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Mehrabi,, N. F., Singh-Bains, M. K., Waldvogel, H. J., & Faull, R. L. M. (2016). Cortico-Basal Ganglia Interactions in Huntington's Disease. *Annals of Neurodegenerative Disorders*, 1(2): 1007, 1-6. Retrieved from <https://www.jscimedcentral.com/NeurodegenerativeDisorders/neurodegenerativedisorders-1-1007.pdf>

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Review Article

Cortico-Basal Ganglia Interactions in Huntington's Disease

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Submitted: 07 July 2016

Accepted: 19 July 2016

Published: 21 July 2016

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OPEN ACCESS**Keywords**

- Huntington's disease
- Cerebral cortex
- Basal ganglia
- Striatum

Abstract

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by involuntary movement, cognitive and psychiatric disturbances. The disease is caused by an expansion of polyglutamine repeats in the N-terminal domain of the huntington protein. Despite the single gene etiology, there is major variability in the neuropathology, as well as major heterogeneity in the symptom profiles. The major pathology occurs in the brain with profound degeneration in the forebrain regions, namely the basal ganglia and the cerebral cortex. In the basal ganglia, the progressive loss of striatal projection neurons, combined with the slow atrophy of other nuclei, were considered as the main neuropathological hallmarks of Huntington's disease. However, it is now well established that the HD symptoms and brain dysfunction result from degeneration in both the cerebral cortex and basal ganglia. This review covers the main cortico-basal ganglia-thalamo-cortical circuits implicated in HD, specifically addressing the relationships between the cerebral cortex and striatum. Furthermore, this review explores the relationships between the pattern of cortical regional degeneration, striatal compartmental degeneration, and the combined contribution of these neuropathological features to the variable symptom phenotypes in HD. Based on the combined and variable contributions of cortical and sub-cortical regional cell loss in HD which links to the heterogeneous symptom profiles in HD patients, this review supports the notion of HD as a multi-system cortico-basal ganglia degenerative disease.

ABBREVIATIONS

HD: Huntington's disease; MSNs: Medium Spiny Neurons

INTRODUCTION

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor disturbances, cognitive loss, and psychiatric manifestations [1,2]. HD is caused by an expansion of CAG trinucleotide repeats in the IT15 [Interesting Transcript 15] gene on chromosome 4, which encodes a mutant protein called huntington [3]. The exact mechanism through which the mutant Huntington causes degeneration and dysfunction of neurons is not entirely understood. However, abnormal depositions of huntington fragments (huntington aggregates) in the nuclei and cytoplasm of neurons have been suggested to initiate a pathogenic cascade leading to neuronal death throughout widespread regions of the forebrain, especially the basal ganglia and the cerebral cortex [4,5].

In the basal ganglia, the progressive loss of medium spiny GABAergic projection neurons of the striatum, with the slow atrophy of other nuclei were considered as the main neuropathological hallmarks of Huntington's disease [6,7]. However, it is now well established that the HD symptoms and brain dysfunction result from degeneration in both the cerebral cortex and basal ganglia [8-11]. The cerebral cortex is closely connected to the striatum via the direct glutamatergic corticostriatal projections. Thus, the degeneration in both of these structures in HD may be very closely linked.

Despite the single-gene etiology, individuals with HD can show clear and considerable phenotypic variability. Previous studies, investigating the relationship between HD symptom phenotype and post-mortem pathology, have established that symptom profile variability correlates very closely with the pattern of cortical and striatal degeneration [12-15]. This review will discuss the cortico-basal ganglia connections within the normal and HD human brain, and how the dysfunction of these

connections may contribute to the variable symptom profiles in HD patients.

