Chapter
Neuropathology of Huntington’s Disease

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Abstract

Huntington’s disease (HD) is a devastating neurodegenerative disease that results in motor, cognitive, and psychiatric impairments. HD results from an autosomal dominant polyglutamine expansion in the huntingtin (HTT) gene that results in a misfolded and aggregated protein. The disease is uniformly fatal and demonstrates characteristic neuropathological changes. While the striatum is preferentially affected, the cortex and many other brain regions are involved in pathogenesis and show progressive changes throughout the disease.

Keywords: Huntington, neuropathology, degeneration, striatum, aggregate

1. Introduction

This chapter summarizes the current knowledge of the neuropathological changes that occur in Huntington’s disease (HD). HD is an autosomal dominant neurodegenerative disease caused by a polyglutamine expansion in the huntingtin gene [1]. The mutation was discovered in 1993 [1], however cases were first documented in 1872 by George Huntington [2]. The disease is characterized by progressive motor, cognitive, and psychiatric impairments and is uniformly fatal [3–6]. Analysis of postmortem brains reveals global atrophy of approximately 19–30% with 29–64% and 23–29% reductions in basal ganglia and cortical volume, respectively [7–9]. HD is thought to preferentially affect medium spiny neurons (MSNs) of the striatum and lead to their degeneration, however the exact reasons why MSNs are so vulnerable is still unknown [7, 10–12]. In addition to the striatum, HD affects other brain areas and peripheral tissues as well, though many of these areas are comparatively less studied.

2. Biological basis and symptomatology of HD

2.1 Biological basis of HD

HD is caused by a polyglutamine (CAG) expansion in exon 1 of the huntingtin gene (HTT). Normal individuals have stable repeat lengths up to 26, whereas repeat lengths from 27 to 35 are potentially unstable. HD is associated with CAG repeats of
40 or more, with repeat lengths of 36–39 demonstrating incomplete penetrance [13]. The expanded CAG repeat produces a dysfunctional, unfolded, and aggregated huntingtin (HTT) protein, called mutant HTT (mHTT) [1]. The normal function of HTT is poorly understood, although some broad functions, such as roles in development, cell adhesion, and brain-derived neurotrophic factor transport and production, have been reported [14–16]. Not only does the expansion disrupt normal HTT functions, but it also exhibits toxic gain-of-function [16, 17]. While HTT is expressed in many cell types, medium spiny neurons (MSNs) of the striatum are particularly vulnerable to mHTT. While the exact mechanisms are still unclear, mHTT causes MSN death and leads to degeneration of the striatum [7, 11, 12].

2.2 HD symptomatology

HD causes motor, cognitive, and psychiatric deficits and the disease is uniformly fatal within a median time from motor symptom onset to death of 18 years [18]. The symptoms are severe and patients often lose independence rapidly, requiring constant care approximately 10 years after motor symptom onset [4]. The motor symptoms come in two broad categories: involuntary movements and impaired voluntary movement [3]. Involuntary movements such as chorea are common in the early stages of HD whereas the impaired voluntary movements, including coordination difficulties and bradykinesia, are often seen in later stages of the disease [4]. In addition, patients also have oculomotor abnormalities and dysdiadochokinesis among other motor symptoms [4]. Patients also experience cognitive symptoms, including personality changes, problems with attention and emotion recognition, cognitive slowing, initiation difficulties, and lack of awareness of deficits [4, 6]. Psychiatric symptoms include depressed mood, anxiety, apathy, irritability, social disengagement, and impulsivity [4, 5].

3. Basal ganglia

3.1 Normal basal ganglia

The basal ganglia is a set of subcortical nuclei located at the base of the forebrain [19]. This region is highly affected in HD [8] and thus, a review on its components, architecture, and circuitry is provided for context.

The basal ganglia is comprised of the striatum, globus pallidus (GP), subthalamic nucleus (STN), and substantia nigra (SN) [20]. The globus pallidus has two components, the internal and external segments (GPi and GPe respectively). The substantia nigra has two components, the pars reticulata (SNr) and the pars compacta (SNC) [19, 20].

