

Peer Review Overview

Manuscript Title: “The Connections of the Insular VEN Area in Great Apes: a Histologically-guided ex vivo Diffusion Tractography Study”

Received	31-Jan-2020
1 st Decision	15-Oct-2020
Revision Submitted	20-Oct-2020
Accepted	31-Oct-2020

Decision Letter

Dear Dr. Cabeen,

Thank you for submitting your manuscript to Progress in Neurobiology. We are very sorry for the delayed decision on your manuscript. Your paper should become acceptable for publication pending suitable minor revision and modification of the article in light of the appended reviewer comments. Specifically, Reviewer #2 has made some important remarks that we ask you to address.

Unfortunately, though, the publication of the Special Issue your ms is planned to be part of, will occur soon. We would therefore highly appreciate it if you could send your response and revised manuscript within 7 days from now. We can otherwise not guarantee that the publication of your manuscript will occur in the Special Issue. We are very sorry that the revision stage has to be so rushed after a very long peer review process. Due to the time constraint, we understand that you would focus your revisions on the most important remarks offered by the Reviewers.

We look forward to receiving your revised manuscript.

Kind regards,

Earl Miller, PhD
Guest Editor, Progress in Neurobiology
Professor of Neuroscience, Massachusetts Institute of Technology

Sabine Kastner, MD, PhD
Editor-in-Chief, Progress in Neurobiology
Professor of Neuroscience, Princeton University

Comments from the Editors and Reviewers:

Reviewer 1

Cabeen et al examined the connectivity of von Economo neuron-rich regions in the orangutan (1), bonobo (1), and gorilla (2), using ex vivo HARDI. They found connections from the insular VEN areas to the frontal and temporal poles, NAcc, ACC, and basal forebrain. Brainstem connections were not identified, but appropriate caveats are acknowledged.

This is a useful and interesting approach to outlining potential VEN connections in non-human primates in which invasive tracer studies are not feasible. Identifying the finer brainstem connections will require axonal tracing. The methods and results are straightforwardly presented, and the Discussion is thoughtful and scholarly. The article is an excellent fit for the journal and the special issue.

Reviewer 2

The review is based on study of Von Economo neurons (VENs) in great apes. The authors used a valuable collection of brains from a bonobo, gorilla and orangutan. Although initially thought to be found exclusively in humans and apes, it is now clear that VENs are seen in monkeys and other mammalian species as well. The authors used high resolution ex vivo tractography in an attempt to study the connections of the principal VEN region in these species.

Tractography as a method has limitations even at high resolution, such as being indeterminate about the direction of a connection, producing false positives or false negatives, but it is still the tool available for the study of connections in humans and apes.

The authors have summarized findings obtained mostly from their labs. But notwithstanding the higher resolution of the method, the review does not venture beyond the authors' prior reviews. The review could be improved considerably with better organization of the findings and their interpretation.

One of the ways to mitigate against the shortcomings of the technique of tractography is to diligently compare the findings with connections in model non-human primate species. Here the authors fall short by selective reference to a limited number of papers. The review could be strengthened by delving more deeply into both the classical and recent literature, which could provide insights.

The same critique applies to the use of select functional imaging data to interpret findings. The references to findings at times are too specific to have generalizable value, and the attribution of function to areas appears at times phrenological. For example, how shall we interpret the idea that lesions of the claustrum lead to loss of consciousness, for a structure found in the midst of numerous pathways that are also destroyed by the lesion?

The applied tractography technique is of bigger concern by the lack of finding well-known connections between the anterior insular area and the thalamus, or the amygdala and hippocampus, which the authors found earlier with less sensitive methods.

There are errors throughout the manuscript, too many to list, but here are some:

In the Figure legend 2, there are references to panels 1A and 1F; similarly, in the legend to Figure 6, there are references to panels 5A, 5B, 5C, etc.

Line 68 says that the brains ".. were obtained from apes in zooms who had died of natural causes.." In spite of the popular dislike of Zoom, it is assumed that the authors mean 'zoos'.

In conclusion, the review could be improved by better organization of the findings and interpretation in the broader context of both anatomical and functional studies from the literature.

Author Response Letter

Dear Dr. Miller and Dr. Kastner,

We greatly appreciate the comments by Reviewer #1, particularly with respect to the organization of our paper and scholarship. We also appreciate the points raised by reviewer #2 and the opportunity to address them within the editorial guidance that time is a very important constraint. We have enclosed a revised manuscript which reflects the critique from the reviewers, in which, the major changes have been highlighted in yellow.

Regarding specific points raised in review, we have set out to address these issues by expanding our discussion and incorporating additional relevant references. We have already done extensive comparisons with the experimental connection literature in macaques and an extensive review of the functional literature in humans and macaques, which can be found in the discussion section. With respect to the claustrum, we appreciate the point raised by the reviewer, and we had expressed some caveats concerning the interpretation of the possible functions of this structure in our original manuscript, and we have further elaborated on these concerns in the revised draft on lines 211-215. We agree that the experimental literature in macaques contains substantial evidence for connections between the anterior insula and the thalamus and amygdala, and we have added additional references to the thalamic connectivity in our revised manuscript on lines 382-385. Nevertheless, the fact remains that we did not find connections between the thalamus and FI in any of the ape brains investigated with the improved methods of diffusion tractography used in our analysis. These improved methods have revealed in detail in ape brains many other connections reported in the experimental literature in macaques, as we discussed throughout the manuscript and especially under the heading, "Expected Tracts Not Found". We have substantially expanded this section to address these issues further on lines 374-401. We also appreciate the correction of typographical errors and have endeavored to correct them throughout. We again thank the reviewers for their time and feedback, which we think have led to an improved manuscript.

Kind regards,

Ryan P. Cabeen, PhD
USC Laboratory of Neuro Imaging (LONI)
USC Mark and Mary Stevens Neuroimaging and Informatics Institute Keck School of
Medicine of USC
University of Southern California, Los Angeles, CA, USA