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Chapter

Neuroimaging Biomarkers for Huntington’s Disease

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Abstract

Biomarkers are of great importance in the prediction of onset and follow-up of patients with Huntington’s disease (HD). Neuroimaging is a convenient biomarker, because of its non-invasive character. Since technology is continuously evolving, we are increasingly able to visualize detailed neural structures and functions. Furthermore, it could also identify new targets for therapeutic interventions. In this chapter, we review findings in neuroimaging research applied to HD. First, we will describe the neuroanatomical structures and cellular processes, which are important in the pathophysiology of HD and are therefore particularly interesting to focus on. We will then discuss the different imaging modalities; from structural to functional, from commonly used to novel imaging strategies. Striatal- and cortical-volume loss on conventional MRI and decrease in uptake of radiotracers on PET are currently the most robust markers of disease progression. The use of other MRI-metabolites, specific PET radioligands, DTI, and fMRI may have the potential to detect HD pathology earlier and more accurately but needs further investigation. These neuroimaging markers, possibly combined, can be useful clinical outcome measures in clinical trials and could improve the management and treatment of future patients.

Keywords: neuroimaging, biomarkers, Huntington’s disease, MRI, fMRI, PET

1. Introduction

Huntington’s disease (HD) is an autosomal dominant inherited neurodegenerative disorder caused by an expansion of a CAG repeat in the huntingtin gene. Therefore, confirmation of carrier ship of an expanded CAG repeat is achieved by a genetic test, which can be performed years before disease onset [1]. The clinical diagnosis and follow-up of the disease are obtained by standardized clinical scales like the Unified Huntington’s Disease Rating Scale (UHDRS) [2]. This assessment consists of a specific neurological exam (e.g. ‘Total Motor Score’, TMS), Total Functional Capacity (TFC), and neuropsychological assessments. During the neuropsychological assessments cognitive, psychological, and psychiatric information is obtained. Clinical diagnosis in research and in clinic is grounded on a clinician’s rating of the diagnostic confidence level. The clinical diagnosis requires a level of 4, on a 0–4 scale, completely based on the motor features of HD. Although these assessments are standardized
and well-known, they have their limitations. In particular, the subjective nature of these assessments contributes to a high inter-rater variability [3]. They also show low sensitivity to longitudinal change and monitoring of treatment effects [4]. There are often many observable clinical and functional changes before motor onset. Since the clinical diagnosis is not made until motor symptoms appear, there is a large gray area where symptoms already exist without being officially classified as ‘manifest’.

At this moment, there is no successful disease-modifying therapy for HD. Nevertheless, research trials are constantly evolving, hoping to find solutions in the near future. Sensitive biomarkers are of great importance in these clinical trials. These are valuable not only for accurate group selection, or deciding when to start therapy, but are also important for evaluating treatment response, which is currently measured by the earlier mentioned clinical scales. The Biomarkers Definitions Working Group defines a biomarker as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’ [5]. A biomarker must be widely available, reliable, reproducible and it should show low variability in the normal population. Besides that, it has to change in relation to disease progression and disease-modifying treatment. An ideal biomarker should be able to predict disease onset and should be obtained in a minimally invasive manner.

Neuroimaging biomarkers are convenient, as they are relatively non-invasive and can provide an accurate picture of the pathophysiology. Currently, there are different types of neuroimaging methods, sequences, and tools available and many of them have been used in observational studies of patients with HD. In this chapter, we summarize the results of different neuroimaging modalities that have been used in HD research. Furthermore, we will discuss the qualities and the limitations of these modalities and appraise which type of methods we should favor for future clinical trials. Before moving to a discussion of the neuroimaging modalities, we first elaborate on the pathophysiology of HD to determine the relevant neuroanatomical structures and cellular processes that neuroimaging modalities should focus on.

2. From neuropathology to scan

HD is a neurodegenerative disease caused by CAG repeat expansion in the huntingtin gene (HTT) on chromosome 4. The number of CAG repeats is associated with an increased accumulation of abnormal huntingtin protein in the neurons. When the CAG-repeat rises above a threshold of 36 repeats, this leads to cumulative toxicity [1]. The CAP score, a statistical prediction tool developed by Penney and colleagues, is an index to estimate the degree of cumulative exposure to the effects of the CAG repeat expansion. The score considers the length of repeats and the lifetime exposure to the disease burden. It can be used to predict the clinical status of HD expanded gene carriers (HDEGC), as it has proven to be a good predictor of HD pathology in post-mortem brains [6]. In general, it is believed that the longer the CAG repeat, the earlier the age of disease onset [7]. However, CAG repeat length is certainly not the only predictor of clinical outcome, as similar CAG repeat lengths can lead to many different manifestations of the disease (e.g. variable age of onset) [8].

An important part of the pathology of HD is the accumulation of mutant huntingtin protein to form intranuclear inclusions, which subsequently leads to loss of GABAergic medium spiny neurons (MSNs) in the neostriatum [9, 10]. This includes the caudate nucleus and the putamen, but also other regions of the basal ganglia, such as the globus pallidus. Multiple studies have shown this striatal atrophy, making it the hallmark of HD’s pathology [11, 12]. Degeneration of inhibitory MSNs leads to
Neuroimaging Biomarkers for Huntington’s Disease
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hyperactivity of the dopaminergic pathway, contributing to chorea [13]. As the pathology progresses, neuronal degeneration spreads to the cortex and other extrastriatal regions [12, 14, 15]. All four cerebral lobes undergo cortical thinning with a layer-specific neuronal loss [16]. Cerebellar symptoms are quite common in HD, including dysarthria and ataxic movements of extremities. Although less studied, recent studies also show a reduction of the cerebellar volume [17]. Considering all these findings, HD is now being viewed as a multisystemic disease [16]. Further research in this area is needed. There is no current explanation why these cortical and subcortical brain regions are selectively affected, ultimately leading to HD-specific neurodegeneration.

