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## Neuroimaging in huntington's disease

 NiccoliniF *et al*. Neuroimaging in HD

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**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.

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**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.

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**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 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 powerful 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 scales (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 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 white-matter 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 componenet 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 (CBVa) was significantly elevated in premanifest *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 medium spiny neurons (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 18F-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 11C-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 11C-SCH23390 is a selective antagonist of D1 receptorswhile 11C-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 the symptoms. Mean 11C-SCH23390 and 11C-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 11C-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 11C-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 11C-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 11C-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 18F-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 18F-FDG and 11C-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 11C-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 H215O 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].

18F-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[89]. 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 18F-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-a and IL-1b). 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 11C-PK11195[97,98]. Using PET with 11C-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 11C-raclopride PET. Additionally, striatal 11C-PK11195 binding correlated with clinical severity as measured with the UHDRS[99]. In premanifest *HD* gene carriers 11C-PK11195 binding was found to be also increased in striatum and cortical regions compared to a group of normal controls, and higher striatal 11C-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, 11C-PK11195 and 11C-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 18FMK-9470[108] and 11C-MePPEP[109,110]. Using PET with 18FMK-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 premanifest HD stages. However, at this stage an integrative multimodal imaging approach, which combines different MRI and PET techniques, could be recommended.

**References**

1 **The Huntington’s Disease Collaborative Research Group**. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* 1993; **72**: 971-983 [PMID: 8458085 DOI: 10.1016/0092-8674(93)90585-E]

2 **Pringsheim T**, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. *Mov Disord* 2012; **27**: 1083-1091 [PMID: 22692795 DOI: 10.1002/mds.25075]

3 **Djoussé L**, Knowlton B, Hayden M, Almqvist EW, Brinkman R, Ross C, Margolis R, Rosenblatt A, Durr A, Dode C, Morrison PJ, Novelletto A, Frontali M, Trent RJ, McCusker E, Gómez-Tortosa E, Mayo D, Jones R, Zanko A, Nance M, Abramson R, Suchowersky O, Paulsen J, Harrison M, Yang Q, Cupples LA, Gusella JF, MacDonald ME, Myers RH. Interaction of normal and expanded CAG repeat sizes influences age at onset of Huntington disease. *Am J Med Genet A* 2003; **119A**: 279-282 [PMID: 12784292 DOI: 10.1002/ajmg.a.20190]

4 **Paulsen JS**, Langbehn DR, Stout JC, Aylward E, Ross CA, Nance M, Guttman M, Johnson S, MacDonald M, Beglinger LJ, Duff K, Kayson E, Biglan K, Shoulson I, Oakes D, Hayden M. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. *J Neurol Neurosurg Psychiatry* 2008; **79**: 874-880 [PMID: 18096682 DOI: 10.1136/jnnp.2007.128728]

5 **Duff K**, Paulsen J, Mills J, Beglinger LJ, Moser DJ, Smith MM, Langbehn D, Stout J, Queller S, Harrington DL. Mild cognitive impairment in prediagnosed Huntington disease. *Neurology* 2010; **75**: 500-507 [PMID: 20610833 DOI: 10.1212/WNL.0b013e3181eccfa2]

6 **Davies SW**, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE, Mangiarini L, Bates GP. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* 1997; **90**: 537-548 [PMID: 9267033 DOI: 10.1016/S0092-8674(00)80513-9]

7 **Li SH**, Cheng AL, Zhou H, Lam S, Rao M, Li H, Li XJ. Interaction of Huntington disease protein with transcriptional activator Sp1. *Mol Cell Biol* 2002; **22**: 1277-1287 [PMID: 11839795 DOI: 10.1128/MCB.22.5.1277-1287.2002]

8 **Browne SE**, Beal MF. Oxidative damage in Huntington's disease pathogenesis. *Antioxid Redox Signal* 2006; **8**: 2061-2073 [PMID: 17034350 DOI: 10.1089/ars.2006.8.2061]

9 **Politis M**, Piccini P. Positron emission tomography imaging in neurological disorders. *J Neurol* 2012; **259**: 1769-1780 [PMID: 22297461 DOI: 10.1007/s00415-012-6428-3]

10 **Phelps ME**. Positron emission tomography provides molecular imaging of biological processes. *Proc Natl Acad Sci USA* 2000; **97**: 9226-9233 [PMID: 10922074 DOI: 10.1073/pnas.97.16.9226]

11 **Harris GJ**, Pearlson GD, Peyser CE, Aylward EH, Roberts J, Barta PE, Chase GA, Folstein SE. Putamen volume reduction on magnetic resonance imaging exceeds caudate changes in mild Huntington's disease. *Ann Neurol* 1992; **31**: 69-75 [PMID: 1531910 DOI: 10.1002/ana.410310113]

12 **Harris GJ**, Aylward EH, Peyser CE, Pearlson GD, Brandt J, Roberts-Twillie JV, Barta PE, Folstein SE. Single photon emission computed tomographic blood flow and magnetic resonance volume imaging of basal ganglia in Huntington's disease. *Arch Neurol* 1996; **53**: 316-324 [PMID: 8929153 DOI: 10.1001/archneur.1996.00550040044013]

13 **Aylward EH**, Codori AM, Barta PE, Pearlson GD, Harris GJ, Brandt J. Basal ganglia volume and proximity to onset in presymptomatic Huntington disease. *Arch Neurol* 1996; **53**: 1293-1296 [PMID: 8970459 DOI: 10.1001/archneur.1996.00550120105023]

