World Journal of Radiology

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DOI: 10.4329/wjr.v6.i6.301

World J Radiol 2014 June 28; 6(6): 301-312
ISSN 1949-8470 (online)

REVIEW

Neuroimaging in Huntington's disease

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Received: December 11, 2013 Revised: February 28, 2014
Accepted: May 8, 2014
Published online: June 28, 2014

Abstract

Huntington's disease (HD) is a progressive and fatal neurodegenerative disorder caused by an expanded trinucleotide CAG sequence in huntingtin gene (HTT) on chromosome 4. HD manifests with chorea, cognitive and psychiatric symptoms. Although advances in genetics allow identification of individuals carrying the *HD* gene, much is still unknown about the mechanisms underlying the development of overt clinical symptoms and the transitional period between premanifestation and manifestation of the disease. HD has no cure and patients rely only in symptomatic treatment. There is an urgent need to identify biomarkers that are able to monitor disease progression and assess the development and efficacy of novel disease modifying drugs. Over the past years, neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) have provided important advances in our understanding of HD. MRI provides information about structural and functional organization of the brain, while PET can detect molecular changes in the brain. MRI and PET are able to detect changes in the brains of *HD* gene carriers years ahead of the manifestation of the disease and have also proved to be powerful in assessing disease progression. However, no single technique has been validated as an optimal biomarker. An integrative multimodal imaging approach, which combines different MRI and PET techniques, could be recommended for monitoring potential neuroprotective and preventive therapies in HD. In this article we review the current neuroimaging literature in HD.

Key words: Huntington's disease; Premanifest Huntington's disease gene carriers; Functional magnetic resonance imaging; Magnetic resonance imaging; Positron emission tomography

Core tip: Huntington's disease (HD) is a hereditary and fatal neurodegenerative disorder. Although advances in genetics allow identification of individuals carrying the *HD* gene, much is still unknown about the mechanisms underlying the development of overt clinical symptoms and the transitional period between premanifestation and manifestation of the disease. Neuroimaging techniques such as magnetic resonance imaging and positron emission tomography may be a suitable biomarker for monitoring disease progression in HD and for assessing the efficacy of future disease modifying therapies. In this article, we provide an overview of the findings from neuroimaging techniques in HD.

Niccolini F, Politis M. Neuroimaging in Huntington's disease. *World J Radiol* 2014; 6(6): 301-312 Available from: URL: http://www.wjgnet.com/1949-8470/full/v6/i6/301.htm DOI: http://dx.doi.org/10.4329/wjr.v6.i6.301

INTRODUCTION

Huntington's disease (HD) is an inherited neurodegenerative disorder characterised by chorea, cognitive dysfunction and psychiatric symptoms caused by an expanded

trinucleotide CAG sequence in huntingtin gene (HTT), which is on chromosome 4[1]. HD prevalence varies by ethnic origin and different genetic profiles, in Caucasian populations of North America and Western Europe is 5.70 per 100000 whereas in Asian population is lower (0.40 per 100000)[2]. Although juvenile onset and late onset of HD are not uncommon, the disease usually appears at mid-40s, and there is an inverse correlation between age of onset and the size of the CAG repeat expansion[3]. However, subclinical changes and pathological processes are thought to precede the initiation of symptoms by several years[4,5].

HD pathology is characterised by the formation of intranuclear inclusions of mutated huntingtin in the brain. These aggregates have been shown to interact and impair the function of a number of transcription factors leading to the loss of GABAergic medium spiny neurons (MSNs) in the striatum but also in cortical areas[6,7]. Currently there is no proven biomarker for HD, no effective treatment, and the disease will eventually lead to death, typically 15-20 years following symptomatic onset[8]. Much is still unknown about the mechanisms that underlie the clinical symptoms and the rate of progression from pre-clinical signs to development of overt symptoms.

Neuroimaging techniques such as magnetic resonance imaging (MRI) and functional MRI (fMRI) have played a critical role in characterizing structural and functional changes in the brain during the asymptomatic and symptomatic stage of the disease. PET imaging, by measuring the distribution of a radionuclide (radioligand) that is introduced into the body on a biologically active molecule, is a powerful technique for investigating *in vivo* abnormalities in brain metabolism and receptor distributions[9]. This analytical imaging method has the potential to give both structural and kinetic information and in comparison with other imaging techniques, provides high sensitivity, and high spatial and temporal resolution[10]. PET with the application of different radioligands has been used to measure metabolic changes in the brain of HD several years before disease onset (Table 1). In this article, we provide an overview of the findings from neuroimaging techniques in HD.

