Review

New Perspectives on the Neuropathology in Huntington's Disease in the Human Brain and its Relation to Symptom Variation

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Abstract. We review recent investigations regarding the relationship between selective neurodegeneration in the human brain and the variability in symptom profiles in Huntington's disease. Huntington's disease is a genetic neurodegenerative disorder caused by an expanded CAG repeat in exon 1 of the *Huntingtin* gene on chromosome 4, encoding a protein called huntingtin. The huntingtin protein is expressed ubiquitously in somatic tissue, however, the major pathology affects the brain with profound degeneration in the striatum and the cerebral cortex. Despite the disease being caused by a single gene, there is a major variability in the neuropathology, as well as major heterogeneity in the symptom profiles observed in Huntington's disease patients. The symptoms may vary throughout the disease course and present as varying degrees of movement disorder, cognitive decline, and mood and behavioral changes. To determine whether there is an anatomical basis underlying symptom variation, recent studies on the post-mortem human brain have shown a relationship between the variable degeneration in the forebrain and the variable symptom profile. In this review, we will summarize the progress relating cell loss in the striatum and cerebral cortex to symptom profile in Huntington's disease.

Keywords: Huntington's disease, human brain, pathology, symptoms, cortex, basal ganglia

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder associated with an unstable expansion of a CAG trinucleotide repeat in the first exon of the *Huntingtin* gene [1]. In humans, exon 1 of the *Huntingtin* gene normally varies between 6–35 CAG repeats, but individuals with more than 36 CAG repeats are at risk for HD. There is a correlation between the number of CAG repeats and the age of onset and disease severity, such that cases with CAG repeat lengths of 36 to 60 typically manifest symptoms in mid-life, whereas CAG repeat lengths of >60 results in more severe juvenile form of the disease [2–8].

The mutant huntingtin is expressed ubiquitously in somatic tissue; however the pathology of HD is most extensively localized in the forebrain. In the brain the neuropathological changes are characterized by extensive degeneration of the striatum (caudate nucleus and putamen) and the cerebral cortex together with involvement in other regions such as the globus pallidus, thalamus, hypothalamus, and white matter [9, 10]. The disease is characterized clinically by involuntary choreiform movements accompanied

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by progressive cognitive impairment and emotional disturbances [11]. One of the most important features of the disease, which has been highlighted by recent studies, is the highly variable nature of the neuropathology and symptomatology in affected individuals despite the single gene etiology of HD [12–15]. Although the age of onset and severity of disease generally correlate with the CAG repeat length, the distinct symptom phenotypes expressed in HD affected individuals show no significant correlation with respect to the size of the CAG expansion. Consequently, there is much interest in whether there are any underlying pathological differences in HD brains which may account for symptom heterogeneity. This review will specifically focus on the possible relationship between symptom profiles of adult onset HD and the variable pattern of degeneration in the striatum and the cerebral cortex [12–15].

CLINICAL FEATURES AND VARIATION IN SYMPTOMS

Huntington's disease is characterized by symptoms affecting motor control, cognition, and behavior. However, the pattern of symptoms exhibited by each individual during the course of the disease as well as at the time of onset can vary considerably. The symptoms typically emerge in mid-life; however the disease can manifest from early childhood to late in life [11, 16]. The disease duration is typically 10–20 years.

The onset of motor symptoms is used to define the clinical onset of HD. Development of involuntary, choreiform movements are one of the most distinctive and well recognized symptoms of HD, which was clearly documented in George Huntington's original work in 1872 [17]. Although useful for diagnosis, chorea is a poor marker of disease severity. Most patients initially display hyperkinetic movements that are progressively replaced by a more hypokinetic (akineto-rigid) syndrome in which bradykinesia, rigidity and dystonia predominate. In addition, the patient's ability to speak and swallow is also often affected thus leaving the patient susceptible to aspiration pneumonia [18–20].

The cognitive disorder begins insidiously with the loss of mental flexibility and progressive decline of intellectual processes that can lead to profound dementia. Early cognitive defects include impaired concentration, dysfunction of short-term memory and impairment of executive functions [21, 22]. As the disease progresses these deficits develop into a more widespread dementia, with the deterioration of verbal

skills such as speech and difficulty in visuospatial functioning [23–25].

Behavioral and psychiatric symptoms are common, but unlike cognition do not show a stepwise progression with disease severity [26]. There is a wide range of associated mood and neuropsychiatric complications. HD patients are afflicted with depression, dysphoria, agitation, irritability, labile mood, apathy, and anxiety [27, 28]. Also, a disproportionately high prevalence of obsessive-compulsive symptoms, sleep disturbances, personality changes, psychotic symptoms, and suicidal tendencies have been previously reported [29–32].

