ADHD and the role of the posterior cingulate cortex in resting state studies of infant volunteers of Latin origin

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Introduction: ADHD is the most common neurological disorder in children and adolescents with prevalence circa 5%. This illness is considered to be in an 80% originated by genetic factors and in a 20% by environmental factors. The Default Mode Network (DMN) is the main network active during rest and covers long areas of the brain. Of special relevance in it are: First, the medial temporal lobe which provides information from prior experiences, to use them for mental simulations (**1**). Second, the medial prefrontal region which facilitates a flexible use of information during the construction of self-relevant mental simulations. These two components of the DMN are integrated mainly in the posterior cingulate cortex (**1**). Patients with mental disorders like Schizophrenia or Autism have this region and its integration function compromised (**2,3**). Finally, most work on the default mode network has been performed in Asia, Europe and North America. Little amount of work to our knowledge exists in Latin America with Latin volunteers (different genetic pool). In this project we compared infant ADHD (AD) patients with healthy (H) ones, all from Latin origin. We assessed the differences with previous studies while focusing in the role of the posterior cingulate cortex.

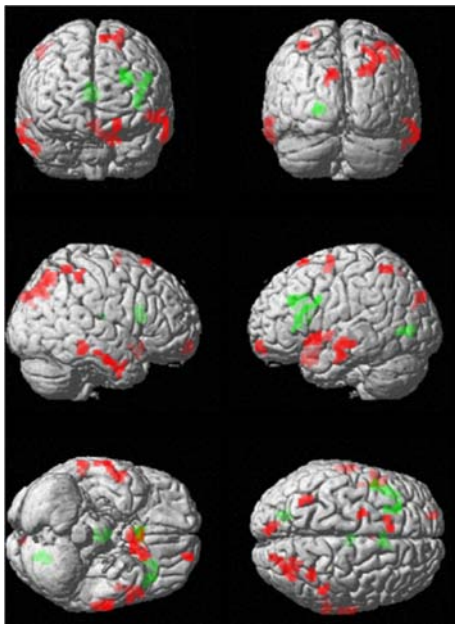
Methods: Experiment: 30 volunteers all of them infants (8.4±2 years) of both sexes (15 males and 15 females) were used in this study. This group was subsequently divided into two cohorts of 15 subjects each, one with AD patients while the remaining 15 subjects were H with no neurological disorder. Protocol: Volunteers laid in the scanner for 7.25 min. in silence and with closed eyes. MRI Hardware: Experiments were performed in a 1.5 T Philips Intera-Achieva scanner using an 8 channel SENSE head-coil. Resting State: 150 brain volumes comprising 35 coronal slices covering the whole of the brain (including cerebellum) were acquired with a Fast-Echo-EPI sequence. TR=2.9 s., TE=50 ms., 64x64 matrix with a 3.6 x 3.6 mm *in-plane* resolution and 4 mm slice thickness (no gap between slices). Resting State analysis was performed using DPARSF software. After slice time correction, realignment, motion correction and smoothing; data was detrended and filtered (keeping frequencies between 0.01 and 0.08 Hz). Regions of homogeneous variance (ReHo) were then calculated together with the amplitude of the low frequencies (Alff). Both groups were threshold at $p<0.05$ with FWE corrections for multiple comparisons. Average results from both groups and analysis were compared with a t-test using 2nd level analysis in SPM8 and projected on a rendered brain in Talairach coordinates. Lateralization of activations was calculated as percentages counting numbers of activated ReHo and Alff voxels in each hemisphere and dividing them buy the total number of voxels.

Results: Figure 1A presents the results of a comparison of ReHo between H and AD patients (H>AD is green and AD>H is red). Figure 1B presents the Alff activations in the same manner as before. H subjects were found to present strong left lateralization (80% vs. 20% structures) in the ReHo analysis while the Alff results were inconclusive in this aspect. AD patients presented in contrast a stronger right lateralization (55% vs. 45%) for both analyses.

Discussion: Disruption of brain asymmetry has been implicated in the pathogenesis of several neurodevelopmental disorders like ADHD (**4,5**). Even if it is generally accepted that AD patients present right hemisphere dominance, previous MR imaging work has just shown lateralization for certain brain regions (**6,7**) but has not studied the brain as a whole. Here we found that AD patients had a larger predominance of right hemisphere activations over left for both ReHo and Alff analysis. Healthy subjects presented the opposite effect. The cuneus and precuneus regions lay together and are thought to be central nodes of the DMN. We found that the cuneus region was part of the resting state networks in both groups but the precunueus was significantly present for AD volunteers but not in H ones. This showed a drift between these node points due to the illness, that made the memory and self-awareness functions of precuneus more prevalent in AD patients. Previous work on resting state analysis (**6**) has reported for Alff studies a strong involvement of the brain stem and the anterior cingulate gyrus for AD patients compared to H. We did not find these representations, but did find strong correlations with the frontal gyrus and especially the posterior cingulate cortex. This result was expected because, as introduced in this abstract, this mayor node of the DMN is known to be affected by mental illnesses. Due to the similar analysis methods used in this study and previous ones, we believe that the differences shown here arise mainly by the different genetic origin of the experimental volunteers.

References: (1) Annals of the New York Academy of Sciences 1124: 1–38. doi:10.1196/annals.1440.011 (**2**) Proceedings of the National Academy of Sciences 106 (4): 1279–84. (**3**) Proc. Natl. Acad. Sci. USA 103: 8275–8280. **(4)** Neurosci Biobehav Rev 2000;24 (1) 13- 19 **(5)** Arch Gen Psychiatry. 2009;66(8):888-896. doi:10.1001/archgenpsychiatry.2009.103 **(6)** Brain Dev 2007 29:83–91. (**7**) Neurosci Lett 2006 400:39–43.

1A



1B

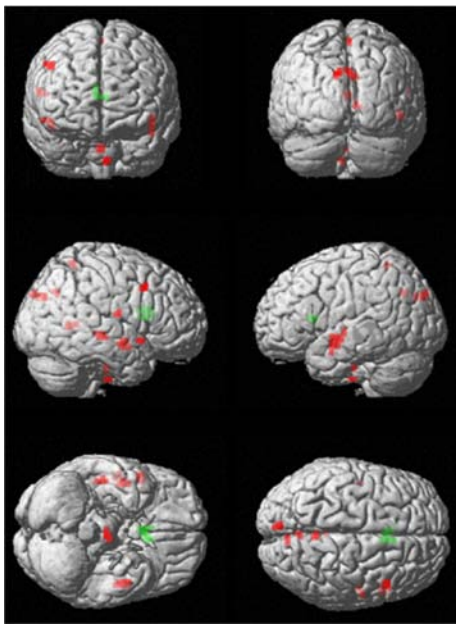


Figure 1. ReHo and Alff results for Healthy and ADHD gropus. Figure 1A shows results of a ReHo analysis for Healthy>ADHD (green) and for ADHD>Healthy (red) comparisons. Figure 1B presents the Alff results in the same manner as Figure 1A.