Neuroimaging as a tool to study the sources of phenotypic heterogeneity in Huntington's disease

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Purpose of review
Huntington's disease is a neurodegenerative disorder characterized by a triad of motor, cognitive and psychiatric disturbances. There is great variability regarding the prominence and evolution of each type of clinical sign. One possible source of phenotypic heterogeneity could be the more prominent degeneration of specific brain circuits. The scope of this review is to highlight the most recent neuroimaging studies that have analysed the relationship between brain changes and motor, cognitive and psychiatric alterations in Huntington's disease.

Recent findings
The results from recent neuroimaging studies are heterogeneous. Although there is a great overlap between the different regions associated with each symptomatic domain, there is some degree of differentiation. For example, the motor network is associated with motor impairment, whereas the ventral striatum is especially involved in emotional deficits related with psychiatric problems.

Summary
Motor, cognitive and psychiatric impairments are associated with structural and functional brain biomarkers. However, the specificity of the regions involved remains unknown, because these studies focused on specific regions and symptoms. In order to tease apart the neural substrates that underlie the phenotypic heterogeneity in Huntington's disease, multivariate approaches combining brain and behavioural measures related to all symptomatic domains should be considered in the future.

Keywords
cortico-striatal circuits, heterogeneity, Huntington's disease, neuroimaging, profiles

INTRODUCTION

Huntington's disease is a neurodegenerative disorder caused by an abnormal expansion of a CAG repeat in the *HTT* gene. Above 35 CAG repeats, the length of the expansion is inversely correlated with the age at onset and positively correlated with the rate of disease progression. A mixture of motor dysfunction, cognitive impairments and psychiatric disturbances characterizes the disease. Huntington's disease gene carriers are clinically diagnosed as manifest patients on the basis of motor dysfunction using the Unified Huntington's Disease Rating Scale total motor score (UHDRS TMS) [1]. However, cognitive impairments and psychiatric problems are common before the onset of motor dysfunction, during what is considered the pre-manifest phase of the disease. Although alterations in all three domains (motor, cognitive and psychiatric) are common, Huntington's disease is characterized by a great heterogeneity in the prominence and evolution of each type of symptom.

The exact relationship between topological brain alterations and the clinical symptoms observed in Huntington's disease still remains unknown. One possible source of the individual differences in the prominence of each symptomatic domain could be the more prominent degeneration of specific brain circuits. In this regard, neuroimaging studies can contribute to the understanding of the neurobiological basis of phenotypic

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KEY POINTS

- Huntington's disease is a neurodegenerative disorder characterized by a mixture of motor, cognitive and psychiatric symptoms.

- There are individual differences in the prominence and evolution of each type of symptom.

- Given the key role of striatal neurodegeneration in Huntington's disease, it is possible that the observed phenotypic variability in Huntington's disease may reflect differences in the degree of degeneration in the different functionally specialized cortico-striatal circuits.

- One way of investigating the sources of phenotypic heterogeneity in Huntington's disease is examining the relationship between the different symptoms and specific brain changes.

- Neuroimaging studies using multivariate approaches that incorporate brain and behavioural measures related to the three types of symptoms can shed light on the neurobiological basis of the observed phenotypic heterogeneity in Huntington's disease.

heterogeneity in Huntington's disease. The scope of this review is to highlight neuroimaging studies from last year that have analysed the relationship between specific brain changes and motor, cognitive and psychiatric alterations in Huntington's disease.

NEUROBIOLOGICAL BASIS OF HUNTINGTON'S DISEASE

Striatal atrophy is considered a hallmark of the disease, being observable between 15 and 20 years before the predicted onset [2–4]. Striatal neuronal loss has been found to be correlated with CAG repeat length [5–8], and also with motor and cognitive dysfunction [9], suggesting an important role of this structure in the pathogenesis of Huntington's disease. Neurodegeneration follows a pattern that starts in the striatum from caudal and dorsal subregions to rostral and ventral areas [6,8,10]. Widespread cortical degeneration is observable in early stages of the disease, with relative sparing of the anterior frontal and lateral temporal regions [6,11,12].