Cortico-basal ganglia- thalamo- cortical circuits in the normal and HD brain

Changes in the anatomy, neurochemistry and cellular morphology of the basal ganglia are known to be the main pathological alterations in HD. The "basal ganglia" refers to a group of large subcortical nuclei located in the base of the forebrain and are involved in modulating motor, mood and cognitive control. The basal ganglia receives a diverse range of inputs from the cerebral cortex and channels this information back to the cerebral cortex through the thalamus, creating a circuit: the cortico-basal ganglia-thalamo-cortical circuit [16]. The projections within the circuit form several functionally segregated and interconnected systems, with the *motor* (indirect and direct) and *limbic* loops being the most characterized cortico-basal ganglia-thalamo-cortical connections [16-18]. Below is a brief description of the *motor* and *limbic* loops, and how alterations in these two loops may lead to the manifestation of variable symptoms in HD. *Motor loop (indirect and direct)* (Figure 1A).

The striatum (caudate nucleus and putamen) receives major excitatory glutamatergic inputs from the cerebral cortex. The cortical information, which is passed to the striatum from the primary motor, primary sensory, premotor and associative motor cortices, can be processed through two different routes:

the direct and indirect pathways. More recent evidence suggests the presence of additional pathways, including a direct pathway from the primary motor cortex to the sub thalamic nucleus of the basal ganglia [19]. It is now known that the basal ganglia forms a complex network, where cortical and sub cortical projections interact with several internal re-entry loops [20]. However, for the purpose of this review, the two major cortico-striatal pathways, notably the direct and indirect pathways, will be discussed. These two major efferent pathways (direct and indirect) are thought to have opposing effects on the output nuclei and the thalamic target nuclei [21-23]. However, recent evidence suggests that these two pathways are more structurally and functionally intertwined. In a holistic fashion, these two pathways work more closely in an integrated manner to influence the control of movements [24]. Furthermore, the neuronal activity of the various cortico-striatal loops work in a complex integrated manner to determine the final movement or behavior [25].

In the indirect pathway, the excitatory corticostriatal projections terminate onto striatal medium spiny neurons (MSNs) that co-express the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and the neuro peptide enkephalin (ENK). The striatal output then projects sequentially to the external segment of the globus pallidus (GPe), sub-thalamic nucleus (STN), and finally to the output nucleus of the basal ganglia (GPi). This increase in the GPi activation leads to reduced thalamic activation of the cortex (a negative feedback loop). In