Disease-specific cellular processes can be investigated using neuroimaging techniques like magnetic resonance spectroscopy (MRS), iron sensitive MRI, and PET-scans. The loss of post-synaptic striatal MSNs results in a decline of post-synaptic dopaminergic neurons. Phosphodiesterase (PDE) is an enzyme that seems to play a role in the pathophysiology of HD. This is an intracellular enzyme that plays an important role in cell signal transduction and in promoting neuronal survival. PDE10A is predominantly expressed in the striatum and has an essential role in regulating dopaminergic signaling. In mutated HD models, it has been shown that mutant huntingtin decreases striatal PDE10A expression [18] and a decreased PDE10A level has been identified before onset of symptoms [19].

Besides the dopaminergic receptors, there are several other receptors suggested to be involved in HD pathophysiology. One of them is the GABA receptor. Studies have shown a decreased GABA receptor density in the caudate, putamen, and the frontal cortex in post-mortem HD brains [20]. In the globus pallidus an increased level of GABA receptors was found [21]. Another common receptor that seems to play a role in HD pathophysiology is the adenosine type 1 receptor, which plays a role in neuroprotection and autoregulation of cerebral blood flow [22]. Cannabinoid type 1 receptors (CB1R) are expressed in the basal ganglia, predominantly in the GABAergic striatal MSNs. They seem to be important for motor and cognitive function and play a protective role against excitotoxicity and promote neuronal survival [23, 24]. Transgenic HD mouse models showed decreased levels of CB1R [25] in both premanifest and manifest stages, with a further decline during the manifest stages [26].

Iron accumulation [27], synaptic dysfunction [28, 29] as well as mitochondrial dysfunction [30] are other mechanisms of HD pathophysiology. Iron accumulation has been correlated with aging and increased accumulation has been found in several neurodegenerative diseases like HD [27]. It is currently unknown whether iron accumulation is a cause or a consequence of neurodegeneration. Iron accumulates in microglia, as has been shown in HD [31]. Microglia cells are also involved in neuroinflammation, another probable pathological process in HD. Activated microglia cells have a neuroprotective effect, but overactivation can result in neuronal damage due to toxic levels of free radicals, nitric oxide and interleukins. Activated microglia have been found in the neostriatum, globus pallidus, cortex, and subcortical white matter in post-mortem human brain tissue in HDEGC [32]. It remains unclear whether this activation is a compensatory mechanism in response to the loss of neurons, or whether microglia activation itself is the cause of pathophysiology.

3. Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) is an imaging method where a magnetic field, magnetic gradients and radiofrequency pulses are used to change the state of
hydrogen atoms in the brain. These changes create energy which is subsequently measured and exported in the form of an MR image [33].

There are different approaches in methodology when analyzing a scan. There is a region-of-interest (ROI) approach and a whole-brain analysis approach. The first one is driven by known pathologically affected structures, the latter is more exploratory, unbiased and does not require a priori assumptions. ROI studies can be useful to study specific hypotheses since they often show high sensitivity for detecting differences between groups and demonstrating longitudinal change. The delineation of ROIs can be performed manually or by using automated software. Although manual delineation of ROIs is the gold standard, it is very time consuming and is susceptible to inter- and intra-rater variability. The automated software can define ROIs on a more consistent level across studies and is therefore likely to be used more frequently in future studies. However, there is an increased level of error to include some of the surrounding tissue in the analysis while working with these automated software methods. ROI approaches are used in volumetric imaging as well as diffusion-weighted imaging (DWI) [34].

Whole-brain-analysis enables exploratory analysis across all brain regions. It has been widely used in HD studies, for example, to measure brain volume. Voxel-based morphometry (VBM) is the most commonly used approach. With this approach volumetric differences in the gray matter, white matter, and cerebrospinal fluid (CSF) can be measured between different groups. It can also be used to make associations between volume and other biomarkers [35]. Cortical thickness is another whole-brain approach, widely used in HD studies. In DWI a whole-brain analysis can be performed by using Tract-Based Spatial Statistics (TBSS). This compares diffusion metrics across the brain. Another type of analysis that is used in DWI is tractography. This is used to measure diffusivity between two or more regions of interest [36].

3.1 Volumetric MRI

Structural or volumetric MRI scans can be used to measure anatomical features of the brain, such as volume and cortical thickness. They are usually 3D T1 weighted sequences, after which volume measurements are made using software packages [37]. Each body tissue has a different relaxation time that is dependent on how tightly bound the protons are in their environment. Volumetric MRI studies were the first and are still the most common in vivo imaging studies in HD research. MRI-based brain volume measurements have been introduced in HD at the beginning of the 1990s. The most common finding is striatal atrophy. Harris et al. were the first to discover a volume loss in the putamen and caudate, comparing 15 symptomatic HDEGC with 19 healthy controls [38]. In 1996, they were able to discriminate manifest HDEGC from healthy controls using volume measurements [39]. In the early years of structural MRI research, Aylward et al. did multiple studies showing that striatal atrophy was already present years before clinical motor diagnosis [40–42]. Contemporary scientists have confirmed these findings, showing volume loss up to 24 years before clinical motor onset [43–45].

Longitudinal studies show reducing striatal volumes with decreasing time to estimated diagnosis, with striatal volumes markedly reduced compared to age-matched controls at the time of clinical motor diagnosis [46–48]. In the past years there have been four large multicentre studies, aimed at identifying sensitive and reliable biomarkers. TRACK-HD is one of these studies, following 120 premanifest and 123 early manifest HDEGC longitudinally [43, 49, 50]. After a 12-month follow-up, they
measured a mean volume loss of 1.4% and 2.9% in the caudate, and 2.3% and 4.5% in the putamen, compared with baseline for the premanifest and manifest HDGC group, respectively [49]. After a 24-month follow-up, this atrophy progressed in both groups [4]. IMAGE-HD, another multicentre longitudinal study, showed that longitudinal volume change in the caudate was the only measure among a range of multi-modal imaging features that discriminated between groups across different disease stages (e.g. >15 years from clinical motor onset, <15 years from clinical motor onset, and after clinical motor onset). Caudate volume showed statistically bigger longitudinal change than putamen volume, over 30 months [51]. This larger difference in caudate volume loss compared to putamen atrophy was confirmed by another multicentre study called PADDINGTON [48].

