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GENETICS AND NEUROPATHOLOGY OF HUNTINGTON'S DISEASE

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Abstract

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disorder that prominently affects the basal ganglia, leading to affective, cognitive, behavioral and motor decline. The basis of HD is a CAG repeat expansion to >35 CAG in a gene that codes for a ubiquitous protein known as huntingtin, resulting in an expanded N-terminal polyglutamine tract. The size of the expansion is correlated with disease severity, with increasing CAG accelerating the age of onset. A variety of possibilities have been proposed as to the mechanism by which the mutation causes preferential injury to the basal ganglia. The present chapter provides a basic overview of the genetics and pathology of HD.

I. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder, characterized by affective, cognitive, behavioral, and motor dysfunctions (Albin and Tagle, 1995; Bruyn and Went, 1986; Wilson *et al.*, 1987). HD has a prevalence of 5–10 per 100,000 in South America, North America, Australia, and most European countries and countries of European descent, but significantly lower in Africa and Asia, with an estimated prevalence of 0.5:100,000 in Japan and China, and even lower in South Africa (Walker, 2007). HD affects males and females at the same frequency, and the mean age of onset is around 40 although it can be as early as 4 and as late as 80 years of age. Epidemiologic studies show that in US, there are about 30,000 HD patients and that there are about 150,000 people at risk of developing the disease (Margolis and Ross, 2003; Walker, 2007). The primary site of neuron loss in HD is the striatal part of the basal ganglia, with striatal projection neurons being nearly completely lost in advanced HD. Early dysfunction and late loss of cortical neurons is prominent as well. Neuron loss is progressive, and the dysfunction and loss account for the cognitive and motor decline, leading to death typically about 20 years after onset in adults. The basis of HD is a CAG repeat expansion to >35 CAG in a gene that codes for a ubiquitous protein known as huntingtin, resulting in an abnormally long polyglutamine tract in the protein N-terminus (HDCRG, 1993). Many possibilities have

been raised as to the means by which mutant huntingtin results in preferential destruction of the striatum and injury to cortex (Reiner *et al.*, 2003). For example, based on the premise that mutant htt injures neurons in a cell autonomous manner, transcriptional dysregulation (Kegel *et al.*, 2002; Luthi-Carter *et al.*, 2002; Ross, 2002), proteosomal dysfunction (Bence *et al.*, 2001; Chai *et al.*, 1999), induction of autophagy (Kegel *et al.*, 2000; Petersén *et al.*, 2001), release of calcium from intracellular stores (Tang *et al.*, 2009), mitochondrial failure (Bossy-Wetzel *et al.*, 2008), induction of apoptosis (Sanchez *et al.*, 1999; Zuccato *et al.*, 2005), and excitotoxicity at extrasynaptic NMDA receptors (Cowan and Raymond, 2006) have been raised as possible mechanisms responsible for striatal and/or cortical neuron death. Additionally, deficient production and transport of BDNF from cortex to striatum (Cattaneo *et al.*, 2005), excessive cortical release of glutamate, and defective glutamate uptake by glia have been invoked as possible pathogenic mechanisms involving an indirect killing action of mutant htt (Behrens *et al.*, 2002; Cepeda *et al.*, 2007; Joshi *et al.*, 2009; Lievens *et al.*, 2001; Rebec *et al.*, 2006). The present review focuses on the genetics and pathology of HD, with comments on pathogenesis as these relate to findings on HD genetics and pathology.

II. The HD Gene

The identification of the HD gene relied strongly on the analyses of a large Venezuelan HD kindred with extremely high HD incidence, due to a high frequency of inbreeding. Using standard linkage analyses, the HD gene was mapped to the tip of the short arm of chromosome 4 in 1983 (Gusella *et al.*, 1983, 1994), but it took scientists another 10 years to isolate it and identify the underlying mutation that causes HD (Fig. 1). In 1993, the HD gene was finally identified by The Huntington's Disease Collaborative Research Group (HDCRG), comprising 58 researchers from six independent research groups. Using haplotype analysis of linkage disequilibrium in HD families of distinct ethnicities, they identified a small segment of 4p16.3 as the likely location of the mutation. A new gene, IT-15 (interesting transcript 15), isolated using cloned trapped exons from the target area, was shown to contain a polymorphic trinucleotide CAG repeat within the coding region of the gene that was expanded and unstable on one of the chromosomes of all 75 HD families examined (HDCRG, 1993). The HD locus was found to span 180 kb, consisting of 67 exons, and encoding a protein (huntingtin, htt) of ~350 kDa. Homologues of the human gene have been identified in several species, including but not limited to pig (Matsuyama *et al.*, 2000), mouse (Barnes *et al.*, 1994; Lin *et al.*, 1995), pufferfish (Baxendale *et al.*, 1995), zebrafish (Karlovich *et al.*, 1998), and *Drosophila* (Li *et al.*, 1999), indicating a conserved essential function of huntingtin through evolution.

