Title: White matter changes in Huntington's disease and the demyelination hypothesis: a critical review of MRI studies

Key words

Huntington's disease, white matter microstructure, myelin, MRI, animal models of Huntington's disease, symptomatic, pre-symptomatic, oligodendrocytes.

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Competing interests

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Abstract

Huntington's disease (HD) is a genetic neurodegenerative disorder, characterised by atrophy of the neostriatum, and cortical grey matter (GM) abnormalities. White matter (WM) alterations have recently been identified as a relevant pathophysiological feature of HD, but the etiology of WM degeneration, and its role in disease pathogenesis and progression remain unclear. An increasing body of research suggests that WM changes in HD are due to alterations in myelin-associated biological processes at the cellular and molecular level. This review first discusses evidence from neurochemical studies lending support to the 'Demyelination hypothesis' of HD, and pointing towards a role for aberrant myelination and changes in oligodendrocytes in HD WM. Next, evidence from neuroimaging studies is reviewed, the limitations of the described methodologies are discussed and suggested interpretations of findings from published studies are challenged. Although our understanding of HD-associated pathological changes in the brain will increasingly rely on neuroimaging techniques, the shortcomings of these methodologies must not be forgotten. Advances in MRI techniques and tissue modeling will enable a better characterization of the biological properties of WM microstructure, and will allow more specific monitoring of longitudinal changes noninvasively. This, in turn, will provide insight into disease pathogenesis and progression and facilitate the identification of disease-related biomarkers and the specification of outcome measures in clinical trials.

Introduction

Huntington's disease (HD) is a genetic, neurodegenerative disorder, leading to debilitating cognitive, psychiatric and motor symptoms. The mutation accountable for

HD is an expansion of the cytosine-adenine-guanine (CAG) repeat within the *huntingtin* (HTT) gene. Clinical diagnosis of 'symptomatic' HD requires the onset of motor abnormalities such as chorea, motor impersistence (i.e. the inability to sustain simple voluntary movements), along with the presence of a family history of the disease (Paulsen et al., 2008). Currently, this devastating disease cannot be cured, and a research priority is to increase the understanding of its pathogenesis and to provide biomarkers for evaluating the efficacy of targeted therapies.

Although HD pathology is tightly associated with degeneration of striatal grey matter (GM) (Weaver et al., 2009), over the past years HD research has identified white matter (WM) changes as relevant pathophysiological features of HD (Bardile et al., 2018; Bartzokis et al., 2007; Beglinger et al., 2007; Ciarmiello et al., 2006; Gregory et al., 2018; Paulsen et al., 2008; Reading et al., 2005; Rosas et al., 2018; Wang & Yang, 2019). However, despite a subcortical WM volume loss of 29-34% already having been reported in post-mortem HD brains over 20 years ago (de la Monte et al., 1988), the etiology of WM degeneration, and its role in disease pathogenesis and progression remain unclear.

While some work suggests that WM damage in HD is secondary to the loss of GM volume in the form of Wallerian degeneration (Di Paola et al., 2014; Gauthier et al., 2004; Rosas et al., 2018; Weaver et al., 2009), there is evidence suggesting that WM aberrations are a feature of HD that occur independent of neuronal cell loss (Beglinger et al., 2007; Mascalchi et al., 2004; Myers et al., 1991; Paulsen et al., 2008; Reading et al., 2005; Rosas et al., 2008; Tabrizi et al., 2009). Accordantly, WM changes are present very early in the disease course, even in pre-symptomatic individuals who are over 15 years away from symptom onset (Aylward et al., 2011; Bartzokis et al., 2007; Tabrizi et al., 2009). Notably, WM is composed of axons as well

as non-neuronal glia cells, such as myelin-producing oligodendrocytes, and it is unclear whether axons, myelin, or both are predominantly responsible for the WM loss (Gregory et al., 2018).

An increasing body of research suggests that WM in HD is subject to alterations in myelin-associated biological processes at the cellular and molecular level (Gómez-Tortosa et al., 2001; Huang et al., 2015; Jin et al., 2015; Myers et al., 1991; Simmons et al., 2007.; Teo et al., 2016). Myelin is an axon wrapping multi-layered sheath and is produced by oligodendrocytes. Myelination of axons is vital during brain development and critical for healthy brain function, as it plays a fundamental role in the regulation of efficiency and speed of action potential propagation during synaptic transmission (Martenson, 1992). Dysfunction of oligodendrocytes and of myelin can slow down or stop otherwise fast axonal transport, which in turn can result in synaptic loss and eventually axonal degeneration (Han et al., 2010). Furthermore, as myelination patterns across the brain enable the temporal synchronisation of information processing, local demyelination can disrupt the performance of functional networks (Nickel & Gu, 2018)

The 'Demyelination Hypothesis' of HD (Bartzokis et al., 2007) suggests that mutant huntingtin (the protein produced by the huntingtin gene) leads to premature myelin breakdown in HD. A dysfunction of oligodendrocytes, in turn, might impair repair of de-myelinated axons, leading to chronic demyelination. Alternatively, as oligodendrocytes are the major iron-containing cells of the central nervous system (CNS), it might be that homeostatic increases in these cells, related to their role in re-myelinating axons, cause significant increases in ferritin iron content. High ferritin iron is proposed to have toxic effects and could further contribute to impairments in WM

and myelination (Bartzokis, et al., 1999; Bartzokis & Tishler, 2000; Bartzokis et al., 2007)

The objective of the present work was to systematically review the impact of HD pathology on WM microstructure, and to evaluate evidence on the ‘Demyelination Hypothesis’ (Bartzokis et al., 2007), which was initially proposed ten years ago.

To look for relevant articles, we performed a search in PUBMED and GoogleScholar.com using the following keywords: Huntington’s Disease, white matter, white matter microstructure, myelin, myelination, diffusion tensor imaging, magnetic resonance imaging, mouse models of Huntington’s Disease, pre-symptomatic, symptomatic, oligodendrocytes, iron. The articles identified were short-listed based on their titles and abstracts. The reference sections of relevant papers were also used to search for additional relevant articles. The criteria for inclusion in this review were: studies describing WM changes in HD mutation carriers either at the pre-symptomatic or symptomatic stage; studies on animal models of HD investigating molecular or cellular processes linked to WM microstructure or assessing HD-related changes in brain structure with magnetic resonance imaging (MRI). A total of 68 studies, published between 1973 and 2019, were reviewed. 43 of these described research involving HD patients.

2. White matter impairment in HD: secondary to, or independent of, neuronal degeneration?

WM changes have been reported both in animal models and in HD human carriers by histopathological postmortem studies (de la Monte et al., 1988; Halliday et al., 1998; Huang et al., 2015; Jin et al., 2015), and MRI studies (Bartzokis et al., 2007; Jin et al., 2015; Meng, Jiang, Bachevalier, Zhang, & Chan, 2017; Rosas et al., 2006,

2018; Tabrizi et al., 2009, 2011). These have shown widespread WM volume loss (Aylward et al., 2011; Beglinger et al., 2007; Ciarmiello et al., 2006; Paulsen et al., 2008; Rosas et al., 2006; Tabrizi et al., 2009, 2012, 2011) and WM alterations at the microstructural and molecular level (Bartzokis et al., 2007; Dumas et al., 2012; Huang et al., 2015, 2015; Jin et al., 2015; Mascalchi et al., 2004; Matsui et al., 2014; Reading et al., 2005; Rosas et al., 2006; Stoffers et al., 2010; Wang & Yang, 2019).