While striatal atrophy can already be detected years before onset, cortical atrophy becomes more apparent after clinical motor diagnosis [52–54]. Atrophy in the frontal lobe has been identified in the moderate and late stages of HD. Volume reductions have been identified in almost all brain structures, including the total cerebrum, cerebral cortex, basal ganglia, amygdala, hippocampus, brainstem, and cerebellum [52, 53]. Another study showed an association between increased losses of gray matter volume in the occipital, parietal, frontal and insular cortices, and disease progression [55]. However, in the TRACK-HD study whole brain and gray matter atrophy were already found in premanifest HDEGC with <10.8 years from predicted symptomatic onset. In the premanifest HD group >10.8 years from predicted symptomatic onset atrophy was limited to the striatum, the white matter surrounding the striatum, the corpus callosum, and the posterior white matter tract [50]. Volume loss in total brain matter and white matter progressed after a 12-month follow-up [49]. The fourth large longitudinal multicentre study, PREDICT-HD, showed volume loss in total brain, white matter, cortical gray matter, thalamus, caudate, and putamen volume in premanifest HDEGC when compared to controls. Striatal volume, especially the putamen, showed the largest loss of volume [46, 47, 56]. White matter atrophy has been identified in more studies, showing volume loss early in the disease, continuing to decline with disease progression [43, 44, 48, 49, 54]. One recent imaging study using both PET and MRI, found significant volume loss in caudate, putamen, and pallidum in premanifest HDEGC. In the early manifest HDEGC, they also found significant atrophy in the thalamus, occipital and frontal cortex, and whole gray matter [57].

Cortical thinning has also been found in early manifest HD, affecting the sensorimotor areas, the occipital, and prefrontal cortices [58–60]. Thinning of the cortical gray matter can be detected before clinical diagnosis, becoming more pronounced and proceeding from posterior to anterior regions as the disease progresses [43, 53, 59, 60].

There is overwhelming evidence showing associations between brain volume loss and clinical outcome measures, showing a decline in performance with reducing volumes. Striatal atrophy has been associated with predicted time to clinical disease onset, age of onset, disease duration, and an increasing CAP score [40, 47, 61]. After a 36-month follow-up, the TRACK-HD study showed progressive whole brain, caudate, putamen, and gray matter atrophy in early manifest HDEGC which correlated to a decreasing TFC score. In the premanifest group with >10.8 years from predicted motor onset, striatal atrophy was not associated with a decline in motor and cognitive performances [50]. This was confirmed by a recent multimodal imaging study, where they also found significant striatal atrophy in premanifest HDEGC which did not correlate to clinical measures [62]. In the TRACK-HD study, the premanifest group within 10.8 years from predicted motor onset did show a significant decline of motor and
cognitive performances. Besides this, TRACK-HD showed that striatal and gray volume measures were sensitive predictors of conversion from the premanifest to manifest HD stage [50]. Furthermore, at the most advanced disease stage (7 ≤ TFC ≤ 10) the caudate volume showed a constant rate of decline over the 12-, 24-, and 36-month follow-up periods. Whole-brain and caudate volumetric MRI measurements have a substantially better power analysis than standard clinical outcome measures used in current clinical trials (TMS and TFC). They only need one-sixth of the sample size to detect the same degree of slowing [63]. The PADDINGTON study, which looked at longitudinal changes in early manifest HDEGC compared to healthy controls, found more MRI changes than changes in clinical outcome measures [64].

In premanifest HDEGC and early HD manifest patients subtle impairments were correlated with regional brain volume, especially in the caudate, putamen, and globus pallidus [65–67]. Regional cortical atrophy has also been correlated with MMSE, TFC, and motor scores [52, 60]. Regional cortical thinning was found to be correlated with cognitive decline [68, 69], depression [69], and TMS [70]. Atrophy in the precentral and parieto-occipital regions correlated with TFC, clinical motor, and cognitive scores [71–73]. Associations have been found between atrophy in the caudate and worse outcome scores on the mini-mental state examination (MMSE) [39], TMS, SDMT, and TFC [74]. A voxel-based morphometry showed an inverse correlation between the TMS and the concentrations of caudate nuclei tissue, internal capsule, occipital lobes, cerebellum, lower brainstem (corrected for age and CAG repeat length) [75]. Increased atrophy in the putamen also correlates with motor impairment [38, 39]. Thalamic atrophy was found to be associated with apathy [76]. Atrophy in the thalamus, insula and white matter volume has been associated with cognitive performance scores in both pre-manifest and manifest HD groups [77, 78].

It can be concluded that volume loss occurs many years before the development of motor signs that mark the clinical diagnosis of HD, starting with striatal atrophy and concomitantly spread over the gray and white matter. To study the microstructural changes that could explain neuronal loss and to find approaches for disease-modifying treatments, other imaging modalities are necessary.

3.2 Diffusion tensor imaging

DWI is a newer MRI technique that has been extensively used in HD research for the past two decades. It is based upon the diffusion properties of protons in the intracellular and extracellular space. In an unrestricted space, water molecules can move in any direction, which is called isotropic movement. When the path of the water molecules is restricted, such as along a white matter tract, water diffuses in an anisotropic way. Diffusion tensor imaging (DTI) is a specific type of DWI that enables a more precise assessment of the direction of diffusion. DTI allows measurement of the orientation, strength, and directionality of the diffusion of water molecules. The measures that can be derived from DTI are mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD). MD represents the speed of diffusion, where a low MD value represents a restricted diffusion and a high MD value an unrestricted diffusion (e.g., CSF). FA represents the strength of the main direction of diffusion. FA values range from 0 to 1. When the FA value is close to 0 there is an equal diffusion in all directions, as is the case in CSF. AD is the diffusion rate along the main axis of diffusion and an increase in AD reflects axonal degeneration and loss. RD is the rate of diffusion in the transverse direction, where an increase in RD reflects the demyelination of white matter tracts [79].
Neuroimaging Biomarkers for Huntington’s Disease
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The advantage of DTI is that it can detect microstructural changes, which precedes the larger changes that appear on a volumetric MRI image [80]. This applies especially to the white matter, due to the white matter tracts.