LITERATURE RESEARCH

PubMed was searched for papers that were published before December 2013. The following key words were used in the search: "Huntington's disease", "positron emission tomography", "magnetic resonance imaging", "functional magnetic imaging". Additional papers were identified from citations in the articles found in PubMed. Only articles published in English were considered. A total number of 37 MRI and 49 PET studies were reviewed.

MRI

Structural MRI studies

The most consistent change in the HD brain is a significant progressive volumetric loss of the striatum[4,11-20]. A reduction of 50%-54% in mean putamen volume and 28%-29% in mean caudate volume has been reported in patients with mild to moderate HD[11,12]. Striatal atrophy has been also documented in early HD patients with Total Functional Capacity (TFC) scores between I-Ⅱ[14,15] and in premanifest *HD* gene carriers who were even 15-20 years before predicted disease onset[4,13,16-20]. The amount of volume loss in the striatum correlates with the age of onset, the disease duration and the CAG repeat length[14,15,21]. While motor impairment correlates with increased putamen atrophy, Mini-Mental Status Examination scores (MMSE) and cognitive assessments are inversely correlated with the amount of caudate volume loss[11,12].

Cortical volume loss has been also reported in HD patients[17-20,22,23]. Cortical thinning occurs early during the course of the disease and seems to be topographically selective proceeding from posterior to anterior cortical regions as the disease progresses[22,23]. Individual variability in regional cortical thinning may also have a role in explaining phenotypic variability. For example, HD patients with more prominent bradykinesia showed significant cortical volume loss in frontal regions including the pre-motor and supplementary motor areas compared to HD patients with chorea[23]. Additionally, regional cortical atrophy correlates with clinical measures such as TFC, Unified HD rating scale (UHDRS) and cognitive tests enhancing the role of this measurement as potential biomarker for assessing neuroprotective therapies[23]. Widespread white matter (WM) atrophy has been identified in HD patients and has been associated with longer CAG length and decline in cognitive and motor performance[24]. Changes in WM volume are detectable up to 12-15 years before the predicted onset and correlate with cognitive functions underlining the role of structural connectivity degeneration in the pathogenesis of HD[25]. Diffusion tensor imaging (DTI) studies have also reported WM tract abnormalities in premanifest *HD* gene carriers and alterations in diffusion indices were correlated with cognitive performance[26-28]. Dumas and coworkers[28] have found abnormal WM connections of the sensori-motor cortex, which correlated with the 5-year probability for symptomatic conversion.

TRACK-HD is a multicentre longitudinal study, which focused in identifying sensitive and reliable biomarkers in premanifest *HD* gene carriers and early HD patients[17-20]. Four groups were enrolled in TRACK-HD: 120 premanifest *HD* gene carriers which were subdivided in pre-HD A and pre-HD B according to the proximity to predicted disease onset (pre-HD A > 10.8 years; pre-HD B < 10.8 years), and 123 early HD patients subdivided in two groups according to the TFC scores (HD stage Ⅰ, HD stage Ⅱ). At 12 months follow-up significantly increased total brain volume atrophy rates were reported in both premanifest *HD* gene carriers and early HD patients. Caudate and putamen volume was reported reduced by 1.4% to 4.5% compared with baseline in premanifest and early HD group. Atrophy of WM was also increased in all groups[18]. Over 24 mo, greater increases

