Enriched environment modulates the development of the brain functional connectivity

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Introduction: Enriched environment (EE) is a condition characterized by increased opportunities for exploratory behavior and sensory stimulation (Hebb, 1947). Several studies have shown that EE improves a set of cognitive and motor skills (Guildi et al, 2014), potentially mediated by neuronal activation and the connectivity between several brain regions. Cognitive and motor performance is associated with the functional connectivity of brain networks such as the Default Mode Network (DMN) and Sensorimotor network (SN). Magnetic resonance imaging (MRI) allows the in-vivo characterization of functional connectivity longitudinally. The effect of EE on functional networks has only been studied in early stages of rodent development, but not throughout the entire span of development. The aim of this work is to show the effect of an enriched environment in the development of functional brain networks from early childhood to adulthood in rats.

Methods: A total of 21 rats, (EE=9, control=12) were scanned postnatally at day 21, 45, and 90 s to characterize the functional connectivity between brain regions of the DMN including retrosplenial cortex (RSCx) and cingulum (Cg1), and SN including left and right motor cortices(M1L-M1R). Control rats were housed in small cages (CB)(34.5 x 49 x 17 cm), while EE rats were reared in bigger cages (45.7 x 41.9 x 76.2 cm) with a training wheel, tunnels, and toys inside the box, the position and form of the latter two were changed every 3 days. . All rats had water and food *ad libitum*, and only 3 rats were housed per cage. Images were acquired in a Bruker Pharmascan 70/16US, 7 Tesla MRI Scanner (Bruker, Ettlingen, Germany). Animals were anesthetized with isoflurane at 2% concentration for induction and positioning in the scanner bed, in which the head was immobilized with a bite bar and the coil head holder, isoflurane was adjusted at 1 % concentration and a single bolus of 0.010 mg/kg of dexmedetomidine (Dexdomitor; Zoetis, México) was administered subcutaneously. Five minutes after the bolus injection, isoflurane was lowered and maintained at 0.5% MRI acquisition started when physiological readings were stabilized (~20 minutes after bolus injection). The animal research protocols were approved by the bioethics committee of the Institute of Neurobiology, UNAM. Images were analyzed with ANTs and FSL routines. A 2x3 way ANOVA was performed to compare the functional connectivity between groups and ages for each network, and a post hoc Tukey test to analyze the differences within and between groups at different ages.

Results: We found that the functional connectivity of the DMN is significantly different between P21-P90 ($p=0.008$) for control rats, and P21-P45($p=<0.001$), P21-P90 ($p=0.002$) for EE rats. No significant differences were found between groups. For the SN we found significant differences between P21-P90 ($p=0.001$) for the control group, while the EE group showed differences between P21-P45 ($p=0.001$), and P21-P90 ($p=0.035$). Functional connectivity was higher for EE rats compared to control ratsa t P45 ($p=0.028$).

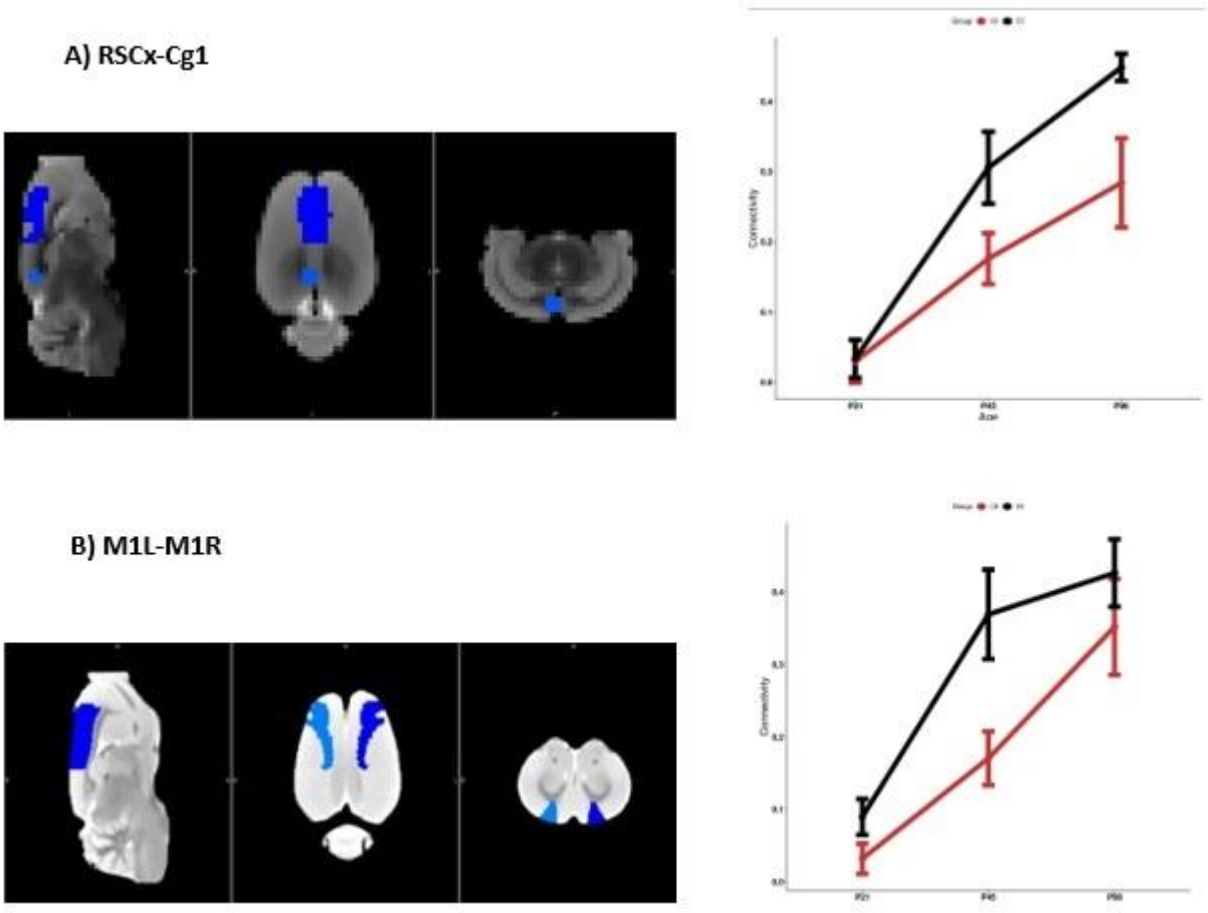

Fig. 1. Panel A shows the average brain connectivity between RSCx-Cg1, across ages 21, 45 and 90 days for the EE (black) and control (red) groups. Panel B shows the average functional connectivity between M1L-M1R regions across ages 21, 45 and 90 daysfor the EE (black) and control (red) groups.

Discussion: Functional networks change with age. An enriched environment accelerates the development of the sensorimotor network, specially throughout adolescence (P45). The development of the functional brain networks is associated with age (Gao, 2015), however, enriched environments influence the acceleration of such development, specially at P45, relatively equivalent to adolescence in humans.

Conclusion: The brain functional connectivity in rats showed significant changes with age, and modulated by the environment.

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