As with structural MRI, diffusion imaging has been used in large multicentre imaging trials like TRACK-HD, TRACK-ON HD, PADDINGTON, IMAGE-HD, and PREDICT-HD. These large MRI datasets are important to improve the technical standardization and statistical power of clinical DTI studies in HD.

Widespread diffusion abnormalities have been demonstrated in both manifest and premanifest HDEGC [81]. Multiple studies have shown a decreased FA and increased AD, RD, and MD in a wide range of white matter regions for HDEGC compared to healthy controls [82–91]. Among these studies three of them included symptomatic HDEGC and healthy controls [87, 89, 91] and three studies compared premanifest HDEGC and controls [83, 84, 90]. There have been many more studies showing a decrease in FA, of which Reading and colleagues were the very first. They showed lower FA values in the precentral cortex of premanifest HDEGC [92]. The TRACK-ON HD study, a longitudinal study of 72 premanifest HDEGC over 24 months, identified that cortico-striatal connections were most affected, followed by interhemispheric and intrahemispheric connections [93]. The corpus callosum has been studied frequently in DTI-studies, probably due to its easy access and well-organized pattern of the pathway. In 2010, Rosas et al. found an increase in AD and RD in fibers of the corpus callosum for the first time, suggesting a cortical disconnection between the prefrontal cortical regions [94]. Also the basal ganglia, the surrounding white matter tracts between these regions and the cortex have been analyzed thoroughly using DTI. There have been studies looking at both white matter and gray matter, showing an increase of FA in the gray matter and a decrease of FA in the white matter for HD patients compared to controls [95–103]. Other studies showed that diffusion imaging could be used as a method to differentiate the subgroup close-to-onset premanifest HDEGC from far-from-onset HDEGC. They showed an increased MD in close-to-onset-HD, compared to far-from-onset and healthy controls [104, 105].

There are also studies with contradictory results. Syka and colleagues did not find any significant difference between FA and MD in the pallidum of symptomatic HDEGC compared to healthy control [106]. Poudel et al. and Matsui et al. have found increased RD without a difference in AD in HDEGC, suggestive of myelination pathology [107, 108].

The longitudinal IMAGE-HD study showed a progressive increase in MD located in the caudate, putamen and corpus callosum of premanifest HDEGC after 18 and 30 months follow-up [51, 109]. Sampedro and colleagues studied 39 HDEGC in different stages and showed correlations between MD and disease progression [110]. Other longitudinal diffusion studies did find cross-sectional differences, but did not find significant longitudinal effects in the included groups [70, 88, 111–113].

Diffusion studies have also tried to correlate diffusion to different phenotypes, clinical signs and genetic variables. Changes in diffusion have been linked to increased impairment in neuropsychological performance [69, 70, 98] and motor assessments [69, 70, 114]. For example, Bohanna et al. showed a positive correlation between motor symptoms and an increase in diffusion in the corpus callosum [91]. Philips and colleagues showed correlations between diffusion and clinical and genetic variables, such as CAG and cognitive assessments [115]. Microstructural dissociation in WM tracts has been associated with depression [69], apathy [116], and irritability [117]. Combining both volumetric and diffusion data sets, Georgiou-Karistianis and his group could accurately detect individuals up to 15 years before onset of symptoms, making it a valuable biomarker [118].
In summary, it seems that MD is increased in widespread regions of the brain and FA is reduced in white matter regions when comparing HDEGC to controls. This difference already begins in the premanifest phase of the disease and increases with disease progression. These results indicate an important role in white matter disorganization in HD.

3.3 Magnetic resonance spectroscopy

MRS is an MRI technique that can look on a microscopic level at the pathophysiology. It uses protons, like hydrogen protons, to measure metabolite concentrations. This modality does not give structural information about the brain tissue, but enables an interpretation of the chemical composition of the tissue. The most common metabolites are N-acetylaspartate (NAA), which is a marker for neuronal and axonal integrity; creatine, reflecting brain energy metabolism; choline, a glial marker; glutamate, a neurotransmitter; lactate, a product of anaerobic glycolysis; and myo-inositol, an astrocyte marker [119]. To date, no previous studies have shown a pathognomic alteration of any metabolite for HD [120]. In manifest HDEGC, lower NAA and creatine have been measured in the putamen and/or caudate nucleus [121–125] and thalamus [126]. Adanyeguh et al. found a significantly higher total creatine in the visual cortex and a significantly lower total creatine in the striatum, in manifest HDEGC compared to controls [127]. This decreased level of total creatine has also been found in premanifest HDEGC in some studies [121, 125], of which one was part of the multicentred TRACK-HD study [121]. Other studies did not show a decreased level in premanifest HDEGC [128, 129]. MRS studies looking at glutamate levels in HDEGC did not demonstrate consistent results either. Some of these studies found increased levels of glutamate [130–132], others found no difference with healthy controls [121, 122] or found a lower level compared to controls [121, 127]. Choline was found to be decreased in the frontal cortex of premanifest HDEGC [128] and the NAA/choline ratio was found to be decreased in the frontal cortex of manifest HDEGC [133]. Furthermore, increased myo-inositol was measured in the putamen of manifest HDEGC [121] and increased lactate has been assessed in the basal ganglia, cerebellum and occipital, parietal, and frontal cortex of manifest HDEGC [123, 124, 133, 134]. Correlations have been made between alterations in metabolites and motor performance [121, 125], neuropsychological performance [128], disease severity [133], and disease burden [121]. So far there have been two longitudinal MRS studies, both showing no longitudinal change of metabolites in their follow-up [135, 136].

