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Structural brain abnormalities and cardiac dysfunction in patients with chronic heart failure

Chronic heart failure (CHF) induces brain structural abnormalities that are associated with depressive symptoms and cognitive impairment.[1–3] We have previously shown that CHF rats have histological abnormalities of the hippocampus characterized by reduction in neurogenesis and neurite outgrowth and increase in the number of astrocytes.[1] Our experimental findings are consistent with clinical studies with brain magnetic resonance imaging (MRI) that demonstrated reduced grey matter volume in several cortical and subcortical regions including the hippocampus in CHF patients.[2,3] A possible mechanism for brain damage in CHF patients is cerebral hypoperfusion due to cardiac dysfunction; decreasing cardiac index (CI), even at normal levels (CI <2.92 L/min/m^2), is associated with reduction in total brain volume.[4] However, it remains unclear which brain regions are susceptible to haemodynamic impairment in CHF patients. In this study, therefore, we examined whether there is a correlation between brain damage (e.g. the hippocampus) and cardiac dysfunction using cardiac and brain MRI recordings that had been acquired in the Brain Assessment and Investigation in Heart Failure Trial (B-HeFT).[5]

We enrolled 40 asymptomatic Stage B and 40 symptomatic Stage C CHF patients aged 45–90 years as described previously.[5] The study protocol was approved by the ethics committee of the Tohoku University Graduate School of Medicine (no. 2012-2-31) and was registered in the University Hospital Medical Information Network (UMIN000008584). We performed cine cardiac (Intera Achiva 1.5 T Nova Dual, Philips Medical Systems, Best, the Netherlands) and structural T1 brain (Signa HDxt 1.5 T GE Medical Systems, Milwaukee, WI, USA) MRI within 6 months in each patient. Left ventricular stroke volume index (LVSVI) and CI were calculated using the Simpson's method and expressed as mean ± standard deviation. We performed pre-processing for brain MRI analyses as described previously.[1,5] Briefly, grey matter maps were segmented from structural brain MRI scans and normalized to the standard Montreal Neurological Institute space to perform voxel-wise statistical analyses. The normalized grey matter maps were unmodulated with Jacobian determinants and were then smoothed with an isotropic Gaussian kernel by convolving a 16 mm full width at half maximum to produce grey matter concentration (GMC) maps. Only voxels with GMC value >0.05 were included.[6]

To explore brain regions associated with cardiac dysfunction, we first performed a voxel-wise regression analysis of the whole brain, which examined correlations between