The earliest WM alterations are seen in HD human carriers years before the onset of signs and symptoms of manifest HD. Prominent areas of damage include the striatum, the corpus callosum (CC) and posterior WM tracts (Di Paola et al., 2014; Dumas et al., 2012; Faria et al., 2016; McColgan et al., 2018; Tabrizi et al., 2011). Furthermore, the severity of WM changes has been shown to correlate with predicted time to symptom onset in pre-manifest patients (Ciarmiello et al., 2006; Paulsen et al., 2008; Stoffers et al., 2010), with measures of motor dysfunction (Rosas et al., 2006), and with cognitive deficits (Bohanna et al., 2008; Rosas et al., 2006).

2.1 Evidence from neurochemical studies

This section reviews evidence for molecular and neurochemical changes in oligodendrocyte lineage cells and myelin sheaths in HD. These changes have been reported in some human subjects and also in studies of animal models of HD.

The phenotype exhibited by each animal model of HD needs to be considered in the context of the different approaches used to generate the respective model (Pouladi, Morton, & Hayden, 2013). Key distinguishing factors are the genetic approach and transgene construct used; for example, the use of full-length or only a fragment of mutant huntingtin (HTT); the length of the CAG repeat incorporated into the genome; the expression of the HD mutation from a transgene versus knock-in of

the mutation into the endogenous HTT locus. In general, since knock-in models carry the mutation in its appropriate genomic and protein context, they are considered as more accurate genetic models of the human condition, as compared to transgenic models (Menalled, 2005).

2.1.1 Abnormalities of oligodendrocyte lineage cells in HD

A dramatically lower number of mature oligodendrocytes during the postnatal myelination period has been shown in the HdhQ250 knock-in mouse model of HD, suggesting deficits in developmental myelination in HD. On the other hand, enhanced proliferation of oligodendrocyte precursor cells (OPCs) was found in adult HdhQ250 mice (Jin et al., 2015). Additionally, Simmons et al. (2007) reported increased immunostaining for ferritin, an iron storage protein that is mostly found in oligodendrocytes, in the striatum, cortex and hippocampus of the R6/2 transgenic mouse model of HD, detectable before any behavioural abnormalities could be observed. Human post-mortem histopathological studies have also demonstrated an increase in the density of oligodendrocytes in the striatum of HD patients compared to healthy controls, years before striatal atrophy or loss of neurons occurs (Gómez-Tortosa et al., 2001; Myers et al., 1991). The increased number of oligodendrocytes observed suggests the presence of a homeostatic myelin repair mechanism, aiming to compensate deficits in myelination that seem to occur in early stages of HD.

In contrast, a study using carbon-14 dating approaches indicated that oligodendrocyte lineage cells are the most depleted cell types amongst all non-neuronal cells in the symptomatic HD brain (Ernst et al., 2014), suggesting that HD might be associated with lack of oligodendrocytes, which cannot repair demyelinated axons. Accordingly, silencing oligodendroglia-specific mutant-HTT (mHTT) expression

in BACHD mice rescues deficits in thickness and compactness of myelin sheaths that otherwise occur in these mice (Bardile et al., 2018), and expressing mHTT selectively in oligodendrocytes of transgenic mice induces impairments in myelination (Huang et al., 2015). Overall, the present findings suggest that there is a relationship between the HD mutation and oligodendrocyte dysfunction.

To summarize, while increased numbers of oligodendrocytes have been observed, their dysfunctionality may lead to unsuccessful myelination. It is also possible that the observed increased levels of oligodendrocytes are helpful at first but eventually lead to toxicity because of increased iron levels. Both explanations fit within the 'Demyelination Hypothesis' (Bartzokis et al., 2007) as they implicate an increasingly unsuccessful compensation for the disease-related myelin loss.

2.1.2 Myelin changes in HD

Reports from human post-mortem studies have demonstrated a striking breakdown of myelin in the HD brain (Bruyn & von Wolferen, 1973). Additionally, some studies on animal models have demonstrated impairments in developmental myelination in HD indirectly: these have shown that the expression of a mutant huntingtin transgene in cells and in R6/2 transgenic mice leads to reduced activity in the cholesterol biosynthesis pathway, leading to lower levels of newly synthesized cholesterol and its intermediates (Valenza et al., 2007, 2005), which are essential for the synthesis of myelin (Dietschy & Turley, 2004).

Electron microscopy investigations have reported thinner myelin sheaths, as reflected by higher g-ratios (the ratio of the inner axonal diameter to the outer diameter), in transgenic BACHD rats and in the HdhQ250 knock-in mouse model (Jin et al., 2015; Teo et al., 2016). HD myelin changes might either represent a breakdown

of myelin into fragments because of toxicity, or thinner myelin sheaths because of a developmental dysfunction in myelination mechanisms. Consistent with the latter, alterations in myelin sheaths are paralleled by reduced expression of myelin-related genes such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) in transgenic R6/2 and HdhQ250 knock-in mice (Blockx et al., 2012; Jin et al., 2015; Xiang et al., 2011). Reduced levels of MBP and MOG in brain regions known to be affected by HD throughout the critical postnatal myelination stage and significantly fewer myelinated axons have been reported in knock-in HdhQ250 mice (Jin et al., 2015). The reduction in myelin proteins may be due to an observed reduced expression of myelin regulatory factor (MRF), a transcription factor which controls expression of myelin-related proteins. Moreover, abnormalities in myelin sheaths and myelin-related gene transcripts in YAC128 transgenic mice are evident well before any striatal neuronal loss can be detected (Teo et al., 2016). These findings imply that a dysregulation of the temporal profile of myelination might underlie WM abnormalities and that disordered myelination during the postnatal period might constitute an important early pathogenic event in HD (Jin et al., 2015).

2.1 Evidence from imaging studies

Neuroimaging techniques enable the assessment of brain structure and function *in vivo* and allow understanding of disease pathology over time.

Structural neuroimaging studies in animal models of HD and in HD carriers have shown that WM atrophy can be found across several WM areas, including the CC, the anterior commissure (AC), internal and external capsules (IC, EC), the cingulum (CG) and that these WM changes happen very early in the disease course (Aylward et al., 2011; Ciarmiello et al., 2006; Di Paola et al., 2014; Ruocco et al., 2008;

Tabrizi et al., 2009). Table 1 summarizes MRI studies reporting WM changes in HD animal models.

Some studies have suggested that WM is more affected than GM in the HD brain. For example, Tabrizi et al. (2012) showed that the rate of change of WM volume over 24 months was greater than that of GM in pre-symptomatic and early HD patients (Tabrizi et al., 2012). Specifically, individuals carrying the mutated Huntingtin gene who were far away from clinical diagnosis showed WM loss only around the striatum and within the CC and posterior WM tracts, while early symptomatic and symptomatic HD patients showed extensive WM loss across the whole brain. Loss of WM volume over this time period ranged between 2% in HD carriers over 10 years away from disease onset and 4% in early HD patients. Effect sizes for atrophy rates between early HD participants and healthy controls were larger in WM (1.70, 1.40 to 2.08) than in GM. Additionally, a 2-year longitudinal study found that, when controlling for normal age-related variations, brain atrophy of pre-symptomatic patients was more pronounced in WM than in striatal GM (Aylward et al., 2011). Similarly, in another patient cohort (Ciarmiello et al., 2006) WM volume was drastically reduced in pre-symptomatic participants as compared to controls (35.3 ± 2.5 mL vs 37.7 ± 2.2 mL), whereas no significant differences were observed for GM volumes.

The findings summarized above suggest that there might be a dissociation between neurodegenerative processes that happen in GM and WM aberrations in HD; further, the temporal pattern of reported WM changes suggests that WM impairment in HD unlikely reflects solely a secondary result of neuronal cell death in GM, and may instead represent an independent factor of HD pathology. Evidence for a link between GM and WM changes comes from studies that show significant atrophy of the cortical mantle of HD patients both cross-sectionally (Douaud et al., 2006; Kassubek et al.,

2004; Rosas et al., 2005, 2002) and longitudinally (Ruocco et al., 2008), suggesting that WM volume loss may be a consequence of the withdrawal of axons projecting from cortical neurons.