The striatum gets input from many cortical areas, integrates the information, and sends it in multiple pathways throughout the basal ganglia [21]. The two major pathways are the direct and indirect pathways. The direct pathway is a monosynaptic pathway from the striatum to the Gpi, whereas the indirect pathway is multisynaptic. The indirect pathway has projections from the striatum to the GPe, the GPe to the STN, and the STN to the Gpi [19, 22–24]. The two pathways converge at Gpi and send inhibitory projections to the ventral anterior and ventral lateral nuclei of the thalamus. Disruption or imbalance of these pathways can lead to motor dysfunction [25].
3.1 Striatum

The dorsal striatum is comprised of the caudate and the putamen, while the ventral striatum is nucleus accumbens. Running between the caudate and the putamen is the internal capsule [26].

The striatum itself is a heterogenous region with two compartments—the matrix and the striosomes. The compartments differ based on their efferent and afferent connections as well as their neurochemical makeup. The striosomes receive inputs from the SNc, prefrontal cortex, and limbic system and they send outputs to the SNc [27]. The matrix compartment receives inputs from motor, somatosensory, frontal, parietal, and occipital cortices and the matrix sends outputs to GPe, GPi, and SNr [27]. The matrix strongly expresses acetylcholinesterase (AChE) whereas the striosomes only weakly stains for AChE [28]. Additionally, there are many other markers that can differentiate between striosome or matrix compartments, such as tyrosine hydroxylase or enkephalin [29].

The striatum contains multiple types of neurons and glial cells [3]. MSNs are GABAergic projection neurons that make up 90–95% of the striatal neuronal population [3, 30]. They receive glutamatergic input from many brain areas including the cortex and some thalamic nuclei [31–33] as well as dopaminergic input from the SN [27, 30]. MSNs that are in the direct pathway and project to the GPi express dopamine D1 receptors while MSNs in the indirect pathway express D2 receptors [22, 30]. Besides MSNs, the striatum also contains several classes of interneurons, the most abundant of which are large cholinergic interneurons [30, 34].

3.2 HD striatum

The dorsal striatum shows significant bilateral atrophy with striking caudate and putamen volume loss (Figure 1A) [7]. The degeneration typically occurs from the tail of the caudate to the head and body (caudal to rostral, dorsal to ventral, and medial to lateral) [36]. The particular sequence of degeneration is described further in Section 8.

Within the striatum, MSNs experience profound degeneration (Figure 1B and C) [3]. In general striatal interneurons are not very affected in HD [3, 37, 38], with the exception of parvalbumin-containing interneurons which degenerate significantly and in a grade-dependent manner [39]. Some cases of HD show rare but distinct, round striatal areas of preservation called islets. They measure 0.5–1.0 mm and show normal neuronal density but increased astrocyte density [40, 41].

Nearly all evidence suggests that cells displaying the classic apoptotic morphology are extremely rare in HD [42]. Remaining MSNs in HD brains appear to be smaller but maintain their normal somatic morphology [36]. Degenerating neurons, called “neostriatal dark neurons” appear darker than healthy neurons and have scalloped cellular membranes, granular dark cytoplasm, and condensed chromatin [29]. These dark neurons are typically present between atrophic and normal areas of the striatum [36]. Besides these atrophic neurons, ballooned neurons are extremely common in affected regions of HD brains. These neurons have enlarged, basophilic cytoplasm with flattened nuclei and Nissl substance and lipofuscin granules at the nuclear periphery [26, 43].

3.2.1 Matrix and striosome

The heterogenous, patchy nature of mHTT reactivity in the striatum of HD patients was observed and determined to reflect the distribution of striatal
compartments. In early studies of HD, HTT was predominantly found in the matrix [44]. Many reports focusing on neurodegeneration found either matrix [45, 46] or striosome [47, 48] predominance, and in particular, discrepancies between compartments were evident in early disease stages. Further investigation into this phenomenon revealed that matrix or striosome predominance correlated with symptom type, where HD patients who showed preferential neuronal loss in striosomes tended to experience more mood dysfunction and HD patients who showed preferential matrix neuronal loss showed mainly motor symptoms [49]. It should be noted that many brains do not show any matrix or striosome predominance, so this phenomenon seems to be ungeneralizable, and it is possible for either compartment to experience predominant neuronal loss.

3.2.2 Indirect and direct pathway

While some studies have shown no differences between indirect and direct pathway MSN degeneration [50], other studies have shown that indirect, D2 receptor-positive MSNs degenerate and show dysfunction prior to direct, D1 receptor-positive MSNs [10, 51–53]. This predominant neuronal loss of indirect pathway MSNs occurs early and by late disease stages, no difference between pathways is noted [51, 52].

