

## Review Article

# Cortico-Basal Ganglia Interactions in Huntington's Disease

Nasim F. Mehrabi<sup>1,2#</sup>, Malvinder K. Singh-Bains<sup>1,2#</sup>, Henry J. Waldvogel<sup>1,2</sup>, and Richard LM Faull<sup>1,2\*</sup>

<sup>1</sup>Centre for Brain Research, University of Auckland, New Zealand

<sup>2</sup>Department of Anatomy with Medical Imaging, University of Auckland, New Zealand

<sup>#</sup>These authors contributed equally to this work

**\*Corresponding author**

Richard L. M. Faull, Centre for Brain Research, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland, New Zealand, Tel: 649 923 6708; Fax: 649 373 7484; Email: rlm.faull@auckland.ac.nz

Submitted: 07 July 2016

Accepted: 19 July 2016

Published: 21 July 2016

**Copyright**

© 2016 Faull et al.

**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.

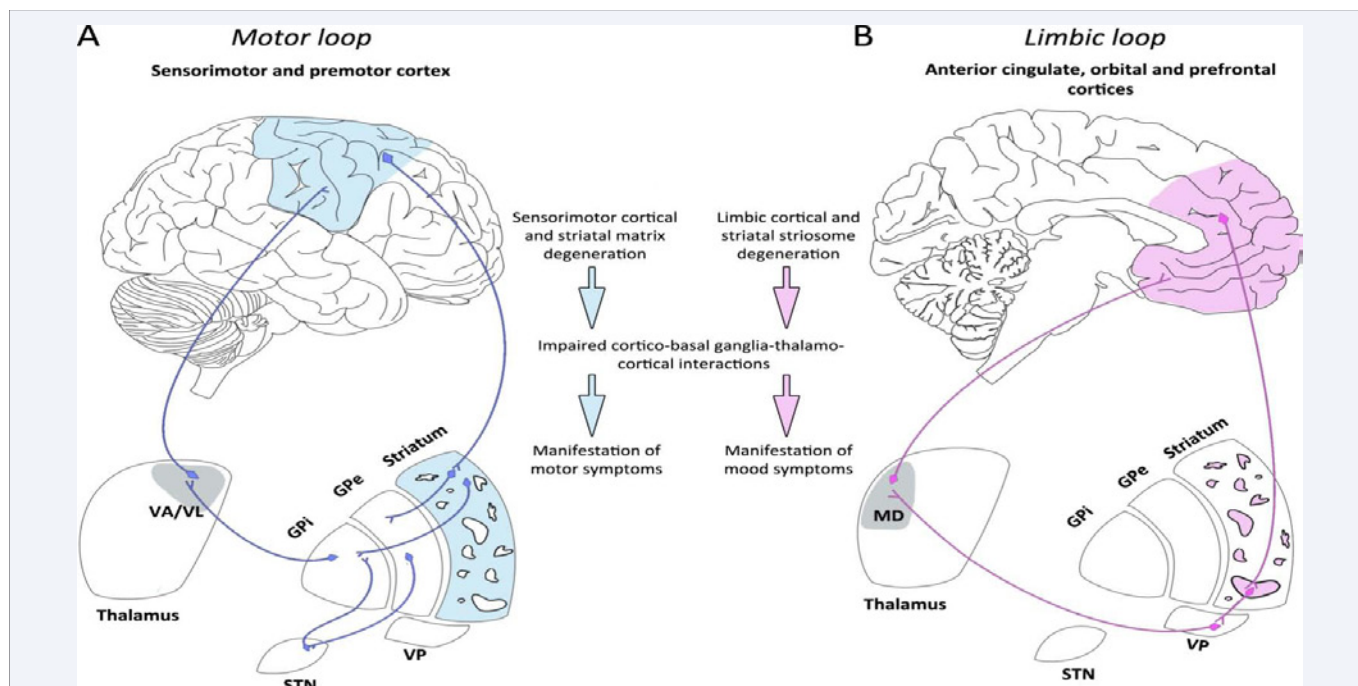
### Cortico-basal ganglia- thalamo- cortical circuits in the normal and HD brain

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.

