Letter to the Editor

New insights into mechanisms of Alzheimer's disease revealed by a dynamic functional magnetic resonance imaging study

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We have read the study by Li *et al*. (1) with great interest and would like to congratulate the authors for the publication of this important study. Based on resting-state functional magnetic resonance imaging (fMRI), they compared the dynamic amplitude of low-frequency fluctuation (dALFF) and dynamic fraction amplitude of low-frequency fluctuation (dfALFF) among 111 patients with Alzheimer's disease (AD), 29 patients with mild cognitive impairment (MCI) and 73 healthy controls (HC). The findings suggest abnormal dynamic features of brain activity in AD patients, which are ignored by conventional static fMRI studies. It gives a new insight into the neurophysiological mechanisms of AD. As such, there are a few points which we would like to bring up.

During the data preprocessing stage, global signal regression (GSR) was not performed in the current work. However, some previous studies have indicated that measures of the dynamic fluctuations in brain activity are sensitive to head motion (2), and GSR is one of the most effective de-noising strategies to diminish motion artifacts (3). For such a reason, although being controversial considering that GSR could exacerbate the impacts of anti-correlations between brain regions (4), more adequate results may be obtained with GSR to minimize the motion-related effects in dynamic fMRI studies. In fact, in many of the recent research on dALFF or dfALFF, the primary analyses were performed with GSR (5-7). Therefore, the authors might benefit from adding complementary analysis with GSR to probe its possible effects on dALFF and dfALFF.

The AD patients showed significantly increased dALFF variabilities within regions of the cerebellum and temporal lobes when compared to HCs, while no significant differences were found between the MCI patients and HCs. Based on such results, the authors concluded that abnormally increased variabilities of brain activity within these regions can be recognized as dementia-specific processes. Nevertheless, it is noteworthy that in the current study, the sample size of MCI group (n=29) is much smaller than those of the AD (n=111) and HC (n=73) groups. Since the reduction in sample size results in a lower statistical power for detecting true effects (8), it is possible that similar alterations are occurring in the MCI patients but can only be detected in a larger sample.

The current study was focused on dALFF and dfALFF, which are both voxel-based measures to assess the dynamic fluctuations of local brain activity. Beyond them, there are measures of brain dynamics with a larger scope, such as the temporal variability of functional connectivity (8,9) and stability of modular structures (10) for large-scale brain networks. In my view, future studies are encouraged to investigate the associations between AD and functional brain dynamics by combining both the dALFF/dfALFF

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and these network-level assessments. This is important since the aberrant dynamic features of brain function in neuropsychiatric disorders are often observed for the entire brain systems (8,9).

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