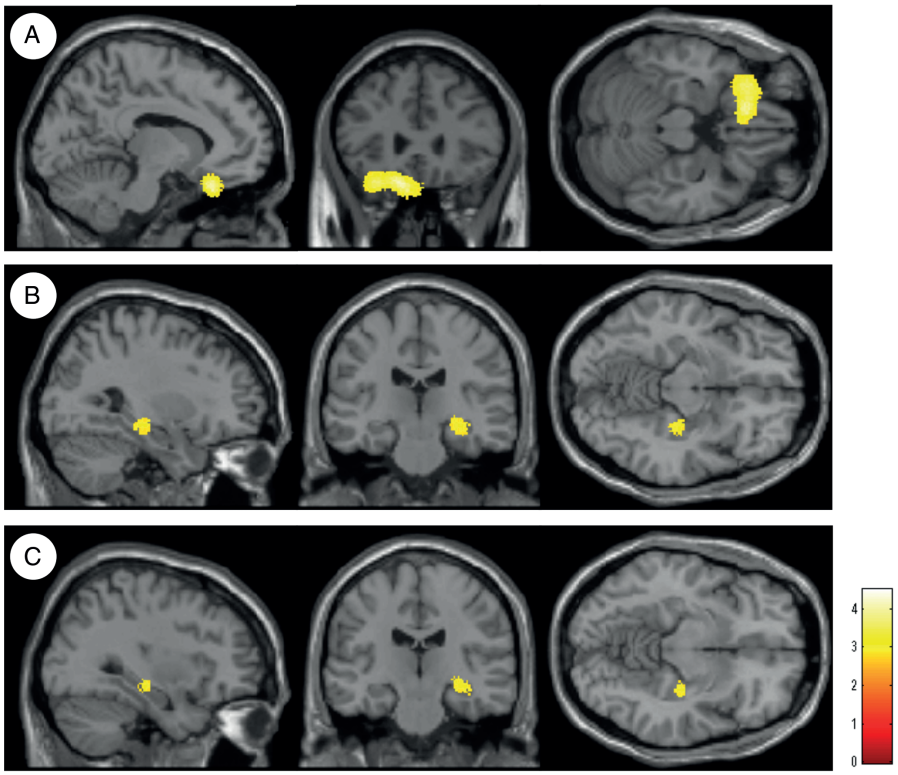

Figure 1 Associations between brain structural abnormalities and haemodynamic impairment. Left ventricular stroke volume index was associated with grey matter concentration of the prefrontal cortex (*A*) and that of the hippocampus (*B*), and cardiac index was associated with that of the hippocampus (*C*) in the Stage B group (orange to yellow regions). The colour calibration bar represents the critical T-score magnitudes.

each voxel consisting of the GMC maps and LVSVI/CI, using Student's *t*-tests. The Stage B and C groups were analysed separately. We then conducted multivariable analyses regressing GMC in brain regions identified in the voxel-wise regression analysis onto variables identified from a stepwise selection—age, sex, educational level, and LVSVI/CI. Parameter estimates (*B*) were reported. All hypothesis testing were two-sided at a significance level of $P < 0.05$ except for the whole-brain analyses, where a significance level was set at a family-wise error-corrected cluster-extent threshold of $P < 0.05$ with an underlying voxel level of $P < 0.005$.[6] A threshold of $P < 0.005$ uncorrected for multiple comparisons was applied to the hippocampus analysis because of our a priori hypothesis.[7]

LVSVI and CI were comparable between the Stage B (LVSVI 37.6 ± 10.0 mL/m^2, CI 2.42 ± 0.72 L/min/m^2) and Stage C (LVSVI 35.7 ± 9.8 mL/m^2, CI 2.41 ± 0.64 L/min/m^2) groups. In the Stage B group, the voxel-wise regression analysis identified the prefrontal cortex and the hippocampus (hippocampus 1), whose GMC was positively correlated with LVSVI. GMC in the hippocampus (hippocampus 2) was also positively correlated with CI (*Figure 1*). The multivariable analyses showed LVSVI was associated with GMC in the prefrontal cortex ($B = 6.9 \times 10^{-4}$), and hippocampus 1 ($B = 5.6 \times 10^{-4}$) and 2 ($B = 4.7 \times 10^{-4}$) (all $P < 0.05$). Associations were also found between CI and GMC in the prefrontal cortex ($B = 5.9 \times 10^{-3}$), and hippocampi 1 ($B = 7.0 \times 10^{-3}$) and 2 ($B = 6.4 \times 10^{-3}$) (all $P < 0.05$). There was no significant association in the Stage C group.

In conclusion, these results were able to demonstrate for the first time that haemodynamic impairment, even at the preserved CI levels (2.42 ± 0.72 L/min/m^2), is associated with structural abnormalities in the prefrontal cortex and the hippocampus in CHF patients.

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References

1. Suzuki H, Sumiyoshi A, Matsumoto Y, Yoshikawa T, Fukumoto Y, Yanai K, Taki Y, Kawashima R, Shimokawa H. Structural abnormality of the hippocampus and depressive symptoms in heart failure rats. *Neuroimage* 2015;**105**:84–92.
2. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol (1985)* 2003; **95**:677–684.
3. Almeida OP, Garrido GJ, Beer C, Lautenschlager NT, Arnolda L, Flicker L. Cognitive and brain changes associated with ischaemic heart disease and heart failure. *Eur Heart J* 2012;**33**: 1769–1776.
4. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S, Gona P, Salton CJ, DeCarli C, O'Donnell CJ, Benjamin EJ, Wolf PA, Manning WJ. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation* 2010;**122**:690–697.
5. Suzuki H, Matsumoto Y, Ota H, Sugimura K, Takahashi J, Ito K, Miyata S, Furukawa K, Arai H, Fukumoto Y, Taki Y, Shimokawa H. Hippocampal blood flow abnormality associated with depressive symptoms and cognitive impairment in patients with chronic heart failure. *Circ J* 2016;**80**: 1773–1780.
6. Takeuchi H, Taki Y, Sassa Y, Hashizume H, Sekiguchi A, Fukushima A, Kawashima R. Regional gray matter volume of dopaminergic system associate with creativity: evidence from voxel-based morphometry. *Neuroimage* 2010;**51**:578–585.
7. Macey PM, Henderson LA, Macey KE, Alger JR, Frysinger RC, Woo MA, Harper RK, Yan-Go FL, Harper RM. Brain morphology associated with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;**166**:1382–1387.