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Functional connectivity modeling of consistent cortico-striatal degeneration in Huntington's disease

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ABSTRACT

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by a complex neuropsychiatric phenotype. In a recent meta-analysis we identified core regions of consistent neurodegeneration in premanifest HD in the striatum and middle occipital gyrus (MOG). For early manifest HD convergent evidence of atrophy was most prominent in the striatum, motor cortex (M1) and inferior frontal junction (IFJ). The aim of the present study was to functionally characterize this topography of brain atrophy and to investigate differential connectivity patterns formed by consistent cortico-striatal atrophy regions in HD. Using areas of striatal and cortical atrophy at different disease stages as seeds, we performed task-free resting-state and task-based meta-analytic connectivity modeling (MACM). MACM utilizes the large data source of the BrainMap database and identifies significant areas of above-chance co-activation with the seed-region via the activation-likelihood-estimation approach. In order to delineate functional networks formed by cortical as well as striatal atrophy regions we computed the conjunction between the co-activation profiles of striatal and cortical seeds in the premanifest and manifest stages of HD, respectively. Functional characterization of the seeds was obtained using the behavioral meta-data of BrainMap. Cortico-striatal atrophy seeds of the premanifest stage of HD showed common co-activation with a rather cognitive network including the striatum, anterior insula, lateral prefrontal, premotor, supplementary motor and parietal regions. A similar but more pronounced co-activation pattern, additionally including the medial prefrontal cortex and thalamic nuclei was found with striatal and IFJ seeds at the manifest HD stage. The striatum and M1 were functionally connected mainly to premotor and sensorimotor areas, posterior insula, putamen and thalamus. Behavioral characterization of the seeds confirmed that experiments activating the MOG or IFJ in conjunction with the striatum were associated with cognitive functions, while the network formed by M1 and the striatum was driven by motor-related tasks. Thus, based on morphological changes in HD, we identified functionally distinct cortico-striatal networks resembling a cognitive and motor loop, which may be prone to early disruptions in different stages of the disease and underlie HD-related cognitive and motor symptom profiles. Our findings provide an important link between morphometrically defined seed-regions and corresponding functional circuits highlighting the functional and ensuing clinical relevance of structural damage in HD.

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1. Introduction

Huntington's disease (HD) is an autosomal-dominantly inherited neurodegenerative disorder caused by an expansion of CAG repeats on chromosome 4p and clinically characterized by a complex phenotype encompassing a triad of motor, psychiatric and cognitive dysfunctions. The neuropathological hallmark of HD is progressive degeneration of the striatum detectable up to two decades prior to the onset of the

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first motor symptoms and leading to widespread brain atrophy with disease progression (Aylward et al., 2004; Paulsen et al., 2010; Tabrizi et al., 2011, 2012, 2013).

Structural brain imaging measures, particularly the assessment of caudate atrophy, have been shown to be predictive of symptom onset and in tracking disease progression (Aylward et al., 2011; Tabrizi et al., 2009, 2011, 2012, 2013). However, the search for reliable and clinically meaningful biomarkers in HD is accompanied by a better understanding of the relationship between (regional) brain volume loss and its contribution to the emergence of clinical symptoms. Importantly, disease-related behavioral manifestations are less likely to be sufficiently explained by distinct regional tissue degeneration, but rather depend on the complex interactions within multiple brain circuits or disruptions of the same — emanating from or even beginning before overt structural atrophy. Hence, the multimodal analysis of dynamic networks and connectivity dysfunctions along with neural cell loss may offer a more comprehensive understanding of the complex neuropathology underlying the heterogeneous nature of HD (Georgiou-Karistianis, 2009; Paulsen, 2009). Particularly in the premanifest stage of HD, where cognitive and psychiatric disturbances seem to precede the motor diagnosis (Paulsen et al., 2006; Paulsen, 2011), characterization of aberrant functional networks has been shown to be more sensitive to detect the earliest changes in HD than those in structural imaging alone (Wolf et al., 2007; Wolf et al., 2008b). Moreover, in manifest HD, when striatal volume loss has already progressed and the degenerative process afflicts widespread brain regions, and thus cortico-striatal projections, the clinical picture becomes more heterogeneous. This raises the need for an appropriate functional differentiation between multiple behavioral outcomes on the neural level and for a better characterization of alterations within these networks in different stages of the disease.