Table 1 Key positron emission tomography imaging studies in Huntington's disease

Ref.	Subjects	PET radiopharmaceutical	Main findings
Dopaminergic system			
Ginovart *et al*[56], 1997	5 HD patients 5 HCs	^{11}C-b-CIT ^{11}C-SCH23390 ^{11}C-raclopride	50% decrease in striatal dopamine transporter (DAT) binding. 40% decrease in striatal D1 and D2 receptors binding. D1 and D2 binding in the striatum was significantly associated with the duration of symptoms Reduced D1 receptors binding in the temporal cortex
Bohnen *et al*[57], 2000	19 HD patients 64 HCs	^{11}C-DTBZ	Reduced nigrostriatal density of VMAT2 (caudate: 33%, putamen: 56%-75%)
Sedvall *et al*[58], 1994	5 HD patients 1 premanifest *HD* gene carrier 5 HCs	^{11}C-SCH 23390	75% reduction in striatal D1 receptor density in HD patients D1 binding in the premanifest *HD* gene carrier was in the lower range of the HCs
Turjanski *et al*[55], 1995	10 HD patients 9 HCs for ^{11}C-raclopride and 6 HCs for ^{11}C-SCH 23390	^{11}C-SCH 23390 ^{11}C-raclopride	Parallel reduction of striatal D1 and D2 receptor binding (31%-39%) with greater loss of mean striatal D1 and D2 binding in the akinetic-rigid patients than those choreic patients without rigidity
Lawrence *et al*[60], 1998	17 premanifest *HD* gene carriers	^{11}C-SCH 23390 ^{11}C-raclopride	Correlation between striatal D1 and D2 receptors binding and cognitive performance
Pavese *et al*[61], 2003	12 HD patients HCs from previous studies	^{11}C-raclopride	4.8% annual reduction in striatal D2 receptor binding D2 reduction receptor density in extrastriatal regions including amygdala, temporal and frontal cortex
Andrews *et al*[64], 1999	9 premanifest *HD* gene carriers 4 HD patients 7 HCs 3 subjects at risk for HD	^{11}C-SCH 23390 ^{11}C-raclopride	Mean annual loss of D1 and D2 binding of 2% and 4% respectively in the group of asymptomatic *HD* gene carriers Mean annual loss of D1 binding of 5% and D2 binding of 3% in symptomatic HD patients UHDRS motor scores and TFC correlated with PET measures of striatal dopamine receptor in both groups Premanifest *HD* gene carriers with active progression had an increased mean annual loss of D1 and D2 receptor binding (5% and 6.5% respectively)
Pavese *et al*[62], 2010	16 HD patients 11 premanifest *HD* gene carriers HCs from previous studies	^{11}C-raclopride	62.5% of symptomatic HD patients and 54.5% of premanifest carriers showed cortical reductions in D2 binding HD patients with decreased cortical D2 binding had worse scores on neuropsychological tests assessing attention and executive functions than subjects without cortical dopamine dysfunction
Antonini *et al*[66], 1998	10 premanifest gene carriers 8 HD patients	^{11}C-raclopride	Correlation between CAG repeat length and the estimated percentage loss of striatal D2 binding after age correction in premanifest *HD* gene carriers and HD patients Rate of disease progression is faster during the earlier asymptomatic stages of the disease
Brain activation and metabolism			
Antonini *et al*[65], 1996	10 premanifest *HD* gene carriers 8 HD patients HCs from previous studies	^{18}F-FDG ^{11}C-raclopride	Annual loss of 2.3% in striatal glucose metabolism and 6.3% annual decline in D2 receptor binding
Kuwert *et al*[75], 1990	23 HD patients 21 HCs	^{18}F-FDG	Decreases of caudate and regional cortical metabolism correlated with cognitive decline
Ciarmiello *et al*[79], 2006	24 premanifest *HD* gene carriers 47 HD patients 30 HCs	^{18}F-FDG	Significant decrease in glucose uptake in the cortex (frontal and temporal lobes) and striatum in both premanifest *HD* gene carriers and HD patients Striatal and cortical hypometabolism in premanfest *HD* gene carriers precedes neuronal loss
Ciarmiello *et al*[80], 2012	43 premanifest *HD* gene carriers	^{18}F-FDG	Premanifest *HD* gene carriers who phenoconverted after five years from the PET scan had a mean glucose uptake in the caudate significantly lower than the those who remained symptom-free after five years
Weeks *et al*[83], 1997	7 HD patients 7 HCs	$H_2{}^{15}O$	Impaired activation of the striatum and its frontal motor projection areas during motor tasks such as paced joystick movements
Tang *et al*[87], 2013	12 premanifest *HD* gene carriers 12 HCs	^{18}F-FDG ^{11}C-raclopride	Network analysis showed a significant spatial covariance pattern characterized by progressive changes in striato-thalamic and cortical metabolic activity network activity increased linearly over 7 yr and was not influenced by intercurrent phenoconversion
Neuroinflammation and activated microglia			
Pavese *et al*[99], 2006	11 HD patients 10 HCs	^{11}C-PK11195 ^{11}C-raclopride	Significant microglial activation in the striatum and cortical regions of HD patients Striatal ^{11}C-PK11195 binding correlates with loss of striatal dopamine D2 binding

