PS: 00 - 04 is the R scripts for the work "Discordance of β-amyloid measured by cerebrospinal fluid and PET imaging shows distinct spatial tau patterns".We conducted the voxel-wise with spm12 in Matlab.

00- This part is about the analysis of demongraphics

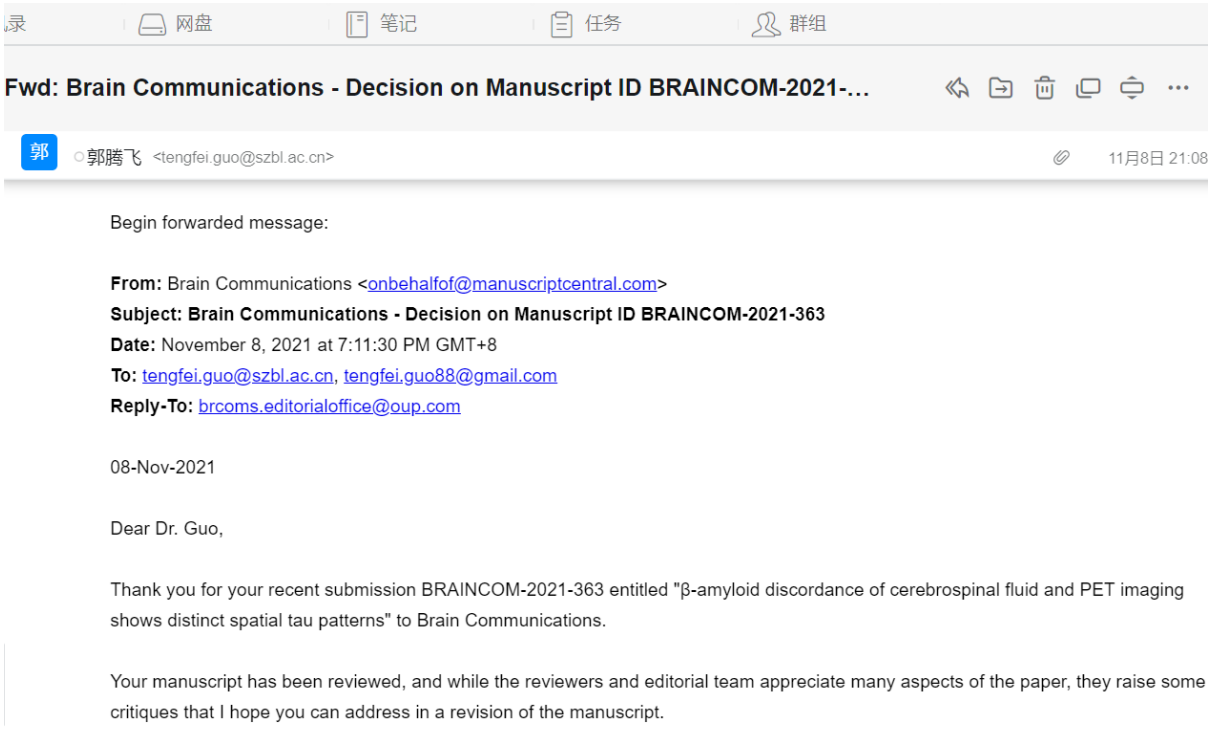
01- This part is to find different corresponding tau pattern of different CSF/PET groups categorized by CSF Abeta and Aβ PET

02- This part is for comparisions Comparisons of cortical tau deposition among different CSF/PET groups

03- This part is for the association analysis of CSF Aβ42/Aβ40, Aβ PET and CSF p-Tau/Aβ40 in early amyloidosis stage

04- This part is for the association analysis of CSF Aβ42/Aβ40, Aβ PET and CSF p-Tau/Aβ40 in late amyloidosis stage

This work is in review in the Journal Brain Communications. The other part is the abstract of the manuscript.



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Fwd: Brain Communications - Decision on Manuscript ID BRAINCOM-2021-...

