

The Neuropathology of Huntington's Disease

Henry J. Waldvogel, Eric H. Kim, Lynette J. Tippett,
Jean-Paul G. Vonsattel and Richard LM Faull

Abstract The basal ganglia are a highly interconnected set of subcortical nuclei and major atrophy in one or more regions may have major effects on other regions of the brain. Therefore, the striatum which is preferentially degenerated and receives projections from the entire cortex also affects the regions to which it targets, especially the globus pallidus and substantia nigra pars reticulata. Additionally, the cerebral cortex is itself severely affected as are many other regions of the brain, especially in more advanced cases. The cell loss in the basal ganglia and the cerebral cortex is extensive. The most important new findings in Huntington's disease pathology is the highly variable nature of the degeneration in the brain. Most interestingly, this variable pattern of pathology appears to reflect the highly variable symptomatology of cases with Huntington's disease even among cases possessing the same number of CAG repeats.

Keywords Human brain • Neuropathology • Neurochemical • Striosomes • Basal ganglia • Striatum • Globus pallidus • Symptomatology

H.J. Waldvogel (✉) • E.H. Kim • R.L. Faull
Centre for Brain Research, Department of Anatomy with Radiology,
University of Auckland, Auckland, New Zealand
e-mail: h.waldvogel@auckland.ac.nz

E.H. Kim
e-mail: e.kim@auckland.ac.nz

R.L. Faull
e-mail: rlm.faull@auckland.ac.nz

J.-P.G. Vonsattel
Department of Pathology, Presbyterian Hospital, Columbia University,
New York NY10032, USA
e-mail: jgv2001@columbia.edu

L.J. Tippett
Centre for Brain Research, Department of Psychology,
University of Auckland, Auckland, New Zealand
e-mail: l.tippett@auckland.ac.nz

Contents

1	Introduction	34
2	Symptomatology	35
3	Pathology in the Basal Ganglia.....	36
3.1	Basal Ganglia Organization	36
3.2	Basal Ganglia Pathways.....	37
4	Neuropathology of the Basal Ganglia.....	39
4.1	Macroscopic Changes	39
4.2	Grading of Striatal Neuropathology	39
5	Cellular and Neurochemical Changes	42
5.1	Striatum	42
5.2	Striosome-matrix Compartmental Degeneration in the Striatum and Its Relation to Symptom Profile.....	47
5.3	Globus Pallidus	51
5.4	Substantia Nigra	51
5.5	Subthalamic Nucleus.....	52
5.6	Cerebral Cortex	52
6	Other Brain Regions	56
6.1	Thalamus	57
6.2	Hypothalamus.....	57
6.3	Hippocampus.....	58
6.4	Cerebellum	58
6.5	Subventricular Zone and Neurogenesis in Huntington's Disease.....	59
7	Gliosis	60
8	Aggregates	61
9	White Matter Changes	64
10	Degeneration in Peripheral Tissues	64
11	Mechanisms of Neuropathology.....	65
	References	67

1 Introduction

This chapter provides an update of the current knowledge of neuropathological changes that occur in the human brain in Huntington's disease (HD), and also an outlook to future studies in human HD neuroanatomy. A HD brain may be about 20–30 % less than a control brain in weight although this will be variable depending on the severity of the disease (Vonsattel and DiFiglia 1998). Major pathology occurs most prominently in the neostriatum which includes the caudate nucleus and putamen but also other regions of the basal ganglia. The basal ganglia are a highly interconnected set of subcortical nuclei and so major atrophy in one or more regions have major effects on the others. Therefore, the striatum which is preferentially degenerated and receives projections from the entire cortex also affects the regions to which it targets especially the globus pallidus and substantia nigra pars reticulata. Additionally, the cerebral cortex is itself severely affected as are many other regions of the brain, especially in more advanced cases. The most important new findings in

HD pathology are the highly variable nature of the degeneration in the brain (Hadzi et al. 2012; Pillai et al. 2012). For instance, there is an overall 21–29 % loss in cross-sectional area of the cerebral cortex but 57 % loss in the caudate nucleus (de la Monte et al. 1988). As discussed later, the cell loss in the cerebral cortex also shows a high degree of variability. Most interestingly, this variable pattern of pathology appears to reflect the highly variable symptomatology of cases with HD even among cases possessing the same number of CAG repeats (Georgiou et al. 1999; Friedman et al. 2005; Gomez-Esteban et al. 2007; Tippet et al. 2007; Thu et al. 2010).

2 Symptomatology

What has been known for a long time is that cases affected by HD express a triad of symptoms which include motor, behavioral, and cognitive deficits, although the defining symptom has always remained that of chorea. However, despite the single-gene etiology of HD, there is remarkable variability in the types of these motor, behavioral, and cognitive symptoms present in different HD cases both at clinical onset, during the disease, and at end stage of the disease. It must be remembered that the vast majority of pathological studies carried out on postmortem HD human brain are at end stage of the disease.

During the lifetime of individuals with HD, some exhibit mainly motor dysfunction at clinical onset, and few if any changes in mood for extended periods of time while, at the other extreme, others show mainly mood and/or cognitive changes, with minimal involuntary movements until the late stages of the disease (Andrew et al. 1993; Claes et al. 1995). Still others experience marked motor, mood, and cognitive symptoms simultaneously (Brandt and Butters 1986; Folstein 1989; Myers et al. 1991; Claes et al. 1995; Zappacosta et al. 1996; Thompson et al. 2002). Interestingly, observations in monozygotic twins who inherited identical *HTT* genes with the same repeat length exhibit marked differences in their symptom profile (Georgiou et al. 1999; Friedman et al. 2005; Gomez-Esteban et al. 2007). The onset of clinical symptoms in individual HD cases is generally correlated with the number of CAG repeats (Wexler et al. 2004), as does the disease severity, but there is no consistent relationship between CAG repeat length and symptom subtype (MacMillan et al. 1993; Telenius et al. 1994; Claes et al. 1995; Zappacosta et al. 1996). Thus, the source of variability in symptom subtypes is not clear. The clinical diagnosis and the onset of the disease are generally based on the onset of the movement disorder termed Huntington's chorea. These characteristic motor symptoms are expressed as a severe "choreoathetotic" disorder, which describes the rapid, irregular, and involuntary movements of HD. In addition, clumsiness and unsteadiness in walking are also early symptoms. Studies on HD populations have indicated that approximately 50–70 % of cases at onset present with chorea (Di Maio et al. 1993; Witjes-Ane et al. 2002) and chorea may develop into rigidity and dystonia later in the disease. However, 30–50 % present first, most commonly with depression followed by cognitive and behavioral changes and emotional problems such as irritability, aggression, anxiety,

and obsessive behavior (Di Maio et al. 1993; Witjes-Ane et al. 2002). There is also considerable phenotypic variation in the pattern of symptomatology during the course of the disease. To be able to more successfully grade HD clinically, several rating scales for HD have been developed, for instance, the Quantitated Neurological Exam (QNE), the HD Functional Capacity Scale (HDFCS), and the HD Motor Rating Scale (HDMRS). Recently, a new combined scale was developed by the Huntington's Study Group to include the four domains in HD: motor function, cognitive function, behavioral abnormalities, and functional capacities and is termed The Unified Huntington's Disease Rating Scale (UHDRS), which aims to be suitable for tracking changes over time (Huntington Study Group 1996).

3 Pathology in the Basal Ganglia

3.1 Basal Ganglia Organization

The basal ganglia are a group of large nuclei located subcortically in the base of the forebrain and are involved with the control of mood and movement. The nuclei belonging to the basal ganglia were originally considered to be the principal components of the "extrapyramidal system" and by convention, the term basal ganglia is now restricted mainly to the striatum (comprised of the caudate nucleus and putamen), globus pallidus segments, the subthalamic nucleus (STN), and the substantia nigra (Carpenter et al. 1976; Smith et al. 1998). The striatum is divided into the two large nuclear masses, the caudate nucleus, which rostrally forms a head, more centrally a body, and posteriorly a tail region which extends dorsally over the thalamus, and the putamen. The caudate nucleus and putamen are separated by the condensed fibers of the internal capsule. The globus pallidus is divided into two parts: the external segment of the globus pallidus (GPe) and the internal segment of the globus pallidus (GPi) (also termed medial and lateral segments). The STN is located medial to the GPi and rostro-dorsal to the substantia nigra. The substantia nigra consists of two parts, the substantia nigra pars reticulata (SNr), which is located ventrally in the midbrain, and the substantia nigra pars compacta (SNc), which in humans and primates are pigmented, and is located as cell clusters in the dorsal regions of the substantia nigra. Although the substantia nigra is located in the midbrain, it is considered part of the basal ganglia due to its close functional and connectional interrelationships with the striatum.

The striatum comprises neurons that fall principally into two classes of neurons—projection neurons and local circuit neurons—and these are subclassified according to their size, neurochemistry, and connectional characteristics. The majority of these neurons (approximately 95 %) are the medium spiny projection neurons using the inhibitory neurotransmitter γ -aminobutyric acid (GABA), which project mainly to the globus pallidus and SNr, and the remaining neurons are a morphologically and neurochemically heterogeneous group of interneurons, which modulate the function of the medium spiny output neurons (see below).

3.2 Basal Ganglia Pathways

The basal ganglia are integrated into a circular interconnected forebrain loop, which forms a cortical/basal ganglia/thalamus/cortical circuit (Nauta and Domesick 1984), (see Fig. 1). The cortex provides a major excitatory glutamatergic input to the caudate nucleus and putamen (Carpenter et al. 1976) that arises bilaterally but with a predominant ipsilateral component from the entire cerebral cortex with a major projection from the sensorimotor cortex (McGeorge and Faull 1989). The projection from the cerebral cortex to the striatum forms the single most extensive afferent connection to the striatum; practically every cortical region projects to the striatum (McGeorge and Faull 1989). In addition, the caudate-putamen receives projections from regions other than the cortex; an excitatory projection from the intralaminar nuclei and other nuclei of the thalamus (Sadikot et al. 1992), an inhibitory feedback loop from the globus pallidus (Bevan et al. 1998), a major dopaminergic projection from the SNc (A9 cell group) plus other afferent connections from diverse nuclei such as the serotonergic dorsal raphe nucleus (Graybiel et al. 1979) and cholinergic and glutamatergic projections from the pedunculopontine nucleus in the midbrain (Mena-Segovia et al. 2004). The main flow of cortical information through the basal ganglia is based on what are termed the “direct” or “indirect” pathways (Albin et al. 1989; Alexander and Crutcher 1990; DeLong 1990; Parent and Hazrati 1993; Graybiel 1995; Yung et al. 1996; Smith et al. 1998), and these are critical to our understanding of HD pathophysiology (see Fig. 1). According to this model, cortical information, which flows to the striatum, is processed and transmitted through the basal ganglia via two routes. First, a direct GABAergic inhibitory pathway flows from the striatum to the GPi and the SNr (*direct pathway*) which also contains the co-transmitter substance P. Secondly, an output from the striatum containing enkephalin projects to the external segment of the GPe, which in turn, sends an inhibitory input to the STN which in turn sends an excitatory projection to the GPi (*indirect pathway*). Thus, the direct and indirect pathways converge on the GPi which provides an inhibitory output projection to the ventral anterior and ventral lateral (VA/VL) nuclear regions of the thalamus. The VA/VL thalamic nucleus that receives most of the input from the GPi and SNr projects an excitatory input mainly to the frontal and premotor cortex (Mehler 1971; Faull and Mehler 1978; Kayahara and Nakano 1996) which then influences the output from the motor cortex. This completes the cerebro-cortical/basal ganglia/thalamus/cortical circuit. This circuit converges on the output of the primary motor cortex and intimately controls the movement of muscles that is critically affected in HD. In addition, a recent pathway termed “the hyperdirect pathway” has been identified which is an excitatory link from the cerebral cortex directly to the STN, which can stimulate subthalamic neurons to give a powerful excitatory drive to the GPi output neurons which inhibit the thalamus, and in this way bypass the striatum, see Fig. 1 (Nambu et al. 2002).

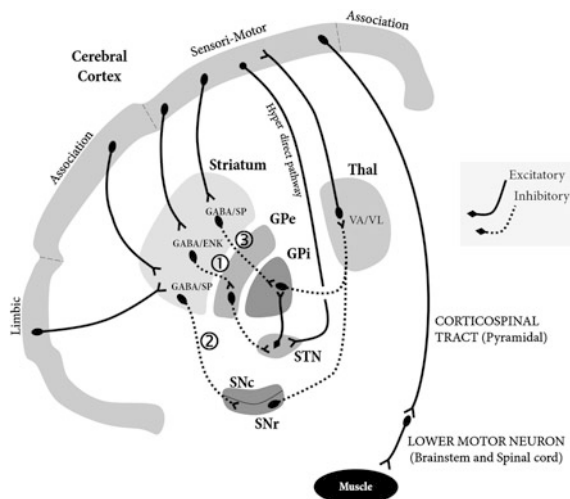


Fig. 1 Schematic diagram of cortico-basal ganglia pathways in Huntington's disease. The projections in the cortico-basal ganglia-thalamo-cortical loop form several functionally segregated parallel and interconnected systems. Prominent among these are the motor circuit, which involves the motor and premotor cortices and the dorsal striatum. In the *indirect pathway* (①), the excitatory corticostriatal projection terminates onto striatal medium spiny neurons that contain GABA/ENK. This striatal output first passes to the inhibitory GPe and then via the excitatory STN to GPi whereby disinhibition of the subthalamic neurons result in excitation of the GPi and hence **inhibition of the VA-VL thalamic nuclei**. In the *direct pathway* (②, ③), the cortical excitatory fibers terminate on the medium spiny striatal projection neurons that contain GABA/SP which project to GPi and SNr. These result in inhibition of the GPi and SNr and disinhibition (i.e., **excitation**) of the **VA/VL thalamic** output to the cerebral cortex. Thus, the result of cortical activation in the direct pathway is opposite to that of the indirect circuit: reinforcement rather than reduction of cortical activity. The hyperdirect pathway originates from the motor regions of the cerebral cortex and terminates in the STN and provides a direct excitatory pathway from the cerebral cortex to the STN. The disruption of the excitatory glutaminergic projection onto the striatum results in dysfunction of the striatal output pathways in HD which ultimately leads to the development of motor dysfunction in both hyperkinetic and dyskinetic movements. In HD, the initial symptoms of hyperkinesia and chorea are caused by the initial preferential damage in the *indirect* GABA/ENK striatopallidal pathway (①) that project from the striatum to the GPe. The loss of striatal neurons that give rise to the indirect pathway reduces the inhibitory action on the GPe which increases inhibition on the STN. The STN then becomes hypofunctional and causes reduced excitation of the inhibitory action of the GPi upon the thalamus. This subsequent disinhibition of the thalamus leads to the overactivation of the motor cortex which results in chorea (hyperactivity). By contrast, the subsequent later loss of *direct* GABA/SP striatopallidal pathway (②, ③) that projects from the striatum to the GPi and SNr causes increased inhibition of the thalamus which decreases the activation of the motor cortex with resultant rigidity (hypoactivity) in the later stages of the disease. The continuous and dotted lines indicate excitatory and inhibitory pathways, respectively. *ENK* enkephalin, *GABA* γ -aminobutyric acid, *GPe* globus pallidus external segment, *GPi* globus pallidus internal segment, *SNc* substantia nigra pars compacta, *SNr* substantia nigra pars reticulata, *SP* substance P, *STN* subthalamic nucleus, *Thal* thalamus, and *VA/VL* ventral anterior/ventral lateral thalamic nuclei

4 Neuropathology of the Basal Ganglia

4.1 *Macroscopic Changes*

Gross examination of postmortem Huntington's diseased human brain demonstrates a striking characteristic bilateral atrophy of the striatum (de la Monte et al. 1988; Aylward et al. 1997; Vonsattel and DiFiglia 1998; Vonsattel et al. 2008). This degeneration generally follows an ordered and topographical distribution. The tail and body of the caudate nucleus show more degeneration than the head in the very early stages of the degenerative process. The pattern of degeneration in the caudate nucleus and the putamen usually progresses from the tail of the caudate nucleus (TCN) to the head and body in the caudo-rostral and simultaneously in the dorsoventral and medio-lateral directions (Vonsattel and DiFiglia 1998).

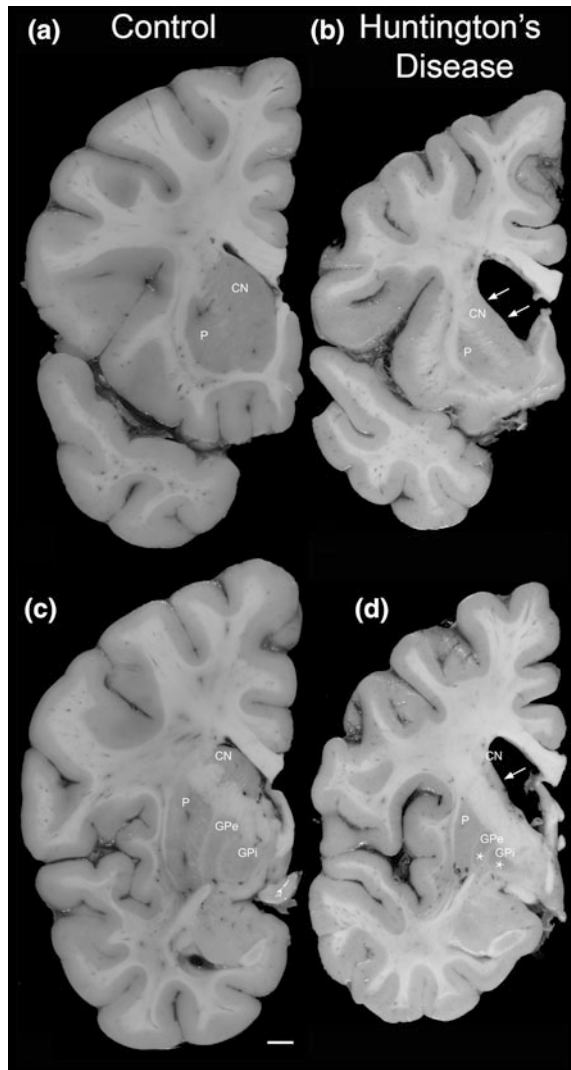
Macroscopically, the volume of the caudate nucleus and putamen is reduced with subsequent alteration of their respective shape (Fig. 2). A study of 30 HD brains showed the putamen had an average 64 % cross-sectional area loss compared with a 57 % cross-sectional area loss in the caudate nucleus (de la Monte et al. 1988). With progression of HD, the caudate nucleus becomes progressively more atrophic changing from the characteristic normal convex shape defining the border of the lateral ventricle to a thinner and ultimately more concave shape with resultant enlargement of the lateral ventricles occurring in parallel. This gradually decreasing volume is due to the loss of especially the medium spiny neurons, and their dendritic arbors and heavily myelinated axonal projections. Combined with the neuronal degeneration, there is also marked gliosis by astrocytes and oligodendrocytes. The extent of the macroscopic shape of the caudate nucleus and associated ventricular enlargement, the microscopic striatal degeneration including the loss of striatal neurons, and extent of gliosis provides the basis of the Vonsattel-grading system which is detailed below (Vonsattel et al. 1985; Vonsattel and DiFiglia 1998).

More recently, studies carried out by in vivo neuroimaging of brains of HD patients have detected early changes in the volume and shape of the basal ganglia, cerebral cortex, and other regions, and these were evident several years prior to symptomatic onset (Reading et al. 2005; Rosas et al. 2005).

4.2 *Grading of Striatal Neuropathology*

Although the degenerative process occurring in HD gradually encompasses the entire brain with regional differential degree of severity, most studies have emphasized that the brunt of the slowly ongoing atrophy involves the neostriatum. As previously stated, the neostriatal neuronal loss and reactive gliosis have an ordered and topographic distribution (Kiessellbach 1914; Lewy 1923; Terplan 1924; Dunlap 1927; Schroeder 1931; Neustaedter 1933; Birnbaum 1941; Hallervorden 1957; McCaughey 1961; Forno and Jose 1973; Roos et al. 1985; Vonsattel et al. 1985).