3.4 Iron sensitive MRI

Various MRI techniques have been used, trying to assess iron accumulation. One of these techniques is the use of relaxation rates R2 and R2* when using the T2 and T2* sequences, respectively. This susceptibility measurement cannot distinguish between paramagnetic or diamagnetic entities and therefore cannot conclude whether there is iron or myeline pathology or calcifications. Susceptibility weighted imaging (SWI) is another widely applied method to visualize iron deposition, although it is not able to provide quantitative measures. One of the more novel techniques to measure magnetic susceptibility is quantified susceptibility mapping (QSM). This technique can differentiate between diamagnetic and paramagnetic and can quantify the iron measures.
Multiple studies have shown increased iron levels in the basal ganglia in early manifest HDEGC compared to controls [137–143]. Some studies also found a decreased level of iron deposition in the frontal white matter [137, 140], parieto-occipital cortex [144], and in the substantia nigra and hippocampus. More novel studies have also included premanifest HDEGC, often showing an increased iron level in the caudate [145], putamen, and globus pallidus [146] as well [142–144, 147]. One study from Sanchez-Castaneda et al. showed an increased iron level in the caudate, staying relatively stable throughout disease progression, whereas iron levels in the putamen and globus pallidus increased progressively [144]. Iron-sensitive MRI studies have found correlations between iron levels and CAG repeat [139, 140, 144, 145, 147], increasing disease severity [138, 139, 141, 142, 144] and were found to be independent of volume [138].

4. Functional MRI

Functional MRI (fMRI) is an imaging technique that measures brain activity by using changes in blood oxygenation due to hemodynamic (blood flow) response to neuronal activity (Blood Oxygen Level-Dependent [BOLD]). This BOLD signal represents the ratio between oxygenated and deoxygenated blood and can be used as a measure of local neural activity. fMRI can be obtained in a resting state (rs-fMRI), where you can analyze the function between interacting regions, focusing on network connectivity or connectomics. Task-Based fMRI is another way to measure neural function connectivity, by doing a particular task or function while being in the MRI-scanner. It investigates the neurovascular response to these tasks [148].

Like in structural MRI there are different ways to investigate the neural activity. Task-based fMRI is usually done on a voxel-by-voxel basis. With rs-fMRI you can use seed-based analyses or independent component analysis. Seed-based analysis is partly hypothesis-driven and looks at a predefined region, compared to the rest of the brain. Independent component analysis is not based on predefined knowledge. Functional connectomics can be made by using both these rs-fMRI methods [149]. Current studies often correct functional connectivity for loss of volume.

Functional activity is highly dependent on the type of task and the region of the brain that is analyzed. Furthermore, when applying task-based fMRI in a multicentre imaging trial, this can entail a higher degree of variability in the performed tasks. Therefore, comparing fMRI studies and interpreting them can be very difficult [81].

4.1 Resting state-fMRI

rs-fMRI studies have been used to examine functional networks in HD populations. They overcome the variability in task performances that come along with task-based fMRI. In recent years, there is an increase in studies looking at the entire connectome. Studies using a seed-based analysis often look at functional networks like known motor and cognitive networks. They also regularly include the default mode network (DMN), a network that becomes active when the brain is at rest. These studies show reduced connectivity in the DMN of HDEGC compared to controls, suggesting a disrupted connection when the brain is at rest [150, 151]. Reduced connectivity in manifest HDEGC has been found within the basal ganglia, between the basal ganglia and the insula and between the primary motor cortex and the insula [97]. Also, premanifest HDEGC has shown reduced connectivity within the primary
motor cortex [152], between the premotor cortex and the caudate nucleus [153], and in the somatosensory cortex [154]. This reduced connectivity in both premanifest and manifest HDEGC correlated with motor performance [97, 152, 154]. Another study showed reduced connectivity between the cerebellum and the paracentral gyrus, which correlated with disease burden and motor signs [155]. Reduced connectivity in the lower fusiform gyrus, which is important in the visual network, correlated with disease burden and symbol digit modality test (SDMT) scores [156]. Functional connectivity was also found to be reduced in the dorsal attention network in both premanifest and manifest HD, correlating with cognitive decline [154].

Studies investigating functional connectivity in the executive network found both reduced [151, 156] and increased connectivity [154, 156, 157] in manifest HD. This difference in connectivity seems to follow different spatial trajectories: parietal cortex and subcortical structures get a decreased connectivity in manifest stages [151, 154, 156], while increased connectivity is measured in the frontal cortex [156–158]. McColgan et al. confirmed this difference in connection per region using connectomics [159]. Increased connectivity was also found in the supplementary motor area (SMA) and motor cortex, correlating with worsening of motor performance, in manifest HD patients [156, 157, 160]. Other regions with increased connectivity in manifest HDEGC were bilateral caudate, inferior and middle frontal cortices [156], striatum, thalamus, and frontal regions [157]. Increased CAG repeat length correlated with increasing fronto-occipital connectivity and decreasing connectivity within the visual cortex [161]. A recent rs-fMRI study, using a 7 T MRI-scanner, found functional connectivity to be decreased between the premotor cortex and the striatum as well as between the SMA and the premotor cortex in both premanifest and manifest HDEGC compared to controls. The connectivity was increased between the striatum and both the frontal inferior and frontal middle region. They also found a significant correlation between the TMS and the connectivity in the premotor regions and between the UDHRS behavioral score and the connectivity in the frontal middle regions. The CAP score and estimated years to onset correlated with functional dysconnectivity between the striatum and frontal region, and between the premotor cortex and the SMA, suggesting a potentially valuable biomarker [162]. Some rs-fMRI studies show an association between increased frontal connectivity and more preserved cognitive function [163, 164], suggesting a compensatory response.