## REFERENCES

- Walker FO. Huntington's disease. *Lancet*. 2007; 369: 218-228.
- Nance MA, Myers RH. Juvenile onset Huntington's disease—clinical and research perspectives. *Mental retardation and developmental disabilities research reviews*. 2001; 7: 153-157.
- Zoghbi HY, Orr HT. Glutamine repeats and neurodegeneration. *Annu Rev Neurosci*. 2000; 23: 217-247.
- DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP, et al. Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science*. 1997; 277: 1990-1993.
- Gutkunst CA, Li SH, Yi H, Mulroy JS, Kuemmerle S, Jones R, et al. Nuclear and neuropil aggregates in Huntington's disease: relationship to neuropathology. *J Neurosci*. 1999; 19: 2522-2534.
- Vonsattel JP, Keller C, Del Pilar Amaya M. Neuropathology of Huntington's disease. *Handb Clin Neurol*. 2008; 89: 599-618.
- Vonsattel JP, DiFiglia M. Huntington disease. *J Neuropathol Exp Neurol*. 1998; 57: 369-384.
- Kassubek J, Bernhard Landwehrmeyer G, Ecker D, Juengling FD, Muehe R, Schuller S, et al. Global cerebral atrophy in early stages of Huntington's disease: quantitative MRI study. *Neuroreport*. 2004; 15: 363-365.
- Rosas HD, Salat DH, Lee SY, Zaleta AK, Hevelone N, Hersch SM. Complexity and heterogeneity: what drives the ever-changing brain in Huntington's disease? *Ann N Y Acad Sci*. 2008; 1147: 196-205.
- Petersén A, Björkqvist M. Hypothalamic-endocrine aspects in Huntington's disease. *Eur J Neurosci*. 2006; 24: 961-967.
- Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology*. 2002; 58: 695-701.
- Tippett LJ, Waldvogel HJ, Thomas SJ, Hogg VM, van Roon-Mom W, Synek BJ, et al. Striosomes and mood dysfunction in Huntington's disease. *Brain*. 2007; 130: 206-221.
- Nana AL, Kim EH, Thu DC, Oorschot DE, Tippett LJ, Hogg VM, et al. Widespread heterogeneous neuronal loss across the cerebral cortex in Huntington's disease. *J Huntingtons Dis*. 2014; 3: 45-64.
- Thu DC, Oorschot DE, Tippett LJ, Nana AL, Hogg VM, Synek BJ, et al. Cell loss in the motor and cingulate cortex correlates with symptomatology in Huntington's disease. *Brain*. 2010; 133: 1094-1110.
- Kim EH, Thu DC, Tippett LJ, Oorschot DE, Hogg VM, Roxburgh R, et al. Cortical interneuron loss and symptom heterogeneity in Huntington disease. *Ann Neurol*. 2014; 75: 717-727.
- Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev*. 1995; 20: 91-127.
- Gerfen CR. The neostriatal mosaic: multiple levels of compartmental organization. *Trends Neurosci*. 1992; 15: 133-139.
- Nieuwenhuys R, Voogd J, van Huijzen C. *The human central nervous system*. Springer Verlag; 2008.
- Strafella AP, Vanderwerf Y, Sadikot AF. Transcranial magnetic stimulation of the human motor cortex influences the neuronal activity of subthalamic nucleus. *Eur J Neurosci*. 2004; 20: 2245-2249.
- Lanciego JL, Luquin N, Obeso JA. Functional neuroanatomy of the