The promoter region of the HD gene has features in common with housekeeping genes that are expressed ubiquitously (multiple G/C rich promoter elements and no TATA box sequence (Coles *et al.*, 1998). The CAG repeat (which encodes polyglutamine) is found within exon 1 of all vertebrate HD homologues. Downstream of the CAG repeat is a stretch of polymorphic CCG (polyproline encoding) repeats, also located within exon 1 (HDCRG, 1993). Although highly conserved across different species, with the exception of HEAT motifs, huntingtin has no homology with other proteins (Andrade and Bork, 1995). The function of huntingtin is currently unknown.

The fact that HD shows autosomal dominant inheritance had long been taken to indicate that the HD mutation acts in a “gain-of-function” manner. Discovery of the HD gene allowed further investigation of this notion, leading to several lines of evidence taken to affirm this view (Sharp and Ross, 1996; Ross, 2002). For example, hemizygous inactivation of the HD gene was found to not cause HD symptoms in humans or mice, despite a reduction in HD gene expression to half of normal (Ambrose *et al.*, 1994; Duyao *et al.*, 1995; Nasir *et al.*, 1995; Zeitlin *et al.*, 1995). Moreover, nullizygous mutant mice were found to die *in utero* (Duyao *et al.*, 1995; Nasir *et al.*, 1995; Zeitlin *et al.*, 1995), whereas humans that are homozygous for the HD mutation are born and do not show profound differences from HD heterozygotes in disease onset or progression (Myers *et al.*, 1989; Wexler *et al.*, 1987).

III. Normal CAG Repeat Length

Early studies by different research groups, involving the analyses of the number of CAG repeats in ~1200 HD individuals and 2000 non-HD individuals, established that the CAG tract in the IT15 gene is polymorphic in the general population, with the normal range of repeat numbers varying from 9 to 11 at the low end and 34–37 at the high end (with an average of 17–20), and that repeat lengths longer than 37 are associated with HD (Read, 1993). Subsequent studies involving large cohorts of individuals who carried between 30 and 40 CAG repeats in the IT15 gene further refined this concept and indicated that repeats up to 35 in length do not cause HD, and that repeat lengths between 36 and 39 are associated with reduced penetrance, meaning that, within this range, some individuals develop HD within their lifetime, while others do not (McNeil *et al.*, 1997; Rubinsztein *et al.*, 1996). Late onset HD with as low as 29 or 34 repeats has, however, been reported (Andrich *et al.*, 2008; Kenney *et al.*, 2006).

IV. CAG Repeat Length and Disease Onset and Progression

The picture that eventually emerged from numerous studies is that the number of CAG repeats is inversely correlated with age of onset of the disease (Andrew *et al.*, 1993; Duyao *et al.*, 1993; Snell *et al.*, 1993; Brinkman *et al.*, 1997). Whereas expansions of 40–50 CAG repeats in the mutant HD allele are usually associated with adult onset, juvenile-onset HD, defined as onset before 20 years of age, is usually associated with expansions above 60 CAG repeats (Fig. 1). Clinical manifestations of the disease also differ depending on the length of the CAG tract. The classical HD presentation—adult-onset with predominant chorea—has an onset of around 40 years of age, and the average repeat length is about 44 (Martin and Gusella, 1986; Kremer *et al.*, 1994; Ross *et al.*, 1997; Margolis and Ross, 2003). In patients displaying the reduced-penetrance repeat lengths (36–38 repeats), HD onset not only occurs late in life (60 years of age and older), but patients may present only mild chorea, and without the cognitive, psychiatric and behavioral abnormalities usually associated with longer repeat tracts (McNeil *et al.*, 1997; Rubinsztein *et al.*, 1996). In contrast, chorea is not a major manifestation of juvenile-onset HD, but rigidity and seizures appear to be the predominant characteristics and are often preceded by abnormal behavior (Nance and Myers, 2001; Ribaï *et al.*, 2007). Note, however, that the rare cases with CAG repeats ranging from 60 to >200 indicate that severity does not increase as prominently with repeat expansion beyond 60 (Fig. 1) (Andresen *et al.*, 2006; Squitieri *et al.*, 2006).