14 **Rosas HD**, Goodman J, Chen YI, Jenkins BG, Kennedy DN, Makris N, Patti M, Seidman LJ, Beal MF, Koroshetz WJ. Striatal volume loss in HD as measured by MRI and the influence of CAG repeat. *Neurology* 2001; **57**: 1025-1028 [PMID: 11571328 DOI: 10.1212/WNL.57.6.1025]

15 **Rosas HD**, Koroshetz WJ, Chen YI, Skeuse C, Vangel M, Cudkowicz ME, Caplan K, Marek K, Seidman LJ, Makris N, Jenkins BG, Goldstein JM. Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. *Neurology* 2003; **60**: 1615-1620 [PMID: 12771251 DOI: 10.1212/01.WNL.0000065888.88988.6E]

16 **Paulsen JS**, Hayden M, Stout JC, Langbehn DR, Aylward E, Ross CA, Guttman M, Nance M, Kieburtz K, Oakes D, Shoulson I, Kayson E, Johnson S, Penziner E. Preparing for preventive clinical trials: the Predict-HD study. *Arch Neurol* 2006; **63**: 883-890 [PMID: 16769871 DOI: 10.1001/archneur.63.6.883]

17 **Tabrizi SJ**, Langbehn DR, Leavitt BR, Roos RA, Durr A, Craufurd D, Kennard C, Hicks SL, Fox NC, Scahill RI, Borowsky B, Tobin AJ, Rosas HD, Johnson H, Reilmann R, Landwehrmeyer B, Stout JC. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol* 2009; **8**: 791-801 [PMID: 19646924 DOI: 10.1016/S1474-4422(09)70170-X]

18 **Tabrizi SJ**, Scahill RI, Durr A, Roos RA, Leavitt BR, Jones R, Landwehrmeyer GB, Fox NC, Johnson H, Hicks SL, Kennard C, Craufurd D, Frost C, Langbehn DR, Reilmann R, Stout JC. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol* 2011; **10**: 31-42 [PMID: 21130037 DOI: 10.1016/S1474-4422(10)70276-3]

19 **Tabrizi SJ**, Reilmann R, Roos RA, Durr A, Leavitt B, Owen G, Jones R, Johnson H, Craufurd D, Hicks SL, Kennard C, Landwehrmeyer B, Stout JC, Borowsky B, Scahill RI, Frost C, Langbehn DR. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurol* 2012; **11**: 42-53 [PMID: 22137354 DOI: 10.1016/S1474-4422(11)70263-0]

20 **Tabrizi SJ**, Scahill RI, Owen G, Durr A, Leavitt BR, Roos RA, Borowsky B, Landwehrmeyer B, Frost C, Johnson H, Craufurd D, Reilmann R, Stout JC, Langbehn DR. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013; **12**: 637-649 [PMID: 23664844]

21 **Aylward EH**, Li Q, Stine OC, Ranen N, Sherr M, Barta PE, Bylsma FW, Pearlson GD, Ross CA. Longitudinal change in basal ganglia volume in patients with Huntington's disease. *Neurology* 1997; **48**: 394-399 [PMID: 9040728 DOI: 10.1212/WNL.48.2.394]

22 **Rosas HD**, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 2002; **58**: 695-701 [PMID: 11889230 DOI: 10.1212/WNL.58.5.695]

23 **Rosas HD**, Salat DH, Lee SY, Zaleta AK, Pappu V, Fischl B, Greve D, Hevelone N, Hersch SM. Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity. *Brain* 2008; **131**: 1057-1068 [PMID: 18337273 DOI: 10.1093/brain/awn025]

24 **Hobbs NZ**, Henley SM, Ridgway GR, Wild EJ, Barker RA, Scahill RI, Barnes J, Fox NC, Tabrizi SJ. The progression of regional atrophy in premanifest and early Huntington's disease: a longitudinal voxel-based morphometry study. *J Neurol Neurosurg Psychiatry* 2010; **81**: 756-763 [PMID: 19955112 DOI: 10.1136/jnnp.2009.190702]

25 **Paulsen JS**, Nopoulos PC, Aylward E, Ross CA, Johnson H, Magnotta VA, Juhl A, Pierson RK, Mills J, Langbehn D, Nance M. Striatal and white matter predictors of estimated diagnosis for Huntington disease. *Brain Res Bull* 2010; **82**: 201-207 [PMID: 20385209 DOI: 10.1016/j.brainresbull.2010.04.003]

26 **Reading SA**, Yassa MA, Bakker A, Dziorny AC, Gourley LM, Yallapragada V, Rosenblatt A, Margolis RL, Aylward EH, Brandt J, Mori S, van Zijl P, Bassett SS, Ross CA. Regional white matter change in pre-symptomatic Huntington's disease: a diffusion tensor imaging study. *Psychiatry Res* 2005; **140**: 55-62 [PMID: 16199141 DOI: 10.1016/j.pscychresns.2005.05.011]

27 **Rosas HD**, Tuch DS, Hevelone ND, Zaleta AK, Vangel M, Hersch SM, Salat DH. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. *Mov Disord* 2006; **21**: 1317-1325 [PMID: 16755582 DOI: 10.1002/mds.20979]

28 **Dumas EM**, van den Bogaard SJ, Ruber ME, Reilman RR, Stout JC, Craufurd D, Hicks SL, Kennard C, Tabrizi SJ, van Buchem MA, van der Grond J, Roos RA. Early changes in white matter pathways of the sensorimotor cortex in premanifest Huntington's disease. *Hum Brain Mapp* 2012; **33**: 203-212 [PMID: 21264990 DOI: 10.1002/hbm.21205]