Figure 1.
Neuropathology of HD. (A) Coronal section of fixed brain at the level of the nucleus accumbens. Note HD grade 4 severe atrophy of the striatum and marked enlargement of the lateral ventricles. Normal (B) and grade 3 HD (C) putamen. Note severe neuron loss and astrogliosis. Immunohistochemical staining with 1C2 antibody against expanded polyglutamine of the TATA binding protein [35] demonstrates intranuclear inclusions, cytoplasmic granules (D and E) and neuritic aggregates (F) in cerebral cortex.
3.3 HD globus pallidus, STN, SN

The GP shows atrophy in grades 3 and 4, with more significant atrophy of the GPe than the GPi [36, 40, 43]. GP volume is decreased significantly [54, 55], but the density of neurons is maintained, suggesting minimal neuronal degeneration [36, 40]. Reactive gliosis is seen in the GPe in late stages of the disease [36].

The STN shows marked atrophy in grades 3 and 4, but no reactive astrocytes are seen in this region [36, 54]. An approximately 20% reduction in STN neuron number are seen in HD brains compared to control brains [56].

The SN pathology differs by component [36]. There is a loss of neurons in the SNr, whereas the SNc is more controversial, appearing thin but with an unchanged number of neurons in some studies [57, 58]. Other studies, however, claim to see a reduction of neuron number in the SNc, although to a lesser degree than in the SNr [59, 60].

3.4 Physiological and neurochemical changes

The loss of MSNs likely causes reductions in NMDA, GABA, and cannabinoid receptor binding in the striatum of HD patients [49, 61–63]. In the GPe, enkephalin staining is diminished as enkephalin-containing MSNs projecting to the GPe are lost and in the GPi and SNr, substance P staining is diminished as substance P-containing MSNs are lost [10, 51, 52, 64]. In addition, urea levels in the brains of HD patients are elevated, even at early disease stages, which suggests disrupted urea metabolism may play a role in neurodegeneration or neurological impairment in HD [65]. Vitamin B5, the precursor for coenzyme A, is reduced in HD patient brains and may contribute to neurodegeneration, as genetic defects in the coenzyme A biosynthetic pathway lead to neurodegeneration [66, 67].

It is thought that excitotoxicity and synaptic changes may play a role in cell death. Many studies using animal models of HD have shown a variety of factors, such as astrocyte dysfunction, defects in energy metabolism, or altered cortical input, that could contribute to the MSN vulnerability to excitotoxicity [68–73]. HD animal models also show early loss of corticostriatal and thalamostriatal synapses [74]. In postmortem brain tissue from HD patients, it was found that bassoon, an anchoring protein in the active zone, and HTT interact and this process draws bassoon into aggregates, causing a reduction of active zone proteins which may impair synaptic function [75].

4. Pathology in other brain regions

In addition to the basal ganglia, HD affects other brain regions such as the cortex, thalamus, cerebellum, brainstem nuclei, subventricular zone, hypothalamus, hippocampus, and white matter. In general, striatal pathology severity correlates well with pathology in other brain regions, though striatal pathology often precedes pathology elsewhere [36].

4.1 Cortex

Cortical pathology is a significant yet disputed component of HD [36]. Early reports on HD pathology either saw significant cortical atrophy [76] or minimal to absent cortical pathology [77]. Currently, the consensus suggests that there is indeed
cortical atrophy, cortical thinning, and cortical volume loss [8, 9, 78]. Exactly which layer of cortical neurons is most affected is still under investigation, as some studies have reported involvement of layers V and VI [79, 80] and others have reported layers III and V [81]. Layers III and V project to the striatum so it has been hypothesized that pathology here could be retrograde from the striatum, however layer VI involvement questions this. It is fairly clear, however, that pyramidal neurons degenerate more than cortical interneurons [81, 82], though there may be heterogenous involvement of cortical interneurons and it may differ by HD patient [29].

Particular cortical regions, such as the motor cortex [82, 83], prefrontal cortex [80, 84], entorhinal cortex [79], cingulate cortex [83], and primary sensory areas [85], have been studied and each shows HD pathology, though it appears to vary between HD patients [86]. It is possible that degeneration and thinning of these particular areas may correlate with specific HD symptoms. One study showed that cases with significant motor cortex pathology showed profound motor dysfunction whereas cases with anterior cingulate cortex pathology showed predominance of mood symptoms [83, 87].

