The Constituents of Default Mode Network in Rats

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Introduction:

The default mode network (DMN) of the brain, first demonstrated in humans[1] and then in non-human primates and rodents[2,3], contains a set of distributed brain regions, that are roughly analogous across these species[3]. Studies of human DMN suggest that DMN is associated with a variety of self-referential functions and failure of these functions is implicated in neurological and psychiatric disorders[4]. Human DMN has been fractionated into subcomponents based on their functional connectivity architecture and their distinct responses to different cognitive tasks[4-6]. However, the partitioning of DMN in animals is much less known[3]. Since rodents have been widely used as translational preclinical models, a thorough understanding of the architecture, and relevant functions, of the DMN in rodents would be important for interpreting resting-state fMRI (rs-fMRI) data of rodent DMN. In this study, we investigate constituents of DMN in rats using rs-fMRI and diffusion tensor imaging (DTI), and discuss their potential functional relevancy.

Materials and methods:

Animals. Thirty-four male Sprague-Dawley rats (275±25 g) were used. All animal procedures were approved by the Institutional Animal Care and Use Committee. Animals were anesthetized with a combination of 0.5-0.75% isoflurane and 0.015 mg/kg/hr dexmedetomidine hydrochloride.

MRI protocol. MRI data were acquired using a Bruker Biospin 9.4 T scanner with a quadrature surface receiver coil and birdcage volume transmit coil. Each rat underwent high-resolution anatomical imaging, DTI and two rs-fMRI. The DTI was acquired using a diffusion-weighted echo-planar imaging (EPI) sequence (TR = 6000 ms, TE = 47 ms, b-value = 0, 1000 and 2000 s/mm^2, 30 directions). The rs-fMRI scans were acquired using a gradient-echo echo-planar imaging (EPI) sequence (TE=15 ms, TR=1,000 ms, FOV=32 mm, matrix size=64*64, slice thickness=1 mm, volumes=520).

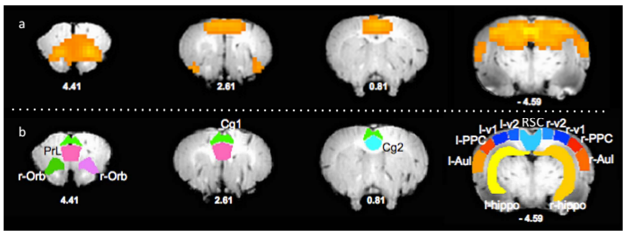

Figure 1. a) Functional connectivity map of DMN from 15 components of ICA analysis. (t>16, p<0.0001) b) 16 ROIs from anatomy

Image processing/analyses. Image processing was carried out using AFNI for motion correction, spatial smoothing (FWHM = 1 mm), detrending and frequency filtering (0.01< f < 0.5 Hz). All 68 rs-fMRI scans (34 rats and 2 rs-fMRI scans) were included in a group independent component analysis (ICA) analysis by MELODIC toolbox in FSL[7]. A dual regression approach was used to reconstruct individual-level functional connectivity components onto each rs-fMRI scan. A one-sample t-test was performed to obtain a robust DMN (Fig. 1a). The overlap of ICA-generated DMN and anatomical region-of-interests (ROIs) of brain structures (Fig. 1b) were selected as nodes for further identifying subcomponents of DMN using graph theory-based modularity analysis. For each rat, we extracted the time course from each node, and computed Pearson correlation between every pair of nodes to construct a resting-state functional connectivity (rsFC) matrix. Next, rsFC matrices were averaged across all subjects to produce a mean rsFC matrix. We then performed modularity analysis on the mean rsFC matrix: 1) without any threshold since all correlations are significant (Bonferroni-corrected p<0.05), and 2) with a threshold of 20% connection density to keep the strongest connections while ensuring 95% nodes in the network were connected. Modules refer to groups of nodes that are highly connected with each other but less connected with other nodes in a network. In addition, the Fiber Assignment by Continuous Tracking (FACT) algorithm of the diffusion toolkit[8] was used to reconstruct the total collection of white matter tracts of the brain. Fiber density index was used to represent the structural connectivity between DMN modules.