The studies summarized above relied on measures of WM volumes. However, WM volume loss as quantified using structural MRI is a rather un-specific marker of disease stage and progression, as it is not sensitive to changes in microstructure. This makes it hard to capture differential effects across the various stages of the disease (Pflanz, 2019). As such, reductions in WM volume observed in structural neuroimaging studies can be the consequence of several factors, including a decrease in the number of axons because of Wallerian degeneration (Douaud et al., 2006; Kassubek et al., 2004; Rosas et al., 2005, 2002; Ruocco et al., 2008), a decrease in axon myelination (Ciarmiello et al., 2006; Squitieri et al., 2009), or a combination of both.

New MRI methods allow to move beyond traditional macrostructural volumetric methods and provide more in-depth information about tissue integrity and organization at the microstructural and biochemical levels.

To date, most neuroimaging studies of WM microstructure have used diffusion tensor MRI (DT-MRI) (Pierpaoli & Basser, 1996) to quantify tissue properties. This technique allows to characterize the three-dimensional diffusion of water as a function of spatial location and it is based on differential diffusion of water molecules depending on tissue type and architecture (Beaulieu, 2002). For example, the molecular diffusion rate (mean diffusivity (MD)), the directional preference of diffusion (fractional anisotropy (FA)), the diffusion rate along the main axis of diffusion (axial diffusivity (AD)), and the rate of diffusion in the transverse direction (radial diffusivity (RD)) can be inferred.

Some evidence from DT-MRI studies suggests that WM aberrations in HD are a consequence of Wallerian axonal degeneration. For example, it has been shown that WM changes correlate with reductions in cerebral GM density (Di Paola et al., 2014; Rosas et al., 2018). Similarly, a DT-MRI study suggested that WM changes in HD are a consequence of axonal injury rather than demyelinating mechanisms, based on the observation of greater changes in axial diffusivity (AD), as compared to radial diffusivity (RD) changes, in the brain of HD patients (Weaver et al., 2009).

On the other hand, there are several DT-MRI studies which have suggested a role for myelin in HD pathology (Bartzokis et al., 2007; Bourbon-Teles et al., 2017; Di Paola et al., 2012, 2014; Mascalchi et al., 2004; Rosas et al., 2018). These studies parallel findings from post-mortem, histopathological studies in HD patients (Bruyn & von Wolferen, 1973). A study employing both structural and DT-MRI found fractional anisotropy (FA) and RD changes in the isthmus of the CC of pre-symptomatic patients, in the absence of any changes in AD (Di Paola et al., 2012). Furthermore, this study found increased RD and decreased AD in the CC in manifest HD patients. Di Paola and colleagues (2012) concluded that these findings suggest demyelination in the pre-symptomatic stage and myelin breakdown and axonal damage in manifest HD. Similarly, Rosas and colleagues (2018) showed increased RD in the WM of pre-symptomatic HD patients, which correlated with impaired performance on neuropsychological tests, and was proposed to reflect early deficits in myelin. On the other hand, they suggested that axonal pathology, as shown by changes in AD, is present only later in the disease course.

All of the above interpretations are based on the assumption of a direct correspondence between a specific microstructural property of WM and variations in DT-MRI metrics. However, although DT-MRI metrics are often regarded as probes of

WM microstructure, these indices do not tap specifically onto biological subcomponents of WM microstructure (Alexander et al., 2007) in that the tensor measured in the DT-MRI model is an average of all the cellular compartments within a specific voxel (Assaf & Basser, 2005). It is therefore very hard to interpret changes in DT-MRI metrics in terms of changes in specific microstructural properties (Jones, Knösche, & Turner, 2013). Very different configurations of, for example, axonal packing, axonal size and myelination may generate very similar outcome measures. Furthermore, the radial and axial diffusivities become hard to interpret when multiple fibre orientations are present within a voxel, such as at fibre bundle crossings (Wheeler-Kingshott & Cercignani, 2009), and this situation affects between one and two thirds of the voxels in a human brain (Behrens et al., 2007; Descoteaux, 2008).

Specifically, these interpretations are based on the assumption that AD and RD are uniquely sensitive to axonal degeneration and demyelination, respectively (Budde et al., 2007; Mac Donald et al., 2007; Song et al., 2002, 2005, 2007; Sun et al., 2006; Wu et al., 2007). Such inferences are based on one study on Shiverer mice, where changes in myelin content were linked to increased RD, but unchanged AD (Song et al. 2002). However, an increase in RD might not necessarily correspond to myelin loss; rather, it can have multiple meanings, including axonal loss (Jones et al., 2013). Furthermore, in regions of crossing fibres, increased RD within a specific tract could be due to a less coherent alignment of fibres, more crossing fibres from other bundles, lower density or less myelination of the fibres, or a combination of any or all these factors (Jones et al., 2013; Wheeler-Kingshott & Cercignani, 2009).

Biophysical models of diffusion MRI, such as neurite orientation and dispersion density imaging (NODDI) (Zhang et al 2012) and the composite hindered and restricted model of diffusion (CHARMED) (Assaf & Basser, 2005), model compartment-specific

water diffusion to dissociate hindered extra-cellular and restricted intra-cellular diffusion properties of WM, and should therefore provide a more biologically specific characterization of WM microstructural organization within the neural system (Alexander et al., 2010).

Zhang et al., (2018) used NODDI to examine WM pathology in pre-manifest HD patients. They reported widespread reductions in the neurite density index (NDI) - a proxy of axonal density - in tracts including the CC and in WM surrounding the basal ganglia of pre-symptomatic HD patients. Importantly, axonal density reductions in callosal regions predicted clinical markers of disease progression. Finally, increased coherence of axonal organization was shown in tracts surrounding the basal ganglia and in the IC and EC, suggesting the presence of possible compensatory pruning of axons in WM regions. Nevertheless, estimation of specific tissue quantities from these models requires simplifying assumptions whose accuracy and generality, in the HD brain especially, are unknown. These techniques indeed still represent a relatively simple approach to modelling neural tissue and therefore cannot fully characterize pathological changes in WM microstructure (Lampinen et al., 2019).

Quantitative magnetization transfer (qMT) imaging has enabled greater sensitivity to myelin content in WM (Ou et al., 2009). This method models the exchange rate between macromolecular protons and protons in surrounding tissue water, when macromolecular protons are subjected to a radiofrequency pulse with a frequency that is off-resonance for protons in free water (Henkelman et al., 1993). One of the outcome measures of qMT, the macromolecular proton fraction (MPF), has been shown to reflect demyelination in Shiverer mice and puppies (Ou et al., 2009; Samsonov et al. 2012), to be sensitive to dysmyelination processes in multiple sclerosis patients (Levesque et al., 2010) and to reflect myelin content of WM in post-

mortem studies of multiple sclerosis brains (Schmierer et al., 2007). A study by Bourbon-Teles et al. (2019) used quantitative magnetization transfer (qMT) to investigate HD-related effects on the MPF, and found pre-symptomatic and early symptomatic HD patients to exhibit MPF reductions in comparison to controls. Furthermore, MPF changes were shown to be related to DT-MRI-based WM measures.

Though the MPF is sensitive to WM myelin, this metric can also be affected by changes in cells and water content due to inflammation (Henkelman, Stanisz, & Graham, 2001). Odrobina and colleagues (2005) for example, measured the MPF *ex vivo* in a demyelinated rat sciatic nerve and confirmed its correlation with myelin content, but also noted the difficulty of separating demyelination from inflammation by qMT alone. Nevertheless, while in manifest HD it is likely that inflammation goes hand in hand with myelin breakdown (Rocha et al., 2016), a recent CSF biomarker study found no evidence of neuro-inflammation in early-manifest HD (Vinther-Jensen et al., 2016). It is therefore plausible that changes in the MPF observed in this study are a reflection of aberrant myelination in these patients.

