, not the ICC itself, as the sentence currently states.
Page 9: The striking left-right asymmetry in the anterior cingulate cortex cannot be ignored. ICC’s of 0.7 strongly support the presence of an actual asymmetry. This was the basis of the handedness comment above. I don’t believe the asymmetry is real, but it can’t be brushed aside without some comment on the statistical implications of this behavior of the data.

Page 10: The discussion of the scale of the measured BP’s is confusing. I didn’t have access to reference 19, but I did access references 13 and 20 (by the way, the citation for reference 20 is garbled), both of which have nearly identical disease-independent demonstrations of a striking age dependence. If anything, the new BP’s are not too small, but too big. The role of resolution is not discussed, except to say that it is different for the various references and this paper. The effect of resolution, however, would be dependent on the ROI sizes and shapes. This entire discussion should be revised. The results (partial volume effects aside) imply that the loss due to aging levels off eventually. This is the point of reference 17, already cited. If the previous data were from another group, the reluctance to combine the results in older subjects with those from younger subjects would be understandable. However, this paper is in a position to say something about the age dependence of receptor density, as the data for other ages was published by the same (or a closely related) group. (Reference 17 makes no mention of an asymmetry in anterior cingulate cortex, of relevance to the previous point.)

Summary comment: The reliability in older subjects is clearly and soundly presented. An opportunity exists to extend the results to new or confirmatory conclusions about age-dependent loss.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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