Given the key role of striatal neurodegeneration in Huntington's disease, it is possible that the observed phenotypic variability in Huntington's disease may reflect individual differences in the degree of degeneration in the different functionally specialized cortico-striatal circuits. Parallel cortico-striatal loops have been proposed to form sensorimotor, associative and limbic circuits [13–16], although further subdivisions have also been suggested [17,18]. Motor, premotor and sensorimotor projections to the dorsolateral striatum form the motor circuit. The associative circuit, devoted to executive functions, consists of dorsolateral and ventrolateral prefrontal cortex projections into the rostral parts of the striatum, mainly the head of the caudate nucleus. The limbic circuit, which is mainly involved in reward and emotional processing, is formed by projections from orbitofrontal, ventromedial prefrontal and anterior cingulate cortices, hippocampus and amygdala into the ventral striatum. Importantly, these circuits partially overlap and interact with each other [16].

RELATIONSHIP BETWEEN NEUROIMAGING AND CLINICAL SYMPTOMS IN HUNTINGTON'S DISEASE

Below, we review recent neuroimaging studies that include correlation analyses between neuroimaging data and clinical scores or behavioural measures, even though in many instances that was not the primary focus of the study. We have subdivided the findings into different sections according to the symptomatic domains that characterize Huntington's disease: motor, cognitive and psychiatric.

Motor domain

Regarding motor disturbances, the most prominent motor sign of Huntington's disease is chorea, which is experienced by more than 90% of the patients [19]. Dystonia and bradykinesia tend to develop in middle to late stages of Huntington's disease, and rigidity is common in advanced stages. Ocular movement abnormalities are also observed during the pre-manifest phase and persist throughout the course of the disease.

The most robust finding from previous neuroimaging studies related to motor disturbances is the correlation between the loss of striatal volume and UHDRS TMS [20–26]. Recent studies have found further functional and structural alterations that correlate with motor impairment. In a study on early Huntington's disease combining diffusion-weighted imaging and resting-state functional magnetic resonance imaging (fMRI), Müller *et al.* [27] found that higher UHDRS TMS, reflecting more severe motor impairment, correlated with reduced strength of functional connectivity of the insula with the motor network and reduced structural connectivity in two motor-related tracts – the cortico-spinal tract and the tract connecting the thalamus to the primary somatosensory cortex. Using a multivariate approach combining functional and structural brain measures in order to

characterize the sensorimotor circuit of manifest and pre-manifest individuals, Orth *et al.* [28**] found that a pattern of loss of caudate, total grey matter and white matter volume and reduced cortical thickness in premotor and somatosensory cortices correlated with worse motor disturbances, measured by UHDRS TMS and grip force – a clinical measure of motor impairment. These results suggest that structural measures of volume and cortical thickness are especially sensitive for the characterization of brain alterations in Huntington's disease. However, measures of individual non-motor brain regions were not included in this study. Therefore, it is not possible to conclude whether the association observed between motor impairment and sensorimotor areas is specific.

It has also been suggested that electroencephalography recordings may be sensitive biomarkers to early disruptions of cortical connectivity in Huntington's disease [29]. In this regard, Turner *et al.* [30] investigated neural sensorimotor integration and motor processing in a motor task. Degenerative changes in the right caudate morphology were associated with a delayed neural-related premotor activation and execution. Better motor performance significantly correlated with larger volumes in the right putamen and the right caudate. However, the authors did not examine the relationship between premotor neural activity and motor performance.

Regarding the interaction between motor and cognitive functions, Holtbernd *et al.* [31] studied the changes in motor learning-related activation in pre-manifest individuals over a period of 18 months using PET. Network analyses were used in order to identify spatial covariance patterns with increasing expression over time such that patient scores were greater for individuals who were nearer to age at onset. The pattern of spatial covariance was characterized by increased learning-related activation in the right orbitofrontal cortex and reductions in the right medial prefrontal and posterior cingulate cortices. Individuals with low performance at baseline exhibited a low network expression at baseline, which increased significantly over time, reaching abnormally elevated levels compared to controls. Learning performance improved over time in the group that showed low performance at baseline. Given that the increase in network activation was accompanied by improvement in learning performance, the authors interpreted these results as reflecting a compensatory mechanism.

