

Quantitative Cerebral Blood Flow Changes in Huntington's Disease Measured using Pulsed Arterial Spin Labeling

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Introduction

Huntington's disease (HD) is a highly debilitating and often fatal neurodegenerative genetic disorder characterized by disrupted motor function as well as cognitive and psychiatric deterioration, typically manifesting by mid-life. Wide-spread cortical thinning and striatal volume reduction have been robustly observed in HD, tentatively linked to mitochondrial oxidative stress [1], a potential cause of which is disruption of cerebral blood flow (CBF) [2,3]. Perfusion studies in HD have predominantly been performed using single-photon emission computed tomography (SPECT) [3,4]. These studies have demonstrated CBF changes in the basal ganglia as well as the cingulate and parietal lobes. However, the results to date have been varied in their reproducibility and spatial specificity. In particular, SPECT suffers from low spatial-resolution, thus limited sensitivity to detect regional effects. In this work, we examine, for the first time, quantitative changes perfusion changes in HD using pulsed arterial-spin labeling (PASL). We show this noninvasive technique to be robustly sensitive to CBF changes in both cortical and sub-cortical brain regions.

Methods

Thirteen middle-aged HD patients (5 men/8 women, age = 50.3±5.5 yrs) and twenty age-matched healthy participants (8 men/12 women, age = 50.0±5.8 yrs) were imaged using a Siemens Trio 3 T system. The scans employed 12-channel phased-array head coil reception and body-coil transmission. Two PWI datasets were obtained for each subject using FAIR QUIPSS II PASL [5] with ¼ partial Fourier EPI readout, matrix=64x64, #slices=24, voxel size=3.4x3.4x5 mm³, #frames=104, T₁/T₂/TE/TR = 600 ms/1600 ms/12 ms/4 s. The tag and control labeling thicknesses were 140 mm and 340 mm, respectively, leaving 100 mm margins at either end of the imaging slab to ensure optimal inversion. The QUIPSS II saturation pulse was applied to a 100 mm slab inferior to the imaging region with a 10 mm gap between the adjacent edges of the saturation and imaging slabs. This PASL sequence was used for calibration (TR = 10 s) for estimating arterial blood magnetization. A 3D anatomical scan (1x1x1 mm³) was acquired using multi-echo MPRAGE [6]. The PWI data were motion- and drift-corrected, and the difference images calculated using surround subtraction, compensating for transit delay. These volumes were averaged across time and datasets to maximize signal-to-noise, following which absolute CBF (qCBF) maps were obtained based on the Standard Kinetic Model and local tissue-based calibration, assuming a 95% labeling efficiency, as well as proton density and T₂* values described previously [7]. The PWI data were registered to the anatomical images using boundary-based registration [8], and subsequently sampled into surface-space at a cortical depth of 50%. All surfaces were registered to a surface-atlas using FreeSurfer, and the difference in cortical grey matter qCBF between HD patients and controls was obtained after removing cortical thickness effects to determine changes in CBF beyond those due to atrophy (partial-voluming). The statistical tests were performed following surface-wise smoothing (FWHM=10mm) and outlier removal, and corrected for multiple comparisons [9]. Cortical and sub-cortical structures were also labeled using probabilistic atlas-based tissue segmentation on multi-echo MPRAGE anatomical data [6], and volume-ROIs for qCBF analysis were selected well within these 3D labels to minimize partial-volume effects. Volume and mean qCBF differences between patients and controls were assessed using 2-way ANOVA.

Results

Significance maps of cortical thickness and qCBF changes are shown with semi-inflated lateral (top) and medial (bottom) surface models in Fig. 1. The pattern of cortical thinning, which appears wide spread over the cortical mantle, overlapped with that of qCBF differences in the lateral-occipital, pre- and postcentral gyri, but voxel-wise correlation analysis showed no significant covariation between cortical thickness and qCBF. The influence of atrophy on CBF was neutralized by regressing out cortical thickness measurements, following which qCBF was found to be most strongly reduced in HD patients in the pre- and postcentral, paracentral, lateral-temporal and lateral-occipital areas (Figure 1b). In addition, significant volume reduction was observed across the cortex ($p=0.05$), in the striatum ($p=1 \times 10^{-9}$), globus pallidum ($p=1 \times 10^{-5}$), amygdala ($p=0.002$) and hippocampus ($p=0.03$). Volume-averaged qCBF values are summarized in Fig. 2. ANOVA showed significant HD-induced qCBF reduction in the cortex ($p=0.009$), striatum ($p=0.0008$) and hippocampus ($p=0.05$), but no salient qCBF change in the pallidum, thalamus and amygdala. Also, no significant gender-dependence in qCBF was found in any of these structures.

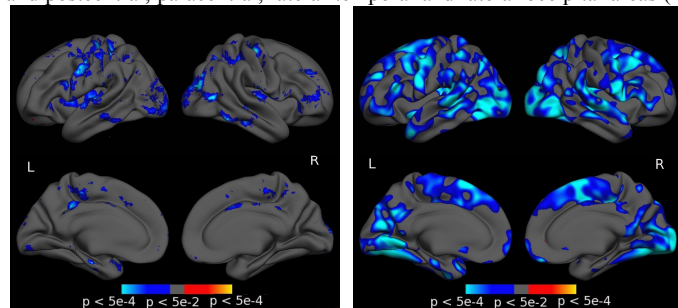


Figure 1. Reductions in cortical qCBF (left, a) due to Huntington's disease remain after the removal of cortical atrophy effects (right, b).

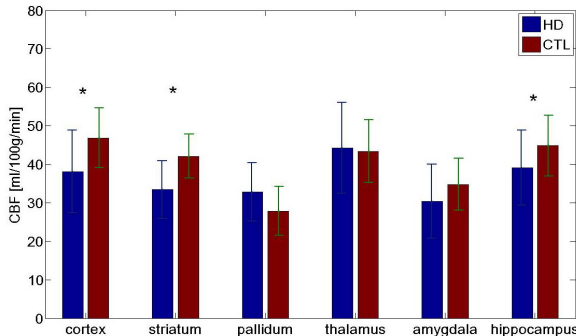


Figure 2. HD was associated with significant (indicated by asterisks) qCBF decrease across the cortex and in the striatum. (HD = Huntington's patients, CTL = healthy controls)

There is a substantial change in quantitative CBF in HD. Our observation of qCBF reduction in the striatum corresponds well with prior reports of reduced CBF [3,4] and glucose metabolism [10] in the region, and the hippocampal hypoperfusion is corroborated by structural atrophy, observed here and in prior studies [1]. Our observation of hypoperfusion in the sensorimotor regions, which has not been reported previously, coincides with cortical thinning patterns as well as the characteristic motor dysfunction. However, hypoperfusion in the superior-temporal region, which is also being observed for the first time, appears to be independent of cortical thinning, suggestive of perfusion deficit preceding structural degeneration. The opposite may be true in the pallidum, amygdala and thalamus, in which perfusion seems preserved despite atrophy, and which were reported to exhibit enhanced metabolism in HD [10]. Finally, we observed no perfusion elevation in any structure in the HD group, in contrast with prior SPECT results [3]. The above differences warrant further investigation, using PASL techniques with improved sensitivity. These results also set the stage for studying perfusion abnormalities in pre-manifest HD-gene carriers, which may further clarify HD pathogenesis.

Conclusion

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References

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