

Format for ANSWERING REVIEWERS



April 28, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2105-edited.doc).

Title: Thickness-based correlations of cortical areas involved in senses, speech and cognitive processes

Authors: Ioannis Mavridis, Konstantinos Lontos, Sophia Anagnostopoulou

Name of Journal: *World Journal of Neurology*

ESPS Manuscript NO: 2105

The manuscript has been improved according to the suggestions of reviewers.

Reviewer 1

In this manuscript the authors measured the thickness of different cortical areas of 38 hemispheres. On the basis of the anatomical results they discussed possible correlations with the cognitive functions of the measured cerebral areas. In my view this manuscript has a number of methodological limits. My first concern is that there is not gender balance (the authors studied only three females' brains). Secondly they did not take into account the problem of cerebral atrophy. Details concerning the age and the manual dominance of the donors are not reported. The discussion is not centered on the aim of the study. From the cognitive point of view the term subconsciously seems quite evasive and scarcely related to specific neuropsychological functions.

The gender limitation of our study is clearly stated in our text. However we added an additional comment. We added comments regarding the limitation of cerebral atrophy too. The latter could be a limitation for absolute thickness volumes but not for the correlations we found, which are obviously much more important. Unfortunately, details concerning the manual dominance of the donors were not available. We added a relative notice. We modified our discussion and we replaced the term "subconsciously".

Reviewer 2

The authors examined cortical thickness in 8 locations of 38 hemispheres. From their results they concluded that "there could be a subconsciously stronger impact for objects placed in the left inferior quarter of the visual field". The question of the study is interesting, but there are several methodological problems that could result in wrong conclusions. 1. The possibility of differential shrinking of cortex during formaldehyde fixation is neither mentioned nor discussed (different regions; surface vs depth of sulci, etc). 2. The age of the subjects and the cause of death are not given. Looking at the tables, those with thinner cortex in one region usually have thinner cortex in other regions as well and vice versa. Among the hemispheres there could have been subjects with significant cortical atrophy. This issue could partly be checked by morphometry of the tissue samples (cell count/density, proportion of volume of glia-neurons, proportion of cell volumes to volumes of extracellular space, etc) 3. The authors performed no functional studies – therefore due to lack of data, nothing supports their conclusion on function 4. There have been several papers published on cortical thickness using MRI. The current results should be compared to in vivo measured data on healthy subjects. Although

mean values are similar, SD values are several fold larger in this study than in MRI morphometric measurements (e.g. Lüsebrink F, Wollrab A, Speck O. Cortical thickness determination of the human brain using high resolution 3T and 7T MRI data. *Neuroimage*. 2013;70:122-131). Reason for this large scatter in the values compared to MRI data should be explained. 5. Cortical thickness usually varied 4 times between minimum and maximum values (usually between 1 – 4 mm), and there were subjects with generally thin and generally thick cortex values. This may mean that brain atrophy affected most regions in the same proportion – thus resulting in tight correlations between several regions. These significant correlations just as well may mean that those with more severe atrophy in one gyrus also have more severe atrophy in the others. As it is known from MRI studies as well that cortical thickness decreases with age, for the analyzed regions a correlation analysis between age and cortical thickness should also be provided. 6. Corrections for multiple comparison should be performed in statistical testing (e.g. Bonferroni). 7. Table 1 is the combination of Tables 2 and 3. Although individual data are worth to show, tables 2 and 3 should be replaced by a graph presenting the 2 sides and the 8 regions with median, interquartile range and min-max values.

We would like to thank the reviewer for finding our manuscript acceptable with revision and for finding the question of our study interesting. 1. The reviewer is right. We added a relative comment. 2. The reviewer is right. We added notices regarding age and cause of death of our study's subjects. We also commented on cortical atrophy as a potential limitation of our study. 3. The lack of functional data is expected in anatomical studies. However we discussed it as limitation of our study. 4. We thank the reviewer for helping us to enrich the used literature as well as our discussion. 5. We commented on cortical atrophy as a potential limitation of our study. 6. We think that such analysis could complicate our article's presentation. 7. We think that our tables are easier to understand than such a graph.

Reviewer 3

The authors present a pathological study of 38 formalin-fixated human cerebral hemispheres from cadaver donors for students' education. The authors reveal several thickness-based correlations among different functional cortical areas. The study is interesting but some aspects of the manuscript may be improved taking into account the following points: 1. From a clinical point of view, readers may be interested to know about the mean age and the percentages of patients with different specific neurologic disorders (Alzheimer disease, acute or chronic lacunes or other stroke subtypes) in the study population. 2. In the presence of cognitive decline, did the authors undergo neuropsychological studies? 3. Delete in Results, statistically ambiguous correlations 4. Write up the Results following the instructions provided in the WJN style guide. 5. In the Discussion section, it would be interesting to include a comment regarding that small subcortical infarcts have remote consequences on gray matter volume. Using MRI scans acquired before and after an incident subcortical infarct, they are able to show that the appearance of a new subcortical infarct is associated with cortical thinning in connected brain regions (*Neurology* 2012; 79: 2025-2028; *Neurology* 2012; 79: 2016-2017)

We would like to thank the reviewer for finding our manuscript acceptable with minor revision and for finding our study interesting. 1. We added information regarding age and cause of death of our study's subjects. Unfortunately details regarding their potential neurological history were not available. 2. Neuropsychological studies are out of the context of a post-mortem anatomical study. 3. We think that ambiguous correlations are worthy to be mentioned. 4. We did so. 5. We thank the reviewer for helping us to enrich the used literature as well as our discussion.