Fig. 2 Pathology of Huntington's diseased brain. Coronal sections at 2 levels through the human brain of **a**, **c** a representative control case the left cerebral hemisphere of a 35-year-old male, and **b**, **d** a Grade 3/4 Huntington's disease case. **a**, **b** are from the level of the striatum and the nucleus accumbens, **c**, **d** are at the level of the globus pallidus. There is major shrinkage of the caudate nucleus and putamen (*arrows*) as well as the globus pallidus (*asterisks*) in the Huntington's disease case. Shrinkage of the cerebral cortex is also evident. CN caudate nucleus, *GPe* globus pallidus external segment, *GPI* globus pallidus internal segment and *P* putamen; Scale bar = 1 cm



Along the sagittal axis of the neostriatum, the TCN is more involved than the body (BCN), which in turn is more involved than the head (HCN). The caudal portion of the putamen is more degenerated than the rostral portion; the transition between the portions is gradual, thus often ill defined.

Along the coronal (or dorsoventral) axis of the neostriatum, the dorsal and rostral neostriatal regions are more involved than the ventral ones including the nucleus accumbens. Along the medio-lateral axis (half brain) or latero-lateral axis (whole brain), the paraventricular half of the CN is more involved than the paracapsular half, the transition between the halves being gradual. As a function of the duration

of the deleterious process, neostriatal degeneration appears to simultaneously move in a caudo-rostral direction, in a dorsoventral direction, and in a medio-lateral direction. Fibrillary astrogliosis parallels the loss of neurons along the caudo-rostral and dorsoventral gradients of decreasing severity. Most neostriatal neurons visible in the postmortem brains are apparently normal, although the lipofuscin might be increased or some neurons might be smaller than normally expected. Clearly, a subset of neostriatal neurons stain darker with Luxol fast blue counterstained with hematoxylin and eosin (LHE), or hematoxylin and eosin (HE), or with cresyl violet (CV) than the apparently healthy, but probably dysfunctional neurons. These neurons are referred to as neostriatal dark neurons (NDN). They have a scalloped cellular membrane, a granular dark cytoplasm, and a nucleus with condensed chromatin. They are scarce, but tend to be clustered, in both the atrophic and in the relatively preserved zones. Less than 5 % of the HD brains show discrete, round 0.5–1.0 mm in diameter islets of relatively intact parenchyma within the anterior neostriatum. The density of neurons in islets is the same as, or slightly lower than that of the control neostriatum, but the density of astrocytes is increased (Vonsattel et al. 1992). Islets are found more frequently in cases with juvenile than adult onset of clinical symptoms.

A neuropathological grading system for HD was developed by Vonsattel based on the pattern of neurodegeneration in the HD striatum of a large number of HD brains (Vonsattel et al. 1985; Glass et al. 2000). The assignment of a grade of neuropathological severity from 0 to 4 is based on gross and microscopic findings using conventional methods of examination obtained from standardized, coronal sections that include the striatum: at the level of the nucleus accumbens (Fig. 2a, b), at the level of the caudal edge of the anterior commissure and globus pallidus (Fig. 2c, d), and at the level of the lateral geniculate body. This grading system applies to brains from individuals diagnosed clinically as having HD, with or without a genetic test.

Grade 0 comprises less than 1 % of all HD brains. Gross examination shows features indistinguishable from control brains. On general survey using LHE- or HE-stained slides alone, neither reactive gliosis nor neuronal loss is reliably detectable. However, further evaluations including cell counts indicate a 30–40 % loss of neurons in the HCN and no visible reactive astrocytosis. Furthermore, a study using immunohistochemistry and sections of three, presymptomatic, gene carriers revealed ubiquitinated, nuclear inclusions in all three brains including one individual, with 37 polyQ, who died putatively 3 decades before the expected age for onset of symptoms. In addition, cell counts of the TCN revealed an increased density of oligodendrocytes among the presymptomatic *HTT* gene carriers (Gomez-Tortosa et al. 2001).

Grade 1 comprises 4 % of all HD brains. The TCN is smaller than control as most likely is the BCN. Neuronal loss and astrogliosis involve the TCN, BCN, and dorsal portion of both the head and nearby dorsal putamen. Cell counts show 50 % or greater loss of neurons in the HCN.

Grade 2 comprises 16 %; those assigned **Grade 3** comprises 52 %; and those assigned **Grade 4** comprises 28 % of all HD brains. Gross striatal atrophy is mild to

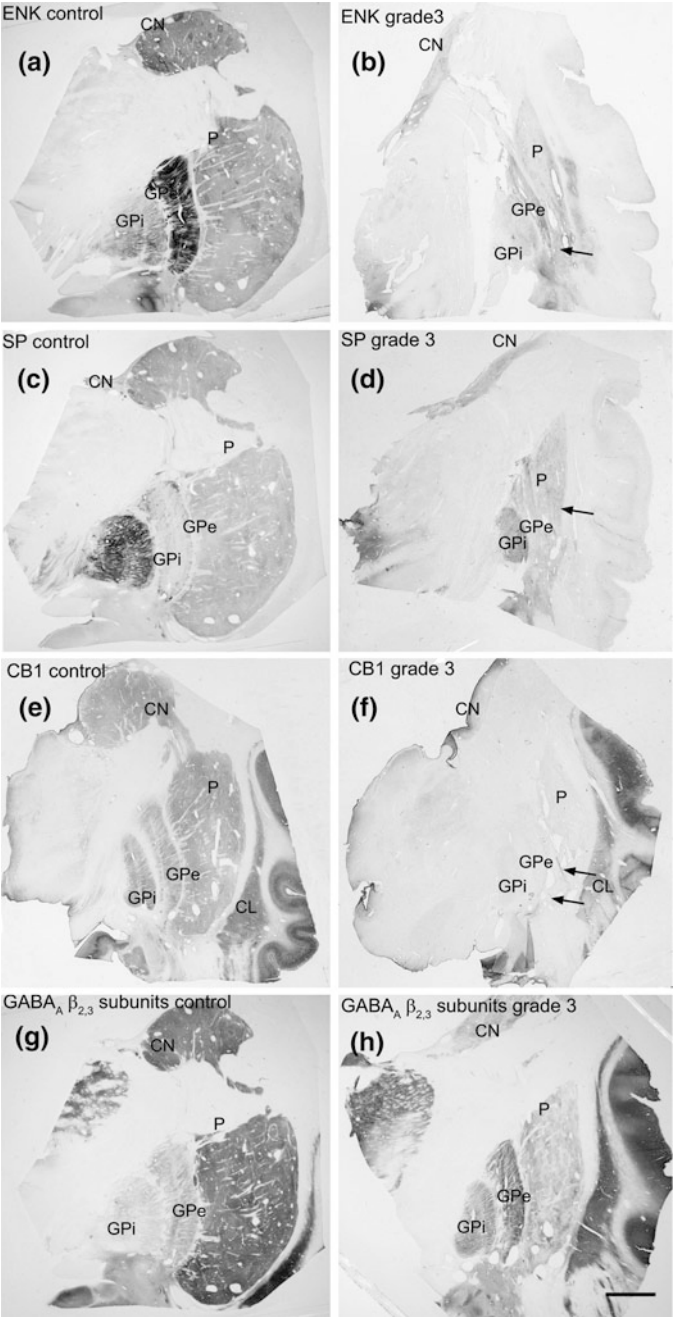
moderate in grade 2 (the medial outline of the HCN is only slightly convex but still bulges into the lateral ventricle) and severe in grade 3 (the medial outline of the HCN forms a straight line or is slightly concave medially). Thus, the microscopical changes in Grade 2 and Grade 3 are more severe than in Grade 1, and less than in Grade 4 brains.

In **Grade 4**, the striatum is severely atrophic (the medial contour of the HCN is concave, as is the CN at the anterior limb of internal capsule). The neostriatum loss is 95 % or more neurons. In at least 50 % of Grade 4 brains, the underlying nucleus accumbens remains relatively preserved, but is not normal.

5 Cellular and Neurochemical Changes

5.1 Striatum

Various autoradiographic, *in situ* hybridization and immunohistochemical studies have documented neuronal and glial changes in the striatum of HD and have reported loss of neurochemicals, neurotransmitters, and neurotransmitter-associated receptors in the HD striatum (Figs. 3, 4, 5; Table 1). The most affected neuronal populations in the HD striatum are the medium-sized spiny projection neurons (MSNs) that constitute ~90–95 % of the total striatal neuronal population. In the human striatum, the cell bodies of these GABAergic inhibitory MSNs can be identified morphologically in histological sections and can also be specifically labeled with antibodies to glutamic acid decarboxylase (GAD, the precursor enzyme for synthesizing GABA), the neuropeptides enkephalin, substance P, dynorphin, and the calcium-binding protein calbindin (CB) (Holt et al. 1996, 1997; Deng et al. 2004) and the dopamine- and cAMP-regulated phosphoprotein 32 kDa, termed DARPP-32. The medium spiny neurons are innervated by excitatory neurons in the cerebral cortex and the thalamus, by dopaminergic neurons in the SNc, and cholinergic and GABAergic interneurons of the striatum. They are therefore associated with a large number of ion channel and metabotropic receptors on their surface membranes including cannabinoid (CB1) (Glass et al. 2000), GABA_A receptors (Waldvogel et al. 1999), glutamate receptors (Dure et al. 1992; Kuppenbender et al. 2000), and dopamine receptors (D1 and D2) (Joyce et al. 1988; Khan et al. 1998). The loss of medium spiny neurons has been shown in immunohistochemical studies using the calcium-binding protein marker CB, which selectively identifies the cell bodies of medium spiny neurons in the matrix compartment (Seto-Ohshima et al. 1988; Goto et al. 1989; Ferrante et al. 1991; Tippet et al. 2007). A recent study showed a loss of 58–76 % DARPP-32 positive neurons in the human HD putamen with increasing grade (Guo et al. 2012). DARPP-32 is a marker for the majority of medium spiny neurons in the rat striatum (Ouimet et al. 1998). The loss of DARPP32 neurons was correlated with the motor impairment score rather than chorea. As mentioned above, there are two major GABAergic populations of MSNs, those that contain



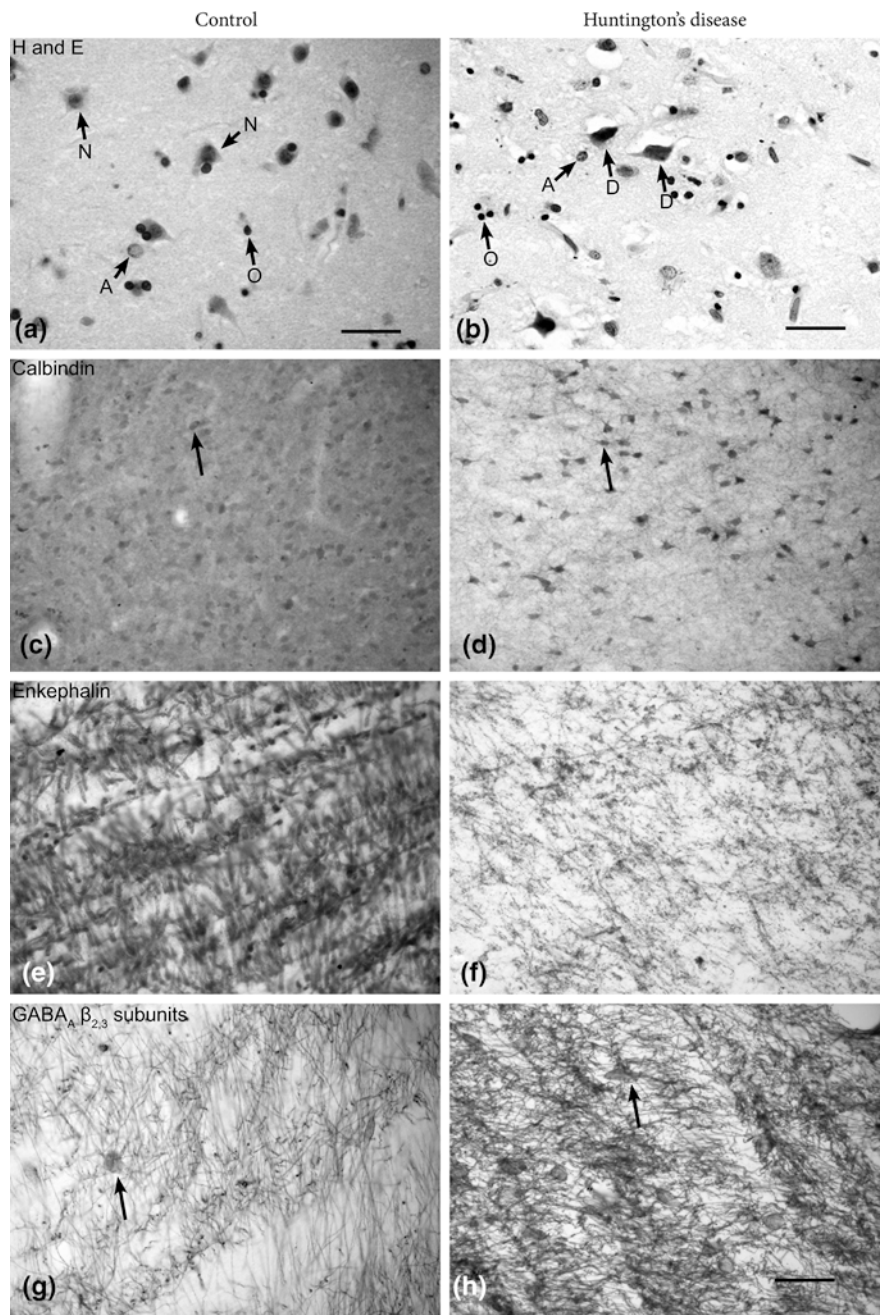
◀ **Fig. 3** Changes in neurochemical markers enkephalin, substance P, cannabinoid CB1, GABA_A receptor α_1 subunit, in the basal ganglia in Huntington's disease human brain. **a, c, e, g** Sections of the control human basal ganglia at the level of the globus pallidus. **b, d, f, h** Sections from Grade 3 Huntington's disease brains at equivalent levels through the globus pallidus. Sections were stained for the following markers: Enkephalin (**a, b**), Substance P (**c, d**), Cannabinoid CB1 receptor (**e, f**), $\beta_{2,3}$ subunit of the GABA_A receptor (**g, h**). In Huntington's disease, there is a major loss of enkephalin in the caudate nucleus, putamen, and GPe. There is also a loss of substance P in the caudate nucleus and putamen and GPi, although the loss is not as marked as that of enkephalin and there is an almost complete loss of CB1 receptors in the caudate nucleus and putamen and both the GPe and GPi. Note for CB1 receptor the adjacent claustrum and insular cortex still show relatively normal levels of staining. There is a major upregulation of the GABA_A $\beta_{2,3}$ receptor subunits in both GPe and GPi in Huntington's disease, but a loss in the putamen. *Arrows* indicate globus pallidus in **b, f**. (Modified from Allen et al. 2009) *CL* claustrum, *CN* caudate nucleus, *ENK* enkephalin, *GPe* globus pallidus external segment, *GPi* globus pallidus internal segment, *P* putamen, *SP* substance P, and Scale bar = 1 cm

enkephalin, and those that contain substance P (see Figs. 1 and 5). In HD, the MSNs degenerate with increasing HD grade (Vonsattel et al. 1985; Vonsattel and DiFiglia 1998). Both enkephalin and substance P neurons are lost (Marshall et al. 1983), but MSNs projecting to the external segment of the GP (indirect pathway) that express enkephalin and dopamine D2 receptors have been shown to be the most vulnerable in the disease process (Reiner et al. 1988; Albin et al. 1992; Augood et al. 1996), and degenerate in advance of the MSNs that express substance P, dynorphin and dopamine D1 receptors that project to the GPi and SNr (direct pathway) (Gerfen et al. 1990; Deng et al. 2004). The disruption of these striatal pathways in HD leads to the development of motor dysfunction including hyperkinetic, hypokinetic, and dyskinetic movements (see Figs. 1 and 5).

Reductions in glutamate NMDA receptor binding, GABA_A receptor binding, and cannabinoid receptor binding are all evident in the HD striatum (Whitehouse et al. 1985; Young et al. 1988; Glass et al. 2000; Tippet et al. 2007), which is most likely due to loss of neurons containing these receptors, but may also represent a dysfunction or downregulation of these receptors.

The projections from the striatum to the output nuclei which contain enkephalin, substance P, and cannabinoid receptors are progressively lost with increasing grade, mirroring the loss of MSNs in the striatum (Figs. 13a–d and 5). Enkephalin staining is dramatically lost in a grade-dependent manner in the GPe reflecting loss of the GABAergic enkephalin-positive pathway to the GPe (indirect pathway) (Figs. 3a, b, and 5). There is also a loss of substance P in the GPi (Figs. 3c, d, and 5) and SNr, reflecting the loss of the GABAergic substance P-positive pathway projecting to these two striatal output nuclei (Reiner et al. 1988; Waters et al. 1988; Albin et al. 1990, 1992; Deng et al. 2004; Allen et al. 2009), and loss of cannabinoid receptors on the presynaptic terminals of both the direct and indirect pathways (Figs. 3e, f and 5).

In addition to the projection neurons, the striatum contains a heterogeneous group of aspiny interneurons, which modulate the activity of medium spiny neurons in a highly complex fashion (Cicchetti et al. 2000). The majority of interneurons contain GABA as their major neurotransmitter, and these are subdivided into groups depending on the calcium-binding proteins they contain, principally



◀ **Fig. 4** Striatal neurons in control and Huntington's disease striatum. Examples of histochemically labeled striatal projection neurons and interneurons in the control striatum (**a**, **c**, **e**, **g**) and Grade 3 Huntington's disease striatum (**b**, **d**, **f**, **h**) from equivalent regions of the striatum. **a**, **b** Hematoxylin- and eosin-stained sections in the region of the (**a**) control human dorsal striatum showing neurons resembling normal medium-sized spiny neurons, astrocytes and oligodendrocytes and (**b**) Huntington's diseased human dorsal striatum showing atrophic neurons, astrocytes, and oligodendrocytes: For **a** and **b**: arrow—A = astrocyte, arrow—D = degenerating neuron, arrow—N = normal neuron, arrow—O = oligodendrocytes. **c**, **d** Medium spiny neurons stained with calbindin from a control case (**c**) and a Grade 3 HD case (**d**) showing marked loss of calbindin-positive neurons and neuropil. **e**, **f** Enkephalin staining of axon terminals in a control GPe (**e**) compared with an HD Grade 3 case showing loss of enkephalin-positive terminal staining on pallidal dendrites (**f**) in the HD case. **g**, **h** (**G**) Illustrates GABA_A receptor $\beta_{2,3}$ subunit staining on pallidal neurons and dendrites in the control GPe from the same case as **e** compared with **h** the same HD Grade 3 case as in **f** showing that associated with the loss of enkephalin terminals there is upregulation of these subunits on pallidal neurons and dendrites in the HD GPe. Scale bars **a**, **b** = 25 μ m **h** represents scale bar for **c**–**h** = 100 μ m

parvalbumin (PV) and calretinin (CR) (Cicchetti et al. 2000). The two other major types of interneurons in the human striatum are the large cholinergic interneurons, which also contain CR and substance P receptors, and the interneurons containing neuropeptide Y, somatostatin, NOS, and NADPH diaphorase (see Figs. 3 and 5).