Human MRI studies have also shown that HD is associated with changes in iron levels across several brain areas (Bartzokis et al., 1999; Bartzokis & Tishler, 2000; Bartzokis et al., 2007; Phillips et al., 2014; Simmons et al., 2006). Tissue iron can be measured by MRI *in vivo* through its effect on transverse relaxation times (T2). Ferritin has been shown to strongly affect the MRI signal and markedly shorten T2 both *in vitro* and *in vivo* (Bartzokis, 1997; Malisch et al., 1991).

Increased ferritin levels are already present in the pre-symptomatic stage of HD (Jurgens et al., 2010; Phillips et al., 2014). As oligodendrocytes contain iron (Connor & Menzies, 1995), the increased density of oligodendrocytes demonstrated in mouse

models of HD should result in significant increases in iron and ferritin content in the HD brain. Evidence for increases in MRI-based iron measures in HD further supports the suggestion for a homeostatic increase in oligodendrocytes as an active repair mechanism in pre-symptomatic HD subjects.

Early and heavily myelinated fibres are the most susceptible to myelin breakdown in HD (Bartzokis et al., 2007), with WM degeneration starting in the caudate and putamen striatum structures and then spreading in a predictable, bilateral and symmetric pattern to involve other earlier-myelinating regions. In turn, later-myelinating regions like the medial temporal lobe, are left much less affected (Bartzokis et al., 1999; DiFiglia et al., 1997). This is consistent with neuroimaging evidence that the earliest WM changes in HD are seen before disease onset, in early myelinating regions, such as around the striatum, within the CC, and in posterior WM tracts (Di Paola et al., 2014; Dumas et al., 2012; Faria et al., 2016; Tabrizi et al., 2011). This spatial pattern of pathology is in contrast with the “last-in-first-out hypothesis” that was proposed for degenerative processes of normal brain aging (Raz, 2000), which postulates that later-myelinating fibres are more vulnerable to insult in later life, as compared to earlier-myelinating ones.

Consistent with the suggestion of a dissociation between early and late myelinating regions in WM impairment in HD (Bartzokis et al., 2007), Bartzokis and colleagues (2007) showed decreased ferritin iron levels in HD in the genu of the corpus callosum and frontal WM (late-myelinating regions), and increased ferritin iron levels in the basal ganglia (an early-myelinating region). Decreased iron levels in late myelinating regions are proposed to be due to suboptimal iron availability, due to a redistribution of iron towards earlier-myelinating regions. Furthermore, although re-myelination processes may successfully compensate for myelin loss during the pre-

symptomatic HD stage, these may start failing in later years, likely explaining evidence of decreases in iron content found between the pre-symptomatic and symptomatic HD subjects (Di Paola et al., 2014; Phillips et al., 2014).

3. Discussion and future directions

In the present review, we discussed evidence of WM abnormalities in HD. Although this disease has been tightly linked to striatal GM degeneration, an accumulating body of evidence suggests that alterations in WM microstructure are present early in HD progression (Aylward et al., 2011; Ciarmiello et al., 2006; Paulsen et al., 2008; Ruocco et al., 2008; Tabrizi et al., 2009), possibly even before any changes can be detected within the striatum (Aylward, et al., 2011). This implies that WM disturbances might independently contribute to HD pathogenesis (Aylward et al., 2011; Bartzokis et al., 2007; Tabrizi et al., 2009) and that, rather than being secondary to axonal insult in the form of Wallerian degeneration (Weaver et al., 2009; Zhang et al., 2018), they might be a direct result of myelin and oligodendrocytes disturbance (Bartzokis et al., 2007; Gómez-Tortosa et al., 2001; Mascalchi et al., 2004; Myers et al., 1991; Radulescu et al., 2018). Demyelination has been associated with severe disabilities in many developmental, psychiatric and neurodegenerative diseases (Martenson, 1992). Therefore, it is possible that also in HD, myelin loss, which leads to altered axonal conduction and axonal damage, may be directly responsible for some of the clinical symptoms. Furthermore, oligodendrocyte dysfunction early in the disease course may impair processes of remyelination and myelin repair (Bartzokis et al., 2007).

A number of studies on HD animal models (Blockx et al., 2011, 2012; Jin et al., 2015; Meng et al., 2017; Xiang et al., 2011) have lent support to the ‘Demyelination

Hypothesis' of HD (Bartzokis et al., 2007). Studies on human HD carriers also suggest the presence of myelin dysfunction (Bartzokis et al., 2007; Bourbon-Teles et al., 2017; Di Paola et al., 2012; Mascalchi et al., 2004; Rosas et al., 2018). However, most studies assessing WM changes *in vivo* have employed DTI-MRI based metrics to quantify these alterations, even though these indices do not tap specifically onto biological subcomponents of WM microstructure (Alexander et al., 2007; Assaf & Pasternak, 2008; De Santis et al., 2014). Recent advances in MRI techniques and tissue modeling enable a better characterization of the biological properties of WM microstructure, and allow more specific monitoring of changes in these properties, both longitudinally and noninvasively (Heath et al., 2018). Longitudinal studies designed to relate specific microstructural changes to the genesis of pathology, while controlling for individual differences such as the impact of environmental factors, will prove particularly useful. Although it is evident that our understanding of the HD brain will increasingly rely on advanced MRI techniques, this reliance highlights the need to remember and address the shortcomings of these methodologies.

Identification of early changes in brain WM micro-structure in HD patients is of fundamental importance as it allows insight into disease pathogenesis and progression and, further, might prove useful for the identification of disease-related biomarkers and in measuring outcomes of clinical trials. In many neurodegenerative diseases such as Alzheimer's and Parkinson's disease, myelin disturbance starts before other pathological changes are evident (Bartzokis, 2007, 2011). Similarly, in HD critical pathogenic events might be present prior to neuronal death, and there might be a decades-long period in which therapeutic intervention could change the course of the disease, before clinical evidence such as behavioral, cognitive and motor decrements, appears. Nonetheless, *in vivo* investigation of demyelination in pre-

symptomatic and symptomatic HD patients remains relatively unexplored when compared to other neurodegenerative diseases such as multiple sclerosis, and very little research has been carried out on the HD brain using these approaches.

To conclude, we have reviewed the evidence that implicates WM aberrations and in particular impaired myelin and oligodendrocytes in HD pathology, and suggests that these could constitute important targets for the study and early treatment of HD.

Table 1. Summary of the reviewed MRI studies assessing WM changes in animal models of HD as compared to wild type (WT). MRI studies on animal models of HD support the hypothesis that WM disturbance is an early pathogenic event in this disease (Blockx et al., 2011, 2012; Carroll et al., 2011; Meng et al., 2017), and suggest distinct developmental trajectories of several WM areas in this disease, as shown by asymmetric age-related changes for various MRI metrics between HD animal models and controls over the lifespan.