4.2 Cerebellum

Cerebellar involvement in HD is rather controversial. The cerebellum plays roles in motor coordination and control, attention, and many other processes [88–90]. Earliest reports of HD neuropathology did not note any cerebellar pathology [77], however recent studies have varied in their assessment of cerebellar atrophy, volume loss, and degeneration [3, 36, 91]. Vonsattel and others reported that the cerebellum displayed normal neuronal density but was atrophied in late stage HD brains [36, 92]. However, other studies were reporting the density of Purkinje cells were reduced by half [3]. A systematic study using serial sections of the cerebellum in HD brains showed widespread loss of Purkinje cells and degeneration of neurons in the deep cerebellar nuclei present at early stages of HD [91]. Interestingly, when HD patients are separated by symptom predominance, those with predominant motor symptoms had significant loss of Purkinje cells whereas those with predominant mood symptoms did not show any loss of Purkinje cells in the neocerebellum [93]. This cerebellar pathology is reminiscent of that seen in spinocerebellar ataxias (1, 2, and 3), and it is possible that HD has more similarities with these diseases than previously thought [94–96]. Classic cerebellar dysfunction signs such as gait abnormalities, dysarthria, oculomotor abnormalities, and fine motor skill impairment have indeed been reported in HD [3, 97–99].

4.3 Other brain areas

HD cases appear to show varied levels of thalamic pathology [100]. The thalamus often appears grossly normal but does show pathology in later stages, though this varies by thalamic nucleus [40]. The thalamus appears normal at early disease stages but at late disease stages, astrocytosis and neuronal loss are seen in the centromedial nucleus [36]. Atrophy has been reported in the centromedial/parafascicular nucleus, the dorsomedial nucleus, and the centromedial/ventrolateral nucleus group [100–102].

The hypothalamus is another area that shows HD pathology [55, 103, 104]. HD patients present with sleep disturbances, altered circadian rhythm, and weight loss
Atrophy, gliosis, and 90% cell loss of the lateral tuberal nucleus has been reported [3]. Other studies have shown a loss of orexin-positive and somatostatin-positive neurons in the lateral hypothalamus [108–110].

Early HD reports did not observe changes in hippocampal density [77], however more recent studies have found a 20% reduction of area [9], 9% reduction of volume [111], and neuronal loss and astrocytosis [36] in the hippocampus. It seems that changes in neuronal density may be restricted to the CA1 region [112].

The subventricular zone (SVZ), which is a region that contains adult stem cells and is located at the edge of the caudate nucleus, shows thickening that progresses with increasing grades of HD [113]. There was increased cell proliferation [113] and altered lipid architecture [114] in the SVZ of HD patients as well.

White matter changes occur in HD and the loss of white matter correlates with amount of gray matter lost [9]. Diffusion tensor imaging and MRI show presymptomatic white matter changes in the microstructure of the corpus callosum and internal capsule [115, 116].

Lastly, brainstem nuclei show pathology in HD. The brainstem shows widespread neuronal loss with particular involvement of the substantia nigra, precerebellar pontine nuclei, inferior olive, oculomotor reticulotegmental nucleus, premotor oculomotor area, raphe interpositus nucleus, auditory superior olive, and the vestibular nuclei [26, 117, 118]. HD patients present with autonomic disturbances and oculomotor dysfunction [4, 119], some of which could be explained by brainstem pathology.

5. Aggregates

Expanded HTT accumulates and forms aggregates and inclusions (Figure 1D–F) [120–122]. Normally, HTT is found mostly in the cytoplasm, dendrites, and axon terminals, but in HD, inclusions are also seen in the nucleus [123]. There are both intranuclear and extranuclear inclusions in HD [124] and they appear round or oblong, ranging from approximately 0.5–20 μm in diameter [123]. mHTT inclusions are found in neurons most commonly but also astrocytes, oligodendrocytes, and microglia [125, 126]. They are found more commonly in gray matter than white matter [123]. The aggregates can be detected prior to symptom onset [127].