Tai *et al*[100], 2007	11 premanifest *HD* gene carriers 10 HCs	^{11}C-PK11195 ^{11}C-raclopride	Striatal ^{11}C-PK11195 binding correlated with UHDRS scores Increased striatal and cortical microglial activation in premanifest *HD* gene carriers Higher striatal ^{11}C-PK11195 binding correlated with lower striatal D2 binding
Politis *et al*[101], 2011	8 premanifest *HD* gene carriers 8 HCs (^{11}C-raclopride) 8 HCs (^{11}C-PK11195)	^{11}C-PK11195 ^{11}C-raclopride	Increased levels of activated microglia in areas of the striatum associated with cognition and other areas related to cognitive function Levels of microglial activation correlated with clinical scales of disease severity and motor dysfunction and with a higher probability of HD onset over the next 5 yr
Cannabinoid system			
Van Laere *et al*[111], 2010	20 HD patients 14 HCs	^{18}FMK-9470	Decrease of CB1 availability throughout the gray matter of the cerebrum, cerebellum, and brain stem in HD patients.

PET: Positron emission tomography; HD: Huntington's disease.

in caudate and putamen atrophy were observed in all four subgroups. Higher rates of whole brain and grey matter (GM) loss were reported in pre-HD B, HD-I and HD-Ⅱ; whereas in the pre-HD A GM atrophy was confined to the striatum. Interestingly, WM atrophy around the striatum and within the corpus callosum and posterior WM tract was observed even in the earliest premanifest stage[19]. At 36 mo, early HD patients showed further significant increases in whole brain, caudate, putamen and GM atrophy and these measures were strongly associated to TFC decline. Although in pre-HD A group increased rates of whole brain, striatal and WM atrophy were observed, these were not accompanied by progressive worsening of motor and cognitive performance. On the contrary, pre-HD B showed higher rates of brain structural loss compared to pre-HD A group and these were associated with significant decline in several motor and cognitive tests. Furthermore, striatal and GM volume measures were sensitive predictors of subsequent clinical diagnosis of HD in the pre-HD B group[20]. Taken together, these findings suggest that MRI measures are able to track pathology in premanifest and manifest *HD* gene carriers and could be useful for the designing of future clinical trials.

Functional MRI studies

There is growing evidence that the severity of clinical manifestations in HD does not depend only on neuronal loss but also on neuronal dysfunction and circuitry reorganization, and these processes may occur at an early stage of the disease, possibly prior to neurodegeneration. Functional neuroimaging approaches such as functional MRI (fMRI) provide a dynamic images of the brain aiding to elucidate neural activity by measuring haemodynamic response (blood flow) of neural activation. Data from manifest HD patients have shown reduced task-activation in several subcortical and cortical regions as well as increased activation in different cortical areas, which were interpreted as a compensatory mechanism for task performances[29-34]. Interestingly, in premanifest *HD* gene carriers further from disease onset increased activation in several brain regions was observed, whereas premanifest *HD* gene carriers closer to disease onset showed reduced activation in the striatum[35-38]. Using fMRI and a group independent component analysis, Unschuld and colleagues[39] investigated networks of functional connectivity while performing a Stroop colour-naming task in both healthy controls and premanifest *HD* gene carriers and correlated with depressive symptoms. Stroop related activity of the ventromedial prefrontal cortex was more significantly correlated with depressive symptoms in premanifest *HD* gene carriers than healthy controls. This correlation was stronger in the premanifest HD subgroup with CAG repeat length greater than 42[39]. Using a Tower of London fMRI task, the same group found significantly reduced functional coupling between the medial prefrontal cortex area and the left premotor cortex in a group of premanifest HD gene carriers and early manifest HD subjects[40]. These findings suggest that impaired brain network connectivity reflects cognitive and mood dysfunction in HD subject even at the earlier stage of the disease. Recently, studies have been focused in investigating functional brain connectivity patterns at rest with fMRI (resting state fMRI). This approach has the potential to give insight into functional changes without the interference of cognitive ability to perform a given task[41,42]. Resting state fMRI data have shown intrinsic reductions in functional connectivity in both premanifest and manifest *HD* gene carriers[43-45]. In premanifest HD gene carriers reduced blood-oxygen-level-dependent (BOLD) synchrony was observed between the caudate and premotor cortex[46]. Using a method that measures changes in synchrony in BOLD signal amplitude and across space, Poudel and coworkers[44] have found several abnormal networks in both premanifest and manifest HD subjects. For example, they have reported a decreased resting state synchronization in the sensori-motor network of premanifest *HD* gene carriers, and interestingly, the level of synchrony was associated with motor performance as measured by speeded self-paced tapping[44]. Overall these findings show abnormal functional network connectivity in both premanifest and manifest HD, suggesting that resting state fMRI may be useful in measuring early neuronal dysfunction and for monitoring progression of the disease.