- basal ganglia. *Cold Spring Harb Perspect Med.* 2012; 2: 009621.
21. Albin RL, Reiner A, Anderson KD, Penney JB, Young AB. Striatal and nigral neuron subpopulations in rigid Huntington's disease: implications for the functional anatomy of chorea and rigidity-akinesia. *Ann Neurol.* 1990; 27: 357-365.
  22. Penney JB Jr, Young AB. Speculations on the functional anatomy of basal ganglia disorders. *Annu Rev Neurosci.* 1983; 6: 73-94.
  23. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* 1990; 13: 281-285.
  24. Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Filippo M. Direct and indirect pathways of basal ganglia: a critical reappraisal. *Nat Neurosci.* 2014; 17: 1022-1030.
  25. Obeso JA, Lanciego JL. Past, present, and future of the pathophysiological model of the Basal Ganglia. *Front Neuroanat.* 2011; 5: 39.
  26. Gerfen CR, Wilson CJ. Chapter II The basal ganglia. *Handbook of chemical neuroanatomy.* 1996; 12: 371-468.
  27. Flaherty AW, Graybiel AM. Input-output organization of the sensorimotor striatum in the squirrel monkey. *J Neurosci.* 1994; 14: 599-610.
  28. Crossman AR, Mitchell IJ, Sambrook MA, Jackson A. Chorea and myoclonus in the monkey induced by gamma-aminobutyric acid antagonism in the lentiform complex. The site of drug action and a hypothesis for the neural mechanisms of chorea. *Brain.* 1988; 111: 1211-1233.
  29. DeLong MR. The basal ganglia. *Principles of neural science.* 2000; 4: 853-867.
  30. Berardelli A, Noth J, Thompson PD, Bollen EL, Currà A, Deuschl G, et al. Pathophysiology of chorea and bradykinesia in Huntington's disease. *Mov Disord.* 1999; 14: 398-403.
  31. Glass M, Dragunow M, Faull RL. The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. *Neuroscience.* 2000; 97: 505-519.
  32. Deng Y, Albin R, Penney J, Young A, Anderson K, Reiner A. Differential loss of striatal projection systems in Huntington's disease: a quantitative immunohistochemical study. *J Chem Neuroanat.* 2004; 27: 143-164.
  33. Heimer L, Switzer TD, Van Hoesen GW. Ventral striatum and ventral pallidum. Component of the motor system? *Trends in Neurosciences.* 1982; 5: 83-87.
  34. Heimer L, Van Hoesen GW, Trimble M, Zahm DS. Anatomy of neuropsychiatry: The new anatomy of the basal forebrain and its implications for neuropsychiatric illness: Access Online via Elsevier. 2007.
  35. Petrasch-Parwez E, Habbes HW, Löbbecke-Schumacher M, Saft C, Niescery J. The Ventral Striatopallidum and Extended Amygdala in Huntington Disease. In: Ferry B, editor. *The Amygdala - A Discrete Multitasking Manager.* 2012.
  36. Cummings JL. Toward a molecular neuropsychiatry of neurodegenerative diseases. *Ann Neurol.* 2003; 54: 147-154.
  37. Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol.* 1993; 50: 873-880.
  38. Chamberlain SR, Sahakian BJ. Cognition in mania and depression: psychological models and clinical implications. *Curr Psychiatry Rep.* 2004; 6: 451-458.
  39. Chamberlain SR, Sahakian BJ. The neuropsychology of mood disorders. *Curr Psychiatry Rep.* 2006; 8: 458-463.
  40. de la Monte SM, Vonsattel JP, Richardson EP Jr. Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. *J Neuropathol Exp Neurol.* 1988; 47: 516-525.
  41. Aylward EH, Li Q, Stine OC, Ranen N, Sherr M, Barta PE, et al. Longitudinal change in basal ganglia volume in patients with Huntington's disease. *Neurology.* 1997; 48: 394-399.
  42. Vonsattel JP, DiFiglia M. Huntington disease. *J Neuropathol Exp Neurol.* 1998; 57: 369-384.
  43. Vonsattel JP, Keller C, Amaya M. Huntington's Disease. In: Duyckaerts C, Litvan I, editors. *Handbook of Clinical Neurology.* 89: Elsevier, BV; 2008; 599-618.
  44. Waldvogel HJ, Kim EH, Tippett LJ, Vonsattel J-PG, Faull RL. The neuropathology of Huntington's disease. *Behavioral Neurobiology of Huntington's Disease and Parkinson's Disease: Springer;* 2014; 33-80.
  45. Parent A, Côté PY, Lavoie B. Chemical anatomy of primate basal ganglia. *Prog Neurobiol.* 1995; 46: 131-197.
  46. Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci.* 1990; 13: 244-254.
  47. Crittenden JR, Graybiel AM. Basal Ganglia disorders associated with imbalances in the striatal striosome and matrix compartments. *Front Neuroanat.* 2011; 5: 59.
  48. Hedreen JC, Peyser CE, Folstein SE, Ross CA. Neuronal loss in layers V and VI of cerebral cortex in Huntington's disease. *Neurosci Lett.* 1991; 133: 257-261.
  49. Sotrel A, Williams RS, Kaufmann WE, Myers RH. Evidence for neuronal degeneration and dendritic plasticity in cortical pyramidal neurons of Huntington's disease: a quantitative Golgi study. *Neurology.* 1993; 43: 2088-2096.
  50. Macdonald V, Halliday G. Pyramidal cell loss in motor cortices in Huntington's disease. *Neurobiol Dis.* 2002; 10: 378-386.
  51. Rosas HD, Salat DH, Lee SY, Zaleta AK, Pappu V, Fischl B, et al. Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity. *Brain.* 2008; 131: 1057-1068.
  52. Haber SN, Lynd E, Klein C, Groenewegen HJ. Topographic organization of the ventral striatal efferent projections in the rhesus monkey: an anterograde tracing study. *J Comp Neurol.* 1990; 293: 282-298.
  53. McGeorge AJ, Faull RL. The organization of the projection from the cerebral cortex to the striatum in the rat. *Neuroscience.* 1989; 29: 503-537.
  54. Cepeda C, Hurst RS, Calvert CR, Hernández-Echeagaray E, Nguyen OK, Jocoey E, et al. Transient and progressive electrophysiological alterations in the corticostriatal pathway in a mouse model of Huntington's disease. *J Neurosci.* 2003; 23: 961-969.
  55. Cepeda C, Wu N, André VM, Cummings DM, Levine MS. The corticostriatal pathway in Huntington's disease. *Prog Neurobiol.* 2007; 81: 253-271.
  56. Gu X, Li C, Wei W, Lo V, Gong S, Li SH, et al. Pathological cell-cell interactions elicited by a neuropathogenic form of mutant Huntingtin contribute to cortical pathogenesis in HD mice. *Neuron.* 2005; 46: 433-444.
  57. Hedreen JC, Roos RAC. Huntington's Disease. *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders: Wiley-Blackwell;* 2011; 258-72.
  58. André VM, Cepeda C, Venegas A, Gomez Y, Levine MS. Altered cortical glutamate receptor function in the R6/2 model of Huntington's disease. *J Neurophysiol.* 2006; 95: 2108-2119.

