FcMRI maps genomic influence on acute alterations of Caudate Putamen functional networks with consomic rat strategy

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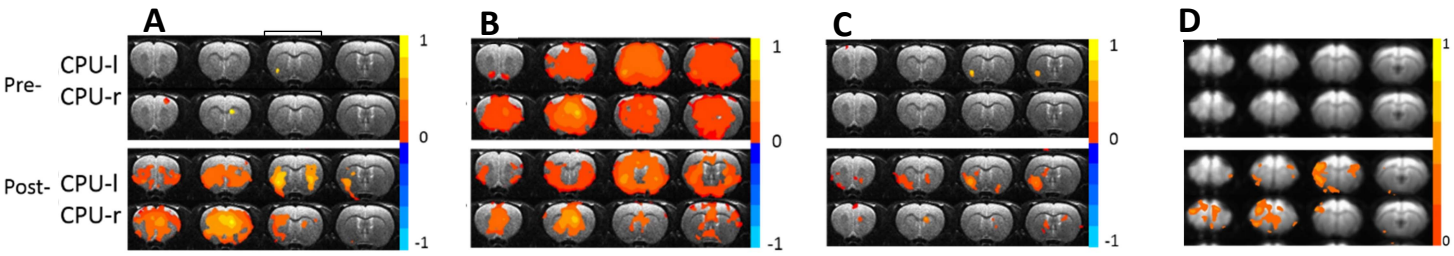
Introduction: A building body of preclinical and clinical studies supports the genetic influence of specific gene variant on the behavioral phenotypes and underlying neural mechanisms(1). However, the penetrance of individual chromosome on brain biology remains poorly understood. Imaging genetics with noninvasive fMRI and fcMRI has provided a novel approach to investigate the genetic impact on normal brain function and disruption due to task or neurological disorders (2). In a Brown Norway (BN)/Dahl salt-sensitive (SS) consomic rat model, we tested the hypothesis that the genomic influence of chromosome 13 on Caudate Putamen(CPU) network alterations due to peripheral sensory stimulation could be unraveled by BOLD-fcMRI. **Materials and Methods**: *Rat strains:* For parental strains, 13 male BN and 10 male SS were included. For consomic strains, 9 male SS-13^{BN}/Mcwi rats were chosen for this study. All studies and protocols were approved by the IACUC of the Medical College of Wisconsin. Rats were maintained on regular normal salt diet before BOLD-fMRI and BOLD-fcMRI experiments. *Anesthesia:* The animals were initially anesthetized with isoflurane. A MR-compatible needle electrode was inserted subcutaneously between the second and fourth digits of left forepaw for electrical stimulation. Oral intubation was used for mechanical ventilation, and tail vein catheterization was used for continuous delivery of Medetomidine (0.05mg/kg/h) and Pancuronium bromide (2mg/kg/h) after isoflurane was tapered off for fMRI. *FcMRI data acquisition*: The animals were imaged in a Bruker 9.4T animal scanner equipped with a Bruker surface linear transmit coil and a Bruker surface receive coil. Gradient echo (single shot EPI, TE= 19.437 ms, TR=2 s. matrix size=96 x 96, FOV= 3.5 cm, number of repetitions = 110, 10 contiguous interleaved 1 mm slices.) were acquired with a total time of 3 min 40 s. Left forepaw was stimulated at 2 mA, 2 mS at 3, 5, 7 and 10 Hz frequencies in a standard fMRI boxcar sequence. Two sets of resting-state fcMRI data were acquired before and 5 minutes after stimulation for each rat (fig.A). Blood oxygen saturation, inspired/expired O2 / CO2, temperature, heart and respirations rate were maintained within physiological ranges. *FcMRI data processing and analysis:* Seed-based resting-state fcMRI analysis was employed to measure the intrinsic functional connectivity of bilateral CPU networks. The common activation foci detected in all strains within CPU were used as seed-region. For both pre- and post-stimulation fcMRI data, a functional connectivity map was generated by cross-correlation between seed and every other BOLD temporal time series in the brain. A band-pass filter was applied to the pre-processed images to keep only low-frequency fluctuations within the frequency range of 0.01–0.1 Hz. For obtaining the network pattern in each strain, a voxel-wise one-sample t-test within group subjects was used against a null hypothesis of no connectivity (P<0.005 with correction). A one-way repeated measures ANOVA was performed (P<0.05 with correction) across the three groups, with rat body weight and age as covariates, to obtain the differential functional connectivity before and after stimulation respectively. **Results:** Before stimulation, no noticeable difference could be observed in the functional connectivity of the 3 rat strains, although BN rats showed a more extensive resting-state network than the other 2 strains. 5 minutes after stimulation, SS and BN strains showed more extensive connectivity in the bilateral CPU and subcortical regions while the SS-13^{bn} consomic strain only showed increased connectivity along the ipsilateral cortex. From ANOVA results with the same threshold, a region –specific difference was detected in the bilateral cortical areas; this regional difference was mainly located in the motor and prefrontal cortices.



Functional connectivity patterns of bilateral Caudate Putamen networks ***before*** (upper panel) and ***After*** (lower panel) left forepaw stimulations in SS (**A**), BN (**B**) and consomic SS-13^{BN} (**C**) rats. **(D)** Differential functional connectivity maps of right S1FL network among three strains before (upper panel) and after (lower panel) stimulation ($p < 0.05$ after correction. The color bar indicates Z-score in figure (**A**,**B** and **C),** and F-score in figure **(D)**.

Discussion and Conclusion Using consomic rat model, we were able to show the genetic components of chromosome 13 that contributed to alterations of brain functional connectivity due to electrical forepaw stimulation. After removing the effects of rat age and body weight, observable results showed that integrating chromosome 13 from the BN to the SS strain's genetic makeup significantly altered the acute response of functional connectivity in the bilateral CPU networks. These alterations might be potentially linked to the underlying functions of the motor and prefrontal cortices.

Reference: 1. Cowley AW, et al. Hypertension. 2001;37(2):456–461 2013;78(9):316–241. 2. Li Z, et al. Neuroimage. 2013; Sep. 29.

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