Neurovascular alterations have been also found in premanifest *HD* gene carriers. Cortical arteriolar cerebral blood volume (CBV_a) was significantly elevated in pre-

manifest *HD* gene carriers compared to normal controls and correlated with genetic measures such as the CAG-age product score and the estimated years to onset[47]. Metabolic brain changes may also occur in premanifest *HD* gene carriers and they may precede structural brain changes[48]. N-acetylaspartate (NAA) and glutamate levels were decreased in the posterior cingulate cortex of 12 premanifest *HD* gene carriers and they correlated with cognitive decline as measured with the Montreal Cognitive Assessment[47]. Neurovascular alterations and metabolic brain changes occurs before substantial brain atrophy suggesting that they may be used as potential biomarker for clinical and therapeutic future studies.

PET

Dopaminergic system

Altered dopamine signalling may play a key role in the pathogenesis of HD[49,50]. In particular, striatal MSNs expressing dopamine receptors are primarily affected in HD, whereas presynaptic dopaminergic nerve terminals are relatively spared[51]. PET studies in premanifest and manifest *HD* gene carriers have shown severe involvement of the postsynaptic dopaminergic system, whereas the dopaminergic nerve terminals seem to be less affected[52-55]. An ^{18}F-fluorodopa case-study did not demonstrate diminished striatal dopamine synthesis capacity suggesting an intact nigrostriatal pathway[52]. However, Ginovart and coworker[56], using PET with ^{11}C-b-CIT, have found a 50% decrease in striatal dopamine transporter (DAT) binding. In line with this finding, nigrostriatal density of the type-2 vesicular monoamine transporter (VMAT2) was found reduced in HD patients[57]. It still remains unclear whether degeneration of nigrostriatal dopaminergic neurons or presynaptic terminal dysfunction takes place in HD.

Investigations of postsynaptic dopaminergic systems, specifically the role of D1 and D2 receptors, which are highly expressed in MSNs, have shown reduced receptor densities and activity in the striatum of HD patients even at the early stage of the disease. The radioligand ^{11}C-SCH23390 is a selective antagonist of D1 receptors while ^{11}C-raclopride is a selective reversible antagonist of D2 receptors. Striatal D1-dopamine receptor density was found reduced by 75% in five HD patients with mild to moderate disease compared to a group of healthy controls[58]. Additionally, one premanifest *HD* gene carrier showed D1 binding in the lower range of the control subjects[58]. Turjanski and colleagues[55] have studied 10 non-neuroleptic treated patients with HD with either the choreic or the akinetic-rigid predominant phenotypes of the disease. They found severe parallel reduction of striatal D1 and D2 receptor binding with greater loss of mean striatal D1 and D2 binding in the akinetic-rigid patients than those choreic patients without rigidity[55]. However, there were no significant correlations between D1 and D2 striatal receptor binding and the duration of symptoms. Mean ^{11}C-SCH23390 and ^{11}C-raclopride binding was found to be reduced by 40% in the striatum of five patients with HD[56]. The degree of the decrease in D1 and D2 binding in the striatum was significantly associated with the duration of symptoms indicating that these two receptors may be reliable quantitative markers for monitoring disease progression[56]. Moreover, a reduction in D1 receptor binding was found also in the temporal cortex suggesting that dopaminergic abnormalities occur in cortical areas and may play a role in the development of cognitive dysfunction observed in HD[56]. Specifically, striatal D1 and D2 receptor density showed strong relationships with performance in several tasks assessing executive function, visuospatial ability, episodic memory, verbal fluency, perceptual speed and reasoning in a group of five HD patients[59]. Thus, cortico-striatal and/or thalamo-cortical circuity may be associated with cognitive impairment in HD[59]. A correlation between striatal D1 and D2 receptors binding, but mainly D2, and cognitive performance was found also in 17 premanifest *HD* gene carriers, in whom both striatal dopamine receptor levels and cognitive performance were lower in the subjects closer to the predicted disease onset[60]. Using ^{11}C-raclopride PET and statistical parametric mapping, Pavese and coworkers[61] have found a reduction in D2 receptor density in cortical regions of symptomatic HD patients, which were also evident in frontal and/or temporal regions in 55% of premanifest *HD* gene carriers[62], suggesting that changes in cortical D2 receptor availability might be an early event in HD pathophysiology. Van Oostrom and colleagues[63] have also reported a reduction in striatal D2 receptor availability in 50% of premanifest *HD* gene carriers and these reductions correlated with increases in cumulative disease load as measured by disease burden (CAG index).