Species/Model	MRI Technique (In vivo/Ex vivo)	Findings	Neurochemical validation	References
R6/2 mice	DT-MRI (Ex vivo)	FA reductions in genu and splenium of the corpus callosum.	Yes	Xiang et al., (2011)
YAC128 mice	Structural MRI (Ex vivo)	Progressive loss of WM volume. Corpus callosum, anterior commissure and fimbria are amongst the most discriminatory areas in genotype separation.	No	Carroll et al., (2011)
YAC128 mice	DT-MRI (In vivo)	FA reductions in the anterior commissure, corpus callosum, internal capsule, external capsule, from 1.5 months of age; in the cingulum and cerebral peduncle from 3 months of age.	Yes	Teo et al., (2016)
BACHD rats	DT-MRI (In vivo)	FA reductions in the anterior corpus callosum, the cingulum and the external capsule at 12 months of age.	Yes	Teo et al., (2016)
TgHD rats	DT-MRI and PET (In vivo)	Increased MD in HD rats at 12 months of age, compared to earlier time points; this parameter remained constant in WT animals. Age-related RD decreases at 6 months of age in HD animals but only at 12 months in WT animals.	Yes	Blockx et al., (2011)
TgHD rats	Diffusion Kurtosis Imaging (In vivo)	Neuronal development in HD rat pups occurs differently compared to controls: higher MD values at P15 but lower MD and AD values at P30 in external capsule.	Yes	Blockx et al., (2012)
rHD1 rhesus monkeys	DT-MRI (In vivo)	Widespread WM changes in FA, MD, and RD. HD monkeys reached the maximal FA value earlier (22.7 ± 4.8 months) compared to controls (47.8 ± 11.7), revealing an arrest of WM maturation in the HD group; across ages, HD monkeys had significantly lower maximal FA values in all areas investigated. Significantly higher minimum RD values of HD monkeys in the striatal bundle.	No	Meng et al., (2017)

Table 2. MRI changes observed in the reviewed in vivo studies in HD patients, interpretations proposed by the respective authors and alternative explanations found in the literature for such changes.

Reported change	Proposed interpretation	Possible Alternative interpretation
Reduced WM volume	Decreased number of axons due to Wallerian degeneration (Douaud et al., 2006; Kassubek et al., 2004; Rosas et al., 2005, 2002; Ruocco et al., 2008).	Decrease in axon myelination (Ciarmiello et al., 2006; Squitieri et al., 2009).
Reduced axial diffusivity	Axonal degeneration (Weaver et al., 2009).	Inflammation, nonuniform axonal oedema, beads, varicosities parallel to the axon segments, microglia/macrophage activation (Xie et al., 2010).
Increased radial diffusivity	Demyelination (Di Paola et al., 2012; H. D. Rosas et al., 2018; Song et al., 2003, 2002, 2005; Weaver et al., 2009).	Less coherent alignment of fibres, more crossing fibres from other bundles, lower density or less myelination of the fibres, or a combination of any or all these factors (Neema et al., 2009).
Reductions in the neurite density index	Decrease in axonal density (Zhang et al., 2018).	Reduced MRI signal because of demyelination (Grussu et al., 2017).
Reductions in MMPF	Demyelination (Bourbon-Teles et al., 2019).	Changes in cells and water content due to inflammation (Henkelman et al., 1993; Odrobina et al., 2005).
Shortened T2	Increased ferritin levels (Jurgens et al., 2010; Phillips et al., 2014).	Remyelination (Stanisz et al., 2004).

References

- Assaf, Y., & Basser, P. J. (2005). Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain. *NeuroImage*, 27(1), 48–58.
<https://doi.org/10.1016/j.neuroimage.2005.03.042>
- Assaf, Y., & Pasternak, O. (2008). Diffusion Tensor Imaging (DTI)-based White Matter Mapping in Brain Research: A Review. *Journal of Molecular Neuroscience*, 34(1), 51–61. <https://doi.org/10.1007/s12031-007-0029-0>
- Aylward, E. H., Nopoulos, P. C., Ross, C. A., Langbehn, D. R., Pierson, R. K., Mills, J. A., ... PREDICT-HD Investigators and Coordinators of Huntington Study Group. (2011). Longitudinal change in regional brain volumes in prodromal Huntington disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 82(4), 405–410.
<https://doi.org/10.1136/jnnp.2010.208264>
- Bardile, C. F., Garcia-Miralles, M., Caron, N., Langley, S., Teo, R. T. Y., Petretto, E., ... Pouladi, M. A. (2018). A43 Intrinsic mutant HTT-mediated defects in oligodendroglia cells contribute to myelin deficits and behavioural abnormalities in huntington disease. *J Neurol Neurosurg Psychiatry*, 89(Suppl 1), A15–A16.
<https://doi.org/10.1136/jnnp-2018-EHDN.41>
- Bartzokis, G., Cummings, J., Perlman, S., Hance, D. B., & Mintz, J. (1999). Increased basal ganglia iron levels in Huntington disease. *Archives of Neurology*, 56(5), 569–574.
- Bartzokis, G., & Tishler, T. A. (2000). MRI evaluation of basal ganglia ferritin iron and neurotoxicity in Alzheimer's and Huntington's disease. *Cellular and Molecular Biology (Noisy-Le-Grand, France)*, 46(4), 821–833.
- Bartzokis, George. (1997). Magnetic Resonance Imaging of Brain Iron. In J. R. Connor (Ed.), *Metals and Oxidative Damage in Neurological Disorders* (pp. 41–56).
https://doi.org/10.1007/978-1-4899-0197-2_3

- Bartzokis, George, Lu, P. H., Tishler, T. A., Fong, S. M., Oluwadara, B., Finn, J. P., ... Perlman, S. (2007). Myelin breakdown and iron changes in Huntington's disease: Pathogenesis and treatment implications. *Neurochemical Research*, 32(10), 1655–1664. <https://doi.org/10.1007/s11064-007-9352-7>
- Beglinger, L. J., Langbehn, D. R., Duff, K., Stierman, L., Black, D. W., Nehl, C., ... Huntington Study Group Investigators. (2007). Probability of obsessive and compulsive symptoms in Huntington's disease. *Biological Psychiatry*, 61(3), 415–418. <https://doi.org/10.1016/j.biopsych.2006.04.034>
- Behrens, T. E. J., Berg, H. J., Jbabdi, S., Rushworth, M. F. S., & Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage*, 34(1), 144–155. <https://doi.org/10.1016/j.neuroimage.2006.09.018>
- Blockx, I., Van Camp, N., Verhoye, M., Boisgard, R., Dubois, A., Jegu, B., ... Van der Linden, A. (2011). Genotype specific age related changes in a transgenic rat model of Huntington's disease. *NeuroImage*, 58(4), 1006–1016. <https://doi.org/10.1016/j.neuroimage.2011.07.007>
- Blockx, I., Verhoye, M., Van Audekerke, J., Bergwerf, I., Kane, J. X., Delgado Y Palacios, R., ... Van der Linden, A. (2012). Identification and characterization of Huntington related pathology: An in vivo DKI imaging study. *NeuroImage*, 63(2), 653–662. <https://doi.org/10.1016/j.neuroimage.2012.06.032>
- Bohanna, I., Georgiou-Karistianis, N., Hannan, A. J., & Egan, G. F. (2008). Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. *Brain Research Reviews*, 58(1), 209–225. <https://doi.org/10.1016/j.brainresrev.2008.04.001>
- Bourbon-Teles, J., Bells, S., Jones, D. K., Coulthard, E., Rosser, A., & Metzler-Baddeley, C. (2017). Myelin breakdown in human Huntington's disease: Multi-modal evidence from diffusion MRI and quantitative magnetization transfer. *Neuroscience*. <https://doi.org/10.1016/j.neuroscience.2017.05.042>

