Hippocampal disconnection predicts cognitive impairment in patients with cerebrovascular disease

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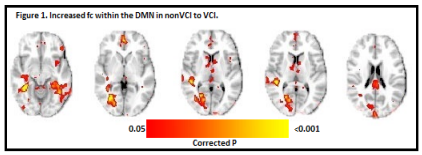
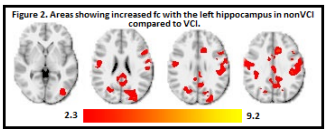
Target audience: Clinical neuroscientists, neuroradiologists

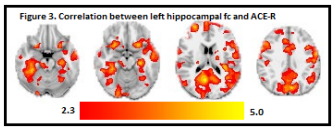
Purpose: Vascular cognitive impairment (VCI) occurs in one cognitive domain in 62% and in two domains in 35% of ischemic stroke patients aged 55 to 85 years[1]. The mechanisms underlying VCI have not been well established. In neurodegenerative dementia and mild cognitive impairment (MCI), dysfunction of the default mode network (DMN) are well established. Furthermore, the hippocampus is considered critical for post-stroke cognitive impairment[2]. We hypothesize that disconnection is a main mechanism underlying VCI, and that in particular reduced activity of the DMN and reduced hippocampal connectivity underpin cognitive deficits in patients with cerebrovascular disease (CVD). The aim of this study was to assess functional connectivity (fc) abnormalities as potential neural substrate of cognitive impairment in patients with recently symptomatic carotid artery disease.

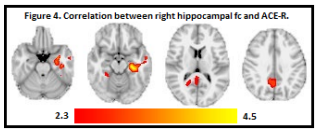
Methods: This prospective study was approved by Local Ethics Committee. 48 patients [age:47-91 (mean 75.4)] with a carotid artery stenosis of >30% with a recent (within last 6 months) non-disabling cerebrovascular event were recruited. Participants underwent a resting-state fMRI scan and Addenbooke's cognitive examination (ACE-R). Participants were divided into VCI and non VCI based on ACE-R scores defining VCI as ACE<82. FC analysis was performed using standard procedures implemented in FSL[3].Independent component analysis (ICA) followed by a dual regression approach was used to assess interrelations of DMN fc with ACE-R, and differences between VCI (n=21) and non VCI (n=27). Seed based analyses were conducted to study the association of fc of the left and right hippocampus with ACE-R using regression and between group comparisons. Signal averaged from the centre deep white matter, over the ventricles, and six parameters obtained by rigid body head motion correction, were removed from the signal time-course of each voxel using the general linear model. FDR corrected P<0.05 was considered significant.

Results: There were no significant differences in age, gender, presenting symptoms, white matter lesion (WML) volume and other risk factors between two groups.**DMN results:** Using ICA with temporal concatenation, we obtained a set of 41 independent components and DMN was selected for further analysis. A Z-score was extracted from each subject's DMN and was correlated with the ACE-R and sub-scores (control for age). We found significant correlation between Z-score and total ACE-R (P=0.018), memory (P=0.028) and fluency (P=0.04). Using the dual regression approach, **Figure 1** shows increased fc within the DMN in non-VCI patients compared with VCI patients. **Seed based hippocampus fc results:** Non-VCI patients showed significantly increased FC compared with VCI patients between the left hippocampus and several brain regions (**Figure 2**). Moreover, we found that the strength of FC in an extended network with the left hippocampus correlated with cognitive performance (**Figure 3**).When right hippocampus was selected as a seed, there were no significant differences between non-VCI and VCI patients regarding the FC between the seed with the rest of the brain. However, the FC between right hippocampus and several brain regions significantly correlated with ACE-R (**Figure 4**).









Discussion: This study provides first fc evidence that VCI can be explained by disconnection of the DMN, left hippocampus and to a lesser extent the right hippocampus. Interestingly, we found that left hippocampus fc was more disrupted in VCI than the right hippocampus fc, suggesting a laterality effect. The correlation of hippocampal fc and cognitive impairment holds promise to improve prediction of VCI that is notoriously difficult based on structural MRI alone. We cannot fully exclude that some of the fc correlation with CI may be explained by co-morbid undiagnosed MCI. However, the rate of 21/48 patients with ACE-R<82 is higher than expected rates for MCI and especially amnestic MCI suggesting predominant vascular cause for the observed CI[4].

Conclusion: Our findings suggest that VCI results from long range disconnection of the left hippocampus fc and DMN. Since resting-state fMRI is easier than task-related fMRI to conduct in patients with CVD, FC assessed by resting-state fMRI has the potential to become a diagnostic marker that may also be useful for the assessment of treatment and rehabilitation.

References: **1.**Pohjasvaara T, et al. Dementia three months after stroke:baseline frequency and effect of different definitions of dementia in the HSAMS cohort. Stroke 1997; 28:785-792. **2.**Grysiewicz R, Gorelick PB. Key neuroanatomical structures for post-stroke cognitive impairment. Curr Neurol Neurosci Rep.2012;12:703-708. **3.** S.M. Smith, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage, 23(S1):208-19, 2004. **4.**Ward, et al. Mild cognitive impairment:disparity of incidence and prevalence extimates.Alzheimers Dement.2012; 8(1):4-21.

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