Some studies have also shown a difference in disconnection between premanifest and manifest expanded gene carriers. While reduced connectivity was found between frontal and motor cortex and within the medial visual network for both premanifest and manifest HDEGC, reduced connectivity in the deep gray matter and occipital cortex was only detected in manifest HDEGC [151]. Other studies have found no difference in the functional connectivity of the visual network between premanifest HDEGC and healthy controls [60, 165]. Coppen and colleagues did find a significant decrease in functional connectivity in this area in the manifest patients [60].

So far, studies have not found a longitudinal change in connectivity [165–167]. One study did a follow-up of a premanifest HDEGC cohort and found no change in connectivity after 3 years [165].

4.2 Task-based fMRI

Multiple task-based fMRI studies have shown changes in activation in manifest HD patients compared to controls, correcting for brain atrophy [168–171]. Something that has been identified more than once is a hyperactivation in certain regions in
premanifest HDEGC, while other regions show a decreased activation. In one study they found a decreased activation in the posterior cingulate and hyperactivation in the left anterior prefrontal cortex in premanifest HDEGC [160]. Klöppel et al. found increased activation in the supplementary motor area (SMA) after a finger tapping task in premanifest HDEGC, especially in the HDEGC subgroup closest to onset [172]. They also found increased activation in the right parietal cortex in response to a working memory task, with a correlation to atrophy [164]. This increased activation suggests compensation in the premanifest phase of the disease. Other studies in premanifest HDEGCs confirmed this hyperactivation. In premanifest HDEGC, hyperactivation was found in the left sensorimotor cortex [173], anterior cingulate and preSMA [174], and subcortical structures [175]. In only one study, hypoactivity was found in the anterior cingulate in premanifest HDEGC far-from-onset [173]. In the premanifest subgroup close-to-onset hypoactivation was found in the subcortical structures [174, 175], SMA, left insula, right inferior frontal gyrus [173], and dorsolateral prefrontal cortex [176]. Besides Klöppel et al. [172], one other study found hyperactivation in premanifest HDEGC close-to-onset, in the left inferior parietal and right superior frontal regions [176]. The multimodal study of Pini et al., where they used volumetric MRI, DTI, and fMRI, confirmed these differences in premanifest HDEGC subgroups. In far-from-onset premanifest HDEGC, there was increased connectivity in the left caudate-cortical functional pathway compared to the healthy controls. No significant differences were found between the close-to-onset subgroup and healthy controls. There was also no difference between the total premanifest group and controls with regard to functional connectivity of the right caudate nucleus, bilateral putamen, and bilateral nucleus accumbens [105]. These differences in activity and locations sometimes differ from each other, partly due to differences in task designs. Therefore, no real conclusion can be made about the exact time point in the premanifest phase when and the brain region where hyperactivation takes place. However, it’s quite clear that there is regional increased activation somewhere during the premanifest phase of the disease, possibly far-from-onset. This is often interpreted as compensation for dysfunctional circuits elsewhere [177].

Several longitudinal fMRI studies have shown none or little evidence of longitudinal changes in activity. Dominguez et al. followed 29 controls, 35 premanifest HDEGC, and 18 manifest HDEGC and showed no changes in activity in either the controls or the premanifest HDEGC after a period of 30 months. The symptomatic HDEGC did show a reduction over time [168]. Poudel and colleagues showed no longitudinal change in activation in early manifest HDEGC and controls after a follow-up of 30 months [178]. However, in the premanifest cohort, there was a progressive increase in activation in the dorsolateral prefrontal cortex and frontal regions over 18 months [179] and over 30 months [178]. Also, Wolf et al. found no evidence of longitudinal changes in activity after a 2-year follow-up of 13 premanifest HDEGC and 13 controls [180].

There have been fMRI studies that relate neural activity to specific symptoms, especially neuropsychiatric symptoms [154]. One study found a positive correlation between depressive symptoms and activation of the ventromedial prefrontal cortex during the Stroop interference task, in premanifest HDEGC [153]. This correlation was more significant with longer CAG repeats. Gray et al. found an association between reduced prefrontal activation in symptomatic HDEGC and severe neuropsychiatric problems such as disinhibition and depression [181]. In the longitudinal study of Dominguez and colleagues, the progressive hypoactivation in the right dorsolateral prefrontal cortex and putamen, in symptomatic HDEGC, was found to be associated with disturbances in executive functioning [168].
fMRI studies have shown us that HD is much more than a basal ganglia disorder. It serves as a tool for a better understanding of the underlying pathophysiological mechanisms, especially concerning different symptoms. Task-based fMRI studies have demonstrated compensatory mechanisms, which may serve as an important marker in the premanifest stage before clinical signs develop.

5. PET-scan

PET is a non-invasive molecular imaging technique for the quantitative imaging of biological functions. It involves the injection of a metabolically active compound labeled with a radioactive isotope, also known as radioligand. This radioligand binds to specific targets and emits gamma rays which are detectable by the gamma camera in the PET scanner. Based on the molecular pathophysiology several radioligands have been identified and used in HD imaging studies [182]. These include tracers for cerebral glucose metabolism, postsynaptic dopaminergic receptors, phosphodiesterase (PDE)10A, cannabinoid receptors, GABA receptors, adenosine A1 receptors, presynaptic terminal marker SV2A, and activated microglia as markers of neuroinflammation.