Clinically manifested HD patients have been shown to have constant loss of D2 receptor availability at around 5% per year in striatal and extrastriatal regions including frontal and temporal cortex, though no correlation between changes in UHDRS motor scores and reductions in striatal binding were observed[61]. Longitudinal ^{11}C-raclopride PET studies in premanifest *HD* gene carriers have reported rates of decline from 4%[64] up to 6.3%[65]. Andrews and coworkers[64] investigated striatal dopamine D1 and D2 receptor binding over a follow-up period of 40 mo in nine premanifest *HD* gene carriers and four symptomatic HD patients. They reported a mean annual loss of D1 and D2 binding of 2% and 4% respectively in the group of premanifest *HD* gene carriers and a mean annual loss of D1 binding of 5% and D2 binding of 3% in symptomatic HD patients[64]. Additionally, UHDRS motor scores and TFC correlated with PET measures of striatal dopamine receptor in both groups. Interestingly, premanifest *HD* gene carriers who demonstrated active progression had an increased mean annual loss of D1 and D2 receptor binding (5% and 6.5% respectively). Thus, the authors conclude that PET measures of striatal D1 and D2 dopamine binding may be used to identify asymptomatic *HD* gene carriers who are actively

progressive[64]. A reduction in the striatal dopamine D2 binding, in particular in the putamen, correlates weakly with the increasing probability of symptomatic conversion within 5 years, as calculated by an age and CAG repeat based model[51]. Although, putaminal D2 binding correlated with predicted time to disease onset, the rate of change of D2 receptor changes were not increased around the onset of HD symptoms[51]. A cross-sectional study by Antonini and colleagues[66] indicated that striatal degeneration in HD patients might proceed in a non-linear fashion. They found a correlation between CAG repeat length and the estimated percentage loss of striatal D2 binding after age correction in premanifest *HD* gene carriers and symptomatic HD patients. While CAG repeat length influenced the rate of disease progression, the slopes of the correlation for asymptomatic mutation carriers and patients were significantly different, implying that the rate of disease progression is faster during the earlier asymptomatic stages of the disease[66]. These data suggest that striatal D2 measures are more sensitive in premanifest HD than later in the disease.

While the loss of striatal dopamine D2 receptors is well known, few studies have addressed the extrastriatal D2 receptor distribution in patients with HD. Statistical parametric mapping of ^{11}C-raclopride binding in patients with HD suggest a loss of cortical dopamine D2 receptors in symptomatic HD patients[61,62]. A significant reduction in postsynaptic dopamine D2 receptor binding was also found in the hypothalamus of nine premanifest HD patients and in 10 asymptomatic *HD* gene carriers[67]. These findings suggest that hypothalamic dysfunction occurs early during the course of the disease and may be responsible for the development of commonly reported nonmotor symptoms in HD including progressive weight loss, alterations in sexual behaviour and disturbances in the wake-sleep cycle[67].

Using PET with ^{11}C-FLB457, a radioligand with high affinity for dopamine D2 receptor, Esmaeilzadeh and coworkers[68] have investigated density of dopamine D2 receptors in extrastriatal brain regions in patients with mild to moderate HD. They found that unlike from striatum, D2 receptors seem to be relatively spared in the brain extrastriatal regions in HD patients suggesting that D2 receptor binding in brain regions outside the striatum may not be a reliable biomarker in HD[68].

Moreover, PET with D1 and D2 receptor radioligands has been used to assess the efficacy of restorative therapy. In 1998, a multicentre open label pilot study was designed to evaluate the safety and efficacy of bilateral fetal striatal transplantation in HD[69]. Five HD patients were transplanted and followed up clinically and with PET over a 3-10 year postoperative period[70,71]. No significant differences were found over time between patients, grafted and non-grafted on the UHDRS and striatal D1 and D2 binding suggesting that there was no obvious surviving striatal graft tissue[70,71].