In general, the striatal interneurons are less affected by the disease process than the medium spiny neurons, especially in lower grades (Ferrante et al. 1987); however, in higher grades, the interneurons are also affected in a differential manner; that is, those containing the calcium-binding protein PV (Harrington and Kowall 1991; Reiner et al. 2013) are consistently lost in the HD striatum, and a recent study shows that the PV-positive fast-spiking interneurons of the striatum are degenerated in a grade-dependent manner, so that by Grade 3, they are severely reduced in number, have a compromised morphology and that they may be linked to those patients developing dystonia (Reiner et al. 2013). The large-sized CR-positive neurons many of which belong to the population of the large-sized cholinergic neurons are generally preserved until the higher grades (Cicchetti and Parent 1996). By contrast, interneurons containing neuropeptide Y/somatostatin or NADPH diaphorase/NOS and the medium-sized CR-positive interneurons are largely spared even in relatively severe cases of striatal degeneration (Dawbarn et al. 1985; Ferrante et al. 1987; Cicchetti and Parent 1996; Cicchetti et al. 2000). The reason for this is not clear, but it has been postulated to be due to either, the pattern of distribution of excitatory receptors, the presence of differential types of calcium-binding proteins which buffer toxic intracellular calcium concentrations, or possibly their genetic fingerprint and susceptibility to the toxic mutant *HTT* gene. The calcium-binding protein CB is however not considered neuroprotective as the MSNs are preferentially affected from the earliest stages of the disease and show massive cell loss. However, the CR-positive medium-sized neurons may be protected by the calcium-binding protein CR, as these are largely preserved in HD.

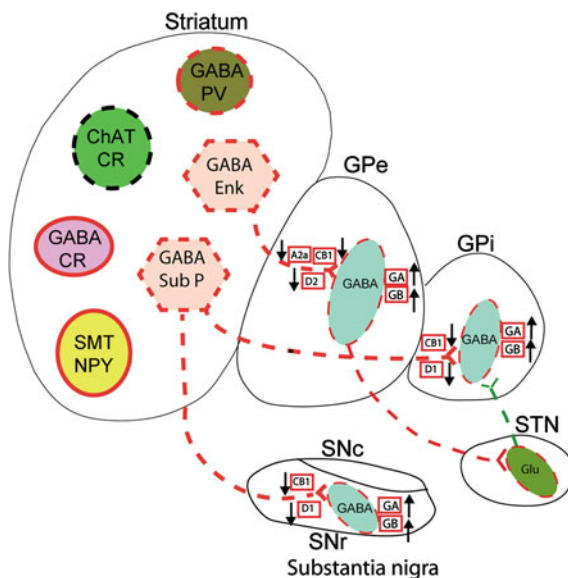


Fig. 5 Cell and receptor changes in the basal ganglia in Huntington's disease. Diagrammatic figure showing the various cell types and receptors in the striatum, globus pallidus external segment (*GPe*), globus pallidus internal segment (*GPi*), substantia nigra (*SN*), and subthalamic nucleus (*STN*). In the striatum, the GABAergic medium spiny projection neurons are divided into 2 groups, those that stain for enkephalin (*Enk*) and those staining for substance P (*Sub P*): These project to the large GABAergic pallidal neurons in the *GPe* and the *GPi* and to GABAergic projection neurons in the *SNr*, respectively. The small boxes near the axon terminals in the *GPe* and *GPi* represent the presynaptic A2a adenosine, D1 or D2 dopamine receptors and CB1 cannabinoid receptors. The boxes on the pallidal cells represent postsynaptic GABA_A receptors (*GA*) and GABA_B receptors (*GB*). The four remaining populations in the striatum are those representing GABAergic interneurons staining for parvalbumin (*PV*), calretinin (*CR*), choline acetyl transferase (*ChAT*) and calretinin, neuropeptide Y (*NPY*), and somatostatin (*SMT*). In Huntington's disease, neurons that degenerate are indicated by dashed lines. These include the medium-sized GABAergic spiny projection neurons containing *Enk* and *Sub P*, the interneurons containing parvalbumin and interneurons containing *ChAT*. Those interneurons containing only calretinin and those containing *NPY/SMT* are relatively spared. Neurons in the output nuclei are also lost, those in the *GPe*, *GPi*, and *STN*. Arrows indicate upregulation or downregulation of receptors in the output nuclei in HD. The GABA/*Enk* striato-*GPe* neurons and their associated receptors are affected in the early stages of the disease while the GABA/*Sub P* (striato-*GPi*, striato-*SNr*) neurons and receptors are affected in HD cases with more advanced pathology. *GPe* globus pallidus external segment, *GPi* globus pallidus internal segment, *STN* subthalamic nucleus, *SNr* substantia nigra pars reticulata, and *SNc* substantia nigra pars compacta

5.2 Striosome-matrix Compartmental Degeneration in the Striatum and Its Relation to Symptom Profile

The mammalian striatum is further subdivided into two major interdigitating compartments: The smaller neurochemically defined islands termed striosomes and the surrounding extrastriosomal region termed the matrix. These compartments

Table 1 Neurochemical changes in the various nuclei in the basal ganglia of the human brain in Huntington's disease

Neurochemical	Region	References
Calbindin	Striatum↓ GPe↓ GPi↓	Seto-Ohshima et al. (1988), Tippet et al. (2007)
Calretinin	Striatum↑	Cicchetti and Parent (1996)
Cannabinoid receptors	Striatum↓	Glass et al. (1993), Richfield and Herkenham (1994), Allen et al. (2009)
<i>Dopamine receptors</i>		
D1	Striatum↓	Reisine et al. (1978), Joyce et al. (1988), Richfield et al. (1991), Weeks et al. (1996)
D2	Striatum↓	Reisine et al. (1978), Joyce et al. (1988), Richfield et al. (1991), Weeks et al. (1996)
DARPP32	Putamen↓ STN↓	Guo et al. (2012)
Enkephalin	Striatum↓ GPe↓	Emson et al. (1980), Deng et al. (2004), Tippet et al. (2007)
GAD	Striatum↓ GPe↓ GPi↓	Bird and Iversen (1974), Spokes (1980), Deng et al. (2004)
GABA _A receptors	Striatum↓	Young et al. (1988), Faull et al. (1993)
<i>GABA_A receptor subunits</i>		
GABA _A α ₁ subunit	GPe↑ GPi↑	Thompson-Vest et al. (2003), Allen et al. (2009)
GABA _A α ₃ subunits	GPe↑ GPi↑	Allen et al. (2009)
GABA _A β _{2,3} subunits	Striatum↓ GPe↑ GPi↑	Tippet et al. (2007), Allen et al. (2009)
GABA _A γ ₂ subunits	Striatum↓ GPe↑ GPi↑	Thompson-Vest et al. (2003), Allen et al. (2009)
GABA _B receptor R1 subunit	GPe↑ GPi↑	Allen et al. (2009)
<i>Glutamate</i>		
<i>Glutamate receptors</i>		
GluA1 (AMPA)	Striatum↓	Dure et al. (1991)
GluN1(NMDA)	Striatum↓	Whitehouse et al. (1985), Young et al. (1988), Albin et al. (1990)
Neuropeptide Y	Striatum↑ (relative to volume)	Ferrante et al. (1987), Albin et al. (1990), Cicchetti and Parent (1996)
Parvalbumin	Striatum↓	Reiner et al. (2013)
Somatostatin	Striatum↑	Albin et al. (1990)
Substance P	Striatum↓ GPi↓ SNr↓	Marshall et al. (1983), Kowall et al. (1993)
Tyrosine hydroxylase	Striatum↑	Ferrante and Kowall (1987), Ferrante et al. (1987)

↓decreased expression ↑increased expression

The up arrows indicate increased protein detected and the down arrows indicate reduced protein detected mainly by immunohistochemical methodologies

were first identified using acetylcholinesterase (AChE) staining which was found mainly in the matrix by Graybiel and Ragsdale (1978). The smaller AChE-weak striosome compartment is identified by high concentrations of distinctive neurochemical markers such as neurotensin, LAMP, dopamine D2 receptors, GABA_A

receptors, substance P, and enkephalin while the larger matrix compartment is characterized by high concentrations of other neurochemicals AChE, tyrosine hydroxylase, somatostatin, the calcium-binding proteins CB, CR, PV, and the glutamatergic NMDA, and AMPA receptors (Faull and Villiger 1986; Voorn et al. 1989; Graybiel 1990; Dure et al. 1991; Waldvogel and Faull 1993; Manley et al. 1994; Holt et al. 1996, 1997; Parent et al. 1996; Prensa et al. 1999).

In HD, variable 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 (Hedreen and Folstein 1995), 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 (Morton et al. 1993; Hedreen and Folstein 1995; Augood et al. 1996). However, other studies show a preferential loss of neurons and neurochemical markers in the matrix compartment with clear sparing of the striosomes (Ferrante et al. 1987; Seto-Ohshima et al. 1988; Faull et al. 1993). 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 SNc (Gerfen 1984; Tokuno et al. 2002; Fujiyama et al. 2011). Therefore, the striosome compartment is thought to play a major “limbic” processing role in modulating mood and other related functions of the basal ganglia. In contrast, the matrix compartment receives topographically organized inputs from especially the sensorimotor and associative cortices, and hence, it is postulated to play a major role in the control of movement (Graybiel 1990; Parent et al. 1995; Parent and Hazrati 1995).

Extending the above observations, Tippet et al. (2007) have shown a differential pattern of degeneration in the two striatal compartments which correlates with the variable symptom profiles in 35 different HD cases (Fig. 6a–d). Some cases showed a selective striosomal loss of striatal neurons, enkephalin, and GABA_A receptors, while others showed selective cellular and GABA_A receptor loss in the matrix compartment. Other cases showed a mixed striosomal/matrix pattern of degeneration. Most importantly, this differential compartmental pattern of striatal degeneration between cases correlated in general principles with the variable symptom profiles between cases; most notably, cases with a profound degeneration in the striosomes correlated with major mood symptoms (Fig. 6c). By contrast, cases with marked degeneration primarily in the matrix compartment often had major motor symptoms (Fig. 6b). 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.

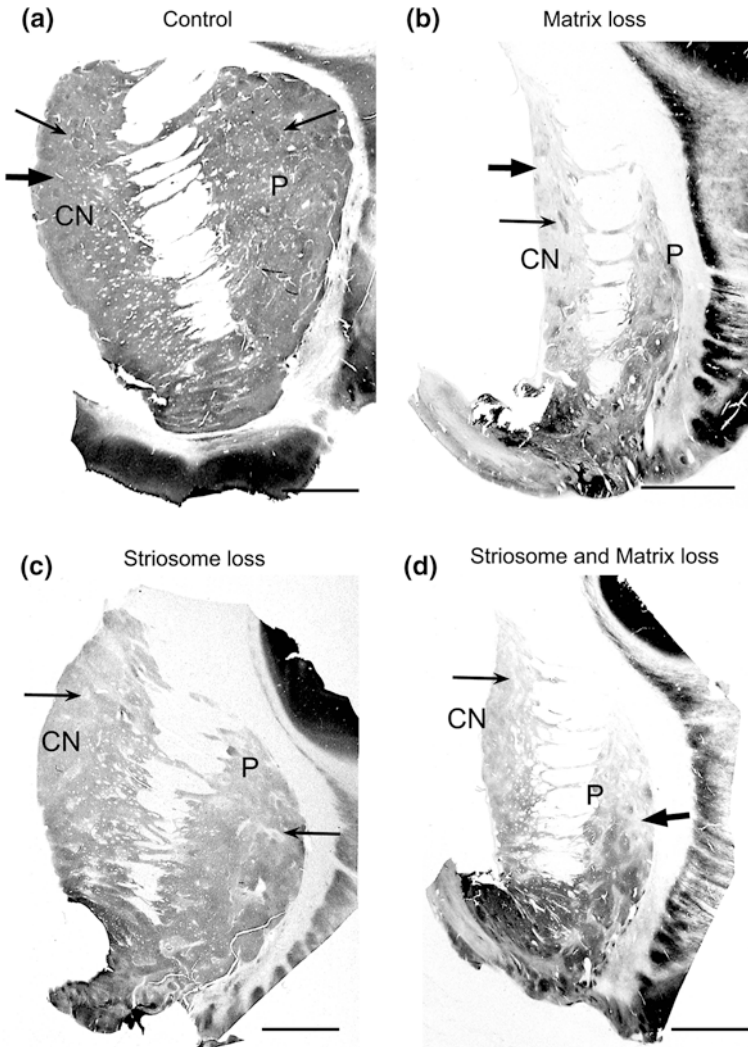


Fig. 6 Variability in the degeneration of the striosome and matrix compartments in different HD cases. Illustrations of the human caudate and putamen striatum stained for GABA_A receptors which are highly expressed on projection neurons and interneurons in the human striatum. **(a)** Control human striatum, showing a relatively homogeneous staining pattern but with higher staining in the striosomes (*large arrows* indicate matrix, *small arrows* indicate striosomes). **(b)** Striatum from a Grade 3 Huntington's disease brain showing predominant matrix loss with preservation of striosomes. **(c)** a Grade 0 case showing predominantly striosome receptor loss with preservation of matrix, and **(d)** a Grade 3 case with a mixed loss of both striosome and matrix compartments. Modified from (Tippett et al. 2007). CN caudate nucleus, P putamen, Scale bar = 5 mm

5.3 *Globus Pallidus*

The globus pallidus shows atrophy and cell loss of approximately 40 % in Grades 3 and 4 with the external segment much more involved than the internal segment. In Grade 4, the GP shows 50 % volume loss (Lange et al. 1976). Using specialized MRI techniques, globus pallidus volume changes of approximately 50 % were detected (Douaud et al. 2006). The external segment is more involved than the internal segment, and atrophy of neurons and reactive astrocytes are discrete especially in Grade 4. These changes are almost constantly observed in Grade 4 brains from cases with juvenile onset (JOHD) of symptoms, or with the rigid-akinetic rather than the choreic form. According to Lange et al. (1976), the absolute number of pallidal neurons decreases up to 40 %, but the neuronal density is up to 42 % higher than in control GPe and 27 % higher in the GPi, reflecting the major atrophy of the globus pallidus in HD. The neurons are smaller and more densely packed than normal in Grade 3, and even more so in Grade 4, suggesting that the onset of the loss of the neuropil might occur before that of the neurons. (Spielmeyer 1926; Schroeder 1931; Neustaedter 1933; Campbell et al. 1961; McCaughey 1961; Vonsattel et al. 1985).

There is also a very marked loss of cannabinoid CB1 receptors in all of the striatal output nuclei (GPe, GPi, and SNr; Fig. 5), which is evident even at Grade 0 where there is minimal cell loss in the striatum (Glass et al. 1993, 2000; Richfield and Herkenham 1994; Allen et al. 2009). This may indicate dysfunction of the cannabinoid system in basal ganglia pathways in the very early stages of HD. On the other hand, associated with the loss of neurotransmitter GABA from the striato-pallidal and striatonigral pathways, there is a major increase in postsynaptic GABA_A (Fig. 3g, h) and GABA_B receptors, which is proposed to be a compensatory upregulatory response of GABA receptors on the pallidal and nigral output neurons (Figs. 3g, h, and 5) (Penney and Young 1982; Faull et al. 1993; Allen et al. 2009).

5.4 *Substantia Nigra*

There is a loss of neurons in the SNr (Lewy 1923; Spielmeyer 1926; Schroeder 1931; Hallervorden 1957; Campbell et al. 1961; Richardson 1990). The SNc is thinner than controls, yet its number of neurons were originally reported to be apparently normal in all grades giving the impression of an increased density of pigmented neurons (Campbell et al. 1961; Richardson 1990). However, other studies on the SNc have found cell loss (Oyanagi and Ikuta 1987; Oyanagi et al. 1989) but less than that of the SNr (Ferrante et al. 1989). In addition, a loss of TH protein and mRNA from the SNc, and loss of TH in the matrix of the striatum has been reported (Ferrante and Kowall 1987). Neurons of the SNc have a major dopaminergic projection to the full extent of the striatal matrix, and these studies suggest that a loss of dopamine in the striatum may contribute to the symptoms of HD (Yohrling et al. 2003).

5.5 Subthalamic Nucleus

In the STN, there is a discrepancy between the marked atrophy present in Grades 3 and 4 (up to 25 % volumetric loss) and the scarcity of the reactive astrocytes (Spielmeyer 1926; Lange et al. 1976). A recent study has measured the loss of neurons in the STN to be on average 20 % less than controls (Guo et al. 2012) although this did not always correlate with cell loss in the putamen, suggesting the STN cell loss trails that of the putamen. Whether the changes involving these structures are due to the mutation alone or secondary to the preponderant involvement of the striatum, or a combination of both remain to be determined. It would be interesting to know to what extent the loss of neurons in the cerebral cortex which form the hyperdirect pathway to the STN would reduce the excitation of the STN in addition to the decreased inhibition of the STN through changes in the indirect pathway due to the loss of striatal neurons in the disease process.

5.6 Cerebral Cortex

Cortical degeneration in HD has been observed and reported over many years and has recently been examined in more detail with the advent of modern imaging techniques and stereological counting techniques.

Cortical atrophy has been observed in HD brains, especially in those in advanced stages of the disease. Many studies of the cortex in HD brains have found evidence of overall cortical volume loss, cortical thinning, and neuronal loss (de la Monte et al. 1988; Cudkowicz and Kowall 1990; Hedreen et al. 1991; Macdonald et al. 1997; Rajkowska et al. 1998; Macdonald and Halliday 2002; Rosas et al. 2002, 2008; Ruocco et al. 2008; Thu et al. 2010).

The earliest accounts of cortical neuropathological features were described by several authors including Bryun (1968), Forno and Jose (1973), Tellez-Nagel et al. (1974), Lange et al. (1976), Hadzi et al. (2012) and Trifiletti et al. (1987). Evidence of global cortical atrophy has been observed by de la Monte et al. (1988) where the authors demonstrated overall morphometric atrophic changes in the brain (30 % of mean brain weight reduction) with 21–29 % reduction in the gray matter and 29–34 % loss in the white matter, and Halliday et al. (1998) showed that the degree of cortical volume loss was similar in the frontal, temporal, parietal, and occipital lobes (19 % reduction of total brain volume) with no major change in volume in the medial temporal lobe. The amount of cortical volume loss was demonstrated to correlate with the degree of striatal atrophy and the number of CAG repeats, suggesting that the disease processes in the striatum and cortex are related. A significant reduction in the frontal lobe volume (17 %) and frontal white matter volume (28 %) was also found (Aylward et al. 1998).

Several detailed investigations of cellular changes in the cerebral cortex in HD brains have shown that neuronal cell body size and cell number are decreased in the

HD cortex (Macdonald et al. 1997; Rajkowska et al. 1998; Macdonald and Halliday 2002), and in some studies, this neuronal loss has been shown to be layer specific (Hedreen et al. 1991; Sotrel et al. 1991, 1993). Laminar-specific neuronal degeneration was found in the HD cortex in 11 HD cases where there was a significant loss of pyramidal projection neurons in layers III and V in the superior frontal cortex and cingulate gyrus (Cudkowicz and Kowall 1990). A study by Hedreen et al. (1991) of five postmortem HD brains showed that significant neuronal loss was present in layers V and VI of prefrontal cortex in Grade 4 HD brains. Layer VI was found to demonstrate the greatest loss in thickness, while layers III and V were also atrophied in HD.

Since neurons from layers III and V project mainly to the striatum, it has been suggested that cortical cell loss in HD is a result of retrograde degeneration secondary to striatal pathology. However, the study by Hedreen et al. (1991) showed that extensive degeneration of layer VI was also present in the cerebral cortex of early-stage HD brains. As neurons in layer VI have major local, subcortical, intracortical projections as well as projections to the thalamus, the claustrum, and other regions of the cortex, this study suggested that cortical cell loss in HD is a disease process parallel to striatal degeneration and not a secondary process as was originally believed (Cudkowicz and Kowall 1990; Hedreen et al. 1991; Sapp et al. 1999). Sotrel et al. (1991) also investigated neuronal degeneration in cortical neurons in the dorsolateral prefrontal cortex in HD. Loss of specific subpopulations of large pyramidal neurons in layers III, V, and VI was demonstrated in an investigation of 81 HD brains, as well as a decrease in the thickness of the cortical layers containing the cell bodies of these neurons with shrunken dendritic trees and sparse spines in advanced stages (Sotrel et al. 1991, 1993; Selemon et al. 2004).