- Bruyn, G. W., & von Wolferen, W. J. (1973). Pathogenesis of Huntington's chorea. *Lancet (London, England)*, 1(7816), 1382.
- Budde, M. D., Kim, J. H., Liang, H.-F., Schmidt, R. E., Russell, J. H., Cross, A. H., & Song, S.-K. (2007). Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. *Magnetic Resonance in Medicine*, 57(4), 688–695.
<https://doi.org/10.1002/mrm.21200>
- Carroll, J. B., Lerch, J. P., Franciosi, S., Spreeuw, A., Bissada, N., Henkelman, R. M., & Hayden, M. R. (2011). Natural history of disease in the YAC128 mouse reveals a discrete signature of pathology in Huntington disease. *Neurobiology of Disease*, 43(1), 257–265. <https://doi.org/10.1016/j.nbd.2011.03.018>
- Ciarmiello, A., Cannella, M., Lastoria, S., Simonelli, M., Frati, L., Rubinsztein, D. C., & Squitieri, F. (2006). Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, 47(2), 215–222.
- Connor, J. R., & Menzies, S. L. (1995). Cellular management of iron in the brain. *Journal of the Neurological Sciences*, 134, 33–44. [https://doi.org/10.1016/0022-510X\(95\)00206-H](https://doi.org/10.1016/0022-510X(95)00206-H)
- de la Monte, S. M., Vonsattel, J. P., & Richardson, E. P. (1988). Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. *Journal of Neuropathology and Experimental Neurology*, 47(5), 516–525.
- De Santis, S., Drakesmith, M., Bells, S., Assaf, Y., & Jones, D. K. (2014). Why diffusion tensor MRI does well only some of the time: Variance and covariance of white matter tissue microstructure attributes in the living human brain. *Neuroimage*, 89(100), 35–44. <https://doi.org/10.1016/j.neuroimage.2013.12.003>
- Descoteaux, M. (2008). *High Angular Resolution Diffusion MRI: From Local Estimation to Segmentation and Tractography* (Theses, Université Nice Sophia Antipolis). Retrieved from <https://tel.archives-ouvertes.fr/tel-00457458>

- Di Paola, M., Luders, E., Cherubini, A., Sanchez-Castaneda, C., Thompson, P. M., Toga, A. W., ... Sabatini, U. (2012). Multimodal MRI analysis of the corpus callosum reveals white matter differences in presymptomatic and early Huntington's disease. *Cerebral Cortex (New York, N.Y.: 1991)*, 22(12), 2858–2866.
<https://doi.org/10.1093/cercor/bhr360>
- Di Paola, M., Phillips, O. R., Sanchez-Castaneda, C., Di Pardo, A., Maglione, V., Caltagirone, C., ... Squitieri, F. (2014). MRI measures of corpus callosum iron and myelin in early Huntington's disease. *Human Brain Mapping*, 35(7), 3143–3151.
<https://doi.org/10.1002/hbm.22391>
- Dietschy, J. M., & Turley, S. D. (2004). Thematic review series: Brain Lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. *Journal of Lipid Research*, 45(8), 1375–1397.
<https://doi.org/10.1194/jlr.R400004-JLR200>
- DiFiglia, M., Sapp, E., Chase, K. O., Davies, S. W., Bates, G. P., Vonsattel, J. P., & Aronin, N. (1997). Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science (New York, N.Y.)*, 277(5334), 1990–1993.
- Douaud, G., Gaura, V., Ribeiro, M.-J., Lethimonnier, F., Maroy, R., Verny, C., ... Remy, P. (2006). Distribution of grey matter atrophy in Huntington's disease patients: A combined ROI-based and voxel-based morphometric study. *NeuroImage*, 32(4), 1562–1575. <https://doi.org/10.1016/j.neuroimage.2006.05.057>
- Dumas, E. M., van den Bogaard, S. J. A., Ruber, M. E., Reilman, R. R., Stout, J. C., Craufurd, D., ... Roos, R. A. C. (2012). Early changes in white matter pathways of the sensorimotor cortex in premanifest Huntington's disease. *Human Brain Mapping*, 33(1), 203–212. <https://doi.org/10.1002/hbm.21205>
- Ernst, A., Alkass, K., Bernard, S., Salehpour, M., Perl, S., Tisdale, J., ... Frisén, J. (2014). Neurogenesis in the Striatum of the Adult Human Brain. *Cell*, 156(5), 1072–1083.
<https://doi.org/10.1016/j.cell.2014.01.044>

- Faria, A. V., Ratnanather, J. T., Tward, D. J., Lee, D. S., van den Noort, F., Wu, D., ... Miller, M. I. (2016). Linking white matter and deep gray matter alterations in premanifest Huntington disease. *NeuroImage: Clinical*, 11, 450–460.
<https://doi.org/10.1016/j.nicl.2016.02.014>
- Gauthier, L. R., Charrin, B. C., Borrell-Pagès, M., Dompierre, J. P., Rangone, H., Cordelières, F. P., ... Saudou, F. (2004). Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell*, 118(1), 127–138. <https://doi.org/10.1016/j.cell.2004.06.018>
- Gómez-Tortosa, E., MacDonald, M. E., Friend, J. C., Taylor, S. A., Weiler, L. J., Cupples, L. A., ... Myers, R. H. (2001). Quantitative neuropathological changes in presymptomatic Huntington's disease. *Annals of Neurology*, 49(1), 29–34.
- Gregory, S., Crawford, H., Seunarine, K., Leavitt, B., Durr, A., Roos, R. A. C., ... Orth, M. (2018). Natural biological variation of white matter microstructure is accentuated in Huntington's disease. *Human Brain Mapping*, 39(9), 3516–3527.
<https://doi.org/10.1002/hbm.24191>
- Grussu, F., Schneider, T., Tur, C., Yates, R. L., Tachrount, M., Ianuș, A., ... Gandini Wheeler-Kingshott, C. A. M. (2017). Neurite dispersion: A new marker of multiple sclerosis spinal cord pathology? *Annals of Clinical and Translational Neurology*, 4(9), 663–679. <https://doi.org/10.1002/acn3.445>
- Grydeland, H., Walhovd, K. B., Tamnes, C. K., Westlye, L. T., & Fjell, A. M. (2013). Intracortical myelin links with performance variability across the human lifespan: Results from T1- and T2-weighted MRI myelin mapping and diffusion tensor imaging. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 33(47), 18618–18630. <https://doi.org/10.1523/JNEUROSCI.2811-13.2013>
- Halliday, G. M., McRitchie, D. A., Macdonald, V., Double, K. L., Trent, R. J., & McCusker, E. (1998). Regional specificity of brain atrophy in Huntington's disease. *Experimental Neurology*, 154(2), 663–672. <https://doi.org/10.1006/exnr.1998.6919>

- Han, I., You, Y., Kordower, J. H., Brady, S. T., & Morfini, G. A. (2010). Differential vulnerability of neurons in Huntington's disease: The role of cell type-specific features. *Journal of Neurochemistry*, 113(5), 1073–1091.
<https://doi.org/10.1111/j.1471-4159.2010.06672.x>
- Heath, F., Hurley, S. A., Johansen-Berg, H., & Sampaio-Baptista, C. (2018). Advances in noninvasive myelin imaging. *Developmental Neurobiology*, 78(2), 136–151.
<https://doi.org/10.1002/dneu.22552>
- Henkelman, R. M., Huang, X., Xiang, Q. S., Stanisz, G. J., Swanson, S. D., & Bronskill, M. J. (1993). Quantitative interpretation of magnetization transfer. *Magnetic Resonance in Medicine*, 29(6), 759–766.
- Henkelman, R. M., Stanisz, G. J., & Graham, S. J. (n.d.). Magnetization transfer in MRI: A review. *NMR in Biomedicine*, 14(2), 57–64. <https://doi.org/10.1002/nbm.683>
- Huang, B., Wei, W., Wang, G., Gaertig, M. A., Feng, Y., Wang, W., ... Li, S. (2015). Mutant huntingtin downregulates myelin regulatory factor-mediated myelin gene expression and affects mature oligodendrocytes. *Neuron*, 85(6), 1212–1226.
<https://doi.org/10.1016/j.neuron.2015.02.026>
- Jin, J., Peng, Q., Hou, Z., Jiang, M., Wang, X., Langseth, A. J., ... Duan, W. (2015). Early white matter abnormalities, progressive brain pathology and motor deficits in a novel knock-in mouse model of Huntington's disease. *Human Molecular Genetics*, 24(9), 2508–2527. <https://doi.org/10.1093/hmg/ddv016>
- Jones, D. K., Knösche, T. R., & Turner, R. (2013). White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*, 73, 239–254.
<https://doi.org/10.1016/j.neuroimage.2012.06.081>
- Jurgens, C. K., Jasinschi, R., Ekin, A., Witjes-Ané, M.-N. W., van der Grond, J., Middelkoop, H., & Roos, R. A. C. (2010). MRI T2 Hypointensities in basal ganglia of premanifest Huntington's disease. *PLoS Currents*, 2. <https://doi.org/10.1371/currents.RRN1173>
- Kassubek, J., Juengling, F. D., Kioschies, T., Henkel, K., Karitzky, J., Kramer, B., ... Landwehrmeyer, G. B. (2004). Topography of cerebral atrophy in early Huntington's

