

DECISION LETTER

I am pleased to inform you that your manuscript is acceptable for publication in the Journal of Alzheimer's Disease pending minor revision.

Below is a link to the decision and reviewers' comments regarding your submission. Please click it to confirm receipt of this letter.

Please revise your manuscript according to the reviewers' suggestions and provide a point-by-point response to the reviews at the beginning of your revised manuscript. Please track changes in your manuscript and submit it to our online submission system (<http://mstracker.com/submit1.php?jc=jad>). Be sure the manuscript is formatted per our instructions to authors (<http://www.j-alz.com/prep>). When resubmitting please mention the reference number in the cover letter. Your revision should be returned within two months.

Sincerely,
George Perry
Editor-in-Chief, JAD

REVIEWER 1

The paper titled "Longitudinal mapping of cortical thickness measurements: an ADNI-based evaluation study" compared 5 different cortical thickness measurement methods: ANTS Cross, ANTS SST, ANTS Native, FreeSurfer-Cross and FreeSurfer Long in terms of the variance ratio, and statistical power for distinguishing LMCI-CN, AD-LMCI, and AD-CN through the linear mixed effect (LME) model. While freesurfer is the most popular tool for cortical thickness analysis, ANTs is now quite popular and their comparisons have done before [26]. I believe that this manuscript's main contribution is introducing the new ANTs longitudinal pipeline first time (though it was released through BioRxiv in 2018) Also, its thorough data analysis including LME, a popular analysis approach for the longitudinal data, raised its value by guiding others to use the longitudinal pipeline and statistical analysis. While the main scientific conclusion of the paper is the importance of longitudinal pipeline, as the author indicates in page 15, Section 2.4 line 8. its real value is not just that. So, I strongly recommend this paper.

I have two major issues.

1. Organization of paper.

1) too much details in the method.

The method has too much details for the journal paper. I think some of them

should move to the appendix: Table 1, Figure 4 and Figure 5.

Figure 1 and 2 look quite interesting but they are not essential for the results.

So, it is recommended to move to the appendix also.

I do not think the figure 9 shows important findings. If it is please clarify in the

text. If not, it is also recommended to move to the appendix.

2) Section 2.3~2.6

I think Section 2.3~2.6 are all about the statistical analysis.

Also Section 2.5 is relatively long since it has two contents in it: review of

LME and variance ratio. I think breaking it into two section will make easier

to read. How about the following organization?

Section 2.1. ADNI

Section 2.2. ANTs

Section 2.3. Statistical analysis

Section 2.3.1. Evaluation between cross-sectional and longitudinal pipelines

Section 2.3.2. Review of LME

Section 2.3.3. variance ratio for between-subject thickness variability evaluation

Section 2.3.4. Regional diagnostic contrasts based on cortical atrophy

3) Better introduction...

I think section 2.4's first paragraph is more clear to understand the real

intention of the paper, compared to the last paragraph of the introduction.

Why don't the authors try to use the wording there for the introduction?

2. The journal scope?

I wonder that it is matched with the journal's scope. This manuscript is rather

methodological paper. Though it uses the ADNI dataset, its main goal is to

introducing ANTs longitudinal process and its superiority in diagnostic performance.

So, I believe that it is more fit to Neuroimage or other methodology-oriented journals.

I just let the editor and other reviewer to decide this.

Minor points.

1. Section 2.5, page 16, line 6: longitudinal mixed effects (LME)

I think generally LME stands for linear mixed effects, and the references are

also used the wording "linear mixed effects". If the author did not used the

non-linear mixed effects, please use the traditional nomenclature.

(well, from the equations, the authors did not use non-linear models.)

2. Section 2.5, page 19, line 4: less less -> less

3. Figure 6 legend on the right,
The topmost markers are ANTs SST and bottommosts are FSCross in the figure,
However, the legend on the right is in the reversed order.
If the order of showing is reversed (matched with the Section 2.4's order)
It is easier to read the figure!

4. Reference 68. Brain Mr Images -> Brain MR images

5. I am not sure JAD allows the reference like 27, 36, 46, 48, 49.

6. In case of the reference 49, there is a formal reference.
Nooner et al, (2012). The NKI-Rockland Sample: A model for accelerating the
pace of discovery science in psychiatry. Frontiers in neuroscience
6, 152.

REVIEWER 2

The manuscript deals with a very important issue of processing longitudinal structural MR images in a robust way. The authors have compared two popular methods in the literature and analyzed the longitudinal data using sound statistical methods. I believe the proposed methods help many researchers in the neuroimaging field.

REVIEWER 3

Manuscript ID#: JAD 19-0283
Title: Longitudinal mapping of cortical thickness measurements: an ADNI-based evaluation study

In this paper, Tustison et al. evaluated the utility of longitudinal FreeSurfer and ANTs surrogate thickness values in the context of a longitudinal mixed-effects (LME) modeling strategy using the first phase of the Alzheimer's Disease Neuroimaging Initiative (ADNI-1) data. This paper is well written and deals with an important methodological issue regarding longitudinal cortical thickness measurement. As this ANTs framework is an open source, it may be useful for future researches.

Major Comments

The advantages of ANTs longitudinal pipeline over other methods were evaluated in a single large cohort. Please acknowledge in the discussion that this has to be replicated in other cohorts as well.

Minor Comments

1. Please write the full term of ANTs in the abstract.
 2. Table 2 and 3 have identical title. Did the authors intend to demonstrate right and left hemisphere for each table?
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