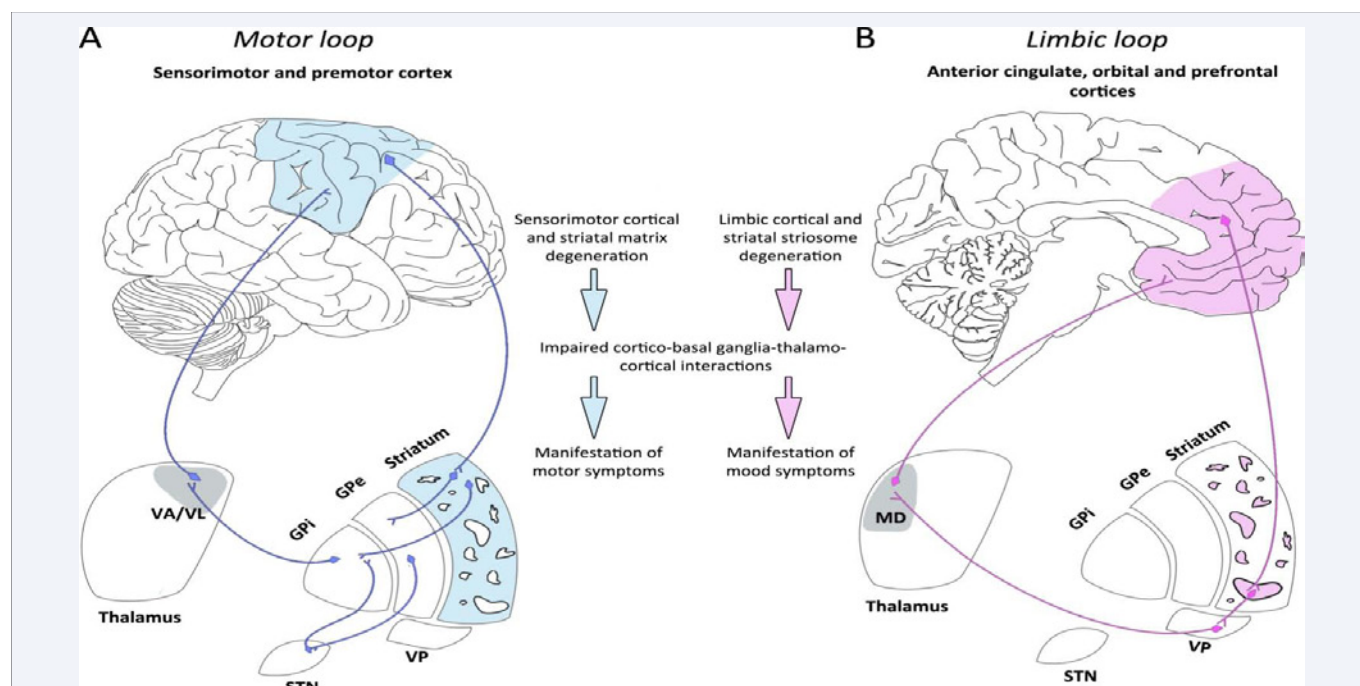


Figure 1 Schematic diagram modeling the hypothesized dysfunction of the two main cortico-basal ganglia-thalamo-cortical loops in the human brain in Huntington's disease.

(A) Motor loop: dysfunction/loss of neurons in the sensorimotor and premotor areas, combined with degeneration of matrix in the striatum (shaded blue), leads to impairment of the basal ganglia- thalamo-cortical motor loop. This will ultimately result in the manifestation of motor symptoms.

(B) Limbic loop: dysfunction/loss of neurons in the anterior cingulate gyrus, orbital and prefrontal cortices, combined with degeneration of striosomes in the striatum (shaded pink), leads to impairment of the basal ganglia-thalamo-cortical limbic loop. This will ultimately result in the manifestation of mood symptoms associated with HD.

Abbreviations: GPe: Globus pallidus External Segment; GPi: Globus pallidus Internal Segment; STN: Sub-Thalamic Nucleus; VP: Ventral Pallidum; VA/VL: Ventral Anterior/Ventral Lateral Nuclei; MD: Mediodorsal Nucleus.

the direct pathway, the excitatory corticostriatal projections terminate onto striatal medium spiny neurons that co-express GABA and the neuropeptide substance-P (SP). The SP expressing neurons then project directly to the GPi (and substantia nigra pars reticulata (SNr)), and thereby inhibit the activity of GPi (and SNr) neurons. Because the GPi (and SNr) neurons are GABAergic, their inhibition leads to an increase in the activity of the excitatory thalamo-cortical projections (a positive feedback loop). Thus, the result of the direct pathway is opposite to that of the indirect pathway [17,22,23,26,27].

In HD, it has been postulated that the disruption of these striatal pathways leads to the development of hyperkinetic (associated with early stages of HD) and dyskinetic movements (associated with advanced HD). Loss of "indirect" GABA/ENK striato-pallidal fibres, that project from the striatum to the GPe leads to a reduction in the inhibitory action upon GPe, which results in over activation of the GABAergic neurons that project from the GPe to the STN. This leads to the reduction of GPi inhibitory action upon the thalamus, resulting in hyperactivity of the cortical sensorimotor areas, and ultimately manifestation of chorea [28, 29]. In contrast, loss of the "direct" GABA/SP striato-pallidal fibres leads to loss of inhibition of the GPi. This, in turn, causes increased inhibition of the excitatory thalamo-cortical projection, and ultimately rigidity [30]. The "indirect" GABA/ENK expressing MSNs have been shown to be most vulnerable to the disease process, as their degeneration precedes that of the "direct" GABA/SP expressing MSNs. Indeed, previous *post-mortem* studies have shown that reduction in ENK staining of the GPe was a prominent feature in early stages of HD (Vonsattel grade 0-1), whereas SP staining in the GPi and SNr was affected only in later stages of the disease (Vonsattel grade 2-4) [31,32]. *Limbic loop* (Figure 1B)