The onset of clinical symptoms pertaining to the motor, cognitive, and behavioral domains and disease course of HD, once manifest, can vary substantially between individual HD patients. For example, some patients show major motor dysfunction at clinical onset with minimal changes in mood or cognitive functions, while at the other extreme, others show major mood and cognitive related changes early in the disease course with minimal motor dysfunction until late stages of the disease. Moreover, remarkable symptom differences have been observed in monozygotic twins that have the same genetic mutation and environmental factors [33–36]. The intricate interaction of this particular genetic defect with innumerable environmental factors and modifier genes may produce a wide range of different possible phenotypes among HD cases [37].

NEUROPATHOLOGY OF THE HUMAN BRAIN

The specific symptoms of HD have been related to the neuropathology, which is characterized by neuronal loss in different functional regions of the brain. An early account of neuropathological abnormalities was described by Meynert in 1877 who proposed that chorea may be explained by lesions in the corpus striatum [38]. The brain weight in end-stage HD is about 300–400 g less than the average brain weight of 1300–1500 g. This gross atrophy of the brain principally results from profound shrinkage of the striatum (caudate-putamen) and thinning in the cerebral cortex [9, 14, 15]. The hippocampus, hypothalamus and thalamus are also affected [9, 10, 39] and the corpus callosum is often atrophic. Most interestingly as detailed below, recent analyses of post-mortem human HD tissue suggest that the variation in clinical symptoms in HD is strongly associated with the variable pattern of neurodegeneration in the striatum and cerebral cortex [12, 13].

Neuropathology in the basal ganglia

Gross examinations of post-mortem human HD tissue and *in vivo* neuroimaging techniques reveal that the disease produces a striking bilateral atrophy of the striatum [9, 40, 41] which generally has an ordered and topographical distribution. The tail and body of the caudate nucleus generally show more degeneration than the head. The pattern of degeneration in the caudate nucleus and the putamen usually progresses in the caudo-rostral and simultaneously in the dorso-ventral and medio-lateral directions [9]. The extent of striatal degeneration established by Vonsattel [42] has been the hallmark grading system to indicate the severity of HD disease pathology. The Vonsattel grading system consists of five grades (0–4) of severity based on both the macroscopic and microscopic histological findings in the striatum. The most affected neuronal populations in the striatum are the GABAergic medium-sized spiny projection neurons (MSNs) that constitute 90–95% of the striatal neuronal population. The MSNs that project to the external segment of the globus pallidus (indirect pathway) are the most vulnerable to the disease process [43, 44]. This population of neurons expresses enkephalin and dopamine D2 receptors and degenerates in advance of the MSNs that project to the internal segment of the globus pallidus and substantia nigra pars reticulata (direct pathway) that express substance P, dynorphin and dopamine D1 receptors [45]. The degree of striatal atrophy is, in part, associated with the degeneration of other nonstriatal basal ganglia regions, e.g., the globus pallidus, substantia nigra, subthalamic nucleus [9, 40]. What is especially interesting is that, as detailed in the next section, recent findings suggest that the pattern of striatal cell death shows regional differences between cases in the functionally and neurochemically distinct striosomal and matrix compartments of the striatum.

Striosome-matrix compartmental degeneration in the striatum and its relation to symptom profile

The mammalian striatum is divided into two major interdigitating compartments first identified using acetylcholinesterase (AChE) by Graybiel and colleagues [46]. The smaller AChE-weak striosome compartment is identified by high concentrations of distinctive neurochemical markers (neurotensin [47], LAMP [48], dopamine D2 receptors [49], GABA$_A$ receptors and kainate receptors [50–53], and substance P and enkephalin [54]) while the larger matrix compartment is characterized by high concentrations of other neurochemicals (AChE, tyrosine hydroxylase, somatostatin, the calcium-binding proteins calbindin, calretinin, parvalbumin, and the glutamatergic NMDA and AMPA receptors [51, 54–61]).