Another study by Rajkowska et al. (1998) investigated neuronal degeneration in the prefrontal cortex in seven HD cases, by measurements of the size and density of both neurons and glial cells in the HD tissue compared to the control tissue. In HD cases, the neuronal size and density of large neurons in the prefrontal cortex was reduced by 9 %; this change was pronounced in pyramidal cell layers III, V, and VI, with no significant decrease in mean cell body size in layer II and VI neurons, and in layer VI, the decrease in size of large neurons was accompanied by a relative increase in the size of small neurons. The density of large glial cells was greatly increased in all layers of the HD prefrontal cortex. As the large neurons showing reduced size and density in the prefrontal cortex in HD are primarily in layers III, V and VI, these cells may be large projection neurons that form corticocortical, corticostriatal, and corticothalamic projections. These studies have focused mainly on the prefrontal cortex, as its role in behavior suggests that neural changes in the prefrontal cortex may contribute to the behavioral aspects of HD (Watkins et al. 2000).

A more detailed quantitative study using stereological cell counting has been addressed by Heinsen et al. (1994), and the authors found a pronounced pyramidal cell loss in the supragranular layers in the primary sensory areas including primary somatosensory cortex (areas 3, 1, 2), primary visual cortex (area 17), primary auditory cortex (area 41), and association areas of the frontal, parietal, and temporal

lobes. Similarly, Macdonald et al. (1997) reported a significant reduction of pyramidal cells across layers III and V, and also found atrophy of cell bodies of the remaining cells in the angular gyrus of the parietal lobe. In the following studies, Macdonald and Halliday (2002) investigated cellular changes in the motor cortical regions, i.e., primary motor cortex (area 4), supplementary and premotor region (area 6), and cingulate motor cortex (posterior part of area 24), and observed a significant reduction of total neuronal number in the primary motor cortex (42 % loss) and the premotor region (49 % loss) in HD. No significant change was observed in the posterior cingulate motor region. In addition, there was a significant loss of pyramidal cells (41 % loss) in the primary motor cortex in HD. Pyramidal cells in the primary motor cortex are involved in the corticostriatal pathways, with the putamen receiving many inputs from the primary and association motor areas. In addition, it has been shown that isolated lesions of the putamen in humans cause chorea in only a few cases. This suggests that corticostriatal degeneration may be important in the development of chorea in HD cases (Bhatia and Marsden 1994; Macdonald and Halliday 2002).

The neuropathological changes in HD have been shown to vary in different areas of the cortex in different stages of the disease, suggesting that they may be related to the symptoms of HD such as motor abnormalities, dementia, apathy, irritability, mood, depression, and visual disturbances (Hedreen et al. 1991; Halliday et al. 1998; Rosas et al. 2002, 2008; Tippett et al. 2007; Thu et al. 2010). More recently, the advances in detailed structural neuroimaging methods have facilitated important steps in elucidating the cortical basis of the clinical heterogeneity in HD patients (Montoya et al. 2006), for example, several authors have demonstrated utilizing in vivo MRI evidence for regional and progressive thinning of the cortical gray matter in both symptomatic and premanifest HD cases which correlates with the clinical expression of the disease (Jernigan et al. 1991; Rosas et al. 2002, 2005, 2008; Kassubek et al. 2004; Douaud et al. 2006; Nopoulos et al. 2007, 2010; Paulsen 2009; Tabrizi et al. 2011). Importantly, Rosas et al. (2002) showed widespread cortical thinning of 11 HD cases with varying clinical severity. The thinning of the cortex appeared to be progressive and followed a posterior to anterior regional pattern of cortical degeneration. Cortical thinning also occurred early in the disease and showed specific regional thinning in different cases. The greatest amount of thinning was observed in the sensorimotor cortex in cases at all stages of the disease. In addition, the primary motor (area 4), sensory (superior portions of areas 3, 2, 1) and visual cortical regions were the most affected, and the thinning was extended to other regions that include posterior superior frontal, posterior middle frontal, superior parietal, and the parahippocampal gyrus (Rosas et al. 2008). The degree of thinning varied between different cortical regions, with the greatest thinning of more than 15 % occurring in the primary visual and primary motor cortices. In addition, the decrease in cortical thickness was found to progress from sensorimotor and primary visual cortical areas to include frontal motor association cortex, parieto-occipital cortex, entorhinal cortex, and eventually the entire cortex. Furthermore, the thinning in the different cortical areas correlated with the varying cognitive deficits and motor disorder of the different individuals with

HD. Also, anterior cingulate cortex atrophy has been found to correlate with emotion and depression clinical scores in HD cases (Hobbs et al. 2011).

In line with the *in vivo* imaging investigations, in a recent pathologic study, the variable neuropathology in the cerebral cortex has been correlated with specific symptoms of HD (Thu et al. 2010) (Fig. 7). Detailed stereological cell counts in motor and cingulate cortical regions of 12 HD cases have shown a variation in the total number of neurons (NeuN) in the primary motor cortex (24 % loss), and anterior cingulate cortex (36 % loss). In addition, the number of SMI32-positive pyramidal neurons was also affected in these regions which followed the pattern of total neuronal loss, with 27–34 % reduction in the pyramidal cell number in the two cortical regions. Interestingly, the loss of total neurons and pyramidal neurons varied between HD cases which expressed different clinical symptoms (Thu et al. 2010). For example, a significant cell loss in the primary motor cortex was associated with HD cases with predominant motor abnormalities (28 % loss in total neuronal population Fig. 7a, b) but no significant cell loss was observed in the motor cortex in HD cases with major mood symptoms (Fig. 7c). In contrast, a significant cell loss in the anterior cingulate cortex was associated with HD cases with dominant mood symptom profiles (54 % loss in total neuronal population Fig. 7f), but no significant loss was observed in the cingulate cortex in HD cases with a dominant motor symptom profile (Fig. 7e). This study clearly illustrated for the first time how cortical degeneration in specific functional brain regions correlates with varying symptom profiles of different HD cases.

Although degeneration of cortical pyramidal neurons in layers III, V, and VI has been well documented, relatively few studies have been conducted in the HD cortex on cortical interneurons. Pathological studies on the cortical interneurons have shown that there was relative sparing of PV and neuropeptide Y (NPY) expressing interneurons in the superior frontal cortex of HD cases (Cudkovicz and Kowall 1990) and Macdonald and Halliday (2002) showed no significant change in the interneuron populations defined by CB, CR, and PV in motor cortical regions in five HD cases examined in their study. In contrast, Ferrer et al. (1994) observed a significant decrease in PV expressing interneurons in the frontal cortex, but significant difference was not observed in the occipital and temporal lobes. These results suggest that there is a heterogeneous topographical pattern of GABAergic interneuron loss in the different functional regions of the cortex in HD.

Extending these observations, our recent preliminary studies on the pattern of cell loss of cortical interneurons in the motor and cingulate cortex demonstrated a heterogeneous loss of interneurons in the two cortical regions in HD cases with different symptom profiles compared to control cases. These findings suggest that the loss of inhibition of pyramidal cells by the death of specific types of interneurons in HD may be a critical determinant in shaping the output activity of the cerebral cortex. The differential loss of inhibition by these interneurons in different cortical regions may lead to hyperexcitability of the pyramidal neurons which may further exacerbate the disease process and contribute to the striatal excitotoxic processes in HD (Beal 1994; Sieradzan and Mann 2001; Cepeda et al. 2007).

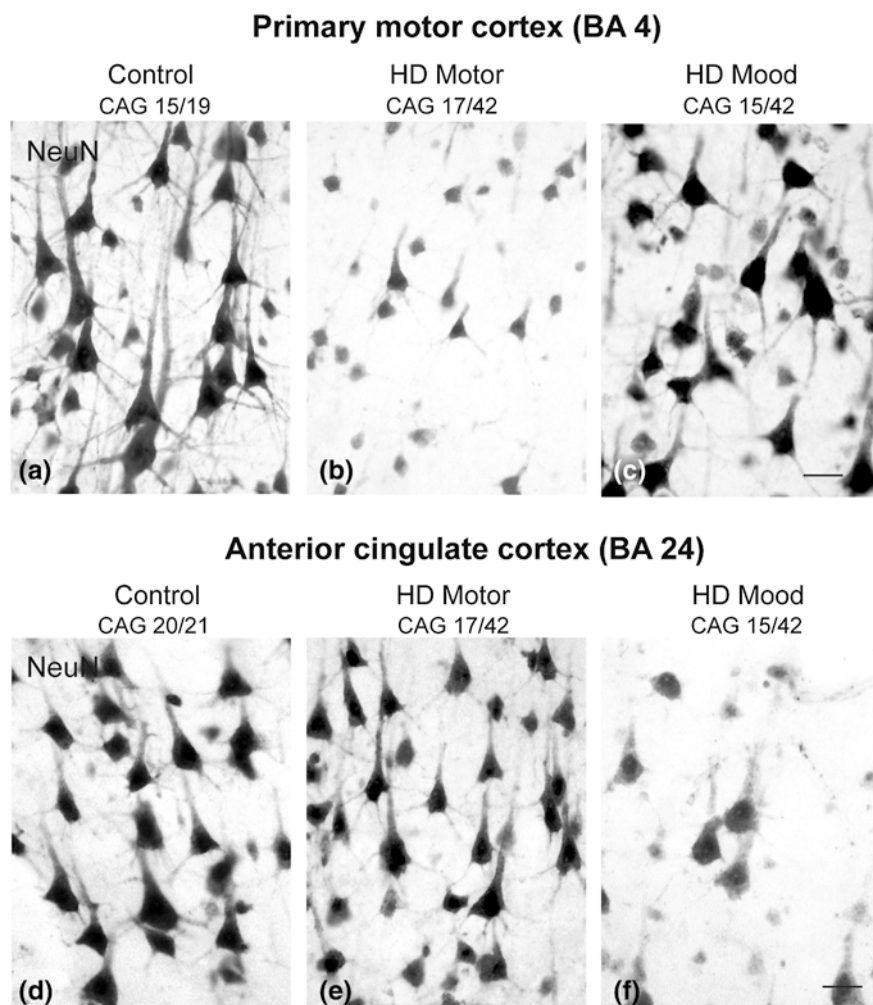


Fig. 7 Cell loss in the primary motor cortex and cingulate cortex in Huntington's disease. **a–c** Illustrates variability in the labeling of cortical neurons stained with neuronal marker Neuronal (NeuN) in the primary motor cortex, showing marked cell loss in the HD motor cortex in *motor* dominant cases (**b**), but no loss in *mood* dominated cases (**c**). **d–f** Variability in the labeling of cortical neurons stained with neuronal marker Neuronal (NeuN) in the anterior cingulate cortex showing marked cell loss in the HD cingulate cortex in *mood* dominated cases (**f**), but no loss in *motor* dominated cases (**e**). Modified from (Thu et al. 2010). Scale bars **a–c**, **d–f** = 30 μ m

6 Other Brain Regions

In general, the grade of striatal degeneration correlates with the atrophy of other brain regions than the striatum in HD. In general, in Grades 1 and 2, non-striatal structures of the brain are apparently normal, or show only mild atrophy, unless

there is age-related volumetric loss, or a superimposed disease, such as Alzheimer disease. However, in Grades 3 and 4, non-neostriatal structures including globus pallidus, neocortex, thalamus, STN, substantia nigra, white matter, and cerebellum are smaller than normally expected. As detailed below, these gray matter structures may show mild or marked neuronal loss usually without reactive astrogliosis, the most frequent exceptions being the GPe and the centromedian nucleus of the thalamus especially in Grade 4, and to a lesser extent in Grade 3.

6.1 *Thalamus*

The thalamus is often within normal limits on gross examination. The centrum medianum shows astrogliosis and neuronal loss especially in Grade 4, and to a lesser extent, in Grade 3; otherwise the thalamus is microscopically normal in lower grades. A recent MRI analysis (Kassubek et al. 2005) shows that there is variability in thalamic degeneration which agrees with neuropathological studies in the post-mortem brain. The main regions of atrophy described in the thalamus so far are that of the dorsomedial nucleus (DM) (Heinsen et al. 1999), the centromedian/ventrolateral nucleus (CM/VLa) nuclear group, and the centromedian/parafascicular nucleus (Heinsen et al. 1996). The parafascicular nucleus is part of the thalamic intralaminar nuclear group which projects to the striatum and its terminals are thought to label specifically for VGluT2 based on animal studies (Doig et al. 2010; Deng et al. 2013). The loss of these terminals is thought to occur in HD, but this is still not confirmed in human HD striatum.

6.2 *Hypothalamus*

The hypothalamus contains a large number of interconnected nuclei involved in regulation of metabolic functions as well as the control of sleep. Sleep disturbances, alterations in circadian rhythm, and weight loss have been found to be altered in HD patients (Morton et al. 2005; Petersen et al. 2005; Petersen and Bjorkqvist 2006; Aziz et al. 2008; Hult et al. 2010). Atrophy of the lateral tuberal nucleus (LTN) in the basolateral region of the hypothalamus in HD cases was described by Vogt and Vogt (1951). Further neuropathological changes were described by Kremer et al. (1990, 1991) and Kremer (1992) with up to 90 % neuronal cell loss as well as gliosis in the LTN of the hypothalamus. Other studies in the lateral hypothalamus have found a loss of orexin (hypocretin)-positive and somatostatin co-expressing neurons in the HD cases (Timmers et al. 1996; Petersen et al. 2005; Aziz et al. 2008). Also gray matter atrophy in the hypothalamus using voxel-based MRI analyses (Kassubek et al. 2004; Douaud et al. 2006) and in vivo PET studies (Politis et al. 2008) have been observed in early stage and symptomatic HD cases. However, the detailed

neuropathology of hypothalamic cell populations in the various hypothalamic nuclei in HD and their role in the overall pathogenetic mechanisms are yet to be determined.

6.3 Hippocampus

Reports on the hippocampal involvement in HD have been outlined in several studies. An early study showed no reduction in cell density in the hippocampus in HD (Dunlap 1927) however a more recent morphometric study has reported a reduction of hippocampal area of about 20 % in 30 HD patients (de la Monte et al. 1988). Also significant volume reductions in the hippocampal region (9 % volume reduction compared to control volume) have been observed early in patients with HD (Rosas et al. 2003). Additionally, Vonsattel and DiFiglia (1998) observed neuronal loss and reactive gliosis in the hippocampal formation in a number of HD cases. A further quantitative stereological technique to assess neuronal populations in four areas of the hippocampus (the granule cell layer of the dentate and CA1, CA3, and CA4 fields) in 11 HD cases showed significant changes in neuronal density restricted to the CA1 region while no significant decrease was observed in the other regions of the hippocampus (Spargo et al. 1993). Selective vulnerability of various regions of the hippocampus in HD is yet to be fully determined, and whether the variation reported in studies to date reflects a variation in cases with different symptom profiles.

6.4 Cerebellum

The neuropathological findings pertaining to the cerebellum in HD were for a longtime controversial, perhaps because they were mainly obtained using conventional methods of neuropathological evaluation. However, Rüb et al. (2013) recently found that the HD mutation is specifically harmful to neurons of the cortical and deep nuclei of the cerebellum. The conflicting findings regarding the HD cerebellum are multifactorial including the use of a wide range of methods applied for the analyses. For example, Dunlap reported that among the 29 cases with chronic chorea (17 with proven family history), only one case with HD had cerebellar atrophy. He identified the fraction of the weight of cerebrum/cerebellum to be 1/5.8 in HD compared to 1/7.2 in controls (Dunlap 1927). Spielmeyer described gliosis involving gray and white matter without systematic selectivity in the cerebella of two cases (Spielmeyer 1926). McCaughey found “possible patchy loss of Purkinje’s cells” in six, and loss of neurons involving the dentate nucleus in nine of his series of 21 HD brains (McCaughey 1961). Rodda found three in “about 300” HD brains, which showed “severe atrophy of the cerebellum” (Rodda 1981). One of those three cases had adult onset symptoms, and no definite family history

of HD. The third patient had a family history of HD, epilepsy, and died at the age of 6 years. Jeste et al. (1984) conducted a quantitative study of the cerebellar cortex of 17 HD cases, two of whom had epilepsy. There was no cerebellar atrophy noticed on gross examination. They found a decrease (up to 50 %) of the density of Purkinje cells but normal thickness of granular and molecular layers. The Purkinje cell loss was variable in its extent in different cases.

Cerebellar atrophy is often reported in cases with JOHD (age of onset <20 year) (Harper et al. 1991). The four cases with JOHD and severe cerebellar atrophy reported by Jervis all had epilepsy (Jervis 1963). The nine-year-old patient reported by Markham and Knox had epilepsy, severe cerebellar atrophy, but “no focal atrophy in Sommer’s sector” (Markham and Knox 1965). Byers et al. reported four juvenile HD cases all with severe cerebellar atrophy (Byers et al. 1973). The hippocampal formation was available in three of the four cases; of these three hippocampi, two showed neuronal loss, and reactive gliosis suggesting that to some extent the cerebellar atrophy may have been secondary to remote hypoxic-ischemic events. Juvenile HD cases are prone to seizures. Thus, seizures may account for some cerebellar or hippocampal neuronal loss, two sites notably vulnerable to hypoxic-ischemic events.

By conventional methods of evaluation, the cerebellum is smaller than normally expected in Grades 3 or 4. Despite this volume loss, neuronal density in the cerebellar cortex frequently appears within normal limits. Segmental loss of Purkinje cells with or without Bergmann gliosis may occur; however, these changes are inconsistent. As mentioned, Rüb et al. (2013) have shown recently with quantitative studies that the cerebellum is a site of primary degeneration in HD and recently were able to find that the HD mutation is specifically harmful to neurons of the cerebellar cortex and all of the deep nuclei of the cerebellum. These investigators compared eight, well-characterized HD cerebella with eight control cerebella using morphometric analysis and immunohistochemistry and found a pronounced loss of neurons especially in the fastigial nucleus as well as loss of CB-labeled Purkinje cells throughout the cerebellum. The Purkinje cells also showed disrupted dendrites and cytoplasmic inclusions.

6.5 Subventricular Zone and Neurogenesis in Huntington's Disease

The subventricular zone (SVZ) which lies along the margin of the caudate nucleus adjacent to the lateral ventricle has become a region of intense interest with the discovery of adult neural stem cells in this region. In the control, human SVZ neural precursors have been identified (Curtis et al. 2005; Kam et al. 2009) using PCNA as a marker for proliferating cells coupled with neuronal stem cell markers to identify their neuronal phenotype. In HD, an increase in cell proliferation was found in the SVZ with evidence for increased neurogenesis and increasing thickness of the SVZ

with increasing grade (Curtis et al. 2003). This raises the exciting possibility of stimulating the production of new neurons through neurogenesis from precursors in the SVZ and subsequent migration directly or via the rostral migratory stream (Curtis et al. 2007) into the cell-depleted HD striatum as a possible therapy for HD. The subsequent integration of these newly formed neurons into the basal ganglia circuitry will be critical. Studies in the rat indicate that stem cells have the ability to migrate into the quinolinic acid lesioned rat striatum (Tattersfield et al. 2004) but further studies are needed to determine whether this is a potentially viable therapy in humans. New research into reprogramming fibroblasts or other cell types to produce new neurons is ongoing (Vierbuchen et al. 2010), with the possibility of transplanting new neurons into regions of neuronal death as a form of treatment for HD.

The other neurogenic region in the human brain is the subgranular zone of the dentate gyrus in the hippocampus where neurogenesis in the human brain was first shown (Eriksson et al. 1998). Intensive research has followed this discovery especially in animals as to what drives this neurogenesis. However, a recent study in the human brain has found no increased neurogenesis in this proliferative zone in the Huntington's diseased brain (Low et al. 2011). This in contrast to the SVZ in the same brains and agrees with animal models of HD, which also tend to show no proliferation in the hippocampus (Curtis et al. 2012).