Brain activation and metabolism

Measurements of cerebral blood flow and glucose metabolism could serve as an index of neuronal integrity and functional state of the synapse[72,73]. Striatal glucose hypometabolism and regional reductions in cortical glucose have been identified in HD patients and have been found to correlate with motor and cognitive symptoms[65,74,75]. Specifically, decreases of caudate and regional cortical metabolism correlated with cognitive decline[75,76], whereas striatal hypometabolism was associated with motor deficits and reduced TFC[77]. Striatal and cortical hypometabolism has been also found in premanifest *HD* gene carriers to precede neuronal loss[78-80]. A recent ^{18}F-FDG PET study has shown that premanifest *HD* gene carriers who became symptomatic after five years from the PET scan had a mean glucose uptake in the caudate significantly lower than those who did not convert, and this difference was independent of mutation size[80]. These findings suggest that reduced glucose levels may be contribute to the time of HD onset. In a combined ^{18}F-FDG and ^{11}C-raclopride longitudinal study, premanifest *HD* gene carriers showed an annual loss of 2.3% in striatal glucose metabolism and 6.3% annual decline in D2 receptor binding[65]. These findings suggest that glucose metabolism is a less sensitive marker of disease progression compared to ^{11}C-raclopride[65]. On the other hand, decreased cortical metabolism in the early stage of HD is indicative of rapid progression[81]. Indeed, cortical metabolism in the frontotemporal and parietal cortices was significantly lower in early HD subjects with faster progression of the disease as measured with the UHDRS and Independence Scale[81].

PET with $H_2{}^{15}O$ has been used to investigate changes of motor-associated cortical activation in HD[82,83]. During motor tasks such as paced joystick movements or sequential finger-to thumb opposition, HD patients showed impaired activation of the striatum and its frontal motor projection areas[82,83] along with enhanced activity of the parietal areas[82] and insular areas[83]. These findings suggest that the loss of MSNs in the striatum leads to impairment of the basal ganglia-thalamo-cortical motor output and may induce a compensatory recruitment of additional accessory motor pathways[82,83]. Moreover, different patterns of brain activation have been showed in HD patients during word generation task[84]. HD patients showed decreased cerebral blood flows in the anterior cingulate and the inferior frontal gyri, which are important in lexical selection and a compensatory activation of the left supramarginal gyrus and the right inferior frontal gyrus, suggesting that compensatory language strategies are present in HD[84].

^{18}F-FDG PET imaging and network approaches have been used to identify spatial covariance patterns in premanifest HD[85-87]. A cross-sectional analysis of metabolic changes from premanifest *HD* gene carriers and healthy controls, has reported a reproducible disease related pattern, characterized by relative bilateral increases in thalamic, occipital, and cerebellar glucose metabolism associated with bilateral decreases in striatal metabolism, which discriminated between the HD and healthy control groups[86]. However, this pattern in *HD* gene carriers

did not show consistent changes over time, thus limiting its utility as a network biomarker of preclinical disease progression[86]. Recently, Tang and coworkers[87] demonstrated the feasibility of network-based approach by using longitudinal metabolic imaging data from premanifest HD carriers to identify and a distinct spatial covariance pattern associated with disease progression. Changes in pattern expression over a seven years period were used to quantify the rate of progression in the preclinical period[87]. They found a significant spatial covariance pattern characterized by progressive changes in striato-thalamic and cortical metabolic activity which increased linearly over 7 years and was not influenced by symptomatic conversion[87]. Additionally, premanifest *HD* gene carriers which showed further increases in metabolic network activity at baseline (> 2 SD above the normal mean) had a greater risk of symptomatic conversion in the following 5-year period[87]. These findings suggest that metabolic network measurements may provide a sensitive tool for evaluating disease progression prior to clinical diagnosis.

Measures of glucose brain metabolism have been used to assess the restoration of striato-cortical function in five HD patients who underwent bilateral striatal transplantation[88,89]. In 2-year follow-up of these five patients, Gaura and colleagues[89] reported that the three patients, who showed clinical improvement or stabilization, had increased in striatal/cortical glucose metabolic rate, which is suggestive of restoration of function of striatal-cortical connections. Conversely, findings from NEST-UK multicentre study failed to show significant change in ^{18}F-FDG uptake over 2 years of follow-up[70]. Thus, the ability of bilateral striatal transplantation to restore striato-cortical pathways remains to be elucidated.

