Deep Anesthesia Provokes Dissimilar Resting State Connectivities in ADHD Rat Model and Normal Control

Sheng-Min Huang[1], Wei-Cheng Lee[1], Kung-Chu Ho[2], and Fu-Nien Wang[1]

[1]*Department of Biomedical Engineering & Environmental Sciences, National Tsing Hua University, Hsinchu, Taiwan,* [2]*Nuclear Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan*

Purpose: Spontaneously hypertensive rat (SHR) has been modeled for attention deficit and hyperactivity disorder (ADHD), a kind of neuropsychiatric disease.[1] Wistar Kyoto rat (WKY) is regarded as the best control in behavioral, genetic and neurobiological consideration. In our previous work, we have discussed the difference in brain network between SHR and WKY through resting state functional MRI (rs-fMRI).[2] However, the entire resting state networks of SHR remains sparsely discovered. Our finding on default mode network abnormality in SHR is submitted in another abstract. Since anesthesia level has noticeable impact on resting state networks[3-5], the control of anesthesia level should be carefully considered in rs-fMRI. In this article we mainly focus on comparing the resistance to anesthesia level between SHR and WKY. It could be interesting to compare the influence of same anesthesia on different strains.

Material & Method: A total of 15 male rats (SHR=10, WKY=5, all 6 weeks) were scanned using 7T Bruker Clinscan with a surface coil for signal receiving. Aneasthesia was induced with isoflurane mixed with O_2. Two anesthesia levels of 1.5±0.2% and 2.6±0.1% were conducted, maintaining the respiratory rate at 65-75 times/min and 40-45 times/min throughout whole experiment, respectively. The body temperature was kept by 37°C water circulation. 525 consecutive volumes with 11 slices were acquired using gradient echo EPI with TE/TR=20ms/1000ms, FOV=30mm, matrix size=64x64 and 1mm slice thickness. All data were pre-processed by tools below: Image registration by Automated Image Registration, slice timing and smoothing (1mm Gaussian kernel) by SPM8, temporal detrend and frequency filtering (0.002 - 0.1Hz) by REST toolkit. Seed-based and other analysis was performed on self-designed Matlab scripts. 25 priori ROIs were defined as seeds according to Paxinos coordinates. Correlation coefficient maps from all animals in each group were subject to one sample t test against 0 and $p<0.005$ was thresholded to generate a 25x25 binary matrix. The element in a binary matrix will be 1 if there is significant correlation between two brain regions and 0 otherwise. The degree of each brain region was calculated by summing up column (or row) in the binary matrix. The diameter of each circle in Fig. 1 is proportional to its degree.

Results: Fig. 1 shows the connectivity map of SHR and WKY under low and high anesthesia levels in dorsal view. For low anesthesia level, the major difference between SHR and WKY is the connection degree of orbital frontal cortex (OFC). When a high dose anesthesia was introduced, the density of connectivity lines decreased obviously, and whole brain connectivity appears to be different in terms of connection distribution. SHR group has a strong cluster around cingulate cortex (Cg), retrosplenial cortex (RSC), thalamus region and ventral posteromedial nucleus (VPM). In contrast, WKY group tends to connect OFC, motor cortex, sensory cortex, insular cortex and Cg together.

Discussions & Conclusion: Consistent with literatures[3,4], the brain connectivity decreased globally under high dose anesthesia. Interestingly, the remaining connection networks under high anesthesia level are not the same in SHR and WKY. Such different responses may suggest that the same brain region or cluster would have different resistances to anesthesia in various strains. For instance, WKY tends to preserve the anterior region of brain (gray dashed line, **Fig.1(c)**), which contains the function of motor, sensory and emotion (insular cortex). SHR kept the central region of brain (purple dashed line, **Fig.1(d)**) including the function of signal transmission, signal integration and consciousness (thalamus). This difference may be one of the origins of functional abnormality in ADHD rat. In another point of view, it is plausible to speculate that the connections in high anesthesia level are very fundamental networks. Relatively lower-degree regions in SHR including SS, insular and motor may imply that these regions are susceptible. This may also suggest that SHR has a weaker organization among these regions. We can therefore consider the possibility of discovering basic brain function difference between SHR and WKY. Though the underlying mechanisms and reasons are not clear, we have shown the difference between SHR and WKY in this study. Advanced investigations such as modularity analysis of brain region can be carried out to give detailed and comprehensive explanations.

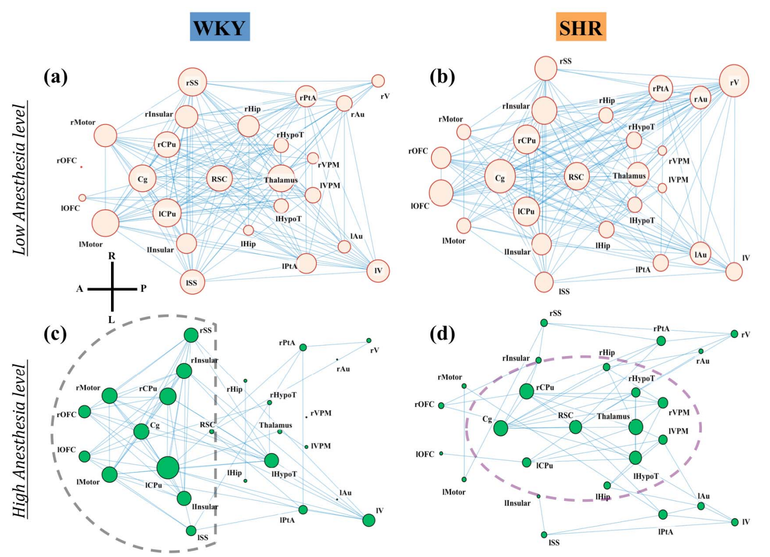

Fig. 1. The connectivity map of SHR and WKY under low and high anesthesia levels in dorsal view. Note the network distribution difference between SHR and WKY under high dose anesthesia.

References: **[1].** Sagvolden T. Validation of Animal Models of ADHD; 2004. 74-78 p. **[2].** Wu YL *et al.* 2013; Proc. of ISMRM. p 3686. **[3].** Liu X *et al.* Brain topography 2013;26(3):363-377. **[4].** Liang Z *et al.* J Neurosci 2012;32(30):10183-10191. **[5].** Wang K *et al.* NMR Biomed 2011;24(1):61-67.