First of all, the most common radioligand is $[^{18}F]FDG$, which traces the uptake of glucose. Multiple studies using $[^{18}F]FDG$-PET scans showed glucose hypometabolism in the caudate [73, 183] and putamen [54, 73, 184–186] in manifest HDEGC compared to healthy controls. A decreased glucose metabolism has also been measured in premanifest HDEGC [54, 185, 187]. Some studies have identified hypometabolism in the cortex as well [54, 73, 183, 187]. Researchers have found a progressive decline in glucose metabolism over the years [185, 188] and could correlate decreased metabolism in the caudate [189] and the putamen [190] with predicted time to symptomatic onset. Some of these studies corrected the measured glucose uptake for volumetric loss and found hypometabolism to be independent of atrophy [54, 73, 184, 191]. This makes it plausible that altered glucose metabolism precedes volumetric loss. If metabolism is not corrected for partial volume, metabolic deficits could simply be a consequence of neuronal atrophy. Furthermore, there have been studies correlating hypometabolism with clinical assessments, such as cognitive decline [183, 192] and severity of motor symptoms [186]. A recent study from Sampedro et al., which corrected for partial volume, found frontotemporal hypometabolism which correlated to the severity of apathy, and striatal hypometabolism which correlated with motor and cognitive UHDRS scores [73]. Limitations in FDG-PET studies are the several influencing factors like hyperglycaemia [193] and psychotropic drugs including benzodiazepine which can decrease the (global) brain activity and thus the glucose metabolism [194].

Other radiotracers which are useful in HD research are the ones that trace postsynaptic dopaminergic receptors. $D_1$ receptors can be investigated using the radioligand $[^{11}C]SCH23390$ and $D_2$ receptors are measured by using $[^{11}C]raclopride$. In PET studies, loss of post-synaptic $D_1$ and $D_2$ receptors has been reported in premanifest [195–197] and manifest HDEGC [198, 199]. Longitudinal studies showed an annual loss of striatal $D_1$ en $D_2$ receptors and this decline seems to be faster during earlier premanifest disease stages [195, 200]. It has been shown that $[^{11}C]raclopride$ is a more sensitive marker of disease progression than glucose metabolism, showing a higher annual loss of $D_2$ receptors than a decline of striatal glucose uptake [185]. Furthermore, it has been shown to precede striatal atrophy [201]. Studies have also
found correlations between dopaminergic receptor loss and CAG repeat (after correcting for age) [201, 202], severity of cognitive function [203], TMS [204], and TFC [195]. Decreased D$_2$ binding in the putamen correlated with higher chorea scores on the TMS and cognitive decline [204]. The specific areas within the striatum have also been linked to specific clinical manifestations. Motor signs have been linked to loss of dopamine receptors in the sensorimotor striatum [200], while the associative striatum, in addition to the temporal cortex, is more involved in cognitive decline [205]. Cortical reduction in D$_2$ receptor binding has also been identified in premanifest HDEGC and manifest HDEGC, where the loss of receptors was correlated with worse attention and executive function [205]. Other regions with loss of dopaminergic receptors are the thalamus [203], hypothalamus [206], and frontal and temporal regions [200].

Radioligands that trace PDE10A have been identified in the last decades, such as $[^{18}F]$MNI-659 and $[^{11}C]$IMA107. Studies in premanifest [207] and manifest HDEGC show a decrease in PDE10A in the caudate and putamen [208], and also in the globus pallidus [209], compared to healthy controls. Two longitudinal studies showed a progressive decrease in these three regions with disease progression, of which decline in the caudate was the most obvious [210, 211]. Fazio et al. showed a slightly more rapid decline from late premanifest to HD stage I, than from early premanifest to late premanifest. Loss of PDE10A has been correlated with more severe motor scores, disease burden, and striatal atrophy [209]. Several studies have shown that annual changes in PDE10A expression were greater than the annual changes in dopamine D$_2$ receptors [185, 195, 200, 211]. This makes PDE10A an even more sensitive marker of disease progression than dopaminergic receptors.

Researchers have identified radiotracers that can detect specific receptors that are related to the HD pathophysiology. Van Laere et al. looked at cannabinoid type receptor (CB$_1$R) levels with the radioligand $[^{18}F]$MK9470 and found a decreased level in the cortex, brainstem, and cerebellum of early manifest HDEGC. They also found an association between the loss of CB$_1$R and increased disease burden scores [212]. Ceccarini and colleagues measured CB$_1$R levels in premanifest HDEGC and found a decreased binding in the prefrontal cortex, which correlated with depression. They included a control group consisting of gene-negative subjects from HD families to control for potential effects of distress caused by growing up in an HD family and undergoing genetic testing [62].

Two PET studies that have looked at GABA receptor expression, using $[^{11}C]$flumazenil, and glucose uptake, using $[^{18}F]$FDG, found a lower level of GABA receptors in the caudate of early manifest HDEGC, compared to healthy controls. Glucose uptake was decreased in the caudate, putamen, and thalamus of these HDEGC [213, 214].

One PET study used $[^{18}F]$CPFPX to look at striatal adenosine A$_1$ receptors and found a decreased level in the caudate and putamen, in manifest HDEGC compared to healthy controls. There was no significant difference in receptor levels in the caudate and putamen of premanifest HDEGC, compared to healthy controls. However, in the thalamus, they did find a significant increase in A$_1$ receptor level in premanifest HDEGC far-from-onset, while there was no significant difference in the group close-to-onset [215].

There is one PET-study looking at synaptic damage using the tracer $[^{11}C]$-UCB-J for the presynaptic terminal marker SV2A. In manifest HDEGC, they found a significant loss of SV2A binding in the putamen, caudate, pallidum, cerebellum and parietal, temporal and frontal cortex, whereas glucose metabolism observed with an $[^{18}F]$-FDG PET was only reduced in the caudate and putamen of these patients. Loss of
SV2A in the putamen correlated with the TMS. In premanifest HDEGC there was only significant decrease in SVA2 in the caudate and putamen [57].

