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A characterization of regional changes in cortical thickness in Huntington's Disease

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Introduction:

Huntington's disease (HD) is a progressive autosomal dominant neurodegenerative disorder characterized by abnormalities of motor function, cognition and behavior(2). HD results from the expansion of trinucleotide (CAG) repeats coding for polyglutamine, the huntingtin protein, on chromosome 4. The mechanisms through which this genetic abnormality leads to the pathogenesis are unclear. Although the pathological hallmark is the progressive degeneration of the striatum, global cerebral atrophy has been demonstrated (1). Several MRI studies have also demonstrated reduction in striatal volumes; one study demonstrated volume loss in the frontal regions. It has been hypothesized that the thickness of the cortical ribbon is reduced in HD; however, the complexity of cortical folding and regional variations in cortical thickness have made accurate ascertainment of these measures extremely difficult. We utilized automated surface reconstruction and high-resolution inter-subject registration procedures (3,4) to determine cortical thickness in ten HD subjects. We found clear, regionally specific, differences in cortical thickness in the HD subjects as compared to normal controls.

Methods:

Subjects: HD subjects were recruited from the Massachusetts General Hospital Huntington's disease Unit. Each subject had a definite clinical signs of HD (2) as well as either a positive family history of a known trinucleotide repeat expansion. Procedures were fully explained to all subjects, and written informed consent was obtained before scanning. Ten HD subjects were scanned; three were female and seven were male. The mean age of HD subjects was 43.8 +/- 10.3. All subjects, except for an andvanced subject, were living independently at the time of scanning. HD subjects were in various stages of disease. The mean age of normal subjects was 33 +/- 11. Imaging: We obtained high-resolution T1-weighted images on a GE 1.5 Tesla Signa. MRI data was analyzed and the surface reconstructed as has been described previously (3,4). The cortical thickness was estimated using the final refined white and pial surfaces; for each point on the white matter surface, the distance closes to the closest point in the pial surfaces is the estimate of the cortical thickness. Thickness maps from different HD individuals were averaged using a high-resolution surface-based averaging technique that aligns cortical folding patterns [3] and compared to thickness maps from group normal control subjects. Results: We were able to demonstrate a statistically significant thinning of the cortical ribbon in HD subjects. A statistical map of the comparison of the averaged nine HD subjects versus normal subjects is displayed on the inflated cortical surface in Figure 1. The statistical cutoff is 10-4. Red and yellow regions represent regions that are thinner in the HD subjects. There is greater thinning more posteriorly. Figure 2 demonstrates a statistical map of the comparison of the averaged nine early to mid-stages of disease HD subjects versus a more advanced subject. The thinning appears to spread more anteriorly. Discussion: We have been able to utilize specialized automated techniques for measuring the thickness of the cortical ribbon. We have shown previously that these measures are accurate and precise. This type of accuracy is critical for understanding intra-cortical and afferent functional connectivity as well as regional atrophy. We have demonstrated cortical thinning in a pilot study of patients with Huntington's disease and have preliminary evidence to suggest a posterior to anterior progressive thinning of the cortical ribbon. This is of interest as Lange et al. [5] have described a more significant occipital lobe than frontal lobe atrophy in an autopsy study. We plan to continue these analyses to determine the regional specificity, if any, and the progression of the changes in respective individuals as they provide non-invasive, reliable and accurate measurements that can be followed over time. These longitudinal studies will be important to determine the nature of the progressive cortical changes that occur during the course of the disease, and their implications for striato-cortical and cortico-cortical connectivity.

References

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