29 **Dierks T**, Linden DE, Hertel A, Günther T, Lanfermann H, Niesen A, Frölich L, Zanella FE, Hör G, Goebel R, Maurer K. Multimodal imaging of residual function and compensatory resource allocation in cortical atrophy: a case study of parietal lobe function in a patient with Huntington's disease. *Psychiatry Res* 1998; **84**: 27-35 [PMID: 9870415 DOI: 10.1016/S0925-4927(98)00040-7]

30 **Clark VP**, Lai S, Deckel AW. Altered functional MRI responses in Huntington's disease. *Neuroreport* 2002; **13**: 703-706 [PMID: 11973474 DOI: 10.1097/00001756-200204160-00033]

31 **Kim JS**, Reading SA, Brashers-Krug T, Calhoun VD, Ross CA, Pearlson GD. Functional MRI study of a serial reaction time task in Huntington's disease. *Psychiatry Res* 2004; **131**: 23-30 [PMID: 15246452 DOI: 10.1016/j.pscychresns.2004.03.002]

32 **Georgiou-Karistianis N**, Sritharan A, Farrow M, Cunnington R, Stout J, Bradshaw J, Churchyard A, Brawn TL, Chua P, Chiu E, Thiruvady D, Egan G. Increased cortical recruitment in Huntington's disease using a Simon task. *Neuropsychologia* 2007; **45**: 1791-1800 [PMID: 17321554 DOI: 10.1016/j.neuropsychologia.2006.12.023]

33 **Georgiou-Karistianis N**, Stout JC, Domínguez D JF, Carron SP, Ando A, Churchyard A, Chua P, Bohanna I, Dymowski AR, Poudel G, Egan GF. Functional magnetic resonance imaging of working memory in Huntington's disease: Cross-sectional data from the IMAGE-HD study. *Hum Brain Mapp* 2014; **35**: 1847-1864 [PMID: 23913754 DOI: 10.1002/hbm.22296]

34 **Thiruvady DR**, Georgiou-Karistianis N, Egan GF, Ray S, Sritharan A, Farrow M, Churchyard A, Chua P, Bradshaw JL, Brawn TL, Cunnington R. Functional connectivity of the prefrontal cortex in Huntington's disease. *J Neurol Neurosurg Psychiatry* 2007; **78**: 127-133 [PMID: 17028117 DOI: 10.1136/jnnp.2006.098368]

35 **Paulsen JS**, Zimbelman JL, Hinton SC, Langbehn DR, Leveroni CL, Benjamin ML, Reynolds NC, Rao SM. fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's Disease. *AJNR Am J Neuroradiol* 2004; **25**: 1715-1721 [PMID: 15569736]

36 **Reading SA**, Dziorny AC, Peroutka LA, Schreiber M, Gourley LM, Yallapragada V, Rosenblatt A, Margolis RL, Pekar JJ, Pearlson GD, Aylward E, Brandt J, Bassett SS, Ross CA. Functional brain changes in presymptomatic Huntington's disease. *Ann Neurol* 2004; **55**: 879-883 [PMID: 15174024 DOI: 10.1002/ana.20121]

37 **Wolf RC**, Vasic N, Schönfeldt-Lecuona C, Landwehrmeyer GB, Ecker D. Dorsolateral prefrontal cortex dysfunction in presymptomatic Huntington's disease: evidence from event-related fMRI. *Brain* 2007; **130**: 2845-2857 [PMID: 17855375 DOI: 10.1093/brain/awm210]

38 **Wolf RC**, Sambataro F, Vasic N, Schönfeldt-Lecuona C, Ecker D, Landwehrmeyer B. Aberrant connectivity of lateral prefrontal networks in presymptomatic Huntington's disease. *Exp Neurol* 2008; **213**: 137-144 [PMID: 18588876 DOI: 10.1016/j.expneurol.2008.05.017]

39 **Unschuld PG**, Joel SE, Pekar JJ, Reading SA, Oishi K, McEntee J, Shanahan M, Bakker A, Margolis RL, Bassett SS, Rosenblatt A, Mori S, van Zijl PC, Ross CA, Redgrave GW. Depressive symptoms in prodromal Huntington's Disease correlate with Stroop-interference related functional connectivity in the ventromedial prefrontal cortex. *Psychiatry Res* 2012; **203**: 166-174 [PMID: 22974690 DOI: 10.1016/j.pscychresns.2012.01.002]

40 **Unschuld PG**, Liu X, Shanahan M, Margolis RL, Bassett SS, Brandt J, Schretlen DJ, Redgrave GW, Hua J, Hock C, Reading SA, van Zijl PC, Pekar JJ, Ross CA. Prefrontal executive function associated coupling relates to Huntington's disease stage. *Cortex* 2013; **49**: 2661-2673 [PMID: 23906595 DOI: 10.1016/j.cortex.2013.05.015]

41 **Fox MD**, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 2007; **8**: 700-711 [PMID: 17704812 DOI: 10.1038/nrn2201]

42 **Greicius M**. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol* 2008; **21**: 424-430 [PMID: 18607202 DOI: 10.1097/WCO.0b013e328306f2c5]

43 **Dumas EM**, van den Bogaard SJ, Hart EP, Soeter RP, van Buchem MA, van der Grond J, Rombouts SA, Roos RA. Reduced functional brain connectivity prior to and after disease onset in Huntington's disease. *Neuroimage Clin* 2013; **2**: 377-384 [PMID: 24179791 DOI: 10.1016/j.nicl.2013.03.001]