In comparison to the dorsal components of the basal ganglia circuitry and their involvement in the direct/indirect motor circuits, the ventral striatum (VS) combined with the ventral pallidum (VP) receive information from the medial, orbitofrontal, and cingulate cortical areas. This information is channeled back to the orbital and medial prefrontal cortical areas (OMPFC) through the mediodorsal (MD) thalamic nucleus. This creates the limbic loop, which is thought to be involved in the regulation of mood and emotion [33-35].

Since many behavioral and mood disorders are associated with the dysfunction of the frontal cortical areas and/or the basal ganglia, the mood and behavioral HD symptoms are postulated to reflect disturbed functioning of the limbic circuit [36,37]. Indeed, some previous studies have suggested a link between HD mood symptoms, including depression, with dysfunction of the cortico-basal ganglia limbic loop [38,39].

Patterns of striatal and cortical degeneration reflect symptom variability in HD (Figure 1)

Pattern of striatal degeneration in Huntington's disease [HD]: Gross examination of the *post-mortem* HD human brain, as well as more recent neuroimaging studies on HD patients, demonstrate striking characteristic bilateral atrophy of the striatum (caudate nucleus and putamen) [40-43]. The major atrophy of the striatum is due to the loss of GABAergic medium-

sized spiny projection neurons (MSNs) which make up ~90-95% of the striatal neuronal population, combined with their dendritic arbors and heavily myelinated axonal projections.

Based on the level of acetyl cholinesterase [ACh] activity, the mammalian striatum can be subdivided into two major interdigitating compartments: The smaller neurochemically defined islands termed striosomes and the surrounding extrastriosomal region termed the matrix [44]. The striosome compartment is believed to connect extensively to the "limbic" cortical areas, namely the prefrontal cortex, thereby playing a major modulatory role in the "limbic" cortico-striatal system. In contrast, the matrix compartment receives inputs from sensorimotor and associative cortical areas, including the primary motor and sensory cortices, in a topographically organized manner; and hence it is thought to play a major role in the control of movement [16,44-47]. This principle has been reinforced by a key study reporting a strong correlation between the general pattern of striatal compartmental degeneration and symptom heterogeneity in HD cases [12]. That is, cases with profound striosome degeneration correlated with major mood symptoms. In comparison, cases with marked degeneration predominantly in the matrix compartment often had major motor symptoms. These findings suggest that the differential compartmental patterns of cell death and degeneration in the HD striatum could contribute significantly to the variability in HD symptomatology.

Pattern of cortical degeneration in Huntington's disease (HD): Due to the complex pathology and variable symptomatology of HD, the hypothesis proposing that the striatum is the main site of pathology in HD has been challenged by several studies. The critical involvement of the cerebral cortex in both "motor" and "limbic" circuits, as outlined above, suggests that some of the clinical symptoms of the disease are, in part, attributed to cortical dysfunction and degeneration. Accumulating evidence from detailed neuroimaging studies has facilitated important steps in elucidating the general regional cortical basis of symptom heterogeneity in HD [9,48-50]. For example, Rosas and colleagues demonstrated a clear correlation between the discrete pattern of cortical grey matter thinning and variable cognitive and motor deficits in HD [9,51]. In line with neuroimaging studies, extensive pathological studies have demonstrated, at the cellular level, a strong association between the pattern of cortical cell loss and variable symptom profiles in HD [13-15]. These studies have shown that loss of pyramidal cells and interneurons in the primary motor cortex is associated with movement abnormalities; whereas pyramidal and interneuron loss in the anterior cingulate gyrus is associated with mood symptoms in HD. These findings in end-stage pathology brains suggest a cellular basis for the clinical heterogeneity in HD. *Cortico-striatal interactions in HD*

