

Resting-State Functional Connectivity in Prodromal Huntington's Disease

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Introduction:

Individuals in the prodromal phase of Huntington's disease (pre-HD) show evidence of abnormal brain activation patterns on task-activated fMRI in the absence of measureable changes on neuropsychological testing and structural brain imaging [1]. Functional connectivity MRI (fcMRI), measured from low-frequency fluctuations in the blood oxygen level dependent (BOLD) timeseries during rest, has the potential to identify disruptions in intrinsic brain connectivity in the prodromal stages of HD. fcMRI may be able to characterize disease progression and serve as a potential biomarker for future HD therapeutics, but to date has not been evaluated in this population.

Methods:

16 gene-positive (mean age 35.63, mean CAP score 342.11, 12 males) and 8 gene-negative participants (mean age 49.5, 6 males) were scanned in an IRB-approved protocol at 3T in a 12-ch receive head coil. Scans included T1-MPRAGE and a resting connectivity fcMRI scan at 2x2x4mm voxels, 1954 Hz/pix BW, 31 axial slices, TR/TE/FA=2800/29/80. All participants performed a time discrimination task as described in [2]. A one-way ANOVA between the gene-positive and gene-negative subjects was used to identify potential seed regions for an fcMRI analysis. The greatest group differences were in the left insula [38 21 5] and right supplementary motor area (SMA) [3 16 46] ($p < 0.01$, corrected). For each area a 4mm in-plane circle was centered at the voxel of highest significance and used to create individual whole-brain seed-based correlation fcMRI maps, as described in [3]. Correlation of low-pass filtered reference timeseries were converted to t-scores, which represent our fcMRI connectivity metric. For the fcMRI analysis, gene positive subjects were split into two groups based on age and CAG repeat size: 8 close to diagnosis of manifest HD (CLOSE, mean age 40.5) and 8 far from diagnosis (FAR, mean age 30.75). fcMRI maps for the three groups were entered into an ANOVA to probe differences in connectivity between gene-negative, FAR, and CLOSE groups.

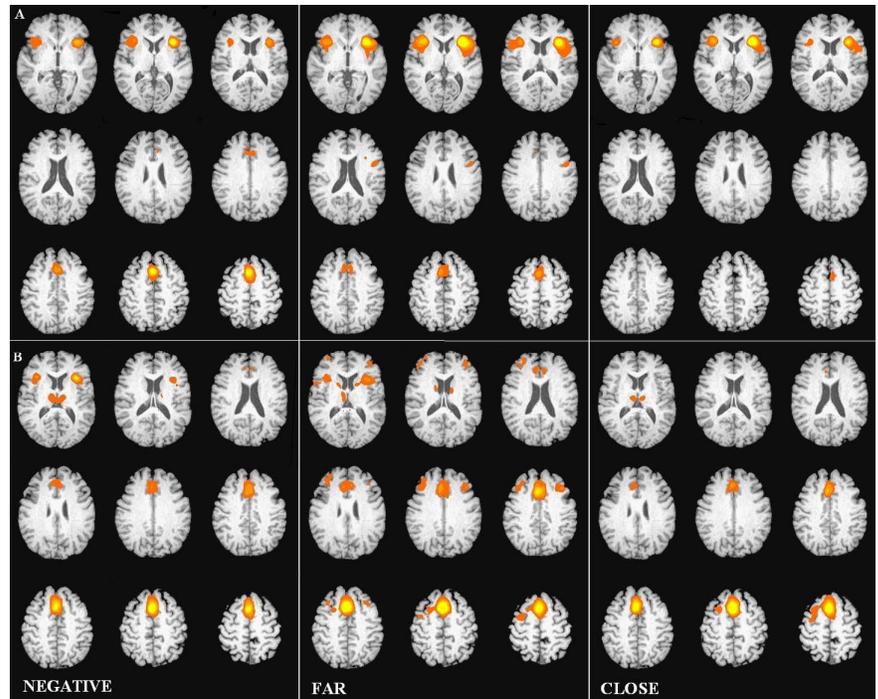


Figure 1. Average fcMRI maps in the Negative, FAR, and CLOSE groups for the A. left insula and B. right SMA. $P < 0.005$, corrected.

Results and discussion:

Connectivity of the left insula to the anterior and posterior cingulate cortices is significantly stronger in the gene-negative group than the FAR group, and stronger in the FAR than in the CLOSE group ($p < 0.01$, corrected). The same pattern was observed for connectivity of the right SMA to the left putamen. Connectivity of the left insula to right medial frontal gyrus and right SMA to right insula was stronger in the FAR group than in the gene-negative and CLOSE groups. This may be associated with hyperactivation observed in the FAR group observed in previous task-related fMRI studies [1]. These results represent the first report of resting-state fcMRI differences in preHD individuals.

References:

[1] Zimelman et al, J of the International Neuropsychological Society, 2007;13:758-769. [2] Rao et al., Nat Neurosci. 2001; 4:317-23. [3] Lowe et al, Hum Brain Mapp. 2008;29:818-27.