In recent years a number of task-based and resting-state imaging studies have investigated functional connectivity changes in HD, if at all mostly after controlling for or partialling out gray matter atrophy (e.g., Dumas et al., 2013; Werner et al., 2014), and only a few addressing the impact of regional volume loss on functional connectivity (Quarantelli et al., 2013; Wolf et al., 2014). However, as functional network connectivity inherently depends on tissue integrity, network analysis based on local volume destruction may predict deviation from normal brain performance due to structural degeneration and enable insights into the underlying neuronal dysfunctions. Modeling of networks co-activating with (or functionally connected to) HD-specific consistently atrophied areas may therefore contribute to a more comprehensive understanding of structural alterations and the complex clinical picture presented in HD. In addition, functional network analysis related to structural damage in HD may increase the predictive value of structural imaging methods by enhancing our knowledge on the ensuing clinical relevance of HD-related tissue destruction. This would ultimately offer a framework to monitor disease progression within these networks and associated clinical manifestations.

In order to synthesize structural magnetic resonance imaging (MRI) findings across the whole brain, we recently performed a coordinate-based meta-analysis of voxel-based morphometry (VBM) studies in HD and delineated a consistent pattern of brain atrophy across studies in premanifest and early manifest patients (Dogan et al., 2013). While marked striatal atrophy was shown to be evident in premanifest HD, we also observed involvement of cortical degeneration in the premanifest stage, particularly in the occipital cortex. After symptom manifestation, which is conventionally defined by the onset of motor symptoms, cerebral atrophy was more pronounced and cortically more widespread. While higher numbers of CAG repeats were associated with striatal degeneration, parameters of disease progression and motor impairment additionally correlated with cortical atrophy, especially in sensorimotor areas (Dogan et al., 2013). We argued that this pattern of structural degeneration may underlie the heterogeneous phenotype in HD and emphasized the need to extend the focus of research from the key region of neuropathology (i.e., degeneration of the striatum) to a more differentiated picture of cortical–subcortical changes and potential disturbances in the networks formed by these regions.

Therefore, our aim in the current study was to functionally characterize the consistent pattern of brain atrophy as observed in our meta-analysis and to probe the ensuing clinical relevance of structural damage in HD. For this, we considered atrophied areas as nodes within dynamic networks and performed functional connectivity analyses to detect which brain areas co-activate with these regions. Connectivity analyses included both a task-based approach *via* the new neuroimaging tool "meta-analytic connectivity modeling" (MACM) as well as a task-free resting-state functional MRI (fMRI). By combining both task-driven and task-independent connectivity modeling tools we aimed to investigate convergent functional networks in different states of brain functioning as well as at rest. In order to integrate connectivity findings and ensuing behavioral correlates, we additionally assessed behavioral domains and paradigm classes associated with regions of consistent atrophy. Connectivity modeling and behavioral decoding of atrophied areas were applied in the following way: As a hallmark of the disease, we were first interested in i) co-activation profiles related to striatal volume loss known to be affected early on in HD. Convergent clusters of striatal atrophy were retrieved from our meta-analysis and used as seeds for functional connectivity modeling. Since the striatum is a key structure in the brain involved in a broad variety of functions, we expected to find a widespread functional network co-activating with HD-related striatal atrophy areas. In a further step we wanted to delineate functional networks formed by both striatal as well as cortical atrophy regions in different stages of the disease, as these networks would be in particular prone to early disease-related disruptions. That is, we considered those brain regions showing common co-activation with both the striatal and cortical atrophy areas. Given that these regions would be connected to atrophy nodes cortically as well as subcortically and therefore highly vulnerable to network disturbances, we aimed to achieve a more reliable inference on the functional role of HD-specific brain structure changes (instead of assessing co-activation profiles separately for each atrophy seed). Thus, we performed functional connectivity modeling of cortical in conjunction with striatal atrophy seeds retrieved from the meta-analysis at the ii) premanifest and iii) manifest HD stages. We hypothesized that connectivity analysis of the cortico-striatal seeds in the premanifest HD stage would reveal a network which mirrors the cognitive disturbances presented at this disease stage, while the seeds of the manifest stage would show more widespread network involvement reflecting cognitive and motor dysfunctions in clinical HD.

2. Methods

2.1. Seed regions: meta-analysis of consistent neurodegeneration in HD

In a recent coordinate-based meta-analysis of VBM studies in HD (Dogan et al., 2013) we identified the core regions of consistent neurodegeneration in premanifest and manifest HD mutation carriers. Drawing on these results, our aim in the current study was to functionally characterize this pattern of brain atrophy and to identify functional networks co-activating with these atrophic regions (seeds) and most likely being disrupted early in HD. Since degeneration of the striatum is the early pathognomonic key marker of the neurodegenerative process in HD, first we performed functional connectivity analysis of convergent striatal atrophy as observed in our meta-analysis encompassing 685 HD mutation carriers and 507 healthy controls. That is, we computed the conjunction between co-activation profiles of the left and right striatal atrophy seeds (cluster volumes: *right* 5872 mm^3; *left* 6880 mm^3; Fig. 1A).

Second, we were interested in modeling networks co-activating with both striatal and cortical atrophy regions in different HD stages, hence being in particular vulnerable to disease-related disruptions.

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