44 **Poudel GR**, Egan GF, Churchyard A, Chua P, Stout JC, Georgiou-Karistianis N. Abnormal synchrony of resting state networks in premanifest and symptomatic Huntington disease: the IMAGE-HD study. *J Psychiatry Neurosci* 2014; **39**: 87-96 [PMID: 24083458 DOI: 10.1503/jpn.120226]

45 **Werner CJ**, Dogan I, Saß C, Mirzazade S, Schiefer J, Shah NJ, Schulz JB, Reetz K. Altered resting-state connectivity in Huntington's Disease. *Hum Brain Mapp* 2013; Epub ahead of print [PMID: 23982979 DOI: 10.1002/hbm.22351]

46 **Unschuld PG**, Joel SE, Liu X, Shanahan M, Margolis RL, Biglan KM, Bassett SS, Schretlen DJ, Redgrave GW, van Zijl PC, Pekar JJ, Ross CA. Impaired cortico-striatal functional connectivity in prodromal Huntington's Disease. *Neurosci Lett* 2012; **514**: 204-209 [PMID: 22425717 DOI: 10.1016/j.neulet.2012.02.095]

47 **Hua J**, Unschuld PG, Margolis RL, van Zijl PC, Ross CA. Elevated arteriolar cerebral blood volume in prodromal Huntington's disease. *Mov Disord* 2014; **29** Suppl 3: 396-401 [PMID: 23847161 DOI: 10.1002/mds.25591]

48 **Unschuld PG**, Edden RA, Carass A, Liu X, Shanahan M, Wang X, Oishi K, Brandt J, Bassett SS, Redgrave GW, Margolis RL, van Zijl PC, Barker PB, Ross CA. Brain metabolite alterations and cognitive dysfunction in early Huntington's disease. *Mov Disord* 2012; **27**: 895-902 [PMID: 22649062 DOI: 10.1002/mds.25010]

49 **Tang TS**, Chen X, Liu J, Bezprozvanny I. Dopaminergic signaling and striatal neurodegeneration in Huntington's disease. *J Neurosci* 2007; **27**: 7899-7910 [PMID: 17652581 DOI: 10.1523/JNEUROSCI.1396-07.2007]

50 **van Oostrom JC**, Dekker M, Willemsen AT, de Jong BM, Roos RA, Leenders KL. Changes in striatal dopamine D2 receptor binding in pre-clinical Huntington's disease. *Eur J Neurol* 2009; **16**: 226-231 [PMID: 19138335 DOI: 10.1111/j.1468-1331.2008.02390.x]

51 **Reiner A**, Albin RL, Anderson KD, D'Amato CJ, Penney JB, Young AB. Differential loss of striatal projection neurons in Huntington disease. *Proc Natl Acad Sci USA* 1988; **85**: 5733-5737 [PMID: 2456581 DOI: 10.1073/pnas.85.15.5733]

52 **Leenders KL**, Frackowiak RS, Quinn N, Marsden CD. Brain energy metabolism and dopaminergic function in Huntington's disease measured in vivo using positron emission tomography. *Mov Disord* 1986; **1**: 69-77 [PMID: 2973559 DOI: 10.1002/mds.870010110]

53 **Hägglund J**, Aquilonius SM, Eckernäs SA, Hartvig P, Lundquist H, Gullberg P, Långström B. Dopamine receptor properties in Parkinson's disease and Huntington's chorea evaluated by positron emission tomography using 11C-N-methyl-spiperone. *Acta Neurol Scand* 1987; **75**: 87-94 [PMID: 2953165 DOI: 10.1111/j.1600-0404.1987.tb07900.x]

54 **Brandt J**, Folstein SE, Wong DF, Links J, Dannals RF, McDonnell-Sill A, Starkstein S, Anders P, Strauss ME, Tune LE. D2 receptors in Huntington's disease: positron emission tomography findings and clinical correlates. *J Neuropsychiatry Clin Neurosci* 1990; **2**: 20-27 [PMID: 1983772]

55 **Turjanski N**, Weeks R, Dolan R, Harding AE, Brooks DJ. Striatal D1 and D2 receptor binding in patients with Huntington's disease and other choreas. A PET study. *Brain* 1995; **118** (Pt 3): 689-696 [PMID: 7600086 DOI: 10.1093/brain/118.3.689]

56 **Ginovart N**, Lundin A, Farde L, Halldin C, Bäckman L, Swahn CG, Pauli S, Sedvall G. PET study of the pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease. *Brain* 1997; **120** (Pt 3): 503-514 [PMID: 9126061 DOI: 10.1093/brain/120.3.503]

57 **Bohnen NI**, Koeppe RA, Meyer P, Ficaro E, Wernette K, Kilbourn MR, Kuhl DE, Frey KA, Albin RL. Decreased striatal monoaminergic terminals in Huntington disease. *Neurology* 2000; **54**: 1753-1759 [PMID: 10802780 DOI: 10.1212/WNL.54.9.1753]

58 **Sedvall G**, Karlsson P, Lundin A, Anvret M, Suhara T, Halldin C, Farde L. Dopamine D1 receptor number--a sensitive PET marker for early brain degeneration in Huntington's disease. *Eur Arch Psychiatry Clin Neurosci* 1994; **243**: 249-255 [PMID: 8172940 DOI: 10.1007/BF02191583]

59 **Bäckman L**, Robins-Wahlin TB, Lundin A, Ginovart N, Farde L. Cognitive deficits in Huntington's disease are predicted by dopaminergic PET markers and brain volumes. *Brain* 1997; **120** (Pt 12): 2207-2217 [PMID: 9448576 DOI: 10.1093/brain/120.12.2207]