In HD, changes in the neurochemicals found in the striosome and the extrastriosomal matrix compartments have been reported. Some studies suggest that neuronal loss and gliosis shown by GFAP staining first appear in the striosomes, indicating that the neurons in striosomes may be more vulnerable at an early stage of HD or lower grades of the disease than those in the matrix [62–64]. However other studies show a preferential loss of neurons and neurochemical markers in the matrix compartment with clear sparing of the striosomes [50, 65, 66]. These findings detailing the heterogeneous pattern of compartmental striatal degeneration in HD are interesting as studies in the rodent and primate brains show that the striosome and matrix compartments have different patterns of connectivity and suggest that the two compartments are functionally different. Evidence from tracing studies suggests that the striosome compartment contains MSNs that receive inputs from the limbic system and these in turn project to the dopamine-containing neurons in the substantia nigra pars compacta [67–69]. Therefore the striosome compartment is thought to play a major "limbic" processing role in modulating mood and other related functions of the basal ganglia. Conversely, the matrix compartment receives inputs from especially the sensori-motor and associative cortices and hence, it is postulated to play a major role in the control of movement [56, 70].

Extending these observations, Tippett and colleagues [13] have shown a differential pattern of degeneration in the two striatal compartments in different HD symptom cases. Some cases showed a selective striosomal loss of striatal neurons, enkephalin and GABA$_A$ receptors (Fig. 1B), others showed selective cellular and GABA$_A$ receptor loss in the matrix compartment (Fig. 1C). Other cases showed a mixed striosomal/matrix pattern of degeneration. Most importantly, this differential compartmental pattern of striatal degeneration between cases correlated generally with the variable symptom profiles between cases; most notably there was a significant association between profound degeneration in the striosomes and pronounced mood symptoms in the patients (Fig. 1B). By contrast, cases with marked degeneration primarily in the matrix compartment often had major motor symptoms (Fig. 1C), although the matrix findings were not statistically significant. These findings particularly the relation between striosome degeneration and mood
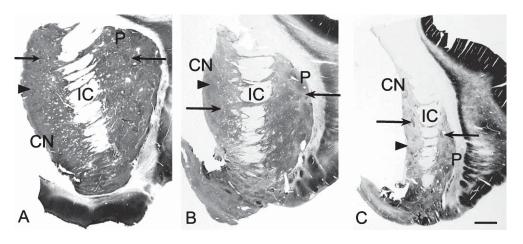
Fig. 1. Comparison of the patterns of GABA$_A$ receptor immunostaining in the striatum of a normal case (A) and two HD cases (B, C), characterized respectively by "mainly mood" symptoms (B) or "motor symptoms" (C). In the normal case GABA$_A$ receptor immunostaining is distributed throughout the striatum (caudate nucleus and putamen) with higher densities in the striosome (arrow) and moderate densities in the matrix (arrowhead) compartments. In the HD case which had predominant mood symptoms there is a major loss of GABA$_A$ receptors in the striosomes (B); whilst the case which has predominant motor symptoms shows extensive receptor loss in the matrix compartment with relative preservation of striosome receptors (C). (In the photomicrographs the matrix is indicated with an arrowhead and the striosomes with an arrow). CN = caudate nucleus; IC = internal capsule; P = putamen. Scale bar = 5 mm.

disturbance suggest that the different compartmental patterns of cell death and degeneration in the HD striatum could contribute significantly to the variability in HD symptomatology.

Neuropathology in the cerebral cortex and its relation to symptom profile

The cerebral cortex shows heterogeneous degeneration throughout different regions of the cerebral cortex in HD. In the cerebral cortex there is overall loss in cortical volume, cortical thinning, neuronal cell loss, neuronal morphological changes, glial cellular changes [12, 14, 15, 41, 71–77]. Recent advances in neuroimaging and detailed pathological analysis of the cerebral cortex in HD cases have also provided further new perspectives on the clinical heterogeneity in HD. Several imaging studies showing striatal and cortical atrophy have been correlated with cognitive deficits such as attention, working memory and executive functions [23]. DTI and tractography studies have shown that the motor circuit between the sensory-motor cortex and the striatum are most affected in HD [78], and these morphological changes correlated with cases showing mainly motor symptoms. Also landmark MRI studies by several authors have demonstrated progressive regional thinning of the cortical grey and white matter in both symptomatic and premanifest HD patients which correlate with varying cognitive, visuomotor

and motor deficits [14, 15, 79, 80]. These findings indicate that cortical changes may contribute to the heterogeneity of symptoms previously ascribed solely to basal ganglia alterations [15, 79, 81–83]. Importantly, the pioneering correlative MRI studies by Rosas and colleagues [14, 15] showed that cases with a prominent choreiform movement disorder presented a major thinning in the sensory-motor cortical region. Furthermore, the cases with more prominent dystonia, bradykinesia and rigidity demonstrated an overlap of thinning in the sensory-motor cortex region but additional thinning was shown in more anterior portions of the frontal cortex including pre-motor and supplementary motor areas.