V. CAG Repeat Instability

In the vast majority (>80%) of the hereditary transmissions from HD parents, the expanded repeat is only mildly altered by one or a few CAG repeats, usually decreasing if transmitted maternally, and increasing if transmitted paternally (Bates *et al.*, 1997; Duyao *et al.*, 1993). However, on occasion, paternal transmissions lead to large intergenerational expansions, causing the phenomenon of anticipation, where the age of onset tends to decrease in successive generations (Vonsattel and DiFiglia, 1998). Hence, juvenile-onset HD is associated with paternal transmission in 80–90% of the cases. So far, the longest CAG expansion reported consists of 250 repeats (Nance *et al.*, 1999).

Due to the high rate of meiotic CAG instability during spermatogenesis, normal fathers can also have affected children. Several studies indicate that CAG repeats between 27 and 35 can also be meiotically unstable during paternal transmission, leading to descendants with HD and carrying CAG expansions of 40 or more repeats (Myers, 2004). About 10–15% of all HD cases, in fact, arise from non-affected parents whose repeat lengths fall within the high end of the normal range (Chong *et al.*, 1997; Maat-Kievit *et al.*, 2001; Semaka *et al.*, 2010). Of particular interest, the highest incidence of HD among populations of European descent correlates with the higher frequency of HD alleles bearing 28–35 repeats in these populations compared to populations in either Asia or Africa (Walker, 2007).

The HD CAG repeat is also somatically unstable and undergoes progressive length increases over time. Analyses of tissues from affected individuals showed that repeat mosaicism is present in all tissues, with the greatest levels detected in sperm and in the brain, and in particular in the areas with more pronounced neuropathology (De Rooij *et al.*, 1995; Telenius *et al.*, 1994). Whether this plays a role in pathogenesis is yet uncertain.

VI. Genetic Modifiers of CAG Repeat Instability

Although paternal transmission has been clearly shown to increase CAG instability, other genetic factors are believed to contribute to CAG instability in HD, including cis-acting factors, such as the size of the CAG tract and HD haplotypes, and trans-acting factors.

Several studies have shown that trinucleotide repeats larger than 28 show instability during replication, and that there is a positive correlation between the instability and the size of the repeat, in particular, in the male germline. Hence, the size of CAG tract is itself a determinant of instability (Leeftang *et al.*, 1999; MacDonald *et al.*, 1993; Wheeler *et al.*, 2007). A very interesting finding is that postzygotic mechanisms also may play a role in triplet repeat instability in HD (this was first observed in mouse models for HD, Kovtun *et al.*, 2000, 2004). In any event, in maternal transmissions, the daughters will more often carry contractions of the CAG repeat, while the sons will more often carry expansions. While with paternal transmissions expansions are equally frequent in male and female offspring, the CAG repeat increases in length significantly more in sons than in daughters (Wheeler *et al.*, 2007).

In addition, HD haplotypes also appear to influence CAG instability. In a recent study, Warby and collaborators (Warby *et al.*, 2009) found that, in spite of the large number of

single nucleotide polymorphisms (SNPs) in the HD gene, disease-associated SNPs form a cluster of similar haplotypes (termed haplogroup A) found in 95% of disease chromosomes. In addition, they found that the same haplogroup is significantly enriched (>80%) in HD genes with intermediate CAG repeats (27–35 CAGs). This finding supports the hypothesis that some variants may have a predisposition for expansion, and that would explain the origin of disease-associated haplotypes.

The availability of mouse models for HD made it possible also to analyze other potential genetic modifiers of CAG repeat instability by assessing the rate of instability in specific gene knockout backgrounds. For instance, somatic CAG instability of transgenic HD mouse models is drastically reduced in mice lacking either the mismatch repair enzyme MSH2 or the base excision repair enzyme OGG1 (Manley *et al.*, 1999; Kovtun *et al.*, 2007). Although the role of Msh2 in CAG repeat expansion is currently not clear, analyses of mice and cell lines lacking OGG1 provided evidence that OGG1 is responsible for initiating an escalating oxidation-excision cycle that leads to progressive age-dependent expansion of the CAG repeats in post-mitotic neurons in HD, and possibly in other trinucleotide disorders as well (Kovtun *et al.*, 2007). Thus, at least one mechanism of CAG expansion appears to involve oxidative DNA damage and single-strand break repair.