60 **Lawrence AD**, Weeks RA, Brooks DJ, Andrews TC, Watkins LH, Harding AE, Robbins TW, Sahakian BJ. The relationship between striatal dopamine receptor binding and cognitive performance in Huntington's disease. *Brain* 1998; **121** (Pt 7): 1343-1355 [PMID: 9679785 DOI: 10.1093/brain/121.7.1343]

61 **Pavese N**, Andrews TC, Brooks DJ, Ho AK, Rosser AE, Barker RA, Robbins TW, Sahakian BJ, Dunnett SB, Piccini P. Progressive striatal and cortical dopamine receptor dysfunction in Huntington's disease: a PET study. *Brain* 2003; **126**: 1127-1135 [PMID: 12690052 DOI: 10.1093/brain/awg119]

62 **Pavese N**, Politis M, Tai YF, Barker RA, Tabrizi SJ, Mason SL, Brooks DJ, Piccini P. Cortical dopamine dysfunction in symptomatic and premanifest Huntington's disease gene carriers. *Neurobiol Dis* 2010; **37**: 356-361 [PMID: 19853661 DOI: 10.1016/j.nbd.2009.10.015]

63 **van Oostrom JC**, Maguire RP, Verschuuren-Bemelmans CC, Veenma-van der Duin L, Pruim J, Roos RA, Leenders KL. Striatal dopamine D2 receptors, metabolism, and volume in preclinical Huntington disease. *Neurology* 2005; **65**: 941-943 [PMID: 16186542 DOI: 10.1212/01.wnl.0000176071.08694.cc]

64 **Andrews TC**, Weeks RA, Turjanski N, Gunn RN, Watkins LH, Sahakian B, Hodges JR, Rosser AE, Wood NW, Brooks DJ. Huntington's disease progression. PET and clinical observations. *Brain* 1999; **122** (Pt 12): 2353-2363 [PMID: 10581228 DOI: 10.1093/brain/122.12.2353]

65 **Antonini A**, Leenders KL, Spiegel R, Meier D, Vontobel P, Weigell-Weber M, Sanchez-Pernaute R, de Yébenez JG, Boesiger P, Weindl A, Maguire RP. Striatal glucose metabolism and dopamine D2 receptor binding in asymptomatic gene carriers and patients with Huntington's disease. *Brain* 1996; **119** (Pt 6): 2085-2095 [PMID: 9010012 DOI: 10.1093/brain/119.6.2085]

66 **Antonini A**, Leenders KL, Eidelberg D. [11C]raclopride-PET studies of the Huntington's disease rate of progression: relevance of the trinucleotide repeat length. *Ann Neurol* 1998; **43**: 253-255 [PMID: 9485067 DOI: 10.1002/ana.410430216]

67 **Politis M**, Pavese N, Tai YF, Tabrizi SJ, Barker RA, Piccini P. Hypothalamic involvement in Huntington's disease: an in vivo PET study. *Brain* 2008; **131**: 2860-2869 [PMID: 18829696 DOI: 10.1093/brain/awn244]

68 **Esmaeilzadeh M**, Farde L, Karlsson P, Varrone A, Halldin C, Waters S, Tedroff J. Extrastriatal dopamine D(2) receptor binding in Huntington's disease. *Hum Brain Mapp* 2011; **32**: 1626-1636 [PMID: 20886576 DOI: 10.1002/hbm.21134]

69 **Rosser AE**, Barker RA, Harrower T, Watts C, Farrington M, Ho AK, Burnstein RM, Menon DK, Gillard JH, Pickard J, Dunnett SB. Unilateral transplantation of human primary fetal tissue in four patients with Huntington's disease: NEST-UK safety report ISRCTN no 36485475. *J Neurol Neurosurg Psychiatry* 2002; **73**: 678-685 [PMID: 12438470 DOI: 10.1136/jnnp.73.6.678]

70 **Furtado S**, Sossi V, Hauser RA, Samii A, Schulzer M, Murphy CB, Freeman TB, Stoessl AJ. Positron emission tomography after fetal transplantation in Huntington's disease. *Ann Neurol* 2005; **58**: 331-337 [PMID: 16049929 DOI: 10.1002/ana.20564]

71 **Barker RA**, Mason SL, Harrower TP, Swain RA, Ho AK, Sahakian BJ, Mathur R, Elneil S, Thornton S, Hurrelbrink C, Armstrong RJ, Tyers P, Smith E, Carpenter A, Piccini P, Tai YF, Brooks DJ, Pavese N, Watts C, Pickard JD, Rosser AE, Dunnett SB. The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. *J Neurol Neurosurg Psychiatry* 2013; **84**: 657-665 [PMID: 23345280 DOI: 10.1136/jnnp-2012-302441]

72 **Sokoloff L**. Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose. *J Cereb Blood Flow Metab* 1981; **1**: 7-36 [PMID: 7035471 DOI: 10.1038/jcbfm.1981.4]

73 **Sokoloff L**. Energetics of functional activation in neural tissues. *Neurochem Res* 1999; **24**: 321-329 [PMID: 9972882 DOI: 10.1023/A: 1022534709672]

74 **Mazziotta JC**, Phelps ME, Pahl JJ, Huang SC, Baxter LR, Riege WH, Hoffman JM, Kuhl DE, Lanto AB, Wapenski JA. Reduced cerebral glucose metabolism in asymptomatic subjects at risk for Huntington's disease. *N Engl J Med* 1987; **316**: 357-362 [PMID: 2949152 DOI: 10.1056/NEJM198702123160701]