Cognitive domain
Cognitive deficits in Huntington's disease may be present more than a decade before motor diagnosis [11,32,33]. The first signs of cognitive dysfunction are usually the deterioration of psychomotor speed and executive functions [34]. Alterations in verbal fluency, cognitive flexibility and planning are amongst the most common deficits regarding executive functions in Huntington's disease [35–40]. Furthermore, Huntington's disease also entails impairments in perception of time [37–40], explicit motor learning [41], episodic memory [42], spatial memory [43], rule learning in language [44–48] and spontaneous speech [49–51].

Converging evidence from previous neuroimaging studies shows an association between reduced striatum volume and global cognitive deficits [24,26,52]. Recently, Kim *et al.* [53▪] examined the regional structural damage of the caudate nucleus using surface-based morphometry in pre-manifest individuals, and observed that deficits in executive functions and working memory significantly correlated with grey matter loss in the anteromedial subregion of the caudate. However, cognitive deficits seem to derive not only from the local atrophy in the caudate, but rather from the effects that it entails in terms of its connectivity with cortical regions. For instance, in a study on grey matter changes in structural covariance networks in manifest and pre-manifest individuals, Coppen *et al.* [54▪▪] found that a network containing the caudate, putamen, nucleus accumbens, pallidum, precuneus and anterior cingulate cortex significantly correlated with both motor scores and executive function scores. Moreover, a network comprising the intracalcarine cortex, parietal and occipital regions was also significantly correlated with cognitive flexibility.

Apart from structural studies, the correlation between brain functional alterations and cognitive measures has also been investigated. In a resting-state fMRI study, Sarappa *et al.* [55] reported that higher activity in the cerebellum and the thalamus was associated with poorer executive functions in pre-manifest individuals. Consistent with the role of the cerebellum in executive functions [56], the authors claim that this result could be driven by a compensatory increase in connectivity of the cerebellar clusters with other brain regions. The lack of correlation with cognitive scores in the manifest Huntington's disease group could indicate a plateau in this phenomenon in more advanced stages of the disease. Likewise, Liu *et al.* [57] investigated the alterations in regional resting-state brain activity in early stages of Huntington's disease and observed that reduced neural activity in the right precuneus and increased activity in the left inferior temporal gyrus correlated with more impaired executive functions in cognitive tests.

Apart from executive functions, the neurobiological basis of the impairment of visuospatial abilities has also been studied in Huntington's disease. In a structural imaging study, Labuschagne *et al.* [58] examined the associations between visuospatial cognition and brain volume and cortical thickness in manifest and pre-manifest individuals, showing that neurodegeneration in striatum and parieto-occipital regions of the brain in Huntington's disease was related to visuospatial performance.

Psychiatric domain

Little attention has been devoted to the neurobiological substrates of psychiatric symptoms in Huntington's disease in comparison with motor and cognitive symptoms.

Psychiatric symptoms, including apathy, depression and irritability, may arise before the onset of motor symptoms [59–61]. Among these, apathy shows the strongest association with disease progression [33,59,62]. Although depression is a common symptom in Huntington's disease, it is not clear whether it is an expression of Huntington's disease itself, or, alternatively, is a reaction to adverse life circumstances [63–65]. In this regard, Gregory *et al.* [66▪] investigated putative microstructural changes associated with depression, apathy and irritability in manifest and pre-manifest individuals, and found that in those individuals close to onset only depression and irritability scores, but not apathy, were associated with reduced structural connectivity, specifically in the posterior corpus callosum and widespread white matter, respectively.

Previous neuroimaging studies on psychiatric-related symptoms in Huntington's disease have focused on emotion and reward processing. Regarding emotion processing and recognition, the most consistent findings are reduced activity and grey matter volume in the insula, especially in the case of disgust [67–71]. During reward processing, reduced ventral striatum activity has been found in Huntington's disease [72].