VII. Genetic Modifiers of HD Age-of-Onset

Although the primary factor that determines whether and when a person will develop HD is the length of the expanded CAG tract, the precise manifestations of the disease and their onset are clearly affected by modifiers that include environmental and other genetic factors. While it is commonly recognized that the correlation of repeat size accounts for about 70% of the variation in age of onset (Gusella and MacDonald, 2009), there is high variation in age of onset among patients with repeat lengths <55 (Myers, 2004). Strong substantiation that heritable components account for the remaining variation in age of onset was first provided by the HD-MAPS (Modifiers of Age at onset in Pairs of Sibs) study involving >600 sibling pairs of multiple ethnicities (Djoussé *et al.*, 2003; Li *et al.*, 2003). These studies and their follow-ups provided strong evidence of linkage between chromosome 6q and 4q to age of onset of neurological symptoms (Li *et al.*, 2006). Analyses of HD Venezuelan kindreds, encompassing >15,000 individuals and comprising 4500 sibships, also confirmed the association of several loci with age of onset and identified significant linkage to chromosomes 2p and 6q, among others (Gayán *et al.*, 2008; Wexler *et al.*, 2004). However, in both cases, the genomic regions are large and so far the specific modifier genes have not been identified. Genome-wide studies using densely spaced single-nucleotide-polymorphisms (SNPS) are currently being applied in an expanded version of the HD-MAPS collaboration to identify the modifier genes in these regions (Gusella and MacDonald, 2009).

The search for genetic modifiers among genes that are connected to pathways and processes thought to be involved in HD also led to the identification of additional candidates. GRIK2 (glutamate receptor ionotropic kainate2, also known as GLUR6) was the earliest reported genetic modifier, and multiple studies have shown that a polymorphic TAA trinucleotide repeat in its 3' untranslated region (3'UTR) is associated with earlier HD onset (Gusella and

MacDonald, 2009; MacDonald *et al.*, 1999; Rubinsztein *et al.*, 1997). The mechanism by which different GRIK2 alleles affect onset is still unknown.

Polymorphisms in huntingtin-associated protein 1 (HAP1) and Atg7 (autophagy-related 7 homolog) genes have also been shown to play a role in onset age in HD. By sequencing the HAP1 gene in unaffected populations, six polymorphisms have been identified, including one that substitutes methionine (M441) for threonine (T441) at amino acid 441. Analyses of 980 European HD patients revealed that patients homozygous for the HAP1 M441 genotype (that substitutes threonine by methionine) showed an 8-year delay in the onset. Functional assays demonstrated that human M441-HAP1 interacts with mutant htt more tightly than does human T441-HAP1 and protects against mutant htt-induced toxicity (Metzger *et al.*, 2008). Using the same approach, the same group reported one polymorphism in the Atg7 gene that substitutes alanine for valine (V471A). This polymorphism showed a significant effect and was associated with an earlier disease onset of 4 years. Although the mechanism by which this polymorphism affects age of onset is unknown, it has been hypothesized that the V471A Atg7 has reduced autophagic function (Metzger *et al.*, 2010).

The hypothesis that somatic instability of the HD CAG repeat is itself a modifier of disease age of onset gained support by the finding that somatic instability is a significant predictor of onset age, with larger repeat length gains associated with earlier disease onset (Swami *et al.*, 2009; Veitch *et al.*, 2007). Hence, factors that are involved in the control of repeat instability may also represent potential genetic modifiers for age of onset.

Analyses of animal models for HD also implicate several other genes as potential genetic modifiers of age of onset. For instance, age of onset is significantly earlier and pathology is exacerbated in mouse models of HD lacking either the heat shock protein Hsp70 (Wacker *et al.*, 2009) or the neurotrophin BDNF (Canals *et al.*, 2004), while inhibition of caspase-1 delays both the age of onset of motor symptoms and the occurrence of other behavioral and neuropathological changes (Ona *et al.*, 1999). The role of any of these genetic factors in HD in humans, however, remains to be verified.