75 **Kuwert T**, Lange HW, Langen KJ, Herzog H, Aulich A, Feinendegen LE. Cortical and subcortical glucose consumption measured by PET in patients with Huntington's disease. *Brain* 1990; **113** (Pt 5): 1405-1423 [PMID: 2147116 DOI: 10.1093/brain/113.5.1405]

76 **Berent S**, Giordani B, Lehtinen S, Markel D, Penney JB, Buchtel HA, Starosta-Rubinstein S, Hichwa R, Young AB. Positron emission tomographic scan investigations of Huntington's disease: cerebral metabolic correlates of cognitive function. *Ann Neurol* 1988; **23**: 541-546 [PMID: 2970247 DOI: 10.1002/ana.410230603]

77 **Young AB**, Penney JB, Starosta-Rubinstein S, Markel DS, Berent S, Giordani B, Ehrenkaufer R, Jewett D, Hichwa R. PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline. *Ann Neurol* 1986; **20**: 296-303 [PMID: 2945510 DOI: 10.1002/ana.410200305]

78 **Hayden MR**, Martin WR, Stoessl AJ, Clark C, Hollenberg S, Adam MJ, Ammann W, Harrop R, Rogers J, Ruth T. Positron emission tomography in the early diagnosis of Huntington's disease. *Neurology* 1986; **36**: 888-894 [PMID: 2940474 DOI: 10.1212/WNL.36.7.888]

79 **Ciarmiello A**, Cannella M, Lastoria S, Simonelli M, Frati L, Rubinsztein DC, Squitieri F. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *J Nucl Med* 2006; **47**: 215-222 [PMID: 16455626]

80 **Ciarmiello A**, Giovacchini G, Orobello S, Bruselli L, Elifani F, Squitieri F. 18F-FDG PET uptake in the pre-Huntington disease caudate affects the time-to-onset independently of CAG expansion size. *Eur J Nucl Med Mol Imaging* 2012; **39**: 1030-1036 [PMID: 22526956 DOI: 10.1007/s00259-012-2114-z]

81 **Shin H**, Kim MH, Lee SJ, Lee KH, Kim MJ, Kim JS, Cho JW. Decreased Metabolism in the Cerebral Cortex in Early-Stage Huntington's Disease: A Possible Biomarker of Disease Progression? *J Clin Neurol* 2013; **9**: 21-25 [PMID: 23346156 DOI: 10.3988/jcn.2013.9.1.21]

82 **Bartenstein P**, Weindl A, Spiegel S, Boecker H, Wenzel R, Ceballos-Baumann AO, Minoshima S, Conrad B. Central motor processing in Huntington's disease. A PET study. *Brain* 1997; **120** (Pt 9): 1553-1567 [PMID: 9313639 DOI: 10.1093/brain/120.9.1553]

83 **Weeks RA**, Ceballos-Baumann A, Piccini P, Boecker H, Harding AE, Brooks DJ. Cortical control of movement in Huntington's disease. A PET activation study. *Brain* 1997; **120** (Pt 9): 1569-1578 [PMID: 9313640 DOI: 10.1093/brain/120.9.1569]

84 **Lepron E**, Péran P, Cardebat D, Démonet JF. A PET study of word generation in Huntington's disease: effects of lexical competition and verb/noun category. *Brain Lang* 2009; **110**: 49-60 [PMID: 19615733 DOI: 10.1016/j.bandl.2009.05.004]

85 **Feigin A**, Leenders KL, Moeller JR, Missimer J, Kuenig G, Spetsieris P, Antonini A, Eidelberg D. Metabolic network abnormalities in early Huntington's disease: an [(18)F]FDG PET study. *J Nucl Med* 2001; **42**: 1591-1595 [PMID: 11696626]

86 **Feigin A**, Tang C, Ma Y, Mattis P, Zgaljardic D, Guttman M, Paulsen JS, Dhawan V, Eidelberg D. Thalamic metabolism and symptom onset in preclinical Huntington's disease. *Brain* 2007; **130**: 2858-2867 [PMID: 17893097 DOI: 10.1093/brain/awm217]

87 **Tang CC**, Feigin A, Ma Y, Habeck C, Paulsen JS, Leenders KL, Teune LK, van Oostrom JC, Guttman M, Dhawan V, Eidelberg D. Metabolic network as a progression biomarker of premanifest Huntington's disease. *J Clin Invest* 2013; **123**: 4076-4088 [PMID: 23985564 DOI: 10.1172/JCI69411]

88 **Bachoud-Lévi AC**, Rémy P, Nguyen JP, Brugières P, Lefaucheur JP, Bourdet C, Baudic S, Gaura V, Maison P, Haddad B, Boissé MF, Grandmougin T, Jény R, Bartolomeo P, Dalla Barba G, Degos JD, Lisovoski F, Ergis AM, Pailhous E, Cesaro P, Hantraye P, Peschanski M. Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. *Lancet* 2000; **356**: 1975-1979 [PMID: 11130527 DOI: 10.1016/S0140-6736(00)03310-9]

89 **Gaura V**, Bachoud-Lévi AC, Ribeiro MJ, Nguyen JP, Frouin V, Baudic S, Brugières P, Mangin JF, Boissé MF, Palfi S, Cesaro P, Samson Y, Hantraye P, Peschanski M, Remy P. Striatal neural grafting improves cortical metabolism in Huntington's disease patients. *Brain* 2004; **127**: 65-72 [PMID: 14607797 DOI: 10.1093/brain/awh003]