7 Gliosis

Reactive gliosis is defined as the increase in number and activation of astrocytes, microglia, and oligodendrocytes and form part of the inflammatory response of the diseased brain. Increases of the three types of glial cells astrocytes, microglia, and oligodendrocytes have been observed in the Huntington's diseased brain in a range of observations starting from the earliest historical studies (Roizin et al. 1976). These studies found a heterogeneous pattern of gliosis throughout the brain. More recent studies found increased gliosis occurred in the dorsal striatum, which was the region of major cell loss in HD (Myers et al. 1991). Additionally, in the caudate nucleus, microglia and astrocytes increased with increasing grade particularly near the ventricular edge and internal capsule, while oligodendrocytes were markedly increased in all grades and were localized throughout the degenerated region of the caudate nucleus. Focal regions of astrocytic gliosis within the striatum that were identified as striosomes were found in lower grades of HD (Hedreen and Folstein 1995), and this finding proposed that the earliest changes in HD were associated with striatal striosomes. More specific markers for microglia found that activated microglia correlated with neuronal loss in the neostriatum, globus pallidus, cerebral cortex, and white matter, but microglia displayed a different morphology in the striatum compared to the cerebral cortex. In the cerebral cortex, they were associated with the dendrites of pyramidal cells (Sapp et al. 2001). Microglia also stain with ferritin, an iron storage protein, and activated microglia were shown to contain abnormally high levels of iron in HD (Simmons et al. 2007). Newer methods using

positive emission topography have investigated microglial activation in the brain of HD and have found widespread microglial activation throughout the striatum, pallidum, frontal and cingulate cortices and brainstem in HD cases, which was evident also in presymptomatic *HTT* gene carriers (Gomez-Tortosa et al. 2000; Pavese et al. 2006; Tai et al. 2007). This close association of neuronal dysfunction and microglial activation needs further investigation. Astrocytes in the white matter of the HD brain were shown to have intranuclear inclusions (Shin et al. 2005), and it was estimated that approximately 12 % of astrocytes have nuclear inclusions in late-stage HD. The metabolism of astrocytes may thus be compromised and therefore may play a role in metabolic dysfunctions of the HD brain.

8 Aggregates

The wild-type huntingtin is a large protein (3144 amino acid residues) expressed mostly in the cytoplasm, dendrites, and axon terminals of neurons in the brain (Trottier et al. 1995; Ferrante et al. 1997). Huntingtin is associated with various intracellular organelles, including endoplasmic reticulum (ER), Golgi apparatus (DiFiglia et al. 1995; Hilditch-Maguire et al. 2000), and microtubules (Li et al. 2003). A small proportion is also found in the nucleus (Kegel et al. 2002). Huntingtin has no clear homology to known proteins, and its normal function is yet to remain fully understood. However, a considerable effort in understanding huntingtin structure and function has led to suggested roles in development (Duyao et al. 1995; Zeitlin et al. 1995), protein trafficking (Huang et al. 2004; Li and Li 2004), anti-apoptotic role (Zeitlin et al. 1995; Lunkes et al. 2002), and transcriptional regulation (Zuccato et al. 2003). The mutant huntingtin (mHtt) shows a similar expression level and regional distribution to the wild-type huntingtin in the brain (Aronin et al. 1995), but a difference in huntingtin epitope localization has been observed, and abnormal accumulation of *N*-terminal fragments of mutant huntingtin form aggregates/inclusions in the nucleus, cytoplasm, and dystrophic neurites in HD brains (Davies et al. 1997; DiFiglia et al. 1997). These protein aggregates are thought to be formed by associations of polyglutamine (polyQ) regions, which act as a “polar zipper” (Perutz et al. 1994; Perutz 1996). Protein aggregates have been observed in immunohistochemical studies using various antibodies directed against the huntingtin *N*-terminal region such as EM48 (Gutekunst et al. 1999; Hodgson et al. 1999), S830 (Landles et al. 2010), huntingtin protein (Goldberg et al. 1996; Zuccato et al. 2001), and antibody 1C2, which is directed against the CAG repeat region of the TATA-binding protein (Trottier et al. 1995; Herndon et al. 2009) (Fig. 8). It has been suggested that the toxic influence of these inclusions leads to a differential loss of specific subsets of neurons; however, this is still a topic of debate as there is evidence for both deleterious and protective effects of huntingtin aggregation (Davies et al. 1999; Arrasate et al. 2004; Reiner et al. 2007). The important steps of the aggregate toxicity hypothesis may involve proteolysis, nuclear translocation, and aggregation. The mHtt possess a higher

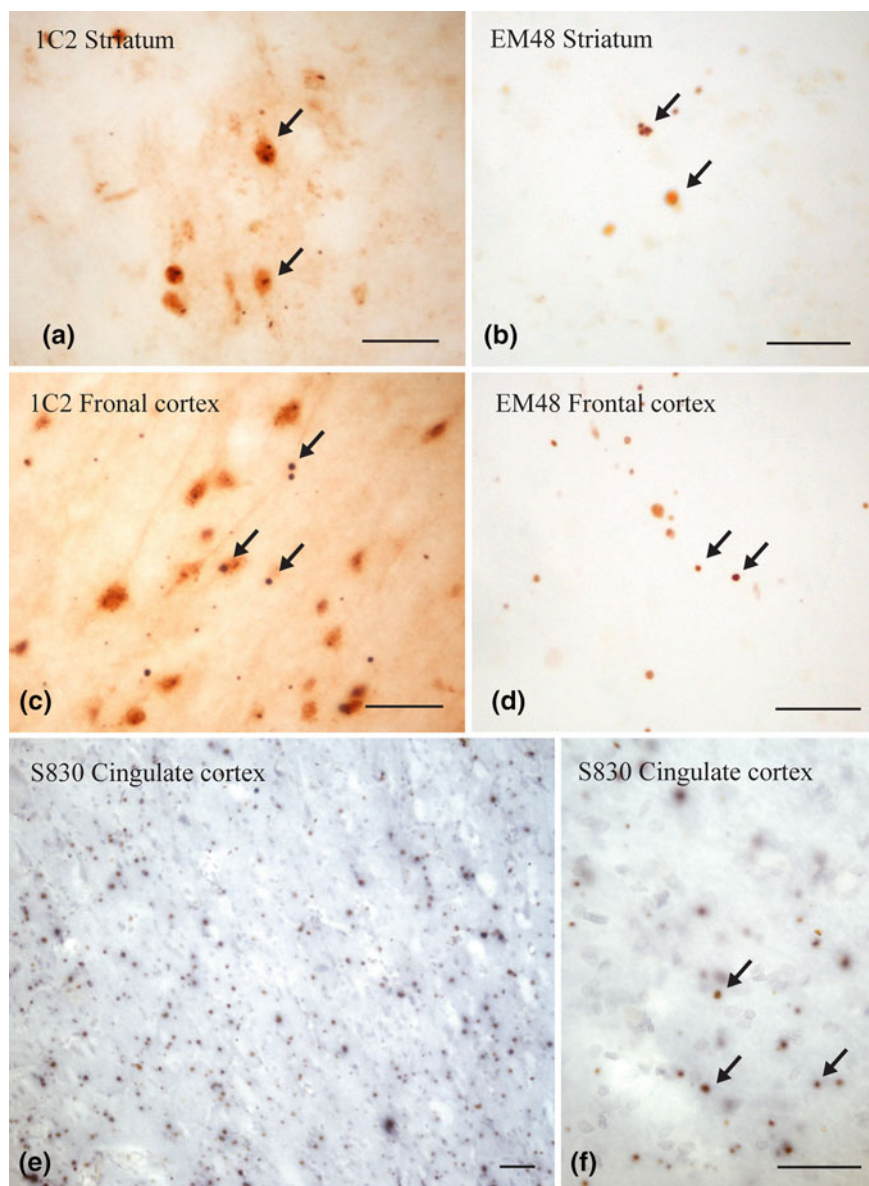


Fig. 8 Aggregates in the human cerebral cortex and striatum in Huntington's disease. Photomicrographs showing various types of aggregate labeling in the human brain in Huntington's disease cases localized with different antibodies directed against the *N*-terminal region of the huntingtin protein (Htt) and the CAG repeat region of the TATA-binding protein. **a, b** Aggregates labeled with **(a)** 1C2 (raised against the expanded CAG repeat in the TATA-binding protein) and **(b)** EM48 (raised against amino acids 1–256 of Htt) (*arrows*) in the striatum of HD brain. **c, d** Aggregates labeled with **(a)** 1C2, **(b)** EM48 shown by *arrows* in sections of the frontal cortex of HD brain. **e, f** S830 directed against the *N*-terminus of human huntingtin exon 1 protein stained in the cingulate gyrus of HD brain **(e)** at low magnification and **(f)** at high magnification, illustrating immunodetection of polyQ aggregates (indicated by *arrows*). Scale bars **a, b, d, f** = 40 μ m; **c, e** = 50 μ m

likelihood of proteolytic cleavage than its wild-type counterpart (Goldberg et al. 1996; Saudou et al. 1998). The smaller cleaved fragments are suggested to be more toxic (Gong et al. 2008), and the toxicity is also associated with nuclear translocation (Martindale et al. 1998; Atwal et al. 2007).

The immunohistochemical analyses of postmortem human HD brain (Fig. 8) have demonstrated the presence of aggregates that can form neuronal intranuclear inclusions (NIIs) or cytoplasmic and neuropil extranuclear inclusions (NEIs), and huntingtin aggregates also form in axons and dendritic spines. The nuclear aggregates were originally mentioned as “filamentous inclusions” examined using electron microscopy in the neuronal nuclei of the human HD brain (Roizin et al. 1979). Thus, aggregates are described as being made of granular and filamentous material, which is not membrane bound. 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 (DiFiglia et al. 1995, 1997; Gutekunst et al. 1999; Maat-Schieman et al. 1999) (see Fig. 8). The inclusions are present prior to symptomatic development of the disease in the HD human brain and found throughout the cortex, but less frequently in the striatum (Becher et al. 1998; Gutekunst et al. 1999; Maat-Schieman et al. 1999; Van Roon-Mom et al. 2006; Herndon et al. 2009). Within the cortex, the cells tend to display combinations of nuclear and cytoplasmic as well as neuropil aggregations (Herndon et al. 2009) with the highest levels of intranuclear inclusions found in juvenile cases, which tend to have relatively very high CAG repeat numbers (Gutekunst et al. 1999). Elucidating the exact molecular mechanisms for mHtt cytotoxicity is an ongoing 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, which elicits a cytotoxic cascade. Indeed, overexpression in various types of cells is cytotoxic (Lievens et al. 2008; Weiss et al. 2009). However, the soluble, non-aggregated forms of mHtt in tissues have been implicated more recently to be the neurotoxic culprit (Saudou et al. 1998; Arrasate et al. 2004; Kitamura et al. 2006; Ratovitski et al. 2009). By contrast, there is also evidence to suggest that the aggregated forms of mHtt may have no effect or even be protective to cells (White et al. 1997; Saudou et al. 1998; Arrasate et al. 2004). 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 (Landles and Bates 2004; Ross and Poirier 2004; Kaltenbach et al. 2007). In addition, the expression of huntingtin does not reflect the distribution of selective vulnerability (Kuemmerle et al. 1999). Some have even presented the view that cortical neurons may actively destroy MSNs in the striatum, rather than the MSN death being due to specifically mHtt itself (Fusco et al. 1999). 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 (Yamamoto et al. 2000; Schiefer et al. 2002; Rodriguez-Lebron et al. 2005; Machida et al. 2006).

9 White Matter Changes

White matter changes have been reported in HD brains, although detailed systematic studies have not been carried out. Earlier studies such as de la Monte et al. (1988) measured 29–34 % changes in overall white matter area in slices through HD brains although these varied with the level measured. The loss of white matter correlated closely with the amount of cerebral cortex gray matter lost, and in addition, the loss of white matter and cerebral cortex correlated more strongly with dementia and depression (de la Monte 1988). Activated microglia and activated astrocytes have been variably reported in the white matter tracts (Vonsattel et al. 2011), but detailed studies of gliosis throughout the white matter have not been reported. Most of the more recent studies on white matter changes in HD have been carried out with neuroimaging techniques such as DTI and MRI. These have shown pre-symptomatic changes in the white matter in the brain throughout different regions. In particular, specific changes are detected in the microstructure of the corpus callosum as well as the internal capsule more than a decade before onset of symptoms which may reflect degeneration of cortical pyramidal neurons, loss of cortical connectivity, and compromised associative processing leading to cognitive deficits in HD (Rosas et al. 2006, 2010). Also disproportionate loss of white matter was found in the prefrontal cortex (Aylward et al. 1998) in HD brains.

10 Degeneration in Peripheral Tissues

Although the most dramatic changes in HD occur in the brain, abnormalities of peripheral tissues have also been recently documented. Non-neurological abnormalities of HD include weight loss, muscle wasting, cardiac problems, insulin sensitivity, and gastrointestinal disorders, and many of these may be due to malfunctions in the peripheral tissues. These are only recently being recognized and documented in studies in humans and in animal models, and is highlighted in a recent review by Van der Burg et al. (2009).

The following peripheral tissues are affected in the disease. The digestive system is known to be affected which may affect nutrient uptake. Patients suffer from xerostomia or dry mouth, which may be due to lack of saliva, and also can affect taste and swallowing, which patients also suffer from. Ghrelin-producing cells, which produce Ghrelin that aids in food intake, are reduced in number in the stomach. The pancreas is affected, and the islet cells are atrophic and contain nuclear inclusions, which may lead to the high incidence of impaired glucose tolerance and diabetes (Podolsky et al. 1972; Andreassen et al. 2002; Hunt and Morton 2005; Lalic et al. 2008). Another major problem in HD patients is skeletal muscle wasting despite being highly active due to hyperkinesia and chorea characteristic of HD, and in HD mice, there are aggregates in the muscle cells (Ribchester et al. 2004); additionally, there are also mitochondrial enzyme dysfunctions in the muscles of HD patients (Arenas et al. 1998).

Cardiac failure is much higher in the HD population with a 30 % incidence compared to 2 % in the normal population and a leading cause of death in HD (Lanska et al. 1988). It is unclear whether this is from the underlying genetic effects on the heart muscle or due to peripheral nerve damage.

The testes are also affected, and this correlates with the very high levels of Htt protein found in testicular tissue. There is testicular degeneration (Van Raamsdonk et al. 2007) with degeneration of the germ cells and thickening of the seminiferous tubes, which appeared to correlate with CAG repeat length.

All of these studies indicate that it is not just the brain that is affected although it is still not clear if these effects are directly gene related or related to endocrine imbalance from the hypothalamus, from peripheral nerve dysfunction or other indirect causes (Van Raamsdonk et al. 2007; Van der Burg et al. 2009) which require further investigation.

11 Mechanisms of Neuropathology

The exact mechanisms of neuronal cell death in HD are currently unclear. What has been observed in recent neuroimaging studies is that the neuropathological changes are occurring up to 10 years before clinical diagnosis and striatal atrophy becomes more severe closer to clinical onset and clinical onset can be predicted within about 2 years (Aylward et al. 2004; Bohanna et al. 2008). Even though only one gene is mutated in HD, the genetics of HD are extremely complex. The expanded CAG repeat of the *HTT* gene is expected to interact with large numbers of other genes as evidenced by the results of gene microarray studies showing large numbers of affected genes in studies on both postmortem HD tissue (Hodges et al. 2006) and mouse models of HD (Luthi-Carter et al. 2000). These interactions lead to a complex set of parameters that may involve transcriptional dysregulation, excitotoxicity, oxidative stress, changes in neurotransmitters, disruption of cortical BDNF production, and breakdown of cellular and vesicular transport mechanisms in neurons of the striatum, cerebral cortex, and other regions throughout the brain (Cha 2000; Cattaneo et al. 2001; Morton et al. 2001; Zuccato and Cattaneo 2007; Rosas et al. 2008; Thu et al. 2010). In the striatum, it is the medium spiny neurons which are the most vulnerable, particularly the subset of enkephalin-containing striatopallidal neurons which are found throughout the striatum; however, the loss of these neurons can be quite variable in relation to the striosome-matrix compartments. Recent transgenic animal studies have implicated dysfunction of the cortex as one of the major indicators of phenotype; this may occur through cortical synaptic dysfunction even before cell death (Cepeda et al. 2007; Cummings et al. 2009) and that dysfunction of the corticostriatal neurons could lead to anterograde neurodegeneration of striatal neurons. Also, abnormal glutamate receptor functions in the cerebral cortex have been implicated in behavioral and motor impairments in transgenic mice with physiological and morphological cortical changes predicting the onset and severity of behavioral deficits (Sapp et al. 1997; Laforet et al. 2001;

Andre et al. 2006). Furthermore, studies in the conditional mouse model where cortical and/or striatal cells selectively express mHtt showed that dysfunction of the cortical neurons was essential to the development of significant behavioral and motor deficits (Gu et al. 2007). Other transgenic mouse studies have implicated dysfunction of both the cortical projection and interneurons of the cerebral cortex in the development of HD pathology (Gu et al. 2005; Spampinato et al. 2008). All of these animal studies provide accumulating mechanistic evidence that the cortex plays a major role in the initiation and development of the HD phenotype and that dysfunction in the corticostriate neurons plays a major role in HD forebrain pathology. The dysfunction of the growth factor BDNF in the glutamatergic cortico-striatal pyramidal neurons has also been implicated in either causing the death of these pyramidal neurons and/or causing a dysfunction of their firing resulting in excess glutamate release causing the death of striatal neurons (Cepeda et al. 2007; Strand et al. 2007; Zuccato and Cattaneo 2007). It has long been known that the cerebral cortex is not a homogeneous structure as evidenced by the different morphological compositions of the Brodmann areas. Furthermore, genetic studies show that neurons in the different regions of the cerebral cortex have a variable genetic expression profile which defines their particular subtype (Molyneaux et al. 2007). This suggests that neurons throughout the brain but particularly in specific cell types throughout the different regions of the cerebral cortex and basal ganglia may interact differently with the mutant *HTT* gene and cause degeneration in variable populations of pyramidal neurons, cortical interneurons, and striatal neurons. This could be an underlying factor in the major susceptibility of the human forebrain to the HD process as well as regional and cellular variability observed within the various regions of the human forebrain.

The neuropathology of HD is constantly being re-evaluated. The most recent studies have shown that the neurodegeneration throughout the brain is highly heterogeneous. Although the most severe pathology occurs in the basal ganglia and cerebral cortex, in the striatum, there is a continuum of degeneration related to the striosome and matrix compartments, in the cerebral cortex, there is a highly variable distribution of degeneration of neurons and related gliosis, and regions of the brain outside of the basal ganglia and cortex such as the thalamus, hypothalamus, cerebellum, and brainstem still await detailed investigation. Additionally, the various inputs to the striatum which have been described recently such as feedback loops from the GPe (Bevan et al. 1998), the thalamic intralaminar nuclei (Smith et al. 2004), and the hyperdirect pathway from the cortex to the STN (Nambu et al. 2002) may all influence basal ganglia pathways in complex ways. The heterogeneous nature of the symptomatology of HD is clearly associated with the heterogeneous nature of the neurodegeneration and major pathways that occur throughout the different regions of the brain in different individuals, and the great challenge is to relate this pattern of heterogeneity to the mutant genotype and its variable effects on gene expression profiles across the entire human genome.

