Huntington's disease (HD) is a progressive neurodegenerative disorder caused by an expanded trinucleotide CAG repeat in the gene coding for the protein huntingtin. The average age of onset is about 37 years of age, and ranges from infancy to the ninth decade. Since the length of the CAG repeat explains less than fifty percent of the variability in the age of onset, other genetic and environmental factors are believed to play important roles. Affected individuals are progressively disabled by early functional decline and require increasing levels of care for another 15-25 years before succumbing to the effects of severe physical and mental deterioration. The earliest and most striking neuropathologic changes are found in the neostriatum [1], but neuronal loss has been identified in many other regions of the brain [2]. Proliferative and degenerative changes [3, 4] in vulnerable neurons suggest that the presence of mutant huntingtin leads to both compensatory and degenerative genetic programs in a prolonged process leading to neuronal dysfunction and death [3], likely occurring long before clinical symptoms become apparent. It is precisely during this period of phenoconversion, the time at which an individual transitions clinically from "health" to illness, presumably due to the cumulative effects of mutant huntingtin, that neuroprotective strategies hold the greatest promise.

Our data highlights several important points. First, HD the involvement of the cortex in HD appears to follow a topologically specific pattern, with early involvement of primary cortical regions and eventually extends to involve unimodal and heteromodal regions. Similarly, basal ganglia structures atrophy very early, but at some point, the rate of atrophy appears to reach a relative floor effect. The hippocampus appears to atrophy prodromally, but progressive atrophy appears to slow in early stages of disease. White matter atrophy is also very significant, appearing to affect some regions before others. These observations demonstrate that the spatial pattern of brain atrophy, therefore, in HD is complex and highly variable, and evolves in time with disease progression.

The development of sensitive, accurate and sophisticated models to fully characterize early and progressive changes in HD is a critical step toward developing neuroimaging biomarkers able to integrate progression in the multiple neurologic domains (e.g. cognition and movements) that together constitute its phenotype. We will discuss some novel approaches that we have applied in the hopes of developing biomarkers of disease onset: measures that are sensitive, reliable, reproducible and clinically relevant.

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