郭 郭腾飞 <tengfei.guo@szbl.ac.cn> 11月8日 21:08

Begin forwarded message:

From: Brain Communications <onbehalfof@manuscriptcentral.com>
Subject: Brain Communications - Decision on Manuscript ID BRAINCOM-2021-363
Date: November 8, 2021 at 7:11:30 PM GMT+8
To: tengfei.guo@szbl.ac.cn, tengfei.guo88@gmail.com
Reply-To: brcoms.editorialoffice@oup.com

08-Nov-2021

Dear Dr. Guo,

Thank you for your recent submission BRAINCOM-2021-363 entitled "β-amyloid discordance of cerebrospinal fluid and PET imaging shows distinct spatial tau patterns" to Brain Communications.

Your manuscript has been reviewed, and while the reviewers and editorial team appreciate many aspects of the paper, they raise some critiques that I hope you can address in a revision of the manuscript.

Discordance of β-amyloid measured by cerebrospinal fluid and PET imaging shows distinct spatial tau patterns

Chengyang Jiang[1], Qingyong Wang[2], Siwei Xie[1], Zhicheng Chen[3], Liping Fu[4], Qiyu Peng[1], Ying Liang[5], Hongbo Guo[6], and Tengfei Guo[1] for the Alzheimer's Disease Neuroimaging Initiative

Abstract

Extracellular β-amyloid-(Aβ) plaques and intracellular neurofibrillary tau tangles are the primary hallmarks of Alzheimer's disease. Aβ pathology can be directly quantified by positron emission tomography (PET) imaging, or indirectly by measuring the decrease of soluble $A\beta_{42}/A\beta_{40}$ ratio in cerebrospinal fluid (CSF). Although these two Aβ biomarkers may be considered interchangeable, they sometimes show discordance, particularly in earlier stage of Alzheimer's disease. Individuals with CSF Aβ positive only (CSF+/PET-) or Aβ PET positive only (CSF-/PET+) may be at early amyloidosis stage comparing to individuals who are negative (CSF-/PET-) or positive (CSF+/PET+) at both CSF Aβ and Aβ PET, probably representing different Aβ pathology progressing pathways. Besides, Aβ pathology may play an initiating role in Alzheimer's disease onset, leading to subsequent tau increases. However, it is still unclear whether individuals with different Aβ pathways have distinct spatial patterns of cortical tau tangles in early amyloidosis stage.

In this study, we analyzed 238 cognitively unimpaired and 77 mild cognitive impairment individuals with concurrent (interval of acquisition < 1 year) ^{18}F-flortaucipir tau PET, Aβ (^{18}F-florbetapir or ^{18}F-florbetaben) PET, and CSF $A\beta_{42}$ and $A\beta_{40}$ and CSF p-Tau, and divided them into 4 different CSF/PET groups based on the abnormal status of CSF $A\beta_{42}/A\beta_{40}$ (CSF±) and Aβ PET (PET±). We determined the cortical regions with significant tau elevations of different CSF/PET groups, and investigated the region-wise and voxel-wise associations of tau PET images with CSF $A\beta_{42}/A\beta_{40}$, Aβ PET and CSF p-Tau/$A\beta_{40}$ in early (CSF+/PET- and CSF-/PET+) and late (CSF+/PET+) amyloidosis stages. By compared to the CSF-/PET- individuals (Ref) without evidence of tau increase measured by CSF or PET, CSF+/PET- individuals showed higher tau in entorhinal but not in $Braak_{III/IV}$ and $Braak_{V/VI}$, whereas CSF-/PET+ individuals had significant tau elevations in $Braak_{V/VI}$ but not in entorhinal and $Braak_{III/IV}$. In contrast, CSF+/PET+ individuals showed significant tau

increases in all the cortical regions than the Ref group. The voxel-wise analyses provided further evidence that lower CSF $A\beta_{42}/A\beta_{40}$ was associated with higher tau in entorhinal while higher Aβ PET was related to higher tau in $Braak_{V/VI}$ regions in early amyloidosis stage, and both of them were correlated with tau aggregation in entorhinal, $Braak_{III/IV}$ and $Braak_{V/VI}$ cortices in late amyloidosis stage.

These findings provide novel insights into the spatial patterns of cortical tau tangles in different amyloidosis stages of Alzheimer's disease, suggesting CSF Aβ and Aβ PET discordant groups may have distinct characteristics of cortical tau tangles in early amyloidosis stage.

