# EARLY ADAPTATION IN RESTING STATE NETWORKS IN MULTIPLE SCLEROSIS IS FOUND USING INDEPENDENT COMPONENT ANALYSIS AND DUAL REGRESSION

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**Introduction:** Task-fMRI studies have shown cortical recruitment in early Multiple Sclerosis (MS)[1], which partly explains the discrepancy between conventional MRI and clinical disability. Task-induced metabolic changes are however relatively small compared to the energy use of the brain during rest[2]. We therefore questioned whether functional changes can also be found in rest in the early phase of MS. For this purpose, resting state fMRI networks were compared between patients with symptoms suggestive of MS (clinically isolated syndrome; CIS), relapsing remitting (RR) MS patients and healthy controls.

**Materials and Methods:** MRI data of fourteen CIS patients, 31 RRMS patients and 41 controls were acquired at 1.5T, and analyzed using FMRIB's Software Library. Resting state fMRI data (200 volumes of echo planar images (EPI); TR 2850 ms, TE 60 ms; 36 axial slices; 211 x 211 $mm^2$ FOV and 3.3 mm isotropic resolution; acquisition time 9.5 minutes) were non-linearly registered to standard space, and analyzed using multi-subject independent component analysis (ICA)[3] and dual regression[4] Eight meaningful resting state networks were identified in our subjects, and compared between the three groups with non-parametric permutation testing, using threshold-free cluster enhancement[5] to correct for multiple comparisons (thresholding at $p<0.05$, corrected). Additionally, measures of structural damage were assessed. Grey and white matter volume, normalized for head size, was measured for each subject using SIENAX. Diffusion tensor measures were voxel-wise compared between groups using tract-based spatial statistics (TBSS)[6]. Cognition was tested for the domains most frequently affected in MS: memory, processing speed and selective attention.

**Results:** CIS patients showed *increased* co-activation in six of the eight networks (Figure 1), including the default mode network, compared to controls and RR patients. No significant *decreases* were found. No significant resting state network differences were found between RR patients and controls. Normalized grey matter volume and fractional anisotropy were significantly decreased in RR patients compared to controls, whereas no atrophy or diffusivity changes were found for the CIS group. RR patients showed significant impairment of processing speed and attention.

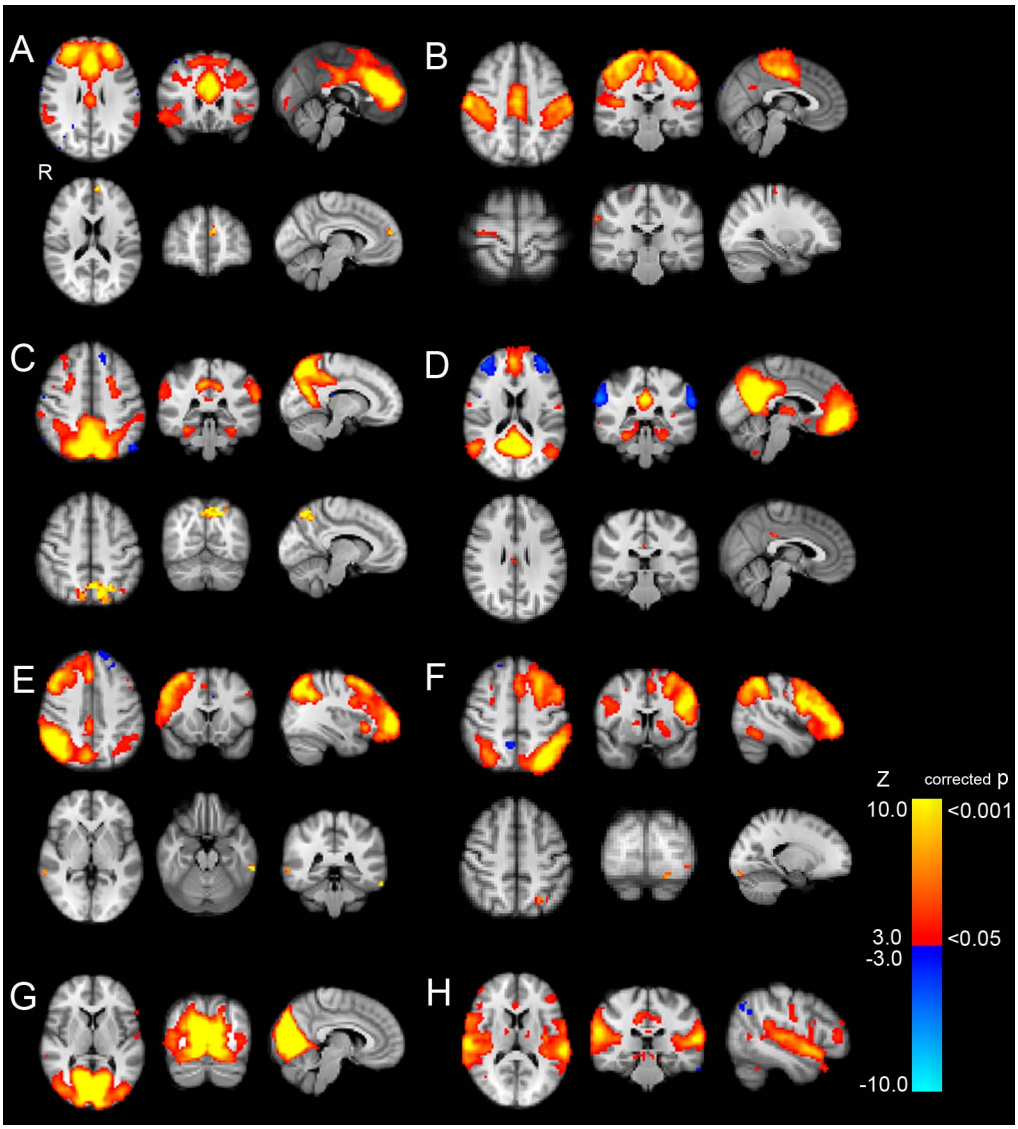


**Figure 1:** Resting state networks (upper rows) and network-specific increased activation in CIS patients (lower rows):

- A: executive functioning; activation was increased compared to healthy controls and RR patients in the left medial prefrontal cortex
- B: sensorimotor network; increased activation compared to controls in the right primary sensorimotor cortex and inferior parietal gyrus
- C: ventral and dorsal attention system; increased activation compared to controls in the bilateral precuneus
- D: default mode network; increased activation compared to RR patients in the posterior cingulate gyrus
- E: right frontoparietal network; increased activation compared to RR patients in the left inferior temporal gyrus and right superior temporal gyrus
- F: left frontoparietal network; increased activation compared to RR patients in the left superior parietal gyrus and the occipital lobe
- G: visual processing and H: auditory and language processing; no significant differences between groups were found in these networks

**Conclusion:** Network-specific resting state changes can already be found in CIS patients, and are lost in MS patients with increasing brain damage and advancing disability.

**References:**

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6. SM Smith et al. NeuroImage 2006. **Acknowledgements:** The MS Center Amsterdam is supported by the Dutch MS Research Foundation (grants no. 02-358-b, 05-358-c and 06-592).