Altered Functional Connectivity in Aged Rat Model of Postoperative Cognitive Dysfunction

P. Xie[1,2], T. Yu[1,2], X-Y. Fu[1,2], Y. Tu[1,2], S. Lui[2], X-N. Zhao[3], H-F. Cheng[4], X-Q. Huang[2], T-J. Zhang[2], X-L. Li[2], Q. Yue[2], D-M. Li[2], and Q-Y. Gong[2,5]

[1]Department of Anesthesiology, Affiliated Hospital of Zunyi Medical College, Zunyi, Guizhou, China, People's Republic of, [2]Department of Radiology, Huaxi MR Research Center (HMRRC),West China Hospital of Sichuan University, Chengdu, Sichuan, China, People's Republic of, [3]Philips Medical System, Beijing, Beijing, China, People's Republic of, [4]School of Science and Technology, University of Electronic Science and Technology, Chengdu, Sichuan, China, People's Republic of, [5]Division of Medical Imaging, Faculty of Medicine, University of Liverpool, Liverpool, United Kingdom

Introduction

Postoperative cognitive dysfunction (POCD) is a common complication occurs after cardiac and major non-cardiac surgery with general anesthesia in the elderly(1), but its causes and mechanism remain unclear to date. Altered functionally connectivity measured by resting-state fMRI has been found in the preclinical phase of some neuro-degenerative diseases such as mild cognitive impairment (MCI)(2) and mild Alzheimer's disease (AD)(3). Present study aims to use resting-state fMRI to explore changes of the functional connectivity, namely the synchronization of low frequency fluctuation (LFF)(4) in animal model of POCD(5) on aged rats genetically predisposed to develop late-onset Alzheimer's disease, and to assess whether it can be used as a marker for postoperative cognitive dysfunction.

Subjects and Methods

The study was approved by the local ethical committee, experiments were conducted in accordance with the guidelines for care and use of laboratory animals. A total of 18 Sprague-Dawley female aged rats (weighing 400–550g, approximately 22 months old) were anesthetized with a combination of 40μg/kg fentanyl and 500μg/kg droperidol (intraperitoneal) for splenectomy. Cognitive function for each rat was assessed using Y maze prior to operation and on postoperative day 1, 3 and 9. Resting-state fMRI data were acquired using a 3.0T MR imaging system (ACHIEVA, Philips, Nederland) with a 4 channel phase array rat head coil. T2-weighted images were acquired using 3D turbo spin echo sequence (TR/TE: 2500/240 ms, slice thickness: 1 mm, matrix size: 224× 224, flip angle: 90°). Functional images were acquired using single shot spin echo EPI sequence (TR/TE: 2000/27 ms, flip angle: 90°, matrix size: 96 × 96, FOV:50× 41mm^2, thickness/gap: 1/0mm, a total of 120 volumes, 20 axial slices per volume to cover whole brain). Data preprocessing was performed using statistical parameter mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm/software/) including slice timing, head-motion correction, spatial normalization to standard rat brain template provided by Adam J. Schwarz(6), and smoothing with the FWHM of 8mm. Further analyses were performed using MarsBar, including selecting seed of interest(ROI) (2×2 pixels) in the left primary somatosensory cortex (SI) and left hippocampus(H), extracting and averaging time courses from these ROIs and band-pass filtering (0.01 - 0.08Hz). The preprocessing time courses were then used as references and cross-correlated on voxel basis with the whole brain to derive corresponding connectivity maps. A correlation coefficient of 0.3 and a cluster size of 4 were used as threshold for the statistical analysis of the functional connectivity maps ($p<4\times10^{-6}$, taking into account the reduced degrees of freedom in the low-pass filtered data)(4).

Results

Table1. Learning and spatial memory for Y maze (mean ±SD, n =18)

Group	Electric stimulation(Voltage)	Learning(Times)
Before operation	35±8	28±7
The 1st day after operation	71±7	69±24★
The 3rd day after operation	62±8	58±19★
The 9th day after operation	41±8	42±12▲

★p< 0.01, ▲P >0.05

The time spent for learning and spatial memorization in Y maze test was significantly longer (p< 0.01) on the 1st and 3rd day after operation than that before operation. Although the learning time was still longer on the 9th day after surgery (42±12 times), this did not differ statistically from that before operation (P >0.05). The results are expressed as mean ± SD (Table1). The group functional connectivity maps showed that significantly correlated voxels (p < 0.001, |T| > 3.16, uncorrected) decreased on both the right primary somatosensory cortex and right hippocampus on the 1st and 3rd day after operation compared with the before operation state, while almost back to normal on the 9th day. (Fig 1).

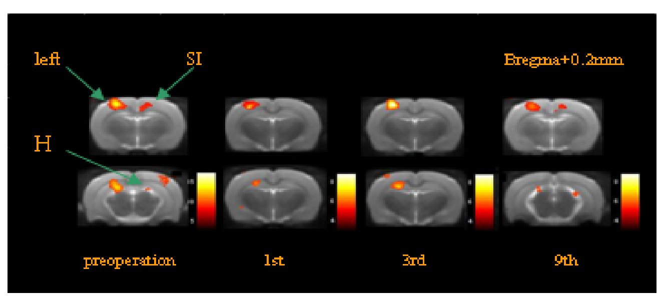

Fig. 1 The average resting-state connectivity map on four scanning days calculated by correlating the time course of pixels with the time course of the seed in primary somatosensory cortex (SI) and with the time course of the seed in hippocampus (H)

Discussion & Conclusion

In the present study, surgery triggers a transient neurocognitive decline in the rat model of POCD. There was a significantly reduced synchronization of temporal correlations in the primary somatosensory cortex and hippocampus on days 1 and 3, compared with that before operation. Our findings implied that the change of functional connectivity in the related cortex and hippocampus maybe one of the underlying causes for the cognitive deficit presented after surgery. Future study on human subjects will be necessary to further our understanding of the POCD.

Reference

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