References

- Albin RL, Reiner A, Anderson KD, Dure LS, Handelin B, Balfour R, Whetsell WO Jr, Penney JB, Young AB (1992) Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. *Ann Neurol* 31(4):425–430
- Albin RL, Reiner A, Anderson KD, Penney JB, Young AB (1990) Striatal and nigral neuron subpopulations in rigid Huntington's disease: implications for the functional anatomy of chorea and rigidity-akinesia. *Ann Neurol* 27(4):357–365
- Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. *Trends Neurosci* 12(10):366–375
- Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* 13(7):266–271
- Allen KL, Waldvogel HJ, Glass M, Faull RLM (2009) Cannabinoid (CB(1)), GABA(A) and GABA(B) receptor subunit changes in the globus pallidus in Huntington's disease. *J Chem Neuroanat* 37(4):266–281
- Andre VM, Cepeda C, Venegas A, Gomez Y, Levine MS (2006) Altered cortical glutamate receptor function in the R6/2 model of Huntington's disease. *J Neurophysiol* 95(4):2108–2119
- Andreassen OA, Dedeglu A, Stanojevic V, Hughes DB, Browne SE, Leech CA, Ferrante RJ, Habener JF, Beal MF, Thomas MK (2002) Huntington's disease of the endocrine pancreas: insulin deficiency and diabetes mellitus due to impaired insulin gene expression. *Neurobiol Dis* 11(3):410–424
- Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, Starr E, Squitieri F, Lin B, Kalchman MA et al (1993) The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet* 4(4):398–403
- Arenas J, Campos Y, Ribacoba R, Martin MA, Rubio JC, Ablanedo P, Cabello A (1998) Complex I defect in muscle from patients with Huntington's disease. *Ann Neurol* 43(3):397–400
- Aronin N, Chase K, Young C, Sapp E, Schwarz C, Matta N, Kornreich R, Landwehrmeyer B, Bird E, Beal MF et al (1995) CAG expansion affects the expression of mutant Huntingtin in the Huntington's disease brain. *Neuron* 15(5):1193–1201
- Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S (2004) Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* 431(7010):805–810
- Atwal RS, Xia J, Pinchev D, Taylor J, Epand RM, Truant R (2007) Huntingtin has a membrane association signal that can modulate huntingtin aggregation, nuclear entry and toxicity. *Hum Mol Genet* 16(21):2600–2615
- Augood SJ, Faull RLM, Love DR, Emson PC (1996) Reduction in enkephalin and substance P messenger RNA in the striatum of early grade Huntington's disease: a detailed cellular in situ hybridization study. *Neuroscience* 72(4):1023–1036
- Aylward EH, Anderson NB, Bylsma FW, Wagster MV, Barta PE, Sherr M, Feeney J, Davis A, Rosenblatt A, Pearlson GD, Ross CA (1998) Frontal lobe volume in patients with Huntington's disease. *Neurology* 50(1):252–258
- Aylward EH, Li Q, Stine OC, Ranen N, Sherr M, Barta PE, Bylsma FW, Pearlson GD, Ross CA (1997) Longitudinal change in basal ganglia volume in patients with Huntington's disease. *Neurology* 48(2):394–399
- Aylward EH, Sparks BF, Field KM, Yallapragada V, Shpritz BD, Rosenblatt A, Brandt J, Gourley LM, Liang K, Zhou H, Margolis RL, Ross CA (2004) Onset and rate of striatal atrophy in preclinical Huntington disease. *Neurology* 63(1):66–72
- Aziz A, Fronczek R, Maat-Schieman M, Unmehopa U, Roelandse F, Overeem S, van Duinen S, Lammers GJ, Swaab D, Roos R (2008) Hypocretin and melanin-concentrating hormone in patients with Huntington disease. *Brain Pathol* 18(4):474–483
- Beal MF (1994) Huntington's disease, energy, and excitotoxicity. *Neurobiol Aging* 15(2):275–276

- Becher MW, Kotzuk JA, Sharp AH, Davies SW, Bates GP, Price DL, Ross CA (1998) Intranuclear neuronal inclusions in Huntington's disease and dentatorubral and pallidoluysian atrophy: correlation between the density of inclusions and IT15 CAG triplet repeat length. *Neurobiol Dis* 4(6):387–397
- Bevan MD, Booth PA, Eaton SA, Bolam JP (1998) Selective innervation of neostriatal interneurons by a subclass of neuron in the globus pallidus of the rat. *J Neurosci* 18(22):9438–9452
- Bhatia KP, Marsden CD (1994) The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain* 117(Pt 4):859–876
- Bird ED, Iversen LL (1974) Huntington's chorea. Post-mortem measurement of glutamic acid decarboxylase, choline acetyltransferase and dopamine in basal ganglia. *Brain* 97(3):457–472
- Birnbaum G (1941) Chronisch-progressive Chorea mit Kleinhirnatrophie. *Archiv für Psychiatrie und Nervenkrankheiten* 114:160–182
- Bohanna I, Georgiou-Karistianis N, Hannan AJ, Egan GF (2008) Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. *Brain Res Rev* 58(1):209–225
- Brandt J, Butters N (1986) The neuropsychology of Huntington's disease. *Trends Neurosci* 9:118–120
- Bryun GW (1968) Huntington's chorea; historical, clinical and laboratory synopsis. In: Vinken PJ, Bruyn GW (eds) *Handbook of clinical neurology*, vol 6. North Holland, Amsterdam, pp 379–396
- Byers RK, Gilles FH, Fung C (1973) Huntington's disease in children. Neuropathologic study of four cases. *Neurology* 23(6):561–569
- Campbell AM, Corner B, Norman RM, Urich H (1961) The rigid form of Huntington's disease. *J Neurol Neurosurg Psychiatry* 24:71–77
- Carpenter MB, Nakano K, Kim R (1976) Nigrothalamic projections in the monkey demonstrated by autoradiographic techniques. *J Comp Neurol* 165(4):401–415
- Cattaneo E, Rigamonti D, Goffredo D, Zuccato C, Squitieri F, Sipione S (2001) Loss of normal huntingtin function: new developments in Huntington's disease research. *Trends Neurosci* 24(3):182–188
- Cepeda C, Wu N, Andre VM, Cummings DM, Levine MS (2007) The corticostriatal pathway in Huntington's disease. *Prog Neurobiol* 81(5–6):253–271
- Cha JH (2000) Transcriptional dysregulation in Huntington's disease. *Trends Neurosci* 23(9):387–392
- Cicchetti F, Parent A (1996) Striatal interneurons in Huntington's disease: selective increase in the density of calretinin-immunoreactive medium-sized neurons. *Mov Disord* 11(6):619–626
- Cicchetti F, Prensa L, Wu Y, Parent A (2000) Chemical anatomy of striatal interneurons in normal individuals and in patients with Huntington's disease. *Brain Res Brain Res Rev* 34(1–2):80–101
- Claes S, Van Zand K, Legius E, Dom R, Malfroid M, Baro F, Godderis J, Cassiman JJ (1995) Correlations between triplet repeat expansion and clinical features in Huntington's disease. *Arch Neurol* 52(8):749–753
- Cudkowicz M, Kowall NW (1990a) Degeneration of pyramidal projection neurons in Huntington's disease cortex. *Ann Neurol* 27(2):200–204
- Cudkowicz M, Kowall NW (1990b) Parvalbumin immunoreactive neurons are resistant to degeneration in Huntington's disease cerebral cortex. *J Neuropathol Exp Neurol* 49:345
- Cummings DM, Andre VM, Uzgil BO, Gee SM, Fisher YE, Cepeda C, Levine MS (2009) Alterations in cortical excitation and inhibition in genetic mouse models of Huntington's disease. *J Neurosci* 29(33):10371–10386
- Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelsø C, Holtas S, van Roon-Mom WM, Bjork-Eriksson T, Nordborg C, Frisen J, Dragunow M, Faull RLM, Eriksson PS (2007) Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. *Science* 315(5816):1243–1249
- Curtis MA, Low VF, Faull RLM (2012) Neurogenesis and progenitor cells in the adult human brain: a comparison between hippocampal and subventricular progenitor proliferation. *Dev Neurobiol* 72(7):990–1005

- Curtis MA, Penney EB, Pearson AG, van Roon-Mom WM, Butterworth NJ, Dragunow M, Connor B, Faull RLM (2003) Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc Natl Acad Sci U S A* 100(15):9023–9027
- Curtis MA, Penney EB, Pearson J, Dragunow M, Connor B, Faull RLM (2005) The distribution of progenitor cells in the subependymal layer of the lateral ventricle in the normal and Huntington's disease human brain. *Neuroscience* 132(3):777–788
- Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE, Mangiarini L, Bates GP (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* 90(3):537–548
- Davies SW, Turmaine M, Cozens BA, Raza AS, Mahal A, Mangiarini L, Bates GP (1999) From neuronal inclusions to neurodegeneration: neuropathological investigation of a transgenic mouse model of Huntington's disease. *Philos Trans R Soc Lond B Biol Sci* 354(1386):981–989
- Dawbarn D, De Quidt ME, Emson PC (1985) Survival of basal ganglia neuropeptide Y-somatostatin neurones in Huntington's disease. *Brain Res* 340(2):251–260
- de la Monte SM, Vonsattel JP, Richardson EP Jr (1988) Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. *J Neuropathol Exp Neurol* 47(5):516–525
- DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 13(7):281–285
- Deng YP, Albin RL, Penney JB, Young AB, Anderson KD, Reiner A (2004) Differential loss of striatal projection systems in Huntington's disease: a quantitative immunohistochemical study. *J Chem Neuroanat* 27(3):143–164
- Deng YP, Wong T, Bricker-Anthony C, Deng B, Reiner A (2013) Loss of corticostriatal and thalamostriatal synaptic terminals precedes striatal projection neuron pathology in heterozygous Q140 Huntington's disease mice. *Neurobiol Dis* 60:89–107
- Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofatter JA, Conneally PM (1993) Onset symptoms in 510 patients with Huntington's disease. *J Med Genet* 30(4):289–292
- DiFiglia M, Sapp E, Chase K, Schwarz C, Meloni A, Young C, Martin E, Vonsattel JP, Carraway R, Reeves SA et al (1995) Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. *Neuron* 14(5):1075–1081
- DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP, Aronin N (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science* 277(5334):1990–1993
- Doig NM, Moss J, Bolam JP (2010) Cortical and thalamic innervation of direct and indirect pathway medium-sized spiny neurons in mouse striatum. *J Neurosci* 30(44):14610–14618
- Douaud G, Gaura V, Ribeiro MJ, Lethimonnier F, Maroy R, Verny C, Krystkowiak P, Damier P, Bachoud-Levi AC, Hantraye P, Remy P (2006) Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study. *Neuroimage* 32(4):1562–1575
- Dunlap CB (1927) Pathologic changes in Huntington's chorea with special reference to the corpus striatum. *Arch Neurol Psychiat* 18:867–943
- Dure LS, Young AB, Penney JB (1991) Excitatory amino acid binding sites in the caudate nucleus and frontal cortex of Huntington's disease. *Ann Neurol* 30 (6):785–793
- Dure LS, Young AB, Penney JB, Jr. (1992) Compartmentalization of excitatory amino acid receptors in human striatum. *Proc Natl Acad Sci U S A* 89 (16):7688–7692
- Duyao MP, Auerbach AB, Ryan A, Persichetti F, Barnes GT, McNeil SM, Ge P, Vonsattel JP, Gusella JF, Joyner AL et al (1995) Inactivation of the mouse Huntington's disease gene homolog Hdh. *Science* 269(5222):407–410
- Emson PC, Arregui A, Clement-Jones V, Sandberg BE, Rossor M (1980) Regional distribution of methionine-enkephalin and substance P-like immunoreactivity in normal human brain and in Huntington's disease. *Brain Res* 199(1):147–160
- Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. *Nat Med* 4(11):1313–1317

- Faull RLM, Mehler WR (1978) The cells of origin of nigroreticular, nigrothalamic and nigrostriatal projections in the rat. *Neuroscience* 3(11):989–1002
- Faull RLM, Villiger JW (1986) Heterogeneous distribution of benzodiazepine receptors in the human striatum: a quantitative autoradiographic study comparing the pattern of receptor labelling with the distribution of acetylcholinesterase staining. *Brain Res* 381(1):153–158
- Faull RLM, Waldvogel HJ, Nicholson LF, Synek BJ (1993) The distribution of GABAA-benzodiazepine receptors in the basal ganglia in Huntington's disease and in the quinolinic acid-lesioned rat. *Prog Brain Res* 99:105–123
- Ferrante RJ, Gutekunst CA, Persichetti F, McNeil SM, Kowall NW, Gusella JF, MacDonald ME, Beal MF, Hersch SM (1997) Heterogeneous topographic and cellular distribution of huntingtin expression in the normal human neostriatum. *J Neurosci* 17(9):3052–3063
- Ferrante RJ, Kowall NW (1987) Tyrosine hydroxylase-like immunoreactivity is distributed in the matrix compartment of normal human and Huntington's disease striatum. *Brain Res* 416(1):141–146
- Ferrante RJ, Kowall NW, Beal MF, Martin JB, Bird ED, Richardson EP Jr (1987) Morphologic and histochemical characteristics of a spared subset of striatal neurons in Huntington's disease. *J Neuropathol Exp Neurol* 46(1):12–27
- Ferrante RJ, Kowall NW, Richardson EP Jr (1989) Neuronal and neuropil loss in the substantia nigra in Huntington's disease. *J Neuropathol Exp Neurol* 48:380
- Ferrante RJ, Kowall NW, Richardson EP Jr (1991) Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28k immunocytochemistry. *J Neurosci* 11(12):3877–3887
- Ferrer I, Kulisevsky J, Gonzalez G, Escartin A, Chivite A, Casas R (1994) Parvalbumin-immunoreactive neurons in the cerebral cortex and striatum in Huntington's disease. *Neurodegeneration* 3:169–173
- Folstein SE (1989) Huntington's disease: a disorder of families. Johns Hopkins University Press, Baltimore
- Forno LS, Jose C (1973) Huntington's chorea: A pathological study. In: Barbeau A, Chase TN, Paulson GW (eds) *Adv Neurol*, vol 1., vol 1 Raven, New York, pp 453–470
- Friedman JH, Trieschmann ME, Myers RH, Fernandez HH (2005) Monozygotic twins discordant for Huntington disease after 7 years. *Arch Neurol* 62(6):995–997
- Fujiyama F, Sohn J, Nakano T, Furuta T, Nakamura KC, Matsuda W, Kaneko T (2011) Exclusive and common targets of neostriatofugal projections of rat striosome neurons: a single neuron-tracing study using a viral vector. *Eur J Neurosci* 33(4):668–677
- Fusco FR, Chen Q, Lamoreaux WJ, Figueredo-Cardenas G, Jiao Y, Coffman JA, Surmeier DJ, Honig MG, Carlock LR, Reiner A (1999) Cellular localization of huntingtin in striatal and cortical neurons in rats: lack of correlation with neuronal vulnerability in Huntington's disease. *J Neurosci* 19(4):1189–1202
- Georgiou N, Bradshaw JL, Chiu E, Tudor A, O'Gorman L, Phillips JG (1999) Differential clinical and motor control function in a pair of monozygotic twins with Huntington's disease. *Mov Disord* 14(2):320–325
- Gerfen CR (1984) The neostriatal mosaic: compartmentalization of corticostriatal input and striatonigral output systems. *Nature* 311(5985):461–464
- Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, Sibley DR (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 250(4986):1429–1432
- Glass M, Dragunow M, Faull RLM (2000) 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* 97(3):505–519
- Glass M, Faull RLM, Dragunow M (1993) Loss of cannabinoid receptors in the substantia nigra in Huntington's disease. *Neuroscience* 56(3):523–527

- Goldberg YP, Nicholson DW, Rasper DM, Kalchman MA, Koide HB, Graham RK, Bromm M, Kazemi-Esfarjani P, Thornberry NA, Vaillancourt JP, Hayden MR (1996) Cleavage of huntingtin by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract. *Nat Genet* 13(4):442–449
- Gomez-Esteban JC, Lezcano E, Zarranz JJ, Velasco F, Garamendi I, Perez T, Tijero B (2007) Monozygotic twins suffering from Huntington's disease show different cognitive and behavioural symptoms. *Eur Neurol* 57(1):26–30
- Gomez-Tortosa E, Irizarry MC, Gomez-Isla T, Hyman BT (2000) Clinical and neuropathological correlates of dementia with Lewy bodies. *Ann N Y Acad Sci* 920:9–15
- Gomez-Tortosa E, MacDonald ME, Friend JC, Taylor SA, Weiler LJ, Cupples LA, Srinidhi J, Gusella JF, Bird ED, Vonsattel JP, Myers RH (2001) Quantitative neuropathological changes in presymptomatic Huntington's disease. *Ann Neurol* 49(1):29–34
- Gong B, Lim MC, Wanderer J, Wytenbach A, Morton AJ (2008) Time-lapse analysis of aggregate formation in an inducible PC12 cell model of Huntington's disease reveals time-dependent aggregate formation that transiently delays cell death. *Brain Res Bull* 75(1):146–157
- Goto S, Hirano A, Rojas-Corona RR (1989) An immunohistochemical investigation of the human neostriatum in Huntington's disease. *Ann Neurol* 25(3):298–304
- Graybiel AM (1990) Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci* 13(7):244–254
- Graybiel AM (1995) The basal ganglia. *Trends Neurosci* 18(2):60–62
- Graybiel AM, Ragsdale CW Jr (1978) Histochemically distinct compartments in the striatum of human, monkeys, and cat demonstrated by acetylthiocholinesterase staining. *Proc Natl Acad Sci U S A* 75(11):5723–5726
- Graybiel AM, Ragsdale CW Jr, Edley SM (1979) Compartments in the striatum of the cat observed by retrograde cell labeling. *Exp Brain Res* 34(1):189–195
- Greenamyre JT, Penney JB, Young AB, D'Amato CJ, Hicks SP, Shoulson I (1985) Alterations in L-glutamate binding in Alzheimer's and Huntington's diseases. *Science* 227(4693):1496–1499
- Gu X, Andre VM, Cepeda C, Li SH, Li XJ, Levine MS, Yang XW (2007) Pathological cell-cell interactions are necessary for striatal pathogenesis in a conditional mouse model of Huntington's disease. *Mol Neurodegener* 2:8
- Gu X, Li C, Wei W, Lo V, Gong S, Li SH, Iwasato T, Itohara S, Li XJ, Mody I, Heintz N, Yang XW (2005) Pathological cell-cell interactions elicited by a neuropathogenic form of mutant Huntingtin contribute to cortical pathogenesis in HD mice. *Neuron* 46(3):433–444
- Guo Z, Rudow G, Pletnikova O, Codispoti KE, Orr BA, Crain BJ, Duan W, Margolis RL, Rosenblatt A, Ross CA, Troncoso JC (2012) Striatal neuronal loss correlates with clinical motor impairment in Huntington's disease. *Mov Disord* 27(11):1379–1386
- Gutkunst CA, Li SH, Yi H, Mulroy JS, Kuemmerle S, Jones R, Rye D, Ferrante RJ, Hersch SM, Li XJ (1999) Nuclear and neuropil aggregates in Huntington's disease: relationship to neuropathology. *J Neurosci* 19(7):2522–2534
- Hadzi TC, Hendricks AE, Latourelle JC, Lunetta KL, Cupples LA, Gillis T, Mysore JS, Gusella JF, Macdonald ME, Myers RH, Vonsattel JP (2012) Assessment of cortical and striatal involvement in 523 Huntington disease brains. *Neurology*
- Hallervorden J (1957) Huntingtonsche Chorea (Chorea chronica progressiva hereditaria). *Handbuch der speziellen pathologischen Anatomie und Histologie* (XIII/1 Bandteil A). Springer Verlag, Berlin. Göttingen. Heidelberg, pp 793–822
- Halliday GM, McRitchie DA, Macdonald V, Double KL, Trent RJ, McCusker E (1998) Regional specificity of brain atrophy in Huntington's disease. *Experimental Neurology* 154(2):663–672
- Harper PS, Morris MR, Quarrell OWJ, Shaw DJ, Tyler A, Youngman S (1991) The clinical neurology of Huntington's disease. *Huntington's Disease Major Problems in Neurology*, 22. W.B. Saunders Company LTD, London Philadelphia Toronto Sydney Tokyo, pp 37–80
- Harrington KM, Kowall NW (1991) Parvalbumin immunoreactive neurons resist degeneration in Huntington's disease striatum. *J Neuropath Exp Neurol* 50:309
- Hedreen JC, Folstein SE (1995) Early loss of neostriatal striosome neurons in Huntington's disease. *J Neuropathol Exp Neurol* 54(1):105–120