- disease: A voxel based morphometric MRI study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 75(2), 213–220.
- Levesque, I. R., Giacomini, P. S., Narayanan, S., Ribeiro, L. T., Sled, J. G., Arnold, D. L., & Pike, G. B. (2010). Quantitative magnetization transfer and myelin water imaging of the evolution of acute multiple sclerosis lesions. *Magnetic Resonance in Medicine*, 63(3), 633–640. <https://doi.org/10.1002/mrm.22244>
- Mac Donald, C. L., Dikranian, K., Song, S. K., Bayly, P. V., Holtzman, D. M., & Brody, D. L. (2007). Detection of traumatic axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury. *Experimental Neurology*, 205(1), 116–131. <https://doi.org/10.1016/j.expneurol.2007.01.035>
- Malisch, T. W., Hedlund, L. W., Suddarth, S. A., & Johnson, G. A. (1991). MR microscopy at 7.0 T: Effects of brain iron. *Journal of Magnetic Resonance Imaging: JMRI*, 1(3), 301–305.
- Martenson, R. E. (1992). *Myelin*. CRC Press.
- Mascalchi, M., Lolli, F., Della Nave, R., Tessa, C., Petralli, R., Gavazzi, C., ... Piacentini, S. (2004). Huntington disease: Volumetric, diffusion-weighted, and magnetization transfer MR imaging of brain. *Radiology*, 232(3), 867–873. <https://doi.org/10.1148/radiol.2322030820>
- Matsui, J. T., Vaidya, J. G., Johnson, H. J., Magnotta, V. A., Long, J. D., Mills, J. A., ... Paulsen, J. S. (2014). Diffusion weighted imaging of prefrontal cortex in prodromal Huntington's disease. *Human Brain Mapping*, 35(4), 1562–1573. <https://doi.org/10.1002/hbm.22273>
- McColgan, P., Gregory, S., Seunarine, K. K., Razi, A., Papoutsis, M., Johnson, E., ... Track-On HD Investigators. (2018). Brain Regions Showing White Matter Loss in Huntington's Disease Are Enriched for Synaptic and Metabolic Genes. *Biological Psychiatry*, 83(5), 456–465. <https://doi.org/10.1016/j.biopsych.2017.10.019>

- Meng, Y., Jiang, J., Bachevalier, J., Zhang, X., & Chan, A. W. S. (2017). Developmental Whole Brain White Matter Alterations in Transgenic Huntington's Disease Monkey. *Scientific Reports*, 7. <https://doi.org/10.1038/s41598-017-00381-8>
- Myers, R. H., Vonsattel, J. P., Paskevich, P. A., Kiely, D. K., Stevens, T. J., Cupples, L. A., ... Bird, E. D. (1991). Decreased Neuronal and Increased Oligodendroglial Densities in Huntington's Disease Caudate Nucleus. *Journal of Neuropathology & Experimental Neurology*, 50(6), 729–742. <https://doi.org/10.1097/00005072-199111000-00005>
- Odrobina, E. E., Lam, T. Y. J., Pun, T., Midha, R., & Stanis, G. J. (n.d.). MR properties of excised neural tissue following experimentally induced demyelination. *NMR in Biomedicine*, 18(5), 277–284. <https://doi.org/10.1002/nbm.951>
- Ou, X., Sun, S.-W., Liang, H.-F., Song, S.-K., & Gochberg, D. F. (2009). The MT pool size ratio and the DTI radial diffusivity may reflect the myelination in shiverer and control mice. *NMR in Biomedicine*, 22(5), 480–487. <https://doi.org/10.1002/nbm.1358>
- Paulsen, J. S., Langbehn, D. R., Stout, J. C., Aylward, E., Ross, C. A., Nance, M., ... Predict-HD Investigators and Coordinators of the Huntington Study Group. (2008). Detection of Huntington's disease decades before diagnosis: The Predict-HD study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 79(8), 874–880. <https://doi.org/10.1136/jnnp.2007.128728>
- Phillips, O., Squitieri, F., Sanchez-Castaneda, C., Elifani, F., Caltagirone, C., Sabatini, U., & Paola, M. D. (2014). Deep White Matter in Huntington's Disease. *PLOS ONE*, 9(10), e109676. <https://doi.org/10.1371/journal.pone.0109676>
- Radulescu, C. I., Garcia-Miralles, M., Sidik, H., Ferrari Bardile, C., Yusof, N. A. B. M., Lee, H. U., ... Pouladi, M. A. (2018). Manipulation of microbiota reveals altered myelination and white matter plasticity in a model of Huntington disease. *BioRxiv*. <https://doi.org/10.1101/413112>

- Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In *The handbook of aging and cognition, 2nd ed* (pp. 1–90). Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers.
- Reading, S. A. J., Yassa, M. A., Bakker, A., Dziorny, A. C., Gourley, L. M., Yallapragada, V., ... Ross, C. A. (2005). Regional white matter change in pre-symptomatic Huntington's disease: A diffusion tensor imaging study. *Psychiatry Research, 140*(1), 55–62. <https://doi.org/10.1016/j.psychresns.2005.05.011>
- Rocha, N. P., Ribeiro, F. M., Furr-Stimming, E., & Teixeira, A. L. (2016). Neuroimmunology of Huntington's Disease: Revisiting Evidence from Human Studies. *Mediators of Inflammation, 2016*. <https://doi.org/10.1155/2016/8653132>
- Rosas, H. D., Hevelone, N. D., Zaleta, A. K., Greve, D. N., Salat, D. H., & Fischl, B. (2005). Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. *Neurology, 65*(5), 745–747. <https://doi.org/10.1212/01.wnl.0000174432.87383.87>
- Rosas, H. D., Liu, A. K., Hersch, S., Glessner, M., Ferrante, R. J., Salat, D. H., ... Fischl, B. (2002). Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology, 58*(5), 695–701.
- Rosas, H. D., Wilkens, P., Salat, D. H., Mercaldo, N. D., Vangel, M., Yendiki, A. Y., & Hersch, S. M. (2018). Complex spatial and temporally defined myelin and axonal degeneration in Huntington disease. *NeuroImage: Clinical, 20*, 236–242. <https://doi.org/10.1016/j.nicl.2018.01.029>
- Rosas, H. Diana, Tuch, D. S., Hevelone, N. D., Zaleta, A. K., Vangel, M., Hersch, S. M., & Salat, D. H. (2006). Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. *Movement Disorders: Official Journal of the Movement Disorder Society, 21*(9), 1317–1325. <https://doi.org/10.1002/mds.20979>
- Ruocco, H. H., Bonilha, L., Li, L. M., Lopes-Cendes, I., & Cendes, F. (2008). Longitudinal analysis of regional grey matter loss in Huntington disease: Effects of the length of

