Functional Interpretations of the Resting-State Networks in Nonhuman Primates

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Introduction Although resting-state networks (RSNs) were originally thought to represent baseline neuronal activity in the absent of external stimuli or goal-directed behavior, they show striking similarity to functional networks extracted from thousands of activation studies (1). This raises the possibility of linking each RSN – or more generally speaking, the functional connectivity networks (FCNs) – with known behavior and/or task, which in turn could provide a more precise assignments of function to individual FCNs (2).

In non-human primates (NHP), it is difficult to map brain functions and individual functional networks by the conventional means (i.e., by evoked responses). Here we explored the possibility of providing functional interpretations of RSNs in baboons by finding similarity of FCNs in humans with known behavioral domains, thereby offering the intriguing opportunity to map brain functions of the entire NHP brain networks without using external stimuli.

Methods Twelve resting-state fMRI scans were acquired from eight normal baboons (12-24 kg). Animals were anesthetized with 0.8~1.0% isoflurane with vecuronium (0.1mg/kg) and mechanically ventilated. A custom holder was used to stabilize the animal in supine position. End-tidal CO_2, O_2 saturation, heart rate, respiration rate, and rectal temperature were monitored continuously and maintained within normal ranges. Resting-state fMRI studies were performed on 3T Siemens TIM TRIO using a 12-channel head coil. Gradient echo EPI was used for BOLD images with the following parameters: TR/TE=3000/30 ms, matrix = 124x124, field of view (FOV) = 12.4x12.4 cm (1x1x1.9 mm), and 27 slices for 30 min.

Human FCNs were extracted from the BrainMap database (http://brainmap.org) with the full behavioral taxonomy (67 descriptors, such as experimental conditions, stimuli, responses, etc.). A total of 8,637 functional brain imaging experiments extracted from 1,840 publications that reported 69,481 activation locations across 31,724 subjects were included to generate a pseudo-image using the peak activations.

Independent component analysis was carried out using MELODIC toolbox in FMRIB Software Library (FSL) as described in (1). Spatial cross correlation coefficients between the FCNs of humans and baboons were calculated after co-registration. Spatially similar pairs were selected by thresholding at a minimum correlation of r=0.25 ($P<10^{-5}$).

Results Spatial correlations between human FCNs and baboon RSNs are shown in **Figure 1**. Seven highly correlated pairs were identified. The human FCNs were grouped using hierarchical cluster analysis of all behavioral metadata, which is not possible with resting-state data itself. Based on the automatic classifications of their functional properties, the functional interpretations for individual FCNs were provided. Three of the identified pairs with the highest *r-values* are those located at the midline, including the frontal network (associated with motor and visuaospatial integration, coordination, and execution), the default mode network, and the central visual network.

Figure 2 shows three pairs of human FCNs and baboon RSNs, these three FCNs are strongly linked to emotion and interoceptions. Interestingly, the only human FCN that was not correlates with baboon RSNs is the left-lateralized fronto-parietal regions (including the Broca's and Wernicke's areas), which is strongly mapped to a host of semantic, phonologic, and orthographic language tasks. Several networks that were not a pure match will benefit from further analysis, such as subdivide the functional/behavioral taxonomy.

Discussion and Conclusions In this study, we provide functional explanations for the baboon RSNs. Most of the RSNs responsible for primary sensory and motor functions were identified. Some of the ICNs are associated with both simple and complex tasks and behaviors, for example, FCN 7 is linked with simple visual task like saccades as well as more complex tasks involve reasoning (Wisconsin Card Sorting) or counting. Other networks linking with higher-level cognitions were also found, although these networks in NHPs may not have similar functions as in humans.

Finding similarity and differences in RSNs between humans and NHPs may provide interesting information regarding the evolutionary changes of brain's intrinsic functional connectivity. This approach sets the stage to explore other unknown networks and provide a guide to invasive probing by electrophysiology to verify functional significance of specific RSNs.

Reference: [1] Smith et al., PNAS (2009). [2] Laird et al., J. Neurosci (2010) *(submitted)*

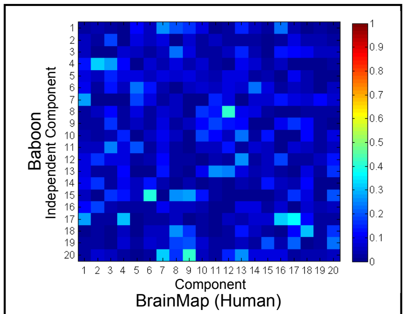

Fig 1. Spatial cross correlations between the human ICNs and baboon RSNs.

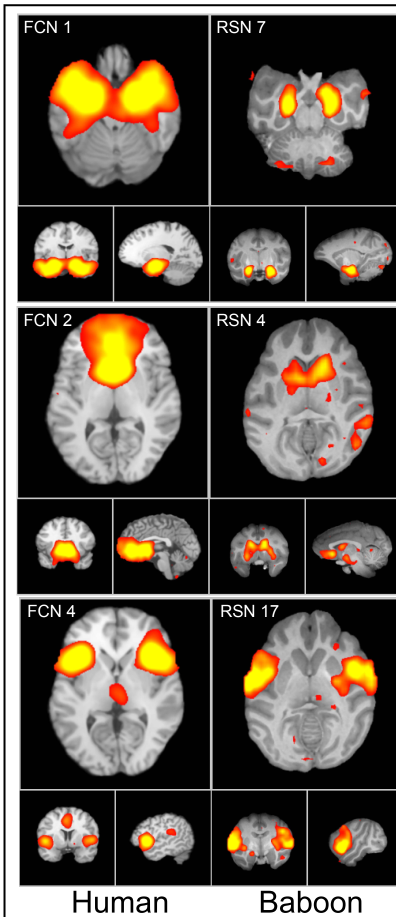

Fig 2. Orthogonal slices of three corresponding human ICN (left) – baboon RSN (right) pairs are also shown.