Neuroinflammation and activated microglia

Recent evidence suggests that microglial activation plays a role in the pathogenesis of HD[90,91]. Microglia constitute about 10% of the total brain cell population, and represent the main immunocompetent phagocytic cells in the central nervous system[92]. Although microglial activation is unlikely to initiate neuronal death, it could contribute to the neurodegenerative processes[93,94]. Indeed, upon exposure to neuronal insults such the presence of abnormal huntingtin protein aggregations, microglia become activated and release pro-inflammatory cytokines (*e.g.*, TNF-α and IL-1β). These cytokines in turn cause further activation of microglia, resulting in a self-propagating inflammatory cascade, which may lead to neuronal death. Microglial activation upregulates the expression of the 18 kDa translocator protein (TSPO) which is involved in the release of proinflammatory cytokines during inflammation and is present at very low levels in the normal healthy CNS[95,96]. The upregulation of TSPO expression can be detected *in vivo* with PET and selective radioligands such as ^{11}C-PK11195[97,98]. Using PET with ^{11}C-PK11195, Pavese and coworkers[99] have found significant microglial activation in the striatum and cortical regions of symptomatic HD patients, and reported that striatal PK binding correlates with loss of striatal dopamine D2 binding as measured with ^{11}C-raclopride PET. Additionally, striatal ^{11}C-PK11195 binding correlated with clinical severity as measured with the UHDRS[99]. In premanifest *HD* gene carriers ^{11}C-PK11195 binding was found to be also increased in striatum and cortical regions compared to a group of normal controls, and higher striatal ^{11}C-PK11195 binding correlated with lower striatal D2 binding[100]. These findings suggest that early and widespread microglial activation occurs in premanifest *HD* gene carriers and it is associated with subclinical striatal neuronal loss of dopamine D2 receptor binding, indicating a potential role of activated microglia in HD pathogenesis.

A more recent multimodal imaging study using MRI, ^{11}C-PK11195 and ^{11}C-raclopride PET, has showed increased levels of activated microglia in several brain areas across *HD* gene carriers who were either premanifest or manifested patients[101]. Of particular interest, high levels of activated microglia were observed in the associative part of the striatum, which is involved in cognitive function. High levels of microglial activation in the associative striatum and in the brain regions related to cognitive function correlated with a higher probability of symptomatic HD onset over the next 5 years in the group of premanifest *HD* gene carriers[101]. These findings highlighted the role of immune response in the pathophysiology and clinical expression of HD.

Cannabinoid system

Dysregulation of the endocannabinoid system may play a critical role in the pathogenesis of HD. The type 1 cannabinoid receptors (CB1R) are expressed in the basal ganglia, mainly in the GABA-ergic striatal MSNs expressing D1 and D2 receptors and are a key modulator of synaptic transmission in the brain[102-104]. Evidences from animal models of HD and postmortem tissue of HD brain have shown that decreased levels of CB1R and CB1 messenger RNA[105-107]. Recently, in vivo imaging of CB1R has become feasible using PET with ^{18}FMK-9470[108] and ^{11}C-MePPEP[109,110]. Using PET with ^{18}FMK-9470, Van Laere and coworkers[111] have investigated the levels of CB1R in the brain of 20 symptomatic HD patients. They found decreased CB1R availability throughout the grey matter of the cerebrum, cerebellum, and brain stem in HD patients. Further studies of CB1R system in premanifest *HD* gene carriers are expected in order to further understand the role of this system in the pathophysiology of HD.

CONCLUSION

Currently, there are no therapies able to slow down progression in HD and symptomatic treatments such as acetylcholinesterase inhibitors have provided limited evidence of their efficacy in HD[112]. Identification of reliable biomarkers of HD progression will be important for the development and evaluation of disease-modifying treatments. Neuroimaging techniques may be a suitable biomarker for monitoring disease progression in HD

and for assessing the efficacy of future disease modifying therapies. Although MRI techniques have shown to be useful for monitoring disease progression, PET imaging is able to detect changes and specific targets early in pre-manifest HD stages. However, at this stage an integrative multimodal imaging approach, which combines different MRI and PET techniques, could be recommended.

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