Reviewer 4

Some observations: ABSTRACT To refer to the area in a unified way; I would suggest to refer always as Brodmann's areas, instead of "area of place memory" and similar interpretative names. The sentences

“Based on our results we suggest that there could be a subconsciously stronger impact for objects placed in the left inferior quarter of the visual field” is completely speculative. It should be deleted.

INTRODUCTION There is not indeed introduction. No previous study is mentioned, and hence, this research as not any background

MATERIALS AND METHODS Again, please refer to the cortical areas as BA, not using interpretative names (such as “area of names understanding” and similar names)

RESULTS Table 1 can be deleted The Tables are presented in a way that is very difficult to understand. Why the same sequence of presentation is not used all the time? (e.g., BA40, BA39, etc); What the numbers mean? Where are explained? The information presented under “Results” is redundant with the information presented in the tables

Correlations could be presented in a table

DISCUSSION It is suggested to follow in the Discussion section the usual sequence of: brief summary of results, how results can be integrated in contemporary literature, proposed interpretation, limitations, and suggestions. The background information about other research in the area is very limited.

CONCLUSIONS This section can be deleted.

We would like to thank the reviewer for finding our manuscript acceptable with revision.

ABSTRACT: The studied areas are more restricted than Brodmann areas. Areas V1 and V2, for example, belong to the same Brodmann area. There are corrections.

INTRODUCTION: Previous studies of cortical thickness measurement are mentioned in our “discussion”. Similar studies of anatomical methodology for such measurement are not reported in the literature.

MATERIALS AND METHODS: The studied areas are more restricted than Brodmann areas.

RESULTS: In our point of view the tables help the presentation of our results. The numbers were used for identification purposes of the specimens.

DISCUSSION: There are corrections. The background information about other research in the area is very limited because of the uniqueness of our methodology. However, we enriched our references regarding recent MRI studies.

CONCLUSIONS: We believe that every article needs to have a conclusion.

Reviewer 5

General: This is an important research since help us to enhance our understanding of how functional brain areas are associated with their structural substrates.

Title: The title is according and reflects the major topic and contents of the study

Abstract Abstract provide a clear delineation of the research background, objectives, materials and methods, results and conclusions

Materials and methods: It is necessary to clarify: Authors do not clarify the normalcy (“healthy”) of the donors before death. Several pathological conditions (neurological or psychological/psychiatric disorders) produce changes in cortical thickness and other morphological measurements. Age and handedness are variables that could influence results as have been commented in the literature. These variables were not clarify.

Results: Results are presented in tables.

1. Clarify which is the meaning of the number in the Hemisphere column (i.e: L8)
2. There are some empty cell in tables, please explain why.
3. Statistical correlation graphs could improve results presentation, at least for the strongest correlated variables

Discussion:

- 1- One of the main results is the statistically significant difference of the V1 MV between right (2.42 ± 0.80 mm) and left (1.87 ± 0.43 mm) hemispheres ($t = 2.11$, degrees of freedom = 28, $p < 0.05$). Authors stressed that the significantly thicker V1 for right hemispheres is an interesting finding. Authors should discuss this finding with more details since in the majority of paper studying normal asymmetries in cortical thickness the presence of occipital asymmetry (left > right) petalias has been the common finding. I relate 3 of these papers: Falk D, Hildebolt C, Cheverud J, Kohn LA, Figiel G, Vannier M (1991) Human cortical asymmetries determined with 3D MR technology. *J Neurosci Methods* 39:185–191. ? K.E. Watkins, T. Paus, J.P. Lerch, , A. Zijdenbos, D.L.Collins, P. Neelin, J. Taylor, K.J. Worsley and A.C. Evans. Structural Asymmetries in the Human Brain: a Voxel-based Statistical Analysis of 142 MRI Scans. *Cerebral Cortex* Sep 2001;11:868–877. ? Toga AW, Thompson PM. 2003. Mapping brain asymmetry. *Nat Rev Neurosci.* 4:37–48.
2. Findings about thickness measurements correlating different cortical areas

suggesting functional connection patterns should be discussed with more details. These findings have been stressed in a number of papers using MRI in healthy subjects, relations among these connection patterns and specific tracts or fibers have been suggested. References are appropriate and updated.

We would like to thank the reviewer for finding our manuscript acceptable and for finding our research important. Materials and methods: We clarified the normalcy of the donors. We commented also on their age and handedness. Results: 1. Hemisphere column numbers are for specimens identifying purposes. We added a clarification. 2. The empty cells in tables are due to local specimen destruction. Discussion: We would like to thank the reviewer for helping us enrich our discussion and references.

Editor

We also modified our text according to the three editorial comments.

We would like to thank you again for publishing our manuscript in the *World Journal of Neurology*.

Sincerely yours,

A handwritten signature in dark ink, appearing to read 'Ioannis N. MAVRIDIS', with a long horizontal stroke extending to the right.

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