90 **Messmer K**, Reynolds GP. Increased peripheral benzodiazepine binding sites in the brain of patients with Huntington's disease. *Neurosci Lett* 1998; **241**: 53-56 [PMID: 9502214 DOI: 10.1016/S0304-3940(97)00967-1]

91 **Sapp E**, Kegel KB, Aronin N, Hashikawa T, Uchiyama Y, Tohyama K, Bhide PG, Vonsattel JP, DiFiglia M. Early and progressive accumulation of reactive microglia in the Huntington disease brain. *J Neuropathol Exp Neurol* 2001; **60**: 161-172 [PMID: 11273004]

92 **Kreutzberg GW**. Microglia: a sensor for pathological events in the CNS. *Trends Neurosci* 1996; **19**: 312-318 [PMID: 8843599 DOI: 10.1016/0166-2236(96)10049-7]

93 **Melton LM**, Keith AB, Davis S, Oakley AE, Edwardson JA, Morris CM. Chronic glial activation, neurodegeneration, and APP immunoreactive deposits following acute administration of double-stranded RNA. *Glia* 2003; **44**: 1-12 [PMID: 12951652 DOI: 10.1002/glia.10276]

94 **Nakanishi H**. Microglial functions and proteases. *Mol Neurobiol* 2003; **27**: 163-176 [PMID: 12777686 DOI: 10.1385/MN: 27: 2: 163]

95 **Banati RB**. Visualising microglial activation in vivo. *Glia* 2002; **40**: 206-217 [PMID: 12379908 DOI: 10.1002/glia.10144]

96 **Wilms H**, Claasen J, Röhl C, Sievers J, Deuschl G, Lucius R. Involvement of benzodiazepine receptors in neuroinflammatory and neurodegenerative diseases: evidence from activated microglial cells in vitro. *Neurobiol Dis* 2003; **14**: 417-424 [PMID: 14678758 DOI: 10.1016/j.nbd.2003.07.002]

97 **Banati RB**, Goerres GW, Myers R, Gunn RN, Turkheimer FE, Kreutzberg GW, Brooks DJ, Jones T, Duncan JS. [11C](R)-PK11195 positron emission tomography imaging of activated microglia in vivo in Rasmussen's encephalitis. *Neurology* 1999; **53**: 2199-2203 [PMID: 10599809 DOI: 10.1212/WNL.53.9.2199]

98 **Banati RB**, Newcombe J, Gunn RN, Cagnin A, Turkheimer F, Heppner F, Price G, Wegner F, Giovannoni G, Miller DH, Perkin GD, Smith T, Hewson AK, Bydder G, Kreutzberg GW, Jones T, Cuzner ML, Myers R. The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity. *Brain* 2000; **123** (Pt 11): 2321-2337 [PMID: 11050032 DOI: 10.1093/brain/123.11.2321]

99 **Pavese N**, Gerhard A, Tai YF, Ho AK, Turkheimer F, Barker RA, Brooks DJ, Piccini P. Microglial activation correlates with severity in Huntington disease: a clinical and PET study. *Neurology* 2006; **66**: 1638-1643 [PMID: 16769933 DOI: 10.1212/01.wnl.0000222734.56412.17]

100 **Tai YF**, Pavese N, Gerhard A, Tabrizi SJ, Barker RA, Brooks DJ, Piccini P. Microglial activation in presymptomatic Huntington's disease gene carriers. *Brain* 2007; **130**: 1759-1766 [PMID: 17400599 DOI: 10.1093/brain/awm044]

101 **Politis M**, Pavese N, Tai YF, Kiferle L, Mason SL, Brooks DJ, Tabrizi SJ, Barker RA, Piccini P. Microglial activation in regions related to cognitive function predicts disease onset in Huntington's disease: a multimodal imaging study. *Hum Brain Mapp* 2011; **32**: 258-270 [PMID: 21229614 DOI: 10.1002/hbm.21008]

102 **Herkenham M**, Lynn AB, de Costa BR, Richfield EK. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Res* 1991; **547**: 267-274 [PMID: 1909204 DOI: 10.1016/0006-8993(91)90970-7]

103 **Mailleux P**, Vanderhaeghen JJ. Localization of cannabinoid receptor in the human developing and adult basal ganglia. Higher levels in the striatonigral neurons. *Neurosci Lett* 1992; **148**: 173-176 [PMID: 1300492 DOI: 10.1016/0304-3940(92)90832-R]

104 **Glass M**, Brotchie JM, Maneuf YP. Modulation of neurotransmission by cannabinoids in the basal ganglia. *Eur J Neurosci* 1997; **9**: 199-203 [PMID: 9058040 DOI: 10.1111/j.1460-9568.1997.tb01390.x]

105 **Glass M**, Dragunow M, Faull RL. The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. *Neuroscience* 2000; **97**: 505-519 [PMID: 10828533 DOI: 10.1016/S0306-4522(00)00008-7]

106 **Casteels C**, Martinez E, Bormans G, Camon L, de Vera N, Baekelandt V, Planas AM, Van Laere K. Type 1 cannabinoid receptor mapping with [18F]MK-9470 PET in the rat brain after quinolinic acid lesion: a comparison to dopamine receptors and glucose metabolism. *Eur J Nucl Med Mol Imaging* 2010; **37**: 2354-2363 [PMID: 20680268 DOI: 10.1007/s00259-010-1574-2]