Our recent detailed quantitative study using stereological cell counting in the post-mortem human HD cortex has complemented and expanded the neuroimaging studies by providing a cortical cellular basis of symptom heterogeneity in HD [12]. In particular, HD cases who were dominated by motor dysfunction showed a major total cell loss (28% loss) in the primary motor cortex but no cell loss in the limbic cingulate cortex, whereas cases where mood symptoms predominated showed a total of 54% neuronal loss in the limbic cingulate cortex but no cell loss in the motor cortex. This suggests that neuronal loss and alterations in the circuitry of primary motor cortex and anterior cingulate cortex may contribute respectively to impairments of motor and mood functions in HD (Fig. 2).

Aggregates in HD

The cell death in HD is accompanied by the presence of intranuclear and cytoplasmic aggregated forms of mutant huntingtin (mHtt) in neurons throughout the brain. The role of inclusions in cell death is controversial as there is evidence for both deleterious and protective effects [84–87]. These protein aggregates are thought to be formed by associations of polyglutamine (polyQ) regions which act as a 'polar zipper' [88, 89]. The immunohistochemical analyses of post-mortem human HD brain has demonstrated the presence of aggregates that can form neuronal intranuclear inclusions (NIIs) or cytoplasmic and neuropil extranuclear inclusions (NEIs). NIIs tend to be round, oval or rod shaped, larger than the nucleolus and more frequent in juvenile than adult onset cases. In contrast, the neuropil aggregates occur more frequently than NIIs in adult cases and tend to be round or oval and may be arranged in thin extensions along a process [90–93]. The inclusions are present prior to symptomatic development of the disease in the human brain and found throughout the cortex, but less frequently in the striatum [92–96]. Within the cortex, the cells tend to display combinations of nuclear and cytoplasmic as well as neuropil aggregations [95] with the highest levels of intranuclear inclusions found in juvenile cases which tend to have relatively very high CAG repeat

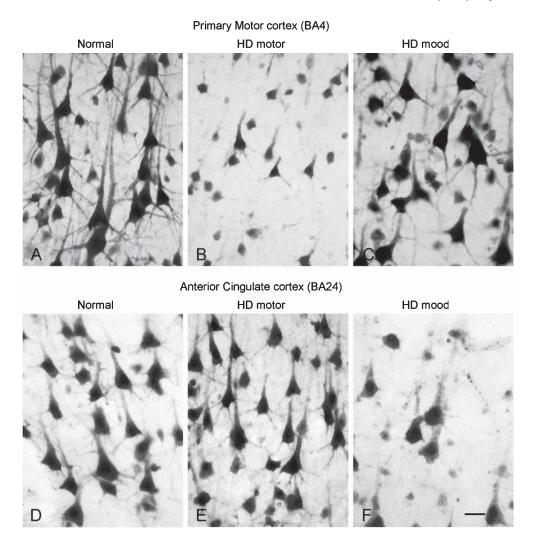Primary Motor cortex (BA4)

Anterior Cingulate cortex (BA24)

Fig. 2. Photomicrographs illustrating the pyramidal neurons in layer III in the primary motor cortex (A–C) and anterior cingulate cortex (D–F) of normal (A, D) and Huntington's disease cases (B, C; E, F). The images illustrate cases with "mainly motor" (B, E), and "mainly mood" (C, F) symptom profiles. In the motor cortex, the case showing predominant motor symptoms (B) shows major cell loss compared to the normal case. In the cingulate cortex the case with predominant mood symptoms (F) shows major cell loss compared to the normal case. Scale bar = 30 μm, modified from Thu et al. [12].

numbers [92]. Elucidating the exact molecular mechanisms for mHtt cytotoxicity has been a challenge. The mHtt aggregates are mostly ubiquitinated and are enriched in truncated polyglutamine containing-fragments generated by several proteases, however the precise mechanisms responsible for the toxicity of these proteolytic products remain elusive. It is generally thought that mHtt confers a toxic gain-of-function to elicit a cytotoxic cascade. Indeed, overexpression in various types of cells is cytotoxic [97, 98]. However, the soluble, non-aggregated forms of mHtt in tissues have been implicated more recently to be the neurotoxic culprit [84, 99–101]. There is also evidence to suggest that the aggregated forms of mHtt may have no effect or even be protective to cells [84, 101, 102]. The substances that are toxic to cells generally elicit a myriad of effects and therefore it is difficult to isolate which are primary, secondary or tertiary [103–105]. In addition, the expression of huntingtin does not reflect the distribution of selective vulnerability [106]. Some have even presented the view that cortical neurons may actively destroy MSNs, rather than these cells being vulnerable to mHtt itself [107]. Nevertheless, inclusions play a role in HD and are commonly used as biological markers for the testing and development of new therapeutic strategies aimed at reducing inclusion formation [108–111].