To study the role of neuroinflammation in cerebral and neurodegenerative diseases, radiotracers that bind to activated microglia can be used, e.g. $[^{11}C]$PK11195. Studies in HD subjects using $[^{11}C]$PK11195 have shown increased microglial activation in striatal and cortical regions in both premanifest and manifest HDEGC, with a correlation to loss of striatal D$_2$ receptors [216, 217]. Increased glial activation has also been found in the putamen and pallidum in HDEGC [218]. Studies found microglial activation to be correlated to the severity of motor symptoms [216, 219], disease severity and higher probability of motor onset over the next 5 years [219], and increased levels of interleukins IL-1$\beta$, IL-6, IL-8, and TNF-$\alpha$ [220]. Regions of increased activation also seem to differ in disease progression. The dorsal striatum, which is involved in motor and cognitive function, is often affected in premanifest stages. The ventral striatum, involved in psychiatric symptoms, is affected later in the manifest phase [219].

6. Conclusion and future perspectives

Based on the cumulative evidence of the imaging studies included in this chapter, it can be concluded that clinical diagnosis of HD is not the starting point, but rather the endpoint of the neuropathophysiological changes. To summarize the current results of all these neuroimaging modalities along the disease course, we made a hypothetical graph (Figure 1). It must be emphasized that this is a hypothetical graph.
and may change as new studies are published in the future. Certain disease stages, such as the more advanced stages, have not been sufficiently studied with neuroimaging to make any conclusions. Nevertheless, it places current findings in perspective, by comparing the changes for each modality set against disease progression.

MRI-based brain volume measurements have already been used since the beginning of the 1990s in HD research and have consistently identified volume loss in multiple regions of the brain. These volume changes seem to start in the striatum, years before clinical onset and spread over the cortex ending up affecting widespread regions of the gray and white matter. Longitudinal studies have shown decreasing volumes of the striatum and specific cortical regions, which correlated with clinical outcome measures and genetic variables. All these factors make structural MRI a valuable technique that is helpful to predict clinical onset before diagnosis, although it is still not applicable on an individual level.

To analyze the microstructural differences, which develop before volume loss, DTI is a better imaging modality. This especially applies to the analysis of white matter changes. DTI studies have identified diffusion abnormalities in widespread regions of the brain, showing certain areas with decreasing diffusion while others have increasing diffusion measures in the same stage. These ratios seem to correlate with certain genetic and clinical variables. These results suggest a more important role for white matter disorganization in HD than we previously thought. A potential application of this knowledge might be in classifying and understanding HD phenotypes according to the differences observed in diffusion maps. Nevertheless, longitudinal diffusion effects have not been consistently proven to date.

Specific MRI sequences have improved our knowledge of the HD pathophysiology, can be used as a biomarker for stage-conversion, and give insights into alternative approaches for disease-modifying treatments. Iron accumulations and metabolic changes seem to precede clinical diagnosis and progress with advancing disease stages. However, longitudinal data and consistent cross-sectional results are still lacking.

fMRI studies have shown that HD is more than just a basal ganglia disorder, even in the premanifest stages of the disease. Using fMRI studies, we have been able to improve our understanding of the disease’s pathophysiology. Increased connectivity after task performance precedes clinical diagnosis, which might be a compensatory mechanism that slows down the conversion into the manifest stage. One of the limitations is that this modality has not been able to consistently detect a significant change over time.

PET-scans can be used to detect early pathophysiological changes before structural changes, like glucose metabolism, neuroinflammation, and receptor level expression. $[^{18}F]$FDG PET is a less sensitive marker compared to dopaminergic D2-receptor ligand $[^{11}C]$raclopride to monitor disease progression. PDE10A expression using different PET-tracers was found to be an even more sensitive marker than dopamine receptor levels. PET-scans improve our knowledge of disease pathophysiology at a molecular level and could help us in evaluating treatment response. At this moment iMagemHTT is in the recruitment phase to study novel mutant huntingtin PET radio-ligands $[^{11}C]$CHDI-00485180-R and $[^{11}C]$CHDI-00485626 and test their suitability for the quantification of aggregated mutant huntingtin in the brain of HDeligible compared to healthy controls [221]. This imaging method combines proteomic knowledge with neuroimaging to improve our knowledge of mHTT aggregation in the brain and it could improve evaluating treatment response.
Multimodal imaging studies, where multiple imaging modalities are used together in one study, are the future of neuroimaging research. To combine these data, researchers have started to use artificial intelligence such as machine learning. It has already been used to develop a multimodality neuroimaging polymarker of HD with the ability to identify HDEGC who are within 5 years of their clinical motor diagnosis. This polymarker consisted of subcortical region volume, cortical thickness, and resting-state functional connectivity [222]. One study used machine learning on neuroimaging datasets to successfully classify between premanifest HDEGC and controls [223]. Mohan et al. recently used machine learning to develop a new disease progression model with nine disease states of increasing severity, based on clinical data only [224]. Another focus in HD-research, requiring artificial intelligence, is the use of network models to explain the pathology of the disease progression and disease phenotypes [158, 225]. However, machine learning algorithms require large amounts of data, before they start to provide useful results, especially when it comes to neural networks. Application in larger imaging studies or the combination of datasets can therefore be expected in the future.

Furthermore, studies should be multicentred to overcome the most common limitation of all included research, which is a small study population. Nevertheless, standardization is not that easy, especially when it concerns advanced MRI-techniques. Despite the excellent performance of different PET-tracers as biomarkers, PET has a major limitation. Not all PET-studies can be performed at every site due to the need for an on-site cyclotron to produce $^{11}$C-labeled radioligands.

Using different imaging modalities new pathophysiological mechanisms have been discovered or hypothesized, such as neuroinflammation, iron deposition, cellular reactions, regional deposition of the huntingtin protein. This shines a new light on therapeutic approaches and could serve as a drug target image technique. The imaging of such biomarkers has also some limitations. A biomarker could be relevant only in specific disease stages, after specific physiological events, or present during a limited period of time [5]. An ideal biomarker should change longitudinally, as time and disease progresses. Therefore, longitudinal imaging studies are of great importance. Another characteristic of an ideal biomarker is that it should change in response to disease-modifying treatment, something quite valuable in future clinical trials.
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