LETTER TO THE EDITOR

Hippocampal functional connectivity in Alzheimer's disease: a resting state 7T fMRI study

Among the range of neuroimaging techniques available that may provide insight into Alzheimer's disease (AD), resting-state functional magnetic resonance imaging (rsfMRI) and functional connectivity has emerged as particularly useful in the early diagnosis of AD (de Vos *et al.*, 2018). Altered functional connectivity of the hippocampus is recognized as an important feature of preclinical AD and found in the early stages of AD (Franzmeier *et al.*, 2019; Scherr *et al.*, 2019; Wang *et al.*, 2006). The hippocampus is one of the earliest affected brain regions in AD (Braak *et al.*, 1993), with its degradation being a hallmark of AD in many structural and functional imaging studies. Thus, we aimed to investigate whether the connectivity of the hippocampus with the rest of the brain is altered in AD patients compared to healthy individuals using a 7-Tesla MRI imaging.

Eleven individuals meeting a NINCDS-ADRDA (McKhann *et al.*, 1984) diagnosis of mild-to-moderate probable AD and 10 non-demented controls (NDC) who were similar in age were recruited for this cross-sectional study from memory services in Leicestershire, United Kingdom. The study had regional Research Ethics Committee approval (12/EM/0007) and all participants provided written informed consent. Mini-mental state examination (MMSE) (Folstein *et al.*, 1975) was used for cognitive assessment.

Resting-state fMRI data acquired using Philips 7-Tesla Achieva scanner (University of Nottingham), with eyes closed and a 2D gradient-echo, echo-planar imaging (GE-EPI) sequence (repetition time = 2000 ms, echo time = 25 ms, nominal flip angle = 75°, 36 slices with $2 \times 2 \times 2$ mm^3 voxels; scan duration = 5:12 min) was preprocessed (realignment, motion correction, and slice timing correction) and functional connectivity analyses were carried out using CONN: Functional Connectivity Toolbox v17 (Whitfield-Gabrieli and Nieto-Castanon, 2012) running in SPM12 (http://www.fil.ion.ucl.ac.uk/spm). rsfMRI volumes were normalized to the standard Montreal Neurological Institute space template, segmented and realignment parameters, white matter, and CSF signals used as covariates-of-no interest in the CONN toolbox(Behzadi *et al.*, 2007). Residual time series of rsfMRI images were then band-pass filtered

$(0.008 < f < 0.09$ Hz) and a seed-based region of interest (ROI) analysis was conducted using the CONN Toolbox. Resting-state BOLD signals from the left and right hippocampal ROIs were defined and correlated with 132 brain regions from the CONN atlas in a 2x132 correlation matrix.

Individuals with AD (36% women; 54–78 years; mean: 61.6 ± 6.3 years) and NDC participants (70% women; 54–77 years; mean: 64.9 ± 6.3 years) were studied. The NDC group (Mean: 29.7 ± 0.7; Median: 30.0 [interquartile range: 29.75, 30.0]) had higher (Mann–Whitney $U = 5.0$, $Z = -3.64$, $p < 0.001$) MMSE score than AD individuals (Mean: 24.9 ± 4.8; Median: 27.0 [interquartile range: 23.0, 29.0]). There was significantly greater functional connectivity (beta= 0.31; $T_{19} = 4.7$; $p_{unc} = 0.000154$; false discovery rate (FDR) corrected $p = 0.020239$; Figure 1; FDR correction applied for each seed separately) of the left hippocampal seed with left superior frontal gyrus (SFG) in NDC compared to AD individuals. MMSE scores positively correlated with hippocampal- SFG functional connectivity (Spearman's $r = 0.629$, $n = 21$, $p \leq 0.002$) in the whole group of participants suggesting lower MMSE scores were associated with reduced connectivity between the left hippocampus and the left SFG. Given the modest sample size, these results are to be considered preliminary and need independent replication in larger samples.

To our knowledge, this is the first functional connectivity report in AD using ultra-high-field strength, 7-Tesla, rsfMRI which provides increased contrast-to-noise ratio and facilitates increased spatial resolution (Li *et al.*, 2012), thus providing increased sensitivity and spatial specificity for the detection of pathological changes that might not be detectable at lower field strengths.

These preliminary findings are consistent with previous evidence of altered hippocampal FC in individuals with AD compared to NDC, in particular altered FC between the hippocampus and frontal lobes (de Vos *et al.*, 2018; Franzmeier *et al.*, 2019; Scherr *et al.*, 2019; Wang *et al.*, 2006). The SFG is thought to be involved in higher cognitive domains and is a critical component of the working memory network. Based on much of the previous literature that has found the hippocampus to be one of the earliest brain areas affected by the accumulation of AD lesions, one may hypothesize that the integrity of functional connectivity between the hippocampus and other brain regions must be compromised in individuals with AD. If these preliminary results can
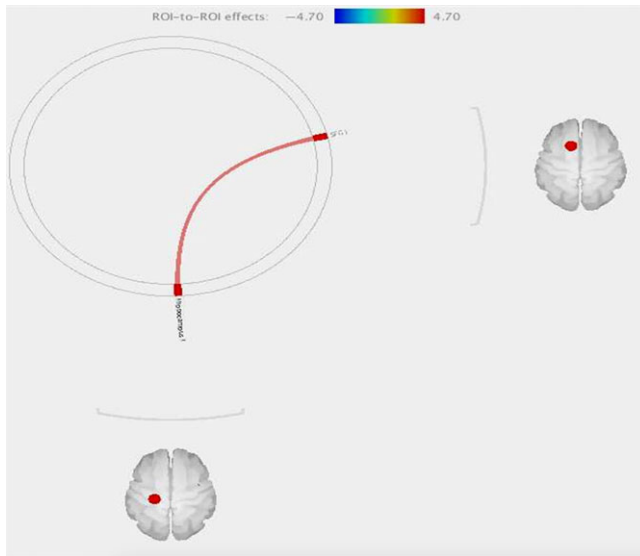
Figure 1. Effect size of hippocampus (L) – superior frontal gyrus (L) functional connectivity.

be validated independently in larger samples, rsfMRI FC measures may have potential as an early diagnostic tool, identifying the presence of AD before demonstrable cognitive deficits arise. It may also have potential as a biomarker for testing novel treatments as well as a surrogate marker for efficacy.

Conflict of interest

None.

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