59. Spampinato J, Gu X, Yang XW, Mody I. Progressive synaptic pathology of motor cortical neurons in a BAC transgenic mouse model of Huntington's disease. *Neuroscience*. 2008; 157: 606-620.
60. Heilman KM, Watson RT. Mechanisms underlying the unilateral neglect syndrome. *Adv Neurol*. 1977; 18: 93-106.
61. Zeron MM, Chen N, Moshaver A, Lee AT, Wellington CL, Hayden MR, et al. Mutant huntingtin enhances excitotoxic cell death. *Mol Cell Neurosci*. 2001; 17: 41-53.
62. Zeron MM, Hansson O, Chen N, Wellington CL, Leavitt BR, Brundin P, et al. Increased sensitivity to N-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntington's disease. *Neuron*. 2002; 33: 849-860.
63. Beal MF. Aging, energy, and oxidative stress in neurodegenerative diseases. *Ann Neurol*. 1995; 38: 357-366.
64. Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB. Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. *Nature*. 1986; 321: 168-171.
65. Strand AD, Baquet ZC, Aragaki AK, Holmans P, Yang L, Cleren C, et al. Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration. *J Neurosci*. 2007; 27: 11758-11768.
66. Altar CA, Cai N, Bliven T, Juhasz M, Conner JM, Acheson AL, et al. Anterograde transport of brain-derived neurotrophic factor and its role in the brain. *Nature*. 1997; 389: 856-860.
67. Conner JM, Lauterborn JC, Yan Q, Gall CM, Varon S. Distribution of brain-derived neurotrophic factor (BDNF) protein and mRNA in the normal adult rat CNS: evidence for anterograde axonal transport. *J Neurosci*. 1997; 17: 2295-2313.
68. Ferrer I, Goutan E, Marín C, Rey MJ, Ribalta T. Brain-derived neurotrophic factor in Huntington disease. *Brain Res*. 2000; 866: 257-261.
69. Cattaneo E, Rigamonti D, Goffredo D, Zuccato C, Squitieri F, Sipione S. Loss of normal huntingtin function: new developments in Huntington's disease research. *Trends Neurosci*. 2001; 24: 182-188.
70. Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, et al. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science*. 2001; 293: 493-498.
71. Fusco FR, Zuccato C, Tartari M, Martorana A, De March Z, Giampà C, et al. Co-localization of brain-derived neurotrophic factor (BDNF) and wild-type huntingtin in normal and quinolinic acid-lesioned rat brain. *Eur J Neurosci*. 2003; 18: 1093-1102.
72. Baquet ZC, Bickford PC, Jones KR. Brain-derived neurotrophic factor is required for the establishment of the proper number of dopaminergic neurons in the substantia nigra pars compacta. *J Neurosci*. 2005; 25: 6251-6259.
73. Gambazzi L, Gokce O, Seredenina T, Katsyuba E, Runne H, Markram H, et al. Diminished activity-dependent brain-derived neurotrophic factor expression underlies cortical neuron microcircuit hypoconnectivity resulting from exposure to mutant huntingtin fragments. *J Pharmacol Exp Ther*. 2010; 335: 13-22.
74. Gorski JA, Balogh SA, Wehner JM, Jones KR. Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. *Neuroscience*. 2003; 121: 341-354.
75. Berghuis P, Agerman K, Dobszay MB, Minichiello L, Harkany T, Ernfors P. Brain-derived neurotrophic factor selectively regulates dendritogenesis of parvalbumin-containing interneurons in the main olfactory bulb through the PLC $\beta$  pathway. *J Neurobiol*. 2006; 66: 1437-1451.
76. Itami C, Kimura F, Nakamura S. Brain-derived neurotrophic factor regulates the maturation of layer 4 fast-spiking cells after the second postnatal week in the developing barrel cortex. *J Neurosci*. 2007; 27: 2241-2252.
77. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res*. 1990; 85: 119-146.
78. Alexander GE. Basal ganglia-thalamocortical circuits: their role in control of movements. *J Clin Neurophysiol*. 1994; 11: 420-431.
79. Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA. Deep brain stimulation: from neurology to psychiatry? *Trends Neurosci*. 2010; 33: 474-484.

#### 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.