Brain Activity in Ateles geoffroyi: Resting-state fMRI of working memory in medial prefrontal cortex.

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Target audience. Functional neuro-imaging groups, researchers of human brain evolution, neuropsychologists, primatologists.

Purpose: Resting state functional images (RsfMRI) measured in absence of a task, aim at detecting low frequency fluctuations (LFFs, less than 0.1 Hz) in the Blood Oxygen Level Dependent (BOLD) signals [1]. Functional connectivity is defined for these studies as the temporal correlations between different brain regions [2,3]. Functional communication between brain regions plays a fundamental role in cognitive processes. Here we have used resting-state areas of the brain to examine intrinsic connectivity networks in a seldom-used primate species, the spider monkey (*Ateles geoffroyi*). Human working memory has been intensively studied but little is known about its evolution. Comparison of connectivity maps in spider monkeys is an initial stage to approach working memory evolution in primates, and thus closes the gap between RsfMRI and cognitive data.

Methods: Subjects: Three healthy adult monkeys were used to acquire whole brain images (2 females and 1 male; 10.5 ± SD 2.5 years). The subjects were housed at the National Institute of Psychiatry, Ramón de la Fuente Muñiz in Mexico City (INP). They were considered an established social group that lives in an outdoor enclosure (6 m in length, 6.3 m in height and 6.2 m wide).

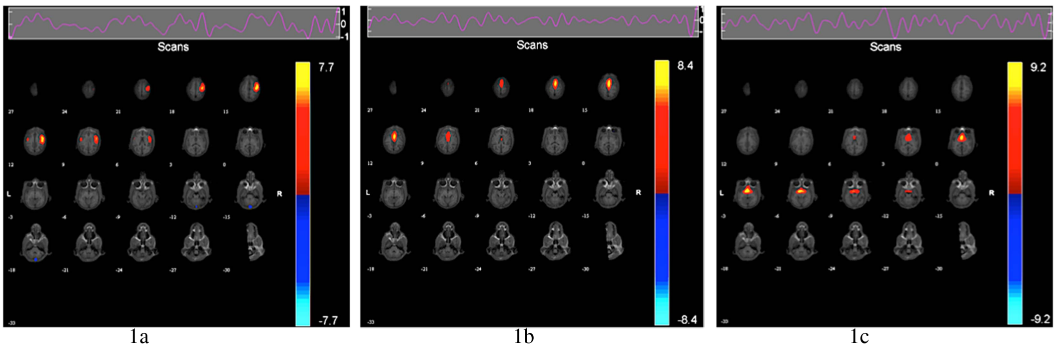
Experimental protocol: Animals were anesthetized before being placed inside the scanner. Anaesthesia was induced with an intramuscular injection of Ketamine (15 mg/kg, Pisa ®) and atropine (0.05 mg/kg, ABBOJECT®) and was then followed with Zoletil 50 Tiletamine-Zolasepan. (0.2 mg/kg, Virbac®). A paediatric head immobilizer (Medihelp®) was used to reduce the motion artefact once animals were placed inside the scanner. This immobilizer used plastic compartments filled with air to fixate the animal's head, ensuring that head motion was in all cases less than 1.5 mm in all directions during the whole of the experimental time (50 minute procedure). Once the experiment was finished and anaesthesia was terminated monkeys were then placed in a restriction cage for a period of 12 hours. Here animals were given time till they were respondent to stimuli and all their vital signs were normal. After this recovery, period animals were finally reintroduced to the colony. During the whole experiment and recovery time, a veterinary was present to measure the physiological parameters and assess animal welfare.

Ethical statement: The research for this study complied with protocols approved by Ethical committee of the National Institute of Psychiatry and National Council for Science and Technology (project 109147), Mexico. In addition, the research adhered to the Principles for the Ethical Treatment of Non Human Primates.

Image acquisition: During a 50-minute procedure, anatomical images followed by resting state sequences were acquired. All MRI studies were performed on a 3T scanner (Philips Achieva, Best, Netherlands). This scanner was equipped with an eight-channel -SENSE knee - RF coil. Gradient echo EPI was used for BOLD resting-state with the following imaging parameters: 20 axial slices covering the whole of the brain, TR/TE=2200/30ms, Averages=1, matrix 128×128 with a 1.88×1.90 mm *in-plane* resolution and slice thickness 3mm (no gap between slices). An anatomical image set, using a T_1-3D-GE sequence, parameters were: TR=10.6ms, TE=5.18ms FOV: 150x150mm, matrix: 256×256, 0.6×0.6 mm *in-plane* resolution with a 1 mm slice thickness and flip angle=8.

Data processing: To estimate functional connectivity, ICA was performed using GIFT (Group ICA of fMRI toolbox: http://icatb.sourceforge.net/). Before the GIFT, data was preprocessed (slice time corrected, realigned, normalized to the first subject and filtered (frequencies between 0.01 and 0.1HZ)). A group ICA was made with Z>3.3. Nine out of 20 components were considered noise and eliminated after visual analysis. The remaining components were projected onto the corresponding T_1 anatomical images.

Results: Figure 1 presents three components in which Motor (Fig. 1a), as well as Executive Control and Working Memory Networks (Fig. 1b and 1c) can be found. These components are similar to those found by Demosieux [4] in healthy humans.



1a 1b 1c

Fig1. Group ICA results for Spider Monkeys. Fig. 1a Motor Network, Fig. 1b and 1c Executive Control and Working Memory Network.

Discussion/Conclusions: Working memory (Wm) involves the brain system that provides temporary storage and manipulation of the information necessary for complex cognitive tasks such as language comprehension, learning, and reasoning. [5,6]. Wm in animals is debated. Most of what we know of Wm and attention system based on cognitive data is limited, and it remains uncertain/unknown; Are the experiments measuring short-term memory instead of Wm [7,8,9] or do primates share similar underlying mechanisms [10]. The memory skills of *Ateles* are reported to exceed those of other primates under experimental conditions [11]. *Ateles* also display complex foraging strategies as well as large social groups. Their brain size and weight is one of the most developed brains of the New World monkeys. Based on the findings of this RsfMRI study in which the Wm appear for the first time, these monkeys are a showing that they can be a strong model in the future for these studies. Data in these primates is important because they shared the same social organization (fusion-fission) as chimpanzees and early hominids. Thus, they can provide unique insights into human brain evolution and also offer information to research neuro-ontogeny and neurodevelopmental disorders associated with working memory.

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