- Hedreen JC, Peyser CE, Folstein SE, Ross CA (1991) Neuronal loss in layers V and VI of cerebral cortex in Huntington's disease. *Neuroscience Letters* 133(2):257–261
- Heinsen H, Rub U, Bauer M, Ulmar G, Bethke B, Schuler M, Bocker F, Eisenmenger W, Gotz M, Korr H, Schmitz C (1999) Nerve cell loss in the thalamic mediodorsal nucleus in Huntington's disease. *Acta Neuropathol* 97(6):613–622
- Heinsen H, Rub U, Gangnus D, Jungkunz G, Bauer M, Ulmar G, Bethke B, Schuler M, Bocker F, Eisenmenger W, Gotz M, Strik M (1996) Nerve cell loss in the thalamic centromedian-parafascicular complex in patients with Huntington's disease. *Acta Neuropathol* 91(2):161–168
- Heinsen H, Strik M, Bauer M, Luther K, Ulmar G, Gangnus D, Jungkunz G, Eisenmenger W, Gotz M (1994) Cortical and striatal neurone number in Huntington's disease. *Acta Neuropathol* 88(4):320–333
- Herndon ES, Hladik CL, Shang P, Burns DK, Raisanen J, White CL 3rd (2009) Neuroanatomic profile of polyglutamine immunoreactivity in Huntington disease brains. *J Neuropathol Exp Neurol* 68(3):250–261
- Hilditch-Maguire P, Trettel F, Passani LA, Auerbach A, Persichetti F, MacDonald ME (2000) Huntingtin: an iron-regulated protein essential for normal nuclear and perinuclear organelles. *Hum Mol Genet* 9(19):2789–2797
- Hobbs NZ, Pedrick AV, Say MJ, Frost C, Santos RD, Coleman A, Sturrock A, Craufurd D, Stout JC, Leavitt BR, Barnes J, Tabrizi SJ, Scahill RI (2011) The structural involvement of the cingulate cortex in premanifest and early Huntington's disease. *Mov Disord* 26(9):1684–1690
- Hodges A, Strand AD, Aragaki AK, Kuhn A, Sengstag T, Hughes G, Elliston LA, Hartog C, Goldstein DR, Thu D, Hollingsworth ZR, Collin F, Synek B, Holmans PA, Young AB, Wexler NS, Delorenzi M, Kooperberg C, Augood SJ, Faull RLM, Olson JM, Jones L, Luthi-Carter R (2006) Regional and cellular gene expression changes in human Huntington's disease brain. *Hum Mol Genet* 15(6):965–977
- Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, Singaraja R, Smith DJ, Bissada N, McCutcheon K, Nasir J, Jamot L, Li XJ, Stevens ME, Rosemond E, Roder JC, Phillips AG, Rubin EM, Hersch SM, Hayden MR (1999) A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. *Neuron* 23(1):181–192
- Holt DJ, Graybiel AM, Saper CB (1997) Neurochemical architecture of the human striatum. *J Comp Neurol* 384(1):1–25
- Holt DJ, Hersch LB, Saper CB (1996) Cholinergic innervation in the human striatum: a three-compartment model. *Neuroscience* 74(1):67–87
- Huang K, Yanai A, Kang R, Arstikaitis P, Singaraja RR, Metzler M, Mullard A, Haigh B, Gauthier-Campbell C, Gutekunst CA, Hayden MR, El-Husseini A (2004) Huntingtin-interacting protein HIP14 is a palmitoyl transferase involved in palmitoylation and trafficking of multiple neuronal proteins. *Neuron* 44(6):977–986
- Hult S, Schultz K, Soylu R, Petersen A (2010) Hypothalamic and neuroendocrine changes in Huntington's disease. *Curr Drug Targets* 11(10):1237–1249
- Hunt MJ, Morton AJ (2005) Atypical diabetes associated with inclusion formation in the R6/2 mouse model of Huntington's disease is not improved by treatment with hypoglycaemic agents. *Exp Brain Res* 166(2):220–229
- Huntington Study Group (1996) Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 11(2):136–142
- Jernigan TL, Salmon DP, Butters N, Hesselink JR (1991) Cerebral structure on MRI, Part II: Specific changes in Alzheimer's and Huntington's diseases. *Biol Psychiatry* 29(1):68–81
- Jervis GA (1963) Huntington's Chorea in childhood. *Arch Neurol* 9:244–257
- Jeste DV, Barban L, Parisi J (1984) Reduced Purkinje cell density in Huntington's disease. *Exp Neurol* 85(1):78–86
- Joyce JN, Lexow N, Bird E, Winokur A (1988) Organization of dopamine D1 and D2 receptors in human striatum: receptor autoradiographic studies in Huntington's disease and schizophrenia. *Synapse* 2(5):546–557

- Kaltenbach LS, Romero E, Becklin RR, Chettier R, Bell R, Phansalkar A, Strand A, Torcassi C, Savage J, Hurlburt A, Cha GH, Ukani L, Chepanoske CL, Zhen Y, Sahasrabudhe S, Olson J, Kurschner C, Ellerby LM, Peltier JM, Botas J, Hughes RE (2007) Huntingtin interacting proteins are genetic modifiers of neurodegeneration. *PLoS Genet* 3(5):e82
- Kam M, Curtis MA, McGlashan SR, Connor B, Nannmark U, Faull RLM (2009) The cellular composition and morphological organization of the rostral migratory stream in the adult human brain. *J Chem Neuroanat* 37(3):196–205
- Kassubek J, Gaus W, Landwehrmeyer GB (2004) Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. *Neurology* 62(3):523–524
- Kassubek J, Juengling FD, Ecker D, Landwehrmeyer GB (2005) Thalamic atrophy in Huntington's disease co-varies with cognitive performance: a morphometric MRI analysis. *Cereb Cortex* 15(6):846–853
- Kayahara T, Nakano K (1996) Pallido-thalamo-motor cortical connections: an electron microscopic study in the macaque monkey. *Brain Res* 706(2):337–342
- Kegel KB, Meloni AR, Yi Y, Kim YJ, Doyle E, Cuiffo BG, Sapp E, Wang Y, Qin ZH, Chen JD, Nevins JR, Aronin N, DiFiglia M (2002) Huntingtin is present in the nucleus, interacts with the transcriptional corepressor C-terminal binding protein, and represses transcription. *J Biol Chem* 277(9):7466–7476
- Khan ZU, Gutierrez A, Martin R, Penafiel A, Rivera A, De La Calle A (1998) Differential regional and cellular distribution of dopamine D2-like receptors: an immunocytochemical study of subtype-specific antibodies in rat and human brain. *J Comp Neurol* 402(3):353–371
- Kiesselbach G (1914) Anatomischer Befund eines Falles von Huntingtonscher Chorea. *Monatsschr Psychiat Neurol* 35:525–543
- Kitamura A, Kubota H, Pack CG, Matsumoto G, Hirayama S, Takahashi Y, Kimura H, Kinjo M, Morimoto RI, Nagata K (2006) Cytosolic chaperonin prevents polyglutamine toxicity with altering the aggregation state. *Nat Cell Biol* 8(10):1163–1170
- Kowall NW, Quigley BJ Jr, Krause JE, Lu F, Kosofsky BE, Ferrante RJ (1993) Substance P and substance P receptor histochemistry in human neurodegenerative diseases. *Regul Pept* 46 (1–2):174–185
- Kremer HP (1992) The hypothalamic lateral tuberal nucleus: normal anatomy and changes in neurological diseases. *Prog Brain Res* 93:249–261
- Kremer HP, Roos RA, Dingjan G, Marani E, Bots GT (1990) Atrophy of the hypothalamic lateral tuberal nucleus in Huntington's disease. *J Neuropathol Exp Neurol* 49(4):371–382
- Kremer HP, Roos RA, Dingjan GM, Bots GT, Bruyn GW, Hofman MA (1991) The hypothalamic lateral tuberal nucleus and the characteristics of neuronal loss in Huntington's disease. *Neurosci Lett* 132(1):101–104
- Kuemmerle S, Gutekunst CA, Klein AM, Li XJ, Li SH, Beal MF, Hersch SM, Ferrante RJ (1999) Huntington aggregates may not predict neuronal death in Huntington's disease. *Ann Neurol* 46 (6):842–849
- Kuppenbender KD, Standaert DG, Feuerstein TJ, Penney JB Jr, Young AB, Landwehrmeyer GB (2000) Expression of NMDA receptor subunit mRNAs in neurochemically identified projection and interneurons in the human striatum. *J Comp Neurol* 419(4):407–421
- Laforet GA, Sapp E, Chase K, McIntyre C, Boyce FM, Campbell M, Cadigan BA, Warzecki L, Tagle DA, Reddy PH, Cepeda C, Calvert CR, Jokel ES, Klapstein GJ, Ariano MA, Levine MS, DiFiglia M, Aronin N (2001) Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. *J Neurosci* 21(23):9112–9123
- Lalic NM, Maric J, Svetel M, Jotic A, Stefanova E, Lalic K, Dragasevic N, Milicic T, Lukic L, Kostic VS (2008) Glucose homeostasis in Huntington disease: abnormalities in insulin sensitivity and early-phase insulin secretion. *Arch Neurol* 65(4):476–480
- Landles C, Bates GP (2004) Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. *EMBO Rep* 5(10):958–963

- Landles C, Sathasivam K, Weiss A, Woodman B, Moffitt H, Finkbeiner S, Sun B, Gafni J, Ellerby LM, Trotter Y, Richards WG, Osmand A, Paganetti P, Bates GP (2010) Proteolysis of mutant huntingtin produces an exon 1 fragment that accumulates as an aggregated protein in neuronal nuclei in Huntington disease. *J Biol Chem* 285(12):8808–8823
- Lange H, Thorner G, Hopf A, Schroder KF (1976) Morphometric studies of the neuropathological changes in choreatic diseases. *J Neurol Sci* 28(4):401–425
- Lanska DJ, Lanska MJ, Lavine L, Schoenberg BS (1988) Conditions associated with Huntington's disease at death. A case-control study. *Arch Neurol* 45(8):878–880
- Lewy FH (1923) Die Histopathologie der choreatischen Erkrankungen. *Zeitschrift für die gesamte Neurologie und Psychiatrie* (Berlin) 85:622–658
- Li JY, Plomann M, Brundin P (2003) Huntington's disease: a synaptopathy? *Trends Mol Med* 9(10):414–420
- Li SH, Li XJ (2004) Huntingtin-protein interactions and the pathogenesis of Huntington's disease. *Trends Genet* 20(3):146–154
- Lievens JC, Iche M, Laval M, Faivre-Sarrailh C, Birman S (2008) AKT-sensitive or insensitive pathways of toxicity in glial cells and neurons in *Drosophila* models of Huntington's disease. *Hum Mol Genet* 17(6):882–894
- Low VF, Dragunow M, Tippet LJ, Faull RLM, Curtis MA (2011) No change in progenitor cell proliferation in the hippocampus in Huntington's disease. *Neuroscience* 199:577–588
- Lunkes A, Lindenberg KS, Ben-Haiem L, Weber C, Devys D, Landwehrmeyer GB, Mandel JL, Trotter Y (2002) Proteases acting on mutant huntingtin generate cleaved products that differentially build up cytoplasmic and nuclear inclusions. *Mol Cell* 10(2):259–269
- Luthi-Carter R, Strand A, Peters NL, Solano SM, Hollingsworth ZR, Menon AS, Frey AS, Spektor BS, Penney EB, Schilling G, Ross CA, Borchelt DR, Tapscott SJ, Young AB, Cha JH, Olson JM (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. *Hum Mol Genet* 9(9):1259–1271
- Maat-Schieman ML, Dorsman JC, Smoor MA, Siesling S, Van Duinen SG, Verschuuren JJ, den Dunnen JT, Van Ommen GJ, Roos RA (1999) Distribution of inclusions in neuronal nuclei and dystrophic neurites in Huntington disease brain. *J Neuropathol Exp Neurol* 58(2):129–137
- Macdonald V, Halliday GM (2002) Pyramidal cell loss in motor cortices in Huntington's disease. *Neurobiology of Disease* 10(3):378–386
- Macdonald V, Halliday GM, Trent RJ, McCusker EA (1997) Significant loss of pyramidal neurons in the angular gyrus of patients with Huntington's disease. *Neuropathol Appl Neurobiol* 23(6):492–495
- Machida Y, Okada T, Kurosawa M, Oyama F, Ozawa K, Nukina N (2006) rAAV-mediated shRNA ameliorated neuropathology in Huntington disease model mouse. *Biochem Biophys Res Commun* 343(1):190–197
- MacMillan JC, Snell RG, Tyler A, Houlihan GD, Fenton I, Cheadle JP, Lazarou LP, Shaw DJ, Harper PS (1993) Molecular analysis and clinical correlations of the Huntington's disease mutation. *Lancet* 342(8877):954–958
- Manley MS, Young SJ, Groves PM (1994) Compartmental organization of the peptide network in the human caudate nucleus. *J Chem Neuroanat* 7(3):191–201
- Markham CH, Knox JW (1965) Observations on Huntington's Chorea in Childhood. *J Pediatr* 67:46–57
- Marshall PE, Landis DM, Zalzneraitis EL (1983) Immunocytochemical studies of substance P and leucine-enkephalin in Huntington's disease. *Brain Res* 289(1–2):11–26
- Martindale D, Hackam A, Wiczorek A, Ellerby L, Wellington C, McCutcheon K, Singaraja R, Kazemi-Esfarjani P, Devon R, Kim SU, Bredesen DE, Tufaro F, Hayden MR (1998) Length of huntingtin and its polyglutamine tract influences localization and frequency of intracellular aggregates. *Nat Genet* 18(2):150–154
- McCaughy WTE (1961) The pathologic spectrum of Huntington's chorea. *J Nerv Ment Dis* 133:91–103
- McGeorge AJ, Faull RLM (1989) The organization of the projection from the cerebral cortex to the striatum in the rat. *Neuroscience* 29(3):503–537

- Mehler WR (1971) Idea of a new anatomy of the thalamus. *J Psychiatr Res* 8(3):203–217
- Mena-Segovia J, Bolam JP, Magill PJ (2004) Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci* 27(10):585–588
- Molyneaux BJ, Arlotta P, Menezes JR, Macklis JD (2007) Neuronal subtype specification in the cerebral cortex. *Nat Rev Neurosci* 8(6):427–437
- Montoya A, Price BH, Menear M, Lepage M (2006) Brain imaging and cognitive dysfunctions in Huntington's disease. *J Psychiatry Neurosci* 31(1):21–29
- Morton AJ, Faull RLM, Edwardson JM (2001) Abnormalities in the synaptic vesicle fusion machinery in Huntington's disease. *Brain Res Bull* 56(2):111–117
- Morton AJ, Nicholson LF, Faull RLM (1993) Compartmental loss of NADPH diaphorase in the neuropil of the human striatum in Huntington's disease. *Neuroscience* 53(1):159–168
- Morton AJ, Wood NI, Hastings MH, Hurelbrink C, Barker RA, Maywood ES (2005) Disintegration of the sleep-wake cycle and circadian timing in Huntington's disease. *J Neurosci* 25(1):157–163
- Myers RH, Sax DS, Koroshetz WJ, Mastromauro C, Cupples LA, Kiely DK, Pettengill FK, Bird ED (1991a) Factors associated with slow progression in Huntington's disease. *Arch Neurol* 48(8):800–804
- Myers RH, Vonsattel JP, Paskevich PA, Kiely DK, Stevens TJ, Cupples LA, Richardson EP Jr, Bird ED (1991b) Decreased neuronal and increased oligodendroglial densities in Huntington's disease caudate nucleus. *J Neuropathol Exp Neurol* 50(6):729–742
- Nambu A, Tokuno H, Takada M (2002) Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. *Neurosci Res* 43(2):111–117
- Nauta WJ, Domesick VB (1984) Afferent and efferent relationships of the basal ganglia. *Ciba Found Symp* 107:3–29
- Neustaedter M (1933) Concerning the striatal localization in chronic progressive chorea. With a report of three cases, two of the Huntington type in siblings and one senile arteriosclerotic, with necropsies. *Journal of Nervous and Mental Disease* 78:470–491
- Nopoulos P, Aylward EH, Ross CA, Johnson HJ, Magnotta VA, Juhl AR, Pierson RK, Mills J, Langbehn DR, Paulsen JS (2010) Cerebral cortex structure in prodromal Huntington disease. *Neurobiol Dis* 40(3):544–554
- Nopoulos P, Magnotta VA, Mikos A, Paulsen H, Andreasen NC, Paulsen JS (2007) Morphology of the cerebral cortex in preclinical Huntington's disease. *Am J Psychiatry* 164(9):1428–1434
- Ouimet CC, Langley-Gullion KC, Greengard P (1998) Quantitative immunocytochemistry of DARPP-32-expressing neurons in the rat caudatoputamen. *Brain Res* 808(1):8–12
- Oyanagi K, Ikuta F (1987) A morphometric reevaluation of Huntington's chorea with special reference to the large neurons in the neostriatum. *Clin Neuropathol* 6(2):71–79
- Oyanagi K, Takeda S, Takahashi H, Ohama E, Ikuta F (1989) A quantitative investigation of the substantia nigra in Huntington's disease. *Ann Neurol* 26(1):13–19
- Parent A, Cote PY, Lavoie B (1995) Chemical anatomy of primate basal ganglia. *Prog Neurobiol* 46(2–3):131–197
- Parent A, Fortin M, Cote PY, Cicchetti F (1996) Calcium-binding proteins in primate basal ganglia. *Neurosci Res* 25(4):309–334
- Parent A, Hazrati LN (1993) Anatomical aspects of information processing in primate basal ganglia. *Trends Neurosci* 16(3):111–116
- Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev* 20(1):91–127
- Paulsen JS (2009) Functional imaging in Huntington's disease. *Exp Neurol* 216(2):272–277
- Pavese N, Gerhard A, Tai YF, Ho AK, Turkheimer F, Barker RA, Brooks DJ, Piccini P (2006) Microglial activation correlates with severity in Huntington disease: a clinical and PET study. *Neurology* 66(11):1638–1643
- Penney JB Jr, Young AB (1982) Quantitative autoradiography of neurotransmitter receptors in Huntington disease. *Neurology* 32(12):1391–1395
- Perutz MF (1996) Glutamine repeats and inherited neurodegenerative diseases: molecular aspects. *Curr Opin Struct Biol* 6(6):848–858

