An investigation of functional connectivity in the cognitive control network in Prodromal Huntington's Disease

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Target audience: This information will be of interest to researchers of Huntington's disease and those using resting state functional connectivity.

Purpose: Functional connectivity MRI, measured from low-frequency fluctuations in the blood oxygen level dependent (BOLD) timeseries during rest (rs-fcMRI), has been used to identify disruptions in intrinsic brain connectivity in the prodromal stages of Huntington's disease (preHD) [1-3], though findings have been mixed. The current study used a seed-based approach to examine rs-fcMRI in the left primary motor cortex (M1). Recent work has shown a relationship between disease burden and the change in functional activation over time in preHD [4].

Using an fMRI study of motor timing for seed selection, we evaluated rs-fcMRI of M1 to determine if it was related to disease progression in preHD.

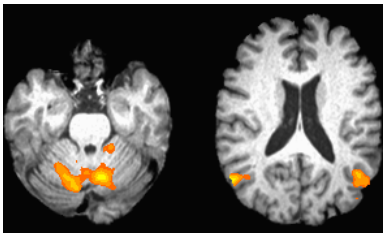
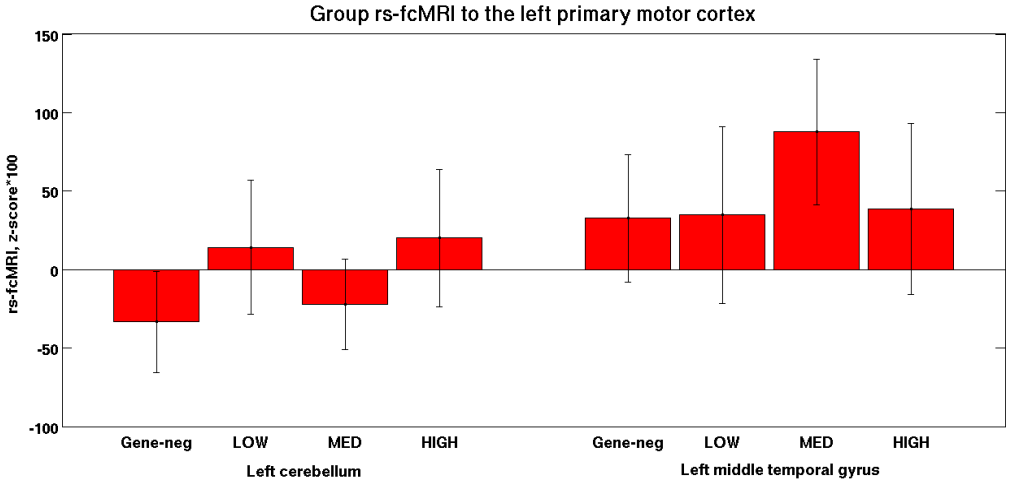


Figure 1. Regions showing group differences in rs-fcMRI to the left primary motor cortex ($p < 0.01$, cluster size 960).

Methods: In an IRB-approved protocol, 48 gene-positive and 16 gene-negative participants (mean age 42.6 ± 9.2, 4 males) were scanned at 3T in a 12-ch receive head coil. Scans included T1-MPRAGE and a rs-fcMRI scan at 2x2x4mm voxels, 1954 Hz/pix BW, 31 axial slices, TR/TE/FA=2800/29/80. All participants performed a motor timing task as described in [5]. Individual activation maps were used to identify the area of highest activation in left M1. A 4mm in-plane circle was centered at the voxel of highest significance and co-registered to the rs-fcMRI scan. Each seed was used to create individual whole-brain fcMRI maps, as described in [6]. For the rs-fcMRI analysis, gene positive subjects were stratified into three groups based on age and CAG repeat length: 16 close to diagnosis of manifest HD (HIGH, mean age 47.1 ± 12.6), 16 far from diagnosis (LOW, mean age 32.6 ± 9.0), and 16 at a middle-distance from diagnosis (MED, mean age 38.3 ± 9.7). rs-fcMRI maps were transformed into common space and a one-way ANOVA based on group was used to determine areas showing differences in connectivity to M1.

Results: Four regions showed significant differences in connectivity to left M1 (Figure 1), including bilateral anterior cerebellar lobes and bilateral middle temporal gyri ($p < 0.01$, cluster size 960). Bilateral cerebellar lobes showed increased connectivity to M1 in both the LOW and HIGH groups as compared to the gene-negative group ($p < 0.0006$), and bilateral middle temporal gyri showed increased connectivity to M1 in the MED group as compared to the LOW and gene-negative groups ($p < 0.0067$). All regions remain significant when age differences are taken into account.



Discussion: Both regions that demonstrate group differences show similar levels of connectivity in the LOW and HIGH groups, with disparate level of connectivity in the MED group. This finding suggests that rs-fcMRI patterns are dependent on time-to-onset. Connectivity to the cerebellum in particular is consistent with a compensatory hypothesis. Those that are far from onset begin to experience neurofunctional changes that normalize over time. As a person moves closerto diagnosis, compensatory processes begin to break down.

Conclusion: With further research into differences in rs-fcMRI, the researchers hope to identify a biomarker of disease progression in preHD.

References: [1] Unschuld et al., Neuroscience Letters. 2012; 514: 204-209. [2] Seibert et al., NeuroImage. 2012; 59: 2452-2460. [3] Dumas et al., Neuroimage Clinical. 2013; 2:377-384. [4] Georgiou-Karistianis et al., Brain Connectivity. 2013; 83(1):80-91. [5] Hinton et al., J Int Neuropsychol Soc. 2007; 13(3):539-543. [6] Lowe et al, Hum Brain Mapp. 2008;29:818-27.

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