The cerebral cortex and striatum form an extensive and highly organized projection system, known as the "corticostriatal pathway". This projection system is arranged in a topographically organized manner [52, 53]. It has been hypothesized that early cortical dysfunction in HD contributes to alterations in the corticostriatal pathway, and thereby influences striatal neurodegeneration [54]. Since the basal ganglia and cortex play an important role in modulating motor and mood functions, the consequent disruption of circuits between them

and neuronal death in both regions must play a major role in symptom phenotypes in HD. Indeed, previous studies using HD mouse models propose that changes in the corticostriatal pathway occurs as early as premanifest HD, and may be a major contributing factor to the initiation of HD pathogenesis [54-56]. Early dysfunction of the corticostriatal pathway is also strongly implicated in striatal excitotoxicity in HD. Participation of excitotoxicity via glutamatergic receptors is also a major theme in the theories of cortical pathogenesis in HD [57]. The medium spiny neurons (MSN) (the most vulnerable striatal neurons) receive excitatory glutamatergic input from different areas of the cortex. Loss of cortical interneuron inhibition results in dysfunction of pyramidal neurons, and alterations in the corticostriatal pathway in early stages of HD is thought to result in excess glutamate release in the striatum, causing NMDA receptor-mediated excitotoxic MSN damage [58-64]. Furthermore, the corticostriatal pathway is thought to be the main tract through which brain-derived neurotrophic factor (BDNF), a growth factor necessary for striatal neuron survival, is transported from the cerebral cortex to the striatum [65]. Previous studies have shown a significant reduction in the production and transportation of BDNF from the cortex to the striatum [66-72]. An *in vitro* study has suggested that early dysregulation of the BDNF gene in HD leads to disruption of the cortical microcircuitry [73]. BDNF has also been shown to be crucial for anatomical and functional maturation of interneurons in different cortical regions [74-76]. Together, these studies highlight the early involvement of the cerebral cortex and the corticostriatal pathway in the pathogenesis of Huntington's disease.

CONCLUSION

Global forebrain considerations of HD pathogenesis

The basal ganglia receive a diverse range of inputs from the cerebral cortex. This information is channeled back to the cortex via the thalamus, creating a circuit: the cortico-basal ganglia-thalamo-cortical circuit [16]. The projections within the circuit form several functionally segregated and interconnected systems, with the *sensorimotor* and *limbic* loops being the major cortico-basal ganglia-thalamo-cortical pathways (Figure 1). The *motor* loop involves the projections from the motor, premotor, and sensory cortical areas to the dorsal striatum; and the *limbic* loop involves the projections from the cingulate, orbital and prefrontal cortices to the ventral striatum [16,77-79]. Due to the strong connections between the different components of the cortico-basal ganglia-thalamo-cortical circuit, the disruption in any component of any of the loops mentioned above, either alone or in combination with cell-autonomous changes, could affect the functionality of the entire circuit. Taking a broad overview, it is clear that the dysfunction and loss of corticostriatal neurons, correlates with dysfunction and loss of striatopallidal projection neurons. That is, differential patterns of cortical neuron degeneration correspond with differential patterns of striatal neuronal degeneration, and this is reflected in variable patterns of symptom manifestations in Huntington's disease.

ACKNOWLEDGEMENTS

This work was supported by the Health Research Council of New Zealand [11-802], Neurological Foundation of New Zealand

(1102-PG), Brain Research New Zealand, as well as funding from the Matthew Oswin Memorial Trust and the TM Pacey Trust, and the Freemasons Foundation of New Zealand.

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Cite this article

Mehrabi NF, Singh-Bains MK, Waldvogel HJ, Faull RLM (2016) Cortico-Basal Ganglia Interactions in Huntington's Disease. *Ann Neurodegener Dis* 1(2): 1007.