Recently, using a reversal learning task during fMRI, Nickchen *et al.* [73] found that the altered reward-related activity and the grey matter density in the left ventral striatum were associated with worse motor abnormalities in Huntington's disease patients. However, the authors did not explore correlations between neuroimaging and behaviour in the reversal learning task or any psychiatric score. Sprengelmeyer *et al.* [74] found that Huntington's disease patients with impaired trustworthiness and dominance recognition showed reduced microstructural integrity (i.e. fractional anisotropy) in the corpus callosum, frontal, parietal and occipital regions, the insula and the cerebellum, which in turn correlated with poorer performance in mood and feelings recognition.

PROFILES IN HUNTINGTON'S DISEASE

Stratification of patients in different profiles using neuroimaging techniques has been proposed in multiple neurodegenerative, psychiatric and neurodevelopmental disorders [75–81]. In contrast, there is a lack of neuroimaging studies that have directly attempted to find profiles or subtypes in Huntington's disease. However, cellular studies on post mortem brain tissue of Huntington's disease patients have found distinctive patterns of neuronal loss associated with motor, mood and mixed profiles [82▪▪,83–85]. Recently, multivariate analysis techniques have been employed to find subtypes in pre-Huntington's disease individuals using the longitudinal trajectories of signs and symptoms of the three domains [86▪▪]. Interestingly, more severe motor signs were accompanied by worse cognitive deficits, but not always by higher levels of depressive symptoms. These findings suggest that Huntington's disease individuals can develop depressive symptoms at any time, regardless of motor or cognitive impairment. Furthermore, individuals with specific genotypes that affect levels of dopaminergic release in the prefrontal cortex are particularly affected in the rate of progression of cognitive impairments [87].

Neuroimaging studies on Huntington's disease have mainly focused on characterizing the disease by comparing patients to healthy controls rather than on finding the source of the symptomatic heterogeneity. Regarding individual differences in Huntington's disease, the focus has been mostly placed on finding biomarkers related to age at onset. One recent study has investigated the longitudinal change of functional connectivity in sensorimotor, associative and limbic cortico-striatal networks [88], and examined correlations with clinical scores. However, this study did not reveal circuit specificity in the association with clinical symptoms, and only included motor and cognitive scores, but no psychiatric measures.

LIMITATIONS AND FUTURE DIRECTIONS

Elucidating the neurobiological source of the phenotypic heterogeneity observed in Huntington's disease would be of paramount relevance for clinical interventions, since this would allow stratifying patients for clinical trials to improve sensitivity. Certain limitations of the current literature should be considered before addressing future directions that can open new avenues.

Analyses of individual differences in neuroimaging studies are typically conducted as a complement to within-patient analyses and are rarely the primary focus of a study. As a result, some of the most common constrains that contribute to losing sensitivity to individual differences are small sample sizes and homogenous samples that include patients in similar disease stages and exclude patients with psychiatric illness.

Equally important is the election of the tasks or clinical tests. Some of the clinical cognitive scores often included in studies have a motor component, which does not allow differentiating between cognitive and motor deficits. In the case of pre-manifest individuals, the standard tests included in the UHDRS scale are often not sensitive enough to detect either differences from controls or individual differences due to ceiling effects. In this regard, experimental tasks can offer more fine-grained measures with more power to detect subtle changes in performance. Motor dysfunction, though subtle in the pre-manifest phase may be also detectable with sensitive tests [89].

Noteworthy, most of the studies only focused on one or two types of symptoms, usually motor and cognitive deficits, overlooking psychiatric symptoms. In order to find specificity in the relation between brain alterations and symptoms, it is important to include measures of the three symptomatic domains in the same study. In this regard, multivariate neuroimaging approaches can be of great relevance. In addition, different neuroimaging techniques could have different sensitivity to small changes in performance. Thus, multimodal studies can provide a more complete picture of the neurobiological basis of individual differences.

CONCLUSION

Recent neuroimaging studies show that motor, cognitive and psychiatric impairments are associated with structural and functional brain biomarkers in Huntington's disease. Although there is a great overlap between the different regions associated with each symptomatic domain, there is some degree of differentiation. However, the specificity of the regions involved remains unknown, since the studies reviewed focused on specific regions and symptoms. In order to tease apart the neural substrates that underlie the phenotypic heterogeneity in Huntington's disease, multivariate approaches should be employed in the future, combining brain and behavioural measures related to the three symptomatic domains.

Conflicts of interest
There are no conflicts of interest.

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