- Perutz MF, Johnson T, Suzuki M, Finch JT (1994) Glutamine repeats as polar zippers: their possible role in inherited neurodegenerative diseases. *Proc Natl Acad Sci USA* 91(12):5355–5358
- Petersen A, Bjorkqvist M (2006) Hypothalamic-endocrine aspects in Huntington's disease. *Eur J Neurosci* 24(4):961–967
- Petersen A, Gil J, Maat-Schieman ML, Bjorkqvist M, Tanila H, Araujo IM, Smith R, Popovic N, Wierup N, Norlen P, Li JY, Roos RA, Sundler F, Mulder H, Brundin P (2005) Orexin loss in Huntington's disease. *Hum Mol Genet* 14(1):39–47
- Pillai JA, Hansen LA, Masliah E, Goldstein JL, Edland SD, Corey-Bloom J (2012) Clinical severity of Huntington's disease does not always correlate with neuropathologic stage. *Mov Disord* 27(9):1099–1103
- Podolsky S, Leopold NA, Sax DS (1972) Increased frequency of diabetes mellitus in patients with Huntington's chorea. *Lancet* 1(7765):1356–1358
- Politis M, Pavese N, Tai YF, Tabrizi SJ, Barker RA, Piccini P (2008) Hypothalamic involvement in Huntington's disease: an in vivo PET study. *Brain* 131(Pt 11):2860–2869
- Prensa L, Gimenez-Amaya JM, Parent A (1999) Chemical heterogeneity of the striosomal compartment in the human striatum. *J Comp Neurol* 413(4):603–618
- Rajkowska G, Selemon LD, Goldman-Rakic PS (1998) Neuronal and glial somal size in the prefrontal cortex: a postmortem morphometric study of schizophrenia and Huntington disease. *Arch Gen Psychiatry* 55(3):215–224
- Ratovitski T, Gucek M, Jiang H, Chighladze E, Waldron E, D'Ambola J, Hou Z, Liang Y, Poirier MA, Hirschhorn RR, Graham R, Hayden MR, Cole RN, Ross CA (2009) Mutant huntingtin N-terminal fragments of specific size mediate aggregation and toxicity in neuronal cells. *J Biol Chem* 284(16):10855–10867
- Reading SA, Yassa MA, Bakker A, Dziorny AC, Gourley LM, Yallapragada V, Rosenblatt A, Margolis RL, Aylward EH, Brandt J, Mori S, van Zijl P, Bassett SS, Ross CA (2005) Regional white matter change in pre-symptomatic Huntington's disease: a diffusion tensor imaging study. *Psychiatry Res* 140(1):55–62
- Reiner A, Albin RL, Anderson KD, D'Amato CJ, Penney JB, Young AB (1988) Differential loss of striatal projection neurons in Huntington disease. *Proc Natl Acad Sci USA* 85(15):5733–5737
- Reiner A, Del Mar N, Deng YP, Meade CA, Sun Z, Goldowitz D (2007) R6/2 neurons with intranuclear inclusions survive for prolonged periods in the brains of chimeric mice. *J Comp Neurol* 505(6):603–629
- Reiner A, Shelby E, Wang H, Demarch Z, Deng Y, Guley NH, Hogg V, Roxburgh R, Tippet LJ, Waldvogel HJ, Faull RL (2013) Striatal parvalbuminergic neurons are lost in Huntington's disease: implications for dystonia. *Mov Disord* 28(12):1691–1699
- Reisine TD, Fields JZ, Bird ED, Spokes E, Yamamura HI (1978) Characterization of brain dopaminergic receptors in Huntington's disease. *Commun Psychopharmacol* 2(2):79–84
- Ribchester RR, Thomson D, Wood NI, Hinks T, Gillingwater TH, Wishart TM, Court FA, Morton AJ (2004) Progressive abnormalities in skeletal muscle and neuromuscular junctions of transgenic mice expressing the Huntington's disease mutation. *Eur J Neurosci* 20(11):3092–3114
- Richardson EP Jr (1990) Huntington's disease: some recent neuropathological studies. *Neuropathol Appl Neurobiol* 16(6):451–460
- Richfield EK, Herkenham M (1994) Selective vulnerability in Huntington's disease: preferential loss of cannabinoid receptors in lateral globus pallidus. *Ann Neurol* 36(4):577–584
- Richfield EK, O'Brien CF, Eskin T, Shoulson I (1991) Heterogeneous dopamine receptor changes in early and late Huntington's disease. *Neurosci Lett* 132(1):121–126
- Rodda RA (1981) Cerebellar atrophy in Huntington's disease. *J Neurol Sci* 50(1):147–157
- Rodriguez-Lebron E, Denovan-Wright EM, Nash K, Lewin AS, Mandel RJ (2005) Intrastriatal rAAV-mediated delivery of anti-huntingtin shRNAs induces partial reversal of disease progression in R6/1 Huntington's disease transgenic mice. *Mol Ther* 12(4):618–633
- Roizin L, Kaufman MA, Willson N, Stellar S, Liu JC (1976) Neuropathologic observations in Huntington's chorea. In: Zimmerman HM (ed) *Progress in neuropathology*, vol 3. Grune and Stratton, New York, pp 447–488

- Roizin L, Stellar S, Liu JC (1979) Neuronal nuclear and cytoplasmic changes in Huntington's chorea: Electron microscope investigations. In: Chase TN, Wexler NS, Barbeau A (eds) Huntington's disease. *Advances in neurology*, vol 23. Raven Press, New York, pp 95–122
- Roos RA, Pruyt JF, de Vries J, Bots GT (1985) Neuronal distribution in the putamen in Huntington's disease. *J Neurol Neurosurg Psychiatry* 48(5):422–425
- Rosas HD, Hevelone ND, Zaleta AK, Greve DN, Salat DH, Fischl B (2005) Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. *Neurology* 65 (5):745–747
- Rosas HD, Koroshetz WJ, Chen YI, Skeuse C, Vangel M, Cudkowicz ME, Caplan K, Marek K, Seidman LJ, Makris N, Jenkins BG, Goldstein JM (2003) Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. *Neurology* 60 (10):1615–1620
- Rosas HD, Lee SY, Bender AC, Zaleta AK, Vangel M, Yu P, Fischl B, Pappu V, Onorato C, Cha JH, Salat DH, Hersch SM (2010) Altered white matter microstructure in the corpus callosum in Huntington's disease: implications for cortical "disconnection". *Neuroimage* 49(4):2995–3004
- Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B (2002) Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 58(5):695–701
- Rosas HD, Salat DH, Lee SY, Zaleta AK, Pappu V, Fischl B, Greve D, Hevelone ND, Hersch SM (2008) Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity. *Brain* 131(Pt 4):1057–1068
- Rosas HD, Tuch DS, Hevelone ND, Zaleta AK, Vangel M, Hersch SM, Salat DH (2006) Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. *Mov Disord* 21(9):1317–1325
- Ross CA, Poirier MA (2004) Protein aggregation and neurodegenerative disease. *Nat Med* 10 (Suppl):S10–17
- Rüb U, Hoche F, Brunt ER, Heinsen H, Seidel K, Del Turco D, Paulson HL, Bohl J, von Gall C, Vonsattel JP, Korf HW, den Dunnen WF (2013) Degeneration of the cerebellum in Huntington's disease (HD): possible relevance for the clinical picture and potential gateway to pathological mechanisms of the disease process. *Brain Pathol* 23(2):165–177
- Ruocco HH, Bonilha L, Li LM, Lopes-Cendes I, Cendes F (2008) Longitudinal analysis of regional grey matter loss in Huntington disease: effects of the length of the expanded CAG repeat. *J Neurol Neurosurg Psychiatry* 79(2):130–135
- Sadikot AF, Parent A, Smith Y, Bolam JP (1992) Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. *J Comp Neurol* 320 (2):228–242
- Sapp E, Kegel KB, Aronin N, Hashikawa T, Uchiyama Y, Tohyama K, Bhide PG, Vonsattel JP, DiFiglia M (2001) Early and progressive accumulation of reactive microglia in the Huntington disease brain. *J Neuropathol Exp Neurol* 60(2):161–172
- Sapp E, Penney J, Young A, Aronin N, Vonsattel JP, DiFiglia M (1999) Axonal transport of N-terminal huntingtin suggests early pathology of corticostriatal projections in Huntington disease. *J Neuropathol Exp Neurol* 58(2):165–173
- Sapp E, Schwarz C, Chase K, Bhide PG, Young AB, Penney J, Vonsattel JP, Aronin N, DiFiglia M (1997) Huntingtin localization in brains of normal and Huntington's disease patients. *Ann Neurol* 42(4):604–612
- Saudou F, Finkbeiner S, Devys D, Greenberg ME (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell* 95 (1):55–66
- Schiefer J, Landwehrmeyer GB, Luesse HG, Sprunken A, Puls C, Milkereit A, Milkereit E, Kosinski CM (2002) Riluzole prolongs survival time and alters nuclear inclusion formation in a transgenic mouse model of Huntington's disease. *Mov Disord* 17(4):748–757
- Schroeder K (1931) Zur Klinik und Pathologie der Huntingtonschen Krankheit. *J Psychol Neurol* 43:183–201

- Selemon LD, Rajkowska G, Goldman-Rakic PS (2004) Evidence for progression in frontal cortical pathology in late-stage Huntington's disease. *J Comp Neurol* 468(2):190–204
- Seto-Ohshima A, Emson PC, Lawson E, Mountjoy CQ, Carrasco LH (1988) Loss of matrix calcium-binding protein-containing neurons in Huntington's disease. *Lancet* 1(8597):1252–1255
- Shin JY, Fang ZH, Yu ZX, Wang CE, Li SH, Li XJ (2005) Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. *J Cell Biol* 171(6):1001–1012
- Sieradzan KA, Mann DM (2001) The selective vulnerability of nerve cells in Huntington's disease. *Neuropathol Appl Neurobiol* 27(1):1–21
- Simmons DA, Casale M, Alcon B, Pham N, Narayan N, Lynch G (2007) Ferritin accumulation in dystrophic microglia is an early event in the development of Huntington's disease. *Glia* 55(10):1074–1084
- Smith Y, Bevan MD, Shink E, Bolam JP (1998) Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* 86(2):353–387
- Smith Y, Raju DV, Pare JF, Sidibe M (2004) The thalamostriatal system: a highly specific network of the basal ganglia circuitry. *Trends Neurosci* 27(9):520–527
- Sotrel A, Paskevich PA, Kiely DK, Bird ED, Williams RS, Myers RH (1991) Morphometric analysis of the prefrontal cortex in Huntington's disease. *Neurology* 41(7):1117–1123
- Sotrel A, Williams RS, Kaufmann WE, Myers RH (1993) Evidence for neuronal degeneration and dendritic plasticity in cortical pyramidal neurons of Huntington's disease: a quantitative Golgi study. *Neurology* 43(10):2088–2096
- Spampanato J, Gu X, Yang XW, Mody I (2008) Progressive synaptic pathology of motor cortical neurons in a BAC transgenic mouse model of Huntington's disease. *Neuroscience* 157(3):606–620
- Spargo E, Everall IP, Lantos PL (1993) Neuronal loss in the hippocampus in Huntington's disease: a comparison with HIV infection. *J Neurol Neurosurg Psychiatry* 56(5):487–491
- Spielmeyer W (1926) Die anatomische Krankheitsforschung am Beispiel einer Huntingtonschen Chorea mit Wilsonschem Symptomenbild. *Zeitschrift für die gesamte Neurologie und Psychiatrie (Berlin)* 101:701–728
- Spokes EG (1980) Neurochemical alterations in Huntington's chorea: a study of post-mortem brain tissue. *Brain* 103(1):179–210
- Strand AD, Baquet ZC, Aragaki AK, Holmans PA, Yang L, Cleren C, Beal MF, Jones L, Kooperberg C, Olson JM, Jones KR (2007) Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration. *J Neurosci* 27(43):11758–11768
- Tabrizi SJ, Scahill RI, Durr A, Roos RA, Leavitt BR, Jones R, Landwehrmeyer GB, Fox NC, Johnson H, Hicks SL, Kennard C, Craufurd D, Frost C, Langbehn DR, Reilmann R, Stout JC (2011) Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol* 10(1):31–42
- Tai YF, Pavese N, Gerhard A, Tabrizi SJ, Barker RA, Brooks DJ, Piccini P (2007) Microglial activation in presymptomatic Huntington's disease gene carriers. *Brain* 130(Pt 7):1759–1766
- Tattersfield AS, Croon RJ, Liu YW, Kells AP, Faull RLM, Connor B (2004) Neurogenesis in the striatum of the quinolinic acid lesion model of Huntington's disease. *Neuroscience* 127(2):319–332
- Telenius H, Kremer B, Goldberg YP, Theilmann J, Andrew SE, Zeisler J, Adam S, Greenberg C, Ives EJ, Clarke LA et al (1994) Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. *Nat Genet* 6(4):409–414
- Tellez-Nagel I, Johnson AB, Terry RD (1974) Studies on brain biopsies of patients with Huntington's chorea. *J Neuropathol Exp Neurol* 33(2):308–332
- Terplan K (1924) Zur pathologischen Anatomie der chronischen progressiven Chorea. *Virchow's Arch f Pathol Anat (Berl)* 252:146–176
- Thompson-Vest NM, Waldvogel HJ, Rees MI, Faull RL (2003) GABA(A) receptor subunit and gephyrin protein changes differ in the globus pallidus in Huntington's diseased brain. *Brain Res* 994(2):265–270

- Thompson JC, Snowden JS, Craufurd D, Neary D (2002) Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. *J Neuropsychiatry Clin Neurosci* 14 (1):37–43
- Thu DCV, Oorschot DE, Tippet LJ, Nana AL, Hogg VM, Synek BJ, Luthi-Carter R, Waldvogel HJ, Faull RLM (2010) Cell loss in the motor and cingulate cortex correlates with symptomatology in Huntington's disease. *Brain* 133(Pt 4):1094–1110
- Timmers HJ, Swaab DF, van de Nes JA, Kremer HP (1996) Somatostatin 1-12 immunoreactivity is decreased in the hypothalamic lateral tuberal nucleus of Huntington's disease patients. *Brain Res* 728(2):141–148
- Tippet LJ, Waldvogel HJ, Thomas SJ, Hogg VM, van Roon-Mom W, Synek BJ, Graybiel AM, Faull RLM (2007) Striosomes and mood dysfunction in Huntington's disease. *Brain* 130(Pt 1):206–221
- Tokuno H, Chiken S, Kametani K, Moriizumi T (2002) Efferent projections from the striatal patch compartment: anterograde degeneration after selective ablation of neurons expressing mu-opioid receptor in rats. *Neurosci Lett* 332(1):5–8
- Trifiletti RR, Snowman AM, Whitehouse PJ, Marcus KA, Snyder SH (1987) Huntington's disease: increased number and altered regulation of benzodiazepine receptor complexes in frontal cerebral cortex. *Neurology* 37(6):916–922
- Trottier Y, Lutz Y, Stevanin G, Imbert G, Devys D, Cancel G, Saudou F, Weber C, David G, Tora L et al (1995) Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. *Nature* 378(6555):403–406
- Van der Burg JM, Bjorkqvist M, Brundin P (2009) Beyond the brain: widespread pathology in Huntington's disease. *Lancet Neurol* 8(8):765–774
- Van Raamsdonk JM, Murphy Z, Selva DM, Hamidzadeh R, Pearson J, Petersen A, Bjorkqvist M, Muir C, Mackenzie IR, Hammond GL, Vogl AW, Hayden MR, Leavitt BR (2007) Testicular degeneration in Huntington disease. *Neurobiol Dis* 26(3):512–520
- Van Roon-Mom WM, Hogg VM, Tippet LJ, Faull RLM (2006) Aggregate distribution in frontal and motor cortex in Huntington's disease brain. *Neuroreport* 17(6):667–670
- Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Sudhof TC, Wernig M (2010) Direct conversion of fibroblasts to functional neurons by defined factors. *Nature* 463(7284):1035–1041
- Vogt C, Vogt O (1951) Precipitating and modifying agents in chorea. *J Nerv Ment Dis* 116:601–607
- Vonsattel JP, DiFiglia M (1998) Huntington disease. *J Neuropathol Exp Neurol* 57(5):369–384
- Vonsattel JP, Keller C, Cortes Ramirez EP (2011) Huntington's disease—neuropathology. *Handb Clin Neurol* 100:83–100
- Vonsattel JP, Keller C, Del Pilar AM (2008) Neuropathology of Huntington's disease. *Handb Clin Neurol* 89:599–618
- Vonsattel JP, Myers RH, Bird ED, Ge P, Richardson EP Jr (1992) Huntington disease: 7 cases with relatively preserved neostriatal islets. *Rev Neurol (Paris)* 148(2):107–116
- Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr (1985) Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol* 44 (6):559–577
- Voom P, Gerfen CR, Groenewegen HJ (1989) Compartmental organization of the ventral striatum of the rat: immunohistochemical distribution of enkephalin, substance P, dopamine, and calcium-binding protein. *J Comp Neurol* 289(2):189–201
- Waldvogel HJ, Faull RLM (1993) Compartmentalization of parvalbumin immunoreactivity in the human striatum. *Brain Res* 610(2):311–316
- Waldvogel HJ, Kubota Y, Fritschy J, Mohler H, Faull RLM (1999) Regional and cellular localisation of GABA(A) receptor subunits in the human basal ganglia: An autoradiographic and immunohistochemical study. *J Comp Neurol* 415(3):313–340
- Waters CM, Peck R, Rossor M, Reynolds GP, Hunt SP (1988) Immunocytochemical studies on the basal ganglia and substantia nigra in Parkinson's disease and Huntington's chorea. *Neuroscience* 25(2):419–438

- Watkins LH, Rogers RD, Lawrence AD, Sahakian BJ, Rosser AE, Robbins TW (2000) Impaired planning but intact decision making in early Huntington's disease: implications for specific fronto-striatal pathology. *Neuropsychologia* 38(8):1112–1125
- Weeks RA, Piccini P, Harding AE, Brooks DJ (1996) Striatal D1 and D2 dopamine receptor loss in asymptomatic mutation carriers of Huntington's disease. *Ann Neurol* 40(1):49–54
- Weiss A, Roscic A, Paganetti P (2009) Inducible mutant huntingtin expression in HN10 cells reproduces Huntington's disease-like neuronal dysfunction. *Mol Neurodegener* 4:11
- Wexler NS, Lorimer J, Porter J, Gomez F, Moskowitz C, Shackell E, Marder K, Penchaszadeh G, Roberts SA, Gayan J, Brocklebank D, Cherny SS, Cardon LR, Gray J, Dlouhy SR, Wiktorski S, Hodes ME, Conneally PM, Penney JB, Gusella J, Cha JH, Irizarry M, Rosas D, Hersch S, Hollingsworth Z, MacDonald M, Young AB, Andresen JM, Housman DE, De Young MM, Bonilla E, Stillings T, Negrette A, Snodgrass SR, Martinez-Jaurrieta MD, Ramos-Arroyo MA, Bickham J, Ramos JS, Marshall F, Shoulson I, Rey GJ, Feigin A, Arnheim N, Acevedo-Cruz A, Acosta L, Alvir J, Fischbeck K, Thompson LM, Young A, Dure L, O'Brien CJ, Paulsen J, Brickman A, Krch D, Peery S, Hogarth P, Higgins DS Jr, Landwehrmeyer B (2004) Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci U S A* 101(10):3498–3503
- White JK, Auerbach W, Duyao MP, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME (1997) Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. *Nat Genet* 17(4):404–410
- Whitehouse PJ, Trifiletti RR, Jones BE, Folstein S, Price DL, Snyder SH, Kuhar MJ (1985) Neurotransmitter receptor alterations in Huntington's disease: autoradiographic and homogenate studies with special reference to benzodiazepine receptor complexes. *Ann Neurol* 18(2):202–210
- Witjes-Anne MN, Zwiderman AH, Tibben A, van Ommen GJ, Roos RA (2002) Behavioural complaints in participants who underwent predictive testing for Huntington's disease. *J Med Genet* 39(11):857–862
- Yamamoto A, Lucas JJ, Hen R (2000) Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell* 101(1):57–66
- Yohrling GJ, Jiang GC, DeJohn MM, Miller DW, Young AB, Vrana KE, Cha JH (2003) Analysis of cellular, transgenic and human models of Huntington's disease reveals tyrosine hydroxylase alterations and substantia nigra neuropathology. *Brain Res Mol Brain Res* 119(1):28–36
- Young AB, Greenamyre JT, Hollingsworth Z, Albin R, D'Amato C, Shoulson I, Penney JB (1988) NMDA receptor losses in putamen from patients with Huntington's disease. *Science* 241(4868):981–983
- Yung KK, Smith AD, Levey AI, Bolam JP (1996) Synaptic connections between spiny neurons of the direct and indirect pathways in the neostriatum of the rat: evidence from dopamine receptor and neuropeptide immunostaining. *Eur J Neurosci* 8(5):861–869
- Zappacosta B, Monza D, Meoni C, Austoni L, Soliveri P, Gellera C, Alberti R, Mantero M, Penati G, Caraceni T, Girotti F (1996) Psychiatric symptoms do not correlate with cognitive decline, motor symptoms, or CAG repeat length in Huntington's disease. *Arch Neurol* 53(6):493–497
- Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A (1995) Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. *Nat Genet* 11(2):155–163
- Zuccato C, Cattaneo E (2007) Role of brain-derived neurotrophic factor in Huntington's disease. *Prog Neurobiol* 81(5–6):294–330
- Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* 293(5529):493–498
- Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, Conti L, Cataudella T, Leavitt BR, Hayden MR, Timmusk T, Rigamonti D, Cattaneo E (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nat Genet* 35(1):76–83

Behavioral Neurobiology of Huntington's Disease and
Parkinson's Disease

Nguyen, H.H.P.; Cenci, M.A. (Eds.)

2015, XIII, 397 p. 95 illus., 25 illus. in color., Hardcover

ISBN: 978-3-662-46343-7