Results:

For the mean rsFC matrix without threshold, modularity analysis revealed that the DMN component constituted two subnetworks (Fig. 2, pink and blue circles). The anterior subnetwork included the cingulate cortex (Cg1 and Cg2), prelimbic cortex (PrL), orbital cortex (Orb), retrosplenial cortex (RSC) and hippocampus (CA1). The posterior subnetwork included visual cortex (V1 and V2), auditory cortex (Aul), and posterior parietal cortex (PPC). Applying the 20% connection density of threshold, the DMN was further partitioned into five modules (Fig. 2). The anterior subnetwork split into two modules: frontal module (including Cg1, Cg2, PrL and Orb) and RSC-hippocampus module (including RSC and CA1). The posterior subnetwork split into three modules: left PPC-visual module (including left-V1, left-V2 and left-PPC), right PPC-visual module (including right-V1, right-V2 and right-PPC) and auditory module (including Aul). Furthermore, the rsFC between modules was correlated with the fiber density index linking the corresponding modules (Fig. 3).

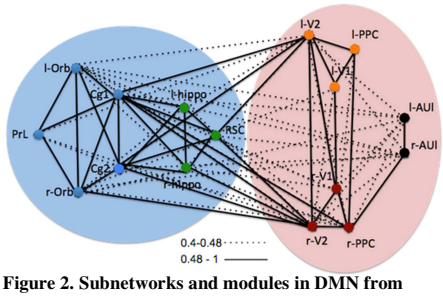

Figure 2. Subnetworks and modules in DMN from modularity analysis. The blue circle and pink circle represent the frontal and posterior subnetworks, respectively. Using 20% connection density threshold, DMN splits into five modules included: blue dots- frontal module; green dots- RSC-hippocampus module; red dots- right PPC-visual module; orange dots- left PPC-visual module; and black dots- auditory module.

Discussion:

In this study, modularity analysis was applied to 16 anatomical nodes in the DMN to examine prominent community structure. The analysis partitioned the DMN into anterior and posterior subnetworks (Fig.2), similar to the subnetworks recently demonstrated in the DMN of humans and rats[3,6]. Moreover, using the 20% connection density threshold in the modularity analysis, five smaller modules were revealed, which was supported by structural connections obtained from DTI-based fiber tracking.

Structures in the frontal module (Orb, PrL, Cg1 and Cg2) belong to the architectonic subdivision of "orbital medial prefrontal cortex" identified in rats and monkeys based on axonal tracing and in humans based on neuroimaging studies [9,10]. These brain structures as a whole receive highly processed sensory afferents, provide cortical influence over visceral functions, and participate in high-level cognitive and emotional processes[10]. The RSC, in the RSC-hippocampus module, is located at the crossroad between the hippocampal formation and areas in the neocortex. Each division of RSC projects to discrete terminal field in the hippocampal formation, suggest important roles of these structures in learning, memory, and emotional behaviors[11]. The visual cortex (V1 and V2), posterior parietal cortex (PPC), and auditory cortex (Aul) were partitioned into three modules in the posterior DMN subnetwork. PPC, characterized by multimodal sensory projections reciprocally connected with the frontal association cortex, has strong connections with visual areas[12,13]. It has been suggested that the role of PPC is to use visual sensory input to help guide movements[12]. Together, the modular architecture of the rodent DMN may support efficient processing by integrating multimodal sensory and affective information to guide bFSLehavior in anticipation of dynamic environmental contingencies[3].

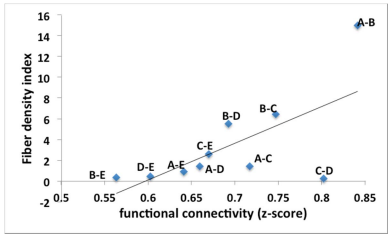

Figure 3. Correlation between functional connectivity and fiber bundle between DMN modules. A: frontal module. B: RSC-hippocampus module. C: right PPC-visual module. D: left PPC-visual module. E: Auditory module. (r = 0.66, p < 0.05, one-tailed)

Reference:

1.Raichle ME et al., PNAS 37:1083-1090 (2001) 2. Vincent JL, et al. Nature 447:83-86 (2007) 3. Lu H, et al. Proc Natl Acad Sci U S A. 109:3979-3984 (2012). 4. Bucner et al., Ann. N Y Acad. Sci. 1124, 1-38 (2008). 5. Hassabis et al., J Neurosci. 28, 14365-14373 (2007). 6. Andrews-Hanna et al., Neuron. 65, 550-562 (2010) 7. Jenkinson M et al. Neuroimaging. 782-90. (2012) 8. Wang et al. ISMRM. (2007) 9. An X et al., J Comp Neurol, 401, 455-79 (1998) 10. Ongur D, et al. Cereb Cortex, 10,206-19 (2000) 11. Wyss JM et al., Hippocampus, 2, 1-11 (1992) 12. Kolb B et al., Behav Brain Res, 23,127-45 (1987) 13. Miller MW et al., J Comp Neurol, 26, 184-202 (1984)

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