- the expanded CAG repeat. *Journal of Neurology, Neurosurgery, and Psychiatry*, 79(2), 130–135. <https://doi.org/10.1136/jnnp.2007.116244>
- Schmierer, K., Tozer, D. J., Scaravilli, F., Altmann, D. R., Barker, G. J., Tofts, P. S., & Miller, D. H. (2007). Quantitative Magnetization Transfer Imaging in Postmortem Multiple Sclerosis Brain. *Journal of Magnetic Resonance Imaging : JMRI*, 26(1), 41–51. <https://doi.org/10.1002/jmri.20984>
- Simmons, D. A., Casale, M., Alcon, B., Pham, N., Narayan, N., & Lynch, G. (n.d.). Ferritin accumulation in dystrophic microglia is an early event in the development of Huntington's disease. *Glia*, 55(10), 1074–1084. <https://doi.org/10.1002/glia.20526>
- Song, S.-K., Sun, S.-W., Ju, W.-K., Lin, S.-J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage*, 20(3), 1714–1722. <https://doi.org/10.1016/j.neuroimage.2003.07.005>
- Song, S.-K., Sun, S.-W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage*, 17(3), 1429–1436.
- Song, S.-K., Yoshino, J., Le, T. Q., Lin, S.-J., Sun, S.-W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, 26(1), 132–140. <https://doi.org/10.1016/j.neuroimage.2005.01.028>
- Squitieri, F., Cannella, M., Simonelli, M., Sassone, J., Martino, T., Venditti, E., ... Ciarmiello, A. (2009). Distinct Brain Volume Changes Correlating with Clinical Stage, Disease Progression Rate, Mutation Size, and Age at Onset Prediction as Early Biomarkers of Brain Atrophy in Huntington's Disease. *CNS Neuroscience & Therapeutics*, 15(1), 1–11. <https://doi.org/10.1111/j.1755-5949.2008.00068.x>
- Stanisz, G. J., Webb, S., Munro, C. A., Pun, T., & Midha, R. (2004). MR properties of excised neural tissue following experimentally induced inflammation. *Magnetic Resonance in Medicine*, 51(3), 473–479. <https://doi.org/10.1002/mrm.20008>

- Stoffers, D., Sheldon, S., Kuperman, J. M., Goldstein, J., Corey-Bloom, J., & Aron, A. R. (2010). Contrasting gray and white matter changes in preclinical Huntington disease. *Neurology*, 74(15), 1208–1216. <https://doi.org/10.1212/WNL.0b013e3181d8c20a>
- Sun, S.-W., Liang, H.-F., Schmidt, R. E., Cross, A. H., & Song, S.-K. (2007). Selective vulnerability of cerebral white matter in a murine model of multiple sclerosis detected using diffusion tensor imaging. *Neurobiology of Disease*, 28(1), 30–38. <https://doi.org/10.1016/j.nbd.2007.06.011>
- Sun, S.-W., Liang, H.-F., Trinkaus, K., Cross, A. H., Armstrong, R. C., & Song, S.-K. (2006). Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. *Magnetic Resonance in Medicine*, 55(2), 302–308. <https://doi.org/10.1002/mrm.20774>
- Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., ... TRACK-HD investigators. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. *The Lancet. Neurology*, 8(9), 791–801. [https://doi.org/10.1016/S1474-4422\(09\)70170-X](https://doi.org/10.1016/S1474-4422(09)70170-X)
- Tabrizi, S. J., Reilmann, R., Roos, R. A. C., Durr, A., Leavitt, B., Owen, G., ... TRACK-HD investigators. (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24 month observational data. *The Lancet. Neurology*, 11(1), 42–53. [https://doi.org/10.1016/S1474-4422\(11\)70263-0](https://doi.org/10.1016/S1474-4422(11)70263-0)
- Tabrizi, S. J., Scahill, R. I., Durr, A., Roos, R. A., Leavitt, B. R., Jones, R., ... TRACK-HD Investigators. (2011). Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: The 12-month longitudinal analysis. *The Lancet. Neurology*, 10(1), 31–42. [https://doi.org/10.1016/S1474-4422\(10\)70276-3](https://doi.org/10.1016/S1474-4422(10)70276-3)
- Teo, R. T. Y., Hong, X., Yu-Taeger, L., Huang, Y., Tan, L. J., Xie, Y., ... Pouladi, M. A. (2016). Structural and molecular myelination deficits occur prior to neuronal loss in

- the YAC128 and BACHD models of Huntington disease. *Human Molecular Genetics*, 25(13), 2621–2632. <https://doi.org/10.1093/hmg/ddw122>
- Valenza, M., Leoni, V., Tarditi, A., Mariotti, C., Björkhem, I., Di Donato, S., & Cattaneo, E. (2007). Progressive dysfunction of the cholesterol biosynthesis pathway in the R6/2 mouse model of Huntington's disease. *Neurobiology of Disease*, 28(1), 133–142. <https://doi.org/10.1016/j.nbd.2007.07.004>
- Valenza, M., Rigamonti, D., Goffredo, D., Zuccato, C., Fenu, S., Jamot, L., ... Cattaneo, E. (2005). Dysfunction of the cholesterol biosynthetic pathway in Huntington's disease. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 25(43), 9932–9939. <https://doi.org/10.1523/JNEUROSCI.3355-05.2005>
- Vinther-Jensen, T., Simonsen, A. H., Budtz-Jørgensen, E., Hjermand, L. E., & Nielsen, J. E. (n.d.). Ubiquitin: A potential cerebrospinal fluid progression marker in Huntington's disease. *European Journal of Neurology*, 22(10), 1378–1384. <https://doi.org/10.1111/ene.12750>
- Wang, N., & Yang, X. W. (2019). Huntington Disease's Glial Progenitor Cells Hit the Pause Button in the Mouse Brain. *Cell Stem Cell*, 24(1), 3–4. <https://doi.org/10.1016/j.stem.2018.12.004>
- Weaver, K. E., Richards, T. L., Liang, O., Laurino, M. Y., Samii, A., & Aylward, E. H. (2009). Longitudinal diffusion tensor imaging in Huntington's Disease. *Experimental Neurology*, 216(2), 525–529. <https://doi.org/10.1016/j.expneurol.2008.12.026>
- Wheeler-Kingshott, C. A. M., & Cercignani, M. (2009). About “axial” and “radial” diffusivities. *Magnetic Resonance in Medicine*, 61(5), 1255–1260. <https://doi.org/10.1002/mrm.21965>
- Wu, Q., Butzkueven, H., Gresle, M., Kirchhoff, F., Friedhuber, A., Yang, Q., ... Kilpatrick, T. J. (2007). MR diffusion changes correlate with ultra-structurally defined axonal degeneration in murine optic nerve. *NeuroImage*, 37(4), 1138–1147. <https://doi.org/10.1016/j.neuroimage.2007.06.029>

- Xiang, Z., Valenza, M., Cui, L., Leoni, V., Jeong, H.-K., Brilli, E., ... Krainc, D. (2011). Peroxisome-proliferator-activated receptor gamma coactivator 1 α contributes to dysmyelination in experimental models of Huntington's disease. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 31(26), 9544–9553. <https://doi.org/10.1523/JNEUROSCI.1291-11.2011>
- Xie, M., Tobin, J. E., Budde, M. D., Chen, C.-I., Trinkaus, K., Cross, A. H., ... Armstrong, R. C. (2010). Rostrocaudal analysis of corpus callosum demyelination and axon damage across disease stages refines diffusion tensor imaging correlations with pathological features. *Journal of Neuropathology and Experimental Neurology*, 69(7), 704–716. <https://doi.org/10.1097/NEN.0b013e3181e3de90>
- Zhang, J., Gregory, S., Scahill, R. I., Durr, A., Thomas, D. L., Lehericy, S., ... Zhang, H. (2018). In vivo characterization of white matter pathology in premanifest huntington's disease. *Annals of Neurology*, 84(4), 497–504. <https://doi.org/10.1002/ana.25309>