A high density of aggregates are homogeneously distributed throughout the striatum of HD brains [123]. No distinction between striosome and matrix compartments were noted in terms of aggregate load [123]. There is a high aggregate load in layers V and VI of the cortex as well [123]. Specifically, the insular and cingulate cortex had a high density of aggregates while other cortical areas and the SN, thalamus, hypothalamus, brainstem nuclei, GP, hippocampus, and cerebellum showed a much lower density [123]. Interestingly, mHTT aggregates are also found in the olfactory bulb of HD patients, though aggregate load here does not correlate with Vonsattel grading score [128].

Polyglutamine proteins can be detected using antibodies that recognize polyglutamine stretches, such as IC2. IC2 is a monoclonal antibody that predominantly binds to pathologic repeat lengths and can therefore detect mHTT [35]. It has consistently been used to detect mHTT aggregates in postmortem HD brains [129, 130]. Other studies have used EM48, an antibody that detects the N-terminal region of HTT, to detect HTT aggregates [123].
6. Pathology in peripheral tissues

HTT is expressed in many tissues and organs outside of the brain [105]. Besides the classic neurological symptoms, HD patients exhibit weight loss, atrophy of skeletal muscle, cardiac dysfunction, testicular atrophy, impaired glucose tolerance, and osteoporosis [105]. While the symptoms have been documented in patients [105, 131, 132], most of the research in peripheral tissue pathology is in HD animal models.

Postmortem samples from HD patients showed testicular atrophy and spermatogenesis deficits, with fewer spermatocytes and spermatids. Additionally, thicker walls and cross-sectional area of the seminiferous tubules were noted. In their study, the patient with the longest repeat length had the most severe testicular pathology [133].

Skeletal muscle atrophy is another hallmark of HD [134]. Muscle cells express mHTT and show inclusion bodies in animal models of HD [135, 136] and in muscle cell cultures from HD patients [137]. In addition to aggregate formation, cultured cells from HD patients also show mitochondrial abnormalities [137–139], and the two may work together to cause muscle wasting in HD.

Cardiac failure is relatively common among HD patients, as it occurs in about 30% of cases [132]. Cardiac tissue expresses HTT and while mHTT inclusions are seen in HD mice [140], no aggregates have been reported in cardiac tissue from HD patients [136]. Altered autonomic input to the heart [141], calcium dysregulation [142], and conduction abnormalities [111] are all seen in HD patients and could contribute to heart conditions.

The exact mechanisms that cause peripheral pathology are not fully understood. It is likely that cells that express aggregates are affected cell-autonomously to at least some extent, but the contribution of brain-derived hormones, signals from affected brain areas, or the degeneration of autonomic nerves is still being uncovered.

7. Gliosis

Gliosis is a significant part of HD pathology [143]. Microglia, astrocytes, and oligodendrocytes all show changes in response to HD [7, 36, 144–146]. The density of oligodendrocytes increases in the striatum of HD brains [36] and is particularly evident in early disease stages [127, 144].

Reactive microglia are seen in the striatum, cortex, and globus pallidus of HD patients in all grades of pathology and their number correlates with the degree of neuronal loss in the striatum [145, 146]. Positron emission tomography scans indicate that progressive microglia activation is also seen in the anterior cingulate cortex and prefrontal cortex [147]. In fact, this microglia activation was even seen in presymptomatic HD patients [148].

In addition to microglia, astrocytes play an important role as well. Glial fibrillary acidic protein (GFAP)-positive astrocytes are a component of the Vonsattel grading system (below) [7]. GFAP-positive astrocytes have traditionally been viewed as the reactive type, although the complexity of astrocyte heterogeneity and reactivity is still being uncovered [143, 149–152]. GFAP-positive astrocyte number in the striatum increases progressively with disease severity and striatal neurodegeneration [7]. Despite cortical atrophy and pathology, no astrocytosis was noted in prefrontal cortex samples from HD patients [84, 143].
8. Grading

The Vonsattel grading system was developed in 1985 and utilizes both macroscopic and microscopic pathology in the striatum to categorize the severity of HD degeneration [7, 26, 36].

Grade 0—These brains show no gross abnormalities despite clinical evidence of HD. There may be up to 30–40% reduction in neuron number in the head of the caudate, though no reactive astrocytes are present at this stage.

Grade 1—Macroscopically, there is mild atrophy of the caudate tail and body. The head of the caudate and the putamen may still appear normal. Microscopically, the neuronal loss and astrocytosis is predominantly in the tail of the caudate nucleus with lesser involvement of the caudate body and head and the nearby putamen.

