

Resting-state Functional Connectivity across Primate Species: Implications of Evolutionary Hemispheric Asymmetry

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Introduction Functional connectivity is inferred from spontaneous BOLD signal fluctuations arising from low frequency (<0.1Hz) brain activity. Spatially distinct regions with synchronized brain activity comprise resting-state networks (RSNs) [1-3]. Altered RSNs are shown in many disorders, such as Alzheimer's, ADHD, among others, although the physiological mechanism underlying RSNs remains elusive. Recently, functional connectivity studies have demonstrated the ability to identify RSNs in anesthetized macaques [4], paving the ground for comprehensive studies on the similarity/discrepancies between NHPs and humans. Herein, we investigate the hypothesis of altered RSNs across species, potentially due to evolutionary processes.

In this study, we aim to identify RSNs of baboons and compare those with the well-documented RSNs in humans. Baboons are large Old World monkeys evolutionarily closest to humans besides Great Apes. We hypothesize that the fundamental RSNs, such as the primary sensory-motor networks and the default mode network, will be most similar between species, while networks related to complex behaviors, such as speech comprehension, will show greatest difference. The information gained might shed light on understanding the origin of RSNs as well as the functional evolution of the brain. This study provides obligatory evidence required before across-species comparisons.

Methods Twelve resting-state fMRI scans were acquired from eight normal baboons (12-24kg). Animals were anesthetized with 0.8-1.0% isoflurane with vecuronium (0.1mg/kg first dose, 0.02 mg/kg supplement dose as needed) and mechanically ventilated. A custom holder was used to stabilize the animal in supine position. End-tidal CO₂, O₂ saturation, heart rate, respiration rate, and rectal temperature were monitored continuously and maintained within normal ranges. Resting state fMRI on humans was derived from de-identified normal subjects (17 males, 26 females, age = 42.1 ± 11.2) whom were instructed close their eyes and rest during rsfMRI.

All MRI studies were performed on a 3T Siemens TIM TRIO using a 12-channel head coil. Gradient echo EPI was used for BOLD images with parameters: TR/TE=3000/30 ms. In baboons, images were acquired with matrix = 124x124, field of view (FOV) = 12.4x12.4 cm (1x1x1.9 mm resolution), and 27 slices for 30 min; in human studies, images were acquired with matrix = 128x128, FOV = 22x22 cm (1.7x1.7x3 mm resolution), and 43 slices for 8.5 min. Data were processed using FMRIB Software Library (FSL). Image pre-processing includes motion correction, brain extraction, temporal band-pass filtering at 0.01-0.08 Hz and spatial smoothing with 4 mm (baboons) or 5 mm (human) FWHM Gaussian kernel. All images were registered to high-resolution brain templates. Temporal-concatenated independent component analysis was performed using the MELODIC toolbox in FSL for statistical analysis as described in [3]. Twenty independent components (IC) were pre-defined for the number of output networks. Spatial correlation coefficients between the ICs of humans and baboons were calculated after co-registration, and were plotted as a matrix shown in figure 1. Lateralization indexes (LI) defined as $LI = (Left - Right) / (Left + Right)$ where Left and Right represents the number of activated voxels in the corresponding hemisphere ($Z > 2.3$) were also calculated for each ICs.

Results Figure 1 shows the spatial correlations of all ICs between humans and baboons. Four of the IC pairs with high correlations were shown in Figure 2. The RSNs including the frontal network (fig 2A), the visual network (fig 2B), the default mode network (fig 2C and 2D), the sensory-motor networks, etc. were identified in both species through visual inspection. However, a subcortical network including the amygdala was shown in baboons but not humans. In contrast, the left and right frontal-parietal networks existed only in humans. The LI demonstrated that the RSNs in humans were more symmetric than those in baboons (mean absolute LIs are 0.19 and 0.28 in humans and baboons respectively). However, a few strongly lateralized RSNs identified in humans, as described previously [3], were also shown in our human population.

Discussion and Conclusions This study demonstrates for the first time the RSNs in anesthetized baboons. Although anesthesia is known to reduce the strength of RSNs [4], many RSNs can be identified robustly. The RSNs of the primary systems and the default mode networks (those localized at the midline, fig 2) are detected in both species. The only two lateralized RSNs in humans are the frontal-parietal networks, which are associated with perception-cognition (right) and language (left). These results suggest that the brain might become more symmetric integrated during evolution. This notion has also been described during human brain maturation [5]. Due to the nature (and function) of these asymmetric RSNs, one would consider that the asymmetric RSNs are formed somewhat later as a result of developmental or evolutionary adaptations. However, more and more recent studies suggested the contrary and conclude that the developments of symmetry and asymmetry functions are equally important to adapt to the environment. Our results support the latter argument. rsfMRI offers a non-invasive approach to map functional connectivity without explicit external stimuli and can be used to probe hemispheric specialization spanning across species associated with evolutionary and/or developmental processes.

References: [1] Biswal et al., MRM (1995). [2] Fox and Raichle. Nat Rev Neurosci (2007). [3] Smith et al., PNAS (2009). [4] Vincent et al. Nature (2007). [5] Fair et al., PNAS (2008).

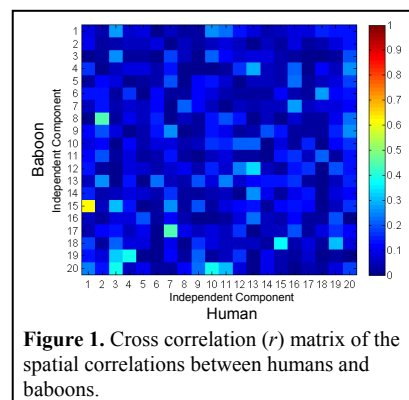


Figure 1. Cross correlation (r) matrix of the spatial correlations between humans and baboons.

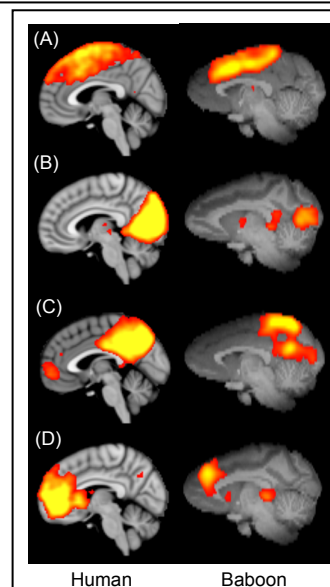


Figure 2. Example RSNs of humans (left) and the corresponding RSNs identified in baboons (right). * color bar: Z-scores from 3 to 8.