POSSIBLE MECHANISMS OF NEURONAL DEGENERATION IN HD

The prevailing questions in the field of HD pathology are: how and when pathological neuronal loss occurs; whether the progressive loss of neurons in the striatum is the primary process or is consequential to cortical cell dysfunction; and also how these changes relate to symptom profiles. Striatal neurons are thought to degenerate through excitotoxic processes or metabolic stress, but whether this is caused by intrinsic mechanisms in those neurons or through excitotoxic mechanisms originating from dysfunction of the cortical pyramidal neurons which project on to the striatum is still unclear. What is clear is that the diverse symptomatology of HD patients appears to have a morphological correlate where the regional distribution of neuronal dysfunction and loss correlates to the pattern of symptomatology in individual cases [12–15]. As the basal ganglia and cortex play an important role in modulating motor and mood functions, the consequent disruption of circuits between the cortex and basal ganglia and neuronal death in both

regions must play a major role in symptom phenotype. It has been suggested that cortical changes [83, 112, 113] are fundamental to the onset and progression of the HD phenotype. For example, the anterior cingulate cortex is the first cortical area to develop nuclear inclusions in the R6/2 HD mice [86] and is the site of ubiquitin-reactive dystrophic neurites in HD patients [114]. Also, in post-mortem HD brains [90, 91, 115] the accumulation of mutant huntingtin is consistently found more frequently in the cortex than in the striatum, and abundant neuropil aggregates have been detected in the cortex of presymptomatic HD cases [92, 116]. The widespread changes in the cortex are further supported by a microarray study in the human primary motor cortex where 3% of the genes (1482 genes) were differentially expressed in the HD cases [117]. These studies showed greater abnormalities in mRNA expression in the motor cortex than in the prefrontal association cortex, suggesting a distinct regional pattern of transcriptional alteration in the cortex of HD. In the cerebral cortex, the large projection neurons in layers V and VI are the most affected [71, 72, 74, 118] and are the principal neuronal type which projects to the striatum. Therefore, as others have suggested, dysfunction and loss of neocortical neurons may contribute to the pathogenesis of cell death in the striatum via the corticostriatal pathway.

Indeed, one of the prevailing mechanisms from mouse models of cell death in HD proposes that early changes in the corticostriatal pathway maybe a major contributing factor to the initiation of the pathogenesis in HD [119–121]. The corticostriatal neurons provide a major excitatory glutamatergic input onto the MSNs in the striatum and dysfunction of the corticostriatal neurons in HD mouse models [122, 123] leads to excess glutamate release in the striatum resulting in NMDA receptor-mediated excitotoxic MSN damage [124]. Furthermore, dysregulation of glutamate release is compounded by loss of dopamine D2, CB1, mGluR2/3 and other presynaptic receptors regulating glutamate release at corticostriatal terminals. Another adverse effect of corticostriatal dysfunction is reduced release of brain-derived neurotrophic factor (BDNF) – a growth factor necessary for striatal neuron survival [125]. The mHtt has been shown to reduce the production and transport of BDNF in the cortex via the corticostriate pathway [126–131]. Also, an early dysregulation of the *BDNF* gene due to mutant huntingtin has been suggested to disrupt microcircuitry in the cerebral cortex in a cellular *in vitro* model of HD leading to dysfunctional signalling in the cerebral cortex [132]. Other mechanisms contributing to cell death

in HD include environmental and epigenetic factors transcriptional dysregulation, oxidative stress, changes in neurotransmitters, and breakdown of cellular and vesicular transport mechanisms in neurons of the striatum and cerebral cortex [129, 133–135].

CONCLUSION

Overall, these studies show that the different patterns of degeneration in the basal ganglia and the cerebral cortex is highly variable and correlates to the variable symptom profiles in HD. Convergent evidence supports both cell-autonomous and non-cell autonomous processes in neuronal dysfunction and degeneration in both the cerebral cortex and striatum. While there is currently no cure, this contemporary evidence suggests that possible genetic therapies aimed at HD gene silencing should be directed towards intervention at both the cerebral cortex and the striatum in the human brain.

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CONFLICT OF INTEREST

None declared.

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