Grade 2—Macroscopically, some atrophy of the caudate is seen with resulting enlargement of the lateral ventricles, although the ventricular surface maintains its convex shape. Microscopically, significant neuronal loss and reactive astrocytosis is seen in the dorsal parts of the caudate and putamen. The globus pallidus begins to show degeneration, with the GPe degenerating before the GPi.

Grade 3—Macroscopically, there is significant atrophy of the caudate, causing the ventricular surface to appear straight as it now parallels the internal capsule boundary. Microscopically, the neuronal loss and reactive astrocytosis is visible throughout the caudate and putamen and becomes severe. This pathology progresses dorsal to ventral, rostral to caudal, and medial to lateral in the striatum. Mild pathology is present in the nucleus accumbens.

Grade 4—Macroscopically, there is severe atrophy of the striatum causing the ventricular surface to become concave. Microscopically, severe striatal neuron loss reaches approximately 95% and there is severe astrocytosis. The globus pallidus volume is reduced by half and the nucleus accumbens may begin to show more significant pathology.

9. Juvenile HD

Juvenile HD occurs when disease onset manifests before 20 years of age [4, 153, 154], 75% of juvenile HD patients have inherited the mutation from their father. Paternal inheritance is associated with increased likelihood of repeat-length expansion, leading to earlier onset in the next generation, referred to as “anticipation” [155]. It is difficult to diagnose because it often presents with minimal chorea. Instead, behavioral symptoms are more prominent than motor symptoms at such early ages [4] and the motor symptoms that do prevail are typically rigidity and bradykinesia [3]. Contrary to adult-onset HD, juvenile cases are prone to seizures as well [3, 153].

Juvenile HD patient brains typically show more severe striatal pathology than adult HD brains [3]. Magnetic resonance imaging (MRI), magnetic resonance spectroscopy, and postmortem brains of juvenile HD patients show severe and early striatal volume loss accompanied by reduced neuronal density but no significant cortical or white matter involvement [156]. Interestingly, juvenile cases of HD show more islets than adult cases [40]. In general, neuronal intranuclear inclusions are more common in juvenile than adult HD [123]. Aggregate load in the striatum is also more significant in juvenile HD brains [157].

Compared to adult onset HD, juvenile HD brains show severe cerebellar atrophy [36, 158]. In one case study involving a father with adult onset HD and a son with
juvenile HD, significantly more cerebellar pathology, including mHTT inclusions in cerebellar neurons, was seen in the juvenile case than the adult case [155]. In addition to the cerebellum, the GPi, thalamus, and nucleus accumbens are also more severely affected in juvenile HD patients [157, 159]. The frontal and parietal regions show gross atrophy and MRI analysis showed more widespread and faster cortical volume loss in juvenile cases compared to adult onset cases [157, 160].

10. Developmental changes

While HD is being increasingly recognized as a developmental disease, few neuropathological studies of developing brains with adult onset HD exist. Using tissue from HD carrier fetuses, it was found that HTT is mislocalized in ventricular zone progenitor cells, which disrupts the neuroepithelial junctional complexes and interkinetic nuclear migration [161]. This causes progenitor cells to prematurely enter into lineage specification [161]. Using imaging approaches, it has been shown that there is an absence of Sylvian fissure asymmetry, which occurs early in development, in the brains of HD patients [162]. Early genetic testing has allowed for imaging studies in children well prior to HD onset. In children with expanded repeats as young as 6 years old, increased connectivity between the striatum and other brain regions is evident [163]. Additionally, imaging has shown that these children have larger striatal volumes early in life, but more rapid decline in volume through aging [164].

Developmental malformations are not uncommon in HD patients. A recent study using a large cohort of autopsy brains found that developmental malformations were found approximately 6 times more frequently in HD-brains than in non HD-brains, with heterotopias being the most common malformation, though other asymmetric and solitary malformations were also seen [165].

11. Conclusion

HD is a complex neurodegenerative disease that involves multiple brain areas. In fact, it has taken decades to firmly establish that HD is not only a basal ganglia disorder, but rather affects many regions in a symptomatically relevant manner. Therefore, the neuropathology of HD is constantly being re-evaluated and studied. It is clear, however, that this disease causes significant striatal atrophy and neuronal loss with concomitant cortical changes that result in devastating motor, cognitive, and psychiatric consequences for HD patients.

Conflict of interest

The authors declare no conflict of interest.
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