Max 3000 char – see below rebuttal guidelines and full reviews.

## Rebuttal

The reviewers highlighted several weaknesses and strengths in our study. The key criticism was that the validation of our Disease Knowledge Transfer (DKT) method is not quantitative and not sufficiently convincing (e.g. trajectories don't match well with experimental data). Another major criticism from reviewer 3 is that some regions in the brain are not affected by measurable pathological processes, and thus the model cannot estimate disease trajectories in such regions. Another issue that came up was that the methods section was not self-contained. In terms of key strengths, reviewers agreed that the problem of knowledge transfer to atypical neurodegenerative diseases is interesting, our proposed DKT method is novel and that the paper is well motivated.

We completely agree with the reviewers and we think the criticism is fair and substantiated. At the time of submission, we were aware of the lack of quantitative metrics for validation, which we didn’t perform due to lack of time. However, we have since done some preliminary performance evaluation and showed that the additional knowledge from typical AD yields better predictions compared to when not using the additional knowledge (RMSE=XX smaller in DKT model compared to simpler model with RMSE=XX, p < 1e-XX). The qualitative validation also did not look very promising, which we attributed to a lack of disease signal in some regions. Another factor biasing the results is that, due to lack of pre-processed ADNI data, DTI measures were estimated only from white matter (WM). These are not straightforwardly mapped to the functional units representing cortical regions, because some of the WM tracts connect regions from different functional units. Ideally, a better validation would use FDG or AV45 cortical measures from PCA patients for which the mapping of such measures to functional units would be simple, but we don’t have such data currently available. Validation of the method is therefore not straightforward due to the lack of comprehensive, longitudinal and multimodal data in atypical neurodegenerative diseases.

Regarding the second criticism -- lack of disease signal in a particular region -- this is a limitation of the input data. However, we believe our model can deal with this in the best way possible by performing extrapolation of the trajectories when required, but also not being prone to overfitting by projecting the data to low-dimensional manifolds. The region with the least disease signal was the cingulate gyrus, which for both PCA and tAD (Fig 2. B-C) has the trajectory that is most flat, which is expected for a region with low disease signal.

Finally, the lack of self-containedness of the methods is because, as explained early in the methods section, our hierarchical approach uses a disease progression model (DPM) as a building block. Several DPMs have already been published in the literature, and any of them can be plugged in our higher-level model. We didn’t describe the DPM model of our choice in detail due to it not being the focus of our work.

## MICCAI Rebuttal guidelines

Your rebuttal is addressed to the Area Chairs only. Reviewers will not see it and will not be able to change their reviews.

The goal of the rebuttal is to inform the Area Chairs of major misunderstandings, in your opinion, in the reviewers’ assessment, or of incorrect statements in the reviews. An effective rebuttal focuses only on major critiques. It is not helpful to try to address every minor point in the reviews. By prioritizing and focusing on the major concerns, and by grouping multiple reviewer comments that generally pertain to the same issue into a few major categories, you are demonstrating to the Area Chair that you understand the high level messages that were provided in the reviews.

It is useful to summarize or rephrase the criticism before you address it, as long as it is clear what comment(s) you are responding to. While the room for rebuttal is limited, if properly utilized by condensing the response down to the essentials, this is an effective way to let the Area Chairs know that you understood the reviewer’s concerns and have valid answers to the questions raised in the reviews, or else to establish that certain reviewer comments were false or unsubstantiated.

An effective rebuttal addresses reviewers' criticisms by explaining where in the paper you had provided the requisite information, perhaps further clarifying it.

It is not helpful to promise to expand your paper to address all the questions raised by the reviewers. The process does not allow you to change an article substantially, and in all likelihood you don't have sufficient room to add to the paper. These promises are likely to not be taken seriously.

A good rebuttal is polite. Being confrontational does not bring any added value to the paper. You should point out however if you feel you have received a review which was not courteous or made false or unsubstantiated arguments that you can succinctly refute.

## Reviews

REVIEWER #1

2. Please list the major strengths of the paper (bulleted list)

- The idea for disease knowledge transfer is novel for modelling the disease progression modelling of the AD.

- The problem is well motivated and the paper is organised well.

- Validation experiment on 20 DTI scans of PCA patients is good, but no quantitative metric was used the evaluate the results and only visual assessment was carried out in the paper.

3. Please list any major weaknesses of the paper (bulleted list)

- Albeit the idea looks interesting, but the validation results in Fig. 4 does not look promising. The predicted trajectories do not match well to the experimental data. This has been mentioned as a limitation of the method by authors in section 5, but this was the initial objective of this paper. What is the benefit of this method then?

- How do you decide the functional units a priori and why should one assume that different types of AD affect the biomarkers in the same way in those selected functional units?

- The paper is not self-contained and one should see the referenced papers to fully understand the method.

4. Please provide detailed and constructive comments for the authors. Please also refer to our Reviewer's guide on what makes a good review: http://www.miccai2018.org/files/downloads/MICCAI2018-Reviewers.pdf

Given your probabilistic formulation, is it possible to model the correlation between biomarkers in the model using a categorical distribution rather assigning them a priori?

REVIEWER #2

2. Please list the major strengths of the paper (bulleted list)

- Very innovative method, which could empower the incomplete datasets of rare diseases by taking advantage of their connections with those well-studied diseases which have more complete data.

- Considering the space limitation, the results are very well presented with proper discussions.

3. Please list any major weaknesses of the paper (bulleted list)

- The methodology part is hard to follow.

4. Please provide detailed and constructive comments for the authors. Please also refer to our Reviewer's guide on what makes a good review: http://www.miccai2018.org/files/downloads/MICCAI2018-Reviewers.pdf

- One concern regarding the results is that SUVR is a normalized ratio and using TIV as covariate may not be appropriate. This could also affect the final estimated trajectory.

- For trajectory estimation, it is better to quantify the fit rather than evaluating it based on visualization.

REVIEWER #3

2. Please list the major strengths of the paper (bulleted list)

This work constructed brain region-specific biomarker progression, by integrating multimodal imaging from different diseases.

3. Please list any major weaknesses of the paper (bulleted list)

Although the region dysfunction can be evaluated from measurements of this region, like atrophy from MRI, amyloid deposit from AV45, not all imaging modalities have changes or have differences between patients and controls. I am afraid using information from the combination of different disease to infer disease-specific progression need more disease specific knowledge.

4. Please provide detailed and constructive comments for the authors. Please also refer to our Reviewer's guide on what makes a good review: http://www.miccai2018.org/files/downloads/MICCAI2018-Reviewers.pdf

This paper explored an interesting problem. However, the validation results cannot confirm me the performance for predicting progression of biomarker from other biomarkers.