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

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Target audience: This information will benefit researchers studying Huntington disease and resting state functional connectivity (rs-fcMRI).

Purpose: Recently, functional connectivity MRI (fcMRI), measured from low-frequency fluctuations in the blood oxygen level dependent (BOLD) timeseries during rest, has been used to identify disruptions in intrinsic brain connectivity in the prodromal stages of Huntington's disease (preHD) [1,2], but with mixed results. The current study used a seed-based approach to examine rs-fcMRI. Seed selection was driven by a task-activated fMRI study of the Stop Signal Task to identify regions involved in the inhibitory control network [3], which is affected in HD. We then evaluated rs-fcMRI for the inhibitory-network seeds to determine if it was a marker of disease progression in the prodromal stage of HD.

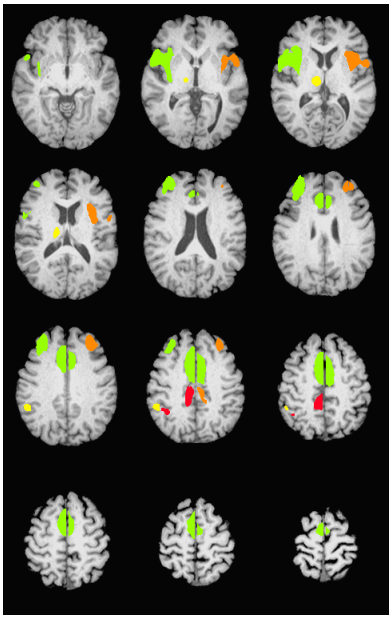

Figure 1. Regions significantly connected to the preSMA and BA 44. Color scale indicates group differences in strength of connectivity to each seed: GREEN: Non-significant. ORANGE: BA 44. YELLOW: preSMA. RED: BA 44 and preSMA.

Methods: In an IRB-approved protocol, 48 gene-positive and 16 gene-negative participants (mean age 47.5 ± 9.6, 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 stop-signal task as described in [4]. Individual activation maps were used to identify the area of highest activation in the right pars opercularis (BA 44) and the right pre-supplementary motor area (preSMA) [3]. For each region 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 [5]. For the fcMRI analysis, gene positive subjects were split into three groups based on age and CAG repeat length: 16 close to diagnosis of manifest HD (HIGH, mean age 48.15 ± 13.7), 16 far from diagnosis (LOW, mean age 33.88 ± 8.0), and 16 a middle-distance from diagnosis (MEDIUM, mean age 35.94 ± 7.3). For each region, average fcMRI maps for the four groups were thresholded and combined so that any area that reached significance in one or more groups was included. The BA 44 mask and preSMA mask were then combined so that only regions that correlated with both seeds were included. The final mask was transformed to individual subject space and mean connectivity to the preSMA and to BA 44 was entered into a one-way group ANOVA test.

Results: 11 regions were significantly connected to both the preSMA and BA 44 (Figure 1). The right inferior parietal lobule showed significantly stronger connectivity in the HIGH group when compared to all other groups ($p<0.006$) for both BA 44 and preSMA. The right posterior cingulate showed the strongest connectivity in the gene-negative group ($p<0.007$) for both BA 44 and preSMA. BA 44 also showed group differences in connectivity to the left middle frontal gyrus ($p=0.005$), the left posterior cingulate ($p=0.03$), and left inferior frontal cortex (0.007). The preSMA showed group differences in connectivity to the right thalamus (0.04) and the right supramarginal gyrus (0.0006).

Discussion and Conclusion: Individuals in the prodromal stage of HD exhibit changes in the strength and the pattern of functional connectivity in the inhibitory control network. The right inferior parietal lobule, which is also active in the Stop Signal Task, has been implicated in motor intention [6]. In this context, the increase in connectivity strength in the HIGH group may indicate a loss of inhibition. Recent research reveals that the dorsal posterior cingulate connects to frontal regions involved in cognitive control [7]. Our findings indicate that connectivity is weakened in this region in individuals in the prodromal stages of HD, perhaps impacting the modulation of attention. With further research into differences in connectivity in the inhibitory control and related networks, we hope to identify a biomarker of disease progression in preHD.

References:

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