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Keywords: Alzheimer's disease; cerebrospinal fluid; PET imaging; β-amyloid; Tau

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; CU = cognitively unimpaired; MCI = mild cognitive impairment; AD = Alzheimer's disease; SUVR = standardized uptake value ratio

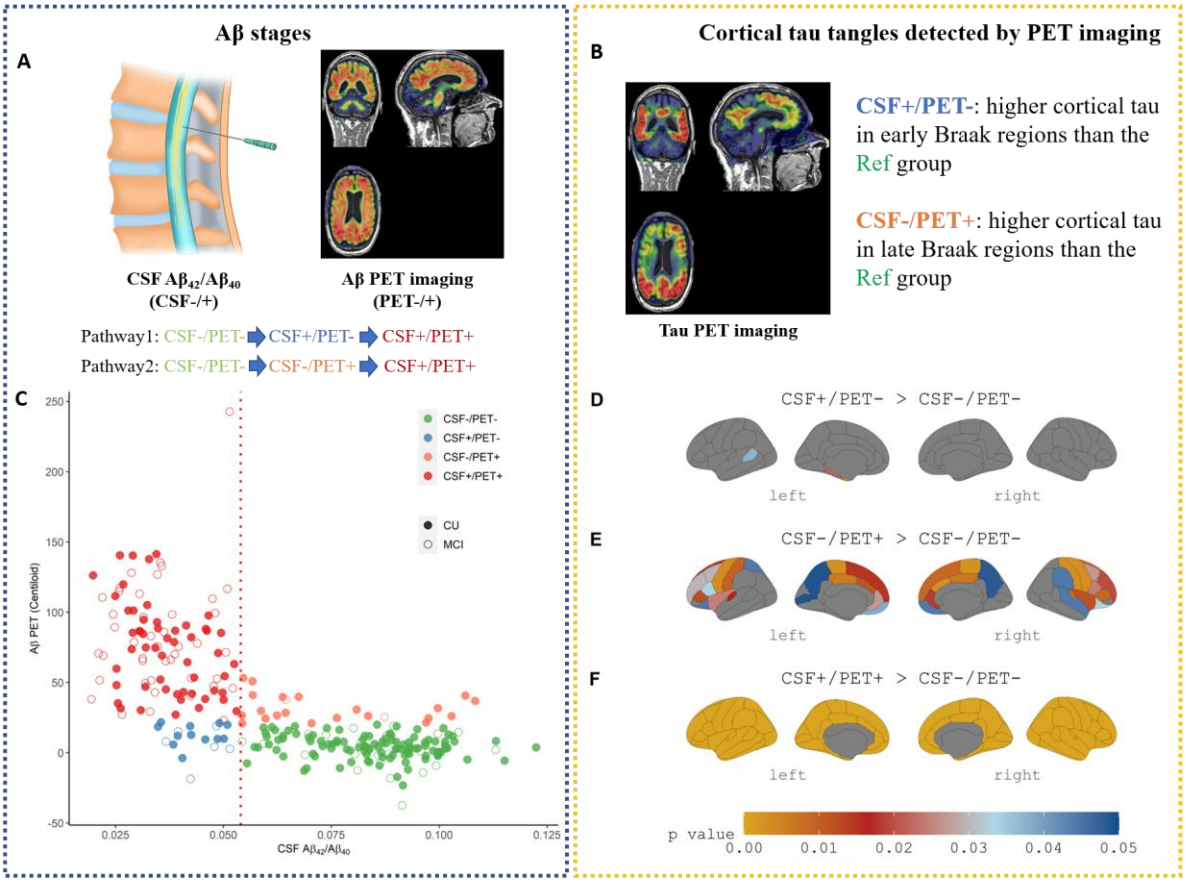

Figure 1 Significant cortical tau elevation of different CSF/PET groups categorized by CSF β-amyloid (Aβ) and Aβ PET. (A) Illustration of lumbar puncture and Aβ PET imaging, (B) Illustration of tau PET imaging, (C) CSF/PET groups defined by CSF $A\beta_{42}/A\beta_{40}$ and Aβ PET, and the vertical red dash line denotes the corresponding thresholds of CSF $A\beta_{42}/A\beta_{40}$ (0.054), (D,E,F) Significant cortical tau elevations of different CSF/PET groups compared with the CSF-/PET- group, and multiple comparisons correction was employed for 68 ROIs by using the Benjamini-Hochberg approach (FDR < 0.05) except for the comparison between CSF+/PET- group and Ref group.