107 **Casteels C**, Vandeputte C, Rangarajan JR, Dresselaers T, Riess O, Bormans G, Maes F, Himmelreich U, Nguyen H, Van Laere K. Metabolic and type 1 cannabinoid receptor imaging of a transgenic rat model in the early phase of Huntington disease. *Exp Neurol* 2011; **229**: 440-449 [PMID: 21459091 DOI: 10.1016/j.expneurol.2011.03.014]

108 **Burns HD**, Van Laere K, Sanabria-Bohórquez S, Hamill TG, Bormans G, Eng WS, Gibson R, Ryan C, Connolly B, Patel S, Krause S, Vanko A, Van Hecken A, Dupont P, De Lepeleire I, Rothenberg P, Stoch SA, Cote J, Hagmann WK, Jewell JP, Lin LS, Liu P, Goulet MT, Gottesdiener K, Wagner JA, de Hoon J, Mortelmans L, Fong TM, Hargreaves RJ. [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. *Proc Natl Acad Sci USA* 2007; **104**: 9800-9805 [PMID: 17535893 DOI: 10.1073/pnas.0703472104]

109 **Yasuno F**, Brown AK, Zoghbi SS, Krushinski JH, Chernet E, Tauscher J, Schaus JM, Phebus LA, Chesterfield AK, Felder CC, Gladding RL, Hong J, Halldin C, Pike VW, Innis RB. The PET radioligand [11C]MePPEP binds reversibly and with high specific signal to cannabinoid CB1 receptors in nonhuman primate brain. *Neuropsychopharmacology* 2008; **33**: 259-269 [PMID: 17392732 DOI: 10.1038/sj.npp.1301402]

110 **Terry GE**, Liow JS, Zoghbi SS, Hirvonen J, Farris AG, Lerner A, Tauscher JT, Schaus JM, Phebus L, Felder CC, Morse CL, Hong JS, Pike VW, Halldin C, Innis RB. Quantitation of cannabinoid CB1 receptors in healthy human brain using positron emission tomography and an inverse agonist radioligand. *Neuroimage* 2009; **48**: 362-370 [PMID: 19573609 DOI: 10.1016/j.neuroimage.2009.06.059]

111 **Van Laere K**, Casteels C, Dhollander I, Goffin K, Grachev I, Bormans G, Vandenberghe W. Widespread decrease of type 1 cannabinoid receptor availability in Huntington disease in vivo. *J Nucl Med* 2010; **51**: 1413-1417 [PMID: 20720046 DOI: 10.2967/jnumed.110.077156]

112 **Vattakatuchery JJ**, Kurien R. Acetylcholinesterase inhibitors in cognitive impairment in Huntington's disease: A brief review. *World J Psychiatry* 2013; **3**: 62-64 [PMID: 24255877 DOI: 10.5498/wjp.v3.i3.62]

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**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 patients5 HCs | 11C-b-CIT11C-SCH23390 11C-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 patients64 HCs | 11C-DTBZ | Reduced nigrostriatal density of VMAT2 (caudate: 33%, putamen: 56-75%). |
| Sedvall *et al*[58], 1994 | 5 HD patients1 premanifest *HD* gene carrier5 HCs | 11C-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 patients9 HCs for 11C-raclopride and 6 HCs for 11C-SCH 23390 | 11C-SCH 2339011C-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 | 11C-SCH 2339011C-raclopride | Correlation between striatal D1 and D2 receptors binding and cognitive performance. |
| Pavese *et al*[61], 2003 | 12 HD patientsHCs from previous studies | 11C-raclopride | 4.8% annual reduction in striatal D2 receptor bindingD2 reduction receptor density in extrastriatal regions including amygdala, temporal and frontal cortex. |
| Andrews *et al*[64], 1999  | 9 premanifest *HD* gene carriers4 HD patients7 HCs3 subjects at risk for HD | 11C-SCH 2339011C-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 patients11 premanifest *HD* gene carriersHCs from previous studies | 11C-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 onneuropsychological tests assessing attention and executive functions than subjects without cortical dopamine dysfunction. |
| Antonini *et al*[66], 1998  | 10 premanifest gene carriers8 HD patients | 11C-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 carriers8 HD patientsHCs from previous studies | 18F-FDG11C-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 patients21 HCs | 18F-FDG | Decreases of caudate and regional cortical metabolism correlated with cognitive decline.  |
| Ciarmiello *et al*[79], 2006  | 24 premanifest *HD* gene carriers47 HD patients30 HCs | 18F-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 | 18F-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 patients7 HCs | H215O | 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 carriers12 HCs | 18F-FDG11C-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 years and was not influenced by intercurrent phenoconversion. |
| **Neuroinflammation and activated microglia** |
| Pavese *et al*[99], 2006 | 11 HD patients10 HCs | 11C-PK1119511C-raclopride | Significant microglial activation in the striatum and cortical regions of HD patients.Striatal 11C-PK11195 binding correlates with loss of striatal dopamine D2 binding.Striatal 11C-PK11195 binding correlated with UHDRS scores. |
|  Tai *et al*[100], 2007  | 11 premanifest *HD* gene carriers10 HCs  | 11C-PK1119511C-raclopride | Increased striatal and cortical microglial activation in premanifest *HD* gene carriers. Higher striatal 11C-PK11195 binding correlated with lower striatal D2 binding. |
| Politis *et al*[101], 2011  | 8 premanifest *HD* gene carriers8 HCs (11C-raclopride)8 HCs (11C-PK11195) | 11C-PK1119511C-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 years. |
| Cannabinoid system |
| Van Laere *et al*[111], 2010  | 20 HD patients14 HCs | 18FMK-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.