

The amygdalar driving effects for overeating in Prader-Willi syndrome

Ju Liu¹, Jianliang Yao¹, Siyou Qiu¹, Yi Zhang¹, and Yijun Liu²

¹School of Life Science and Technology, Xidian University, Xi'an, Shanxi, China, ²Department of Biomedical Engineering, Peking University, Beijing 100871, China

Background

Prader-Willi syndrome (PWS) is a genetic imprinting disorder characterized mainly by hyperphagia and early childhood obesity [1]. Previous fMRI studies examined the activation of eating-related neural circuits in PWS patients with or without exposures to food cues and found an excessive hunger signal and a reduced inhibitory control of cognitive processing of food [2]. However, the effective connectivity between various brain areas or neural circuitry critically implicated in both the biological and behavioral control of overeating in PWS is largely unexplored.

Methods

A total of 27 patients with PWS and 21 of their siblings participated in the study. The experiments were carried out on a 3.0 Tesla head-dedicated Siemens Allegra MRI scanner. Before the fMRI scan, all of the subjects were fasting for average 3 hours. A set of T1-weighted high-resolution structural images were acquired using an MPRAGE sequence with matrix size = 512 x 512, TR = 1500 ms, TE = 4.38 ms, FOV = 240 x 240 mm², flip angle = 8 degree and 160 continuous axial slices. Then, a gradient echo T2*-weighted EPI sequence was used for acquiring resting state functional images with the following parameter: TR = 3000 ms, TE = 25 ms, flip angle = 90 degree; matrix size = 64 x 64, FOV = 240 x 240 mm², in-plane resolution of 3.75 x 3.75 mm², 36 axial slices. The scan for RS-fMRI lasted for 300 seconds, containing 100 brain volumes. The current study combined the resting-state fMRI and Granger causality analysis (GCA) techniques to investigate the interactive causal influences among key neural pathways underlying overeating in PWS. We first defined the regions of interest (ROIs) that demonstrated significant alterations of the baseline brain activity levels in children with PWS as compared to that of their normal siblings controls, and then carried out GCA to characterize the region-to-region interactions among these ROIs.

Results

Compared with the controls, the PWS patients exhibited altered ALFF in the MPFC (BA 9/10), ACC (BA 32/24), parahippocampus (PHIPP, BA 28/34), hippocampus (HIPPP), amygdala, insula, thalamus, caudate, hypothalamus, pre- and postcentral gyri, precuneus, cuneus and fusiform gyrus ($P < 0.05$, $n = 21$, FDR correct). Among these brain areas showing enhanced baseline activities, the bilateral MPFC, ACC, amygdala and the hypothalamus were chosen as the ROIs because they are the major components of a specific neural circuitry for controlling and regulating eating (Fig. 1). One pair of the ROIs showing significant increase in Granger causality influence is from the amygdala to the hypothalamus. In fact, the causal influence from the rAMY to the hypothalamus increased from 4.60 to 7.59 and the causal influence from the lAMY to the hypothalamus increased from 5.87 to 10.49 (Fig. 2A). Abnormal driving effects were also found from the MPFC and ACC to the rAMY. The causal influence from the MPFC to the rAMY increased from 2.35 to 4.60, and that from the ACC to the rAMY increased from 3.20 to 5.70 (Fig 3A). Moreover, the strength and directionality alterations (Fig 2B) of the region-to-region causal influence revealed a dysfunctional inhibitory control that persisted in the absence of food cues in PWS patients.

Conclusions

Our data demonstrate unusual driving forces from the amygdala to the hypothalamus and from the MPFC and ACC to the amygdala in PWS. These findings implicate that the long-term effect of the aberrant learned cues generated from amygdala may override the normal function of the hypothalamus, resulting in deregulation of homeostatic energy intake and dysfunction of inhibitory control.

References

- [1] Ledbetter, D. H., Riccardi, V. M., Youngbloom, S. A., Strobel, R. J., Keenan, B. S., Crawford, J. D. & Louro, J. M. (1980). Deletion (15q) as a cause of the Prader-Willi syndrome. American Journal Of Human Genetics, 77A.
- [2] Dimitropoulos, A. & Schultz, R. T. (2008). Food-related neural circuitry in Prader-Willi syndrome: response to high- versus low-calorie foods. J Autism Dev Disord, 38, 1642-1653.

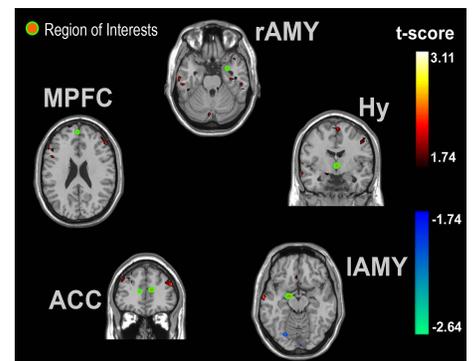


Fig.1 The functional mapping of the brain areas demonstrating significant ALFF alterations between the PWS and control groups during resting state.

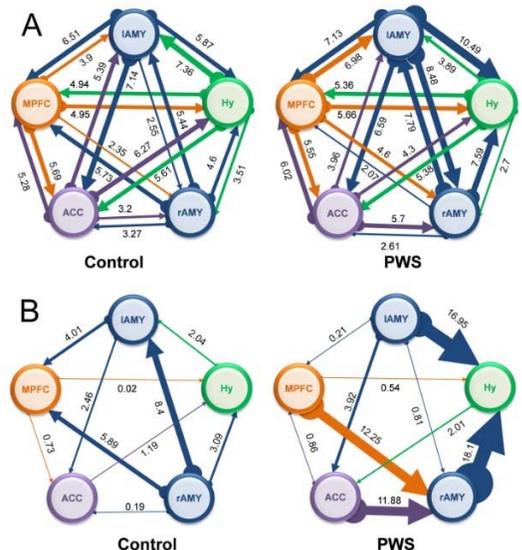


Fig.2 Granger causal influences between select pair-wise ROIs demonstrating