VIII. HD: A True Dominant Gain-of-Function Disorder?

HD is one of a group of inherited neurodegenerative disorders, commonly referred to as “trinucleotide repeat disorders,” caused by expansions of trinucleotide repeats in distinct genes. In at least nine of these diseases, including HD, these expansions involve CAG repeats that are present in the coding region of the gene and are translated into polyglutamine stretches. Although the mutant protein of the distinct disorders do not share any homology or sequence similarity, except for the presence of the polyglutamine tract, all of them have similar features (for example, repeat length—onset age correlation, and dominant inheritance) and are likely to possess some similarities in their pathogenic mechanisms. Since neuronal degeneration occurs in different areas of the brain in these different CAG repeat diseases, there clearly are also disease mechanisms specific to each disorder that impart the differential regional vulnerability. The dominant pattern of inheritance of HD strongly indicates that HD, like all other polyglutamine disorders, is

caused by a gain-of-function mechanism and that the expanded polyglutamine stretch is responsible for the pathogenesis.

Homozygous HD patients are rare, and there is still controversy over whether homozygosity for the mutation in HD is associated with a more severe phenotype. Most information on homozygosity in HD has come from analyses of probable homozygous offspring within the Venezuelan kindreds (Wexler *et al.*, 1987) or from other sporadic cases in which both parents are affected (Alonso *et al.*, 2002; Dürr *et al.*, 1999; Myers *et al.*, 1989). In all these reports, the age-at-onset appeared similar in homozygotes and heterozygotes, and both progression and severity of the disease were in some cases actually worse in the heterozygotes. Together, these reports led to the conclusion that HD displays complete dominance. However, this conclusion was based on clinical evaluation of eight potential homozygous and only two confirmed cases, and did not take into account differences in CAG tract sizes between siblings, or other possible genetic modifiers. In contrast, a more detailed comparison between a large homozygous patients' series and their heterozygous counterparts in a multicenter study revealed significant clinical and neuropathological differences between the two groups (Squitieri *et al.*, 2003). In this study, not only the disease progression was more rapid in homozygous patients, but also homozygous patients appeared to have a wider spectrum of neurological symptoms. More recent work involving cell lines derived from heterozygous and homozygous HD patients (Mormone *et al.*, 2006; Squitieri *et al.*, 2010; Varani *et al.*, 2003) and analyses of mouse models for HD (Fossale *et al.*, 2002; Graham *et al.*, 2006; Lin *et al.*, 2001) also support the notion that HD is more severe in homozygosity. Thus, more recent work is consistent with the notion that, like other triplet repeat disorders, HD is not a true dominant disorder, and that gain of function is only one of the facets of this devastating disease.

IX. Expression of Huntingtin in Normal and HD Human brain

Huntingtin mRNA and protein are widely distributed in mammalian brain, and almost no brain region is devoid of huntingtin-containing perikarya—although glial cells typically show only low levels (Bhide *et al.*, 1996; Fusco *et al.*, 1999; Gutekunst *et al.*, 1995; Landwehrmeyer *et al.*, 1995; Li *et al.*, 1993; Sapp *et al.*, 1997; Sharp and Ross, 1996; Strong *et al.*, 1993; Vonsattel and DiFiglia, 1998). Large neuronal perikarya tend to be richer in huntingtin than medium-sized or small neuronal perikarya, and huntingtin-positive neurons are especially abundant in the telencephalon and thalamus, but seemingly sparse in the hypothalamus. Within telencephalon, the highest density of huntingtin-rich neurons is in cerebral cortex, in which pyramidal neurons of layers 3 and 5 are especially rich (Fig. 2), and in hippocampus, in which the pyramidal neurons of CA2–CA3 are labeled intensely for huntingtin. The vast majority of striatal projection neurons are, however, only moderate in huntingtin, but scattered large neurons in striatum and the large neurons of globus pallidus externus, the ventral pallidum, basal nucleus of Meynert, and the globus pallidus internus are rich (Fig. 2) (Bhide *et al.*, 1996; Fusco *et al.*, 1999; Gutekunst *et al.*, 1995; Landwehrmeyer *et al.*, 1995). The disease-producing mutation in the HD gene does not appear to affect its regional expression in brain (Bhide *et al.*, 1996; Gourfinkel-An *et al.*, 1997; Landwehrmeyer *et al.*, 1995; Sapp *et al.*, 1997; Schilling *et al.*, 1995; Vonsattel and DiFiglia, 1998). Thus, while the widespread distribution of huntingtin in brain indicates that

it possesses a role in the functioning of many brain neurons, this function is not limited to the brain regions and neurons that are the major target of HD, and huntingtin expression is not obviously selectively impaired in the regions or neuron types most affected by the HD mutation. At the cellular level, huntingtin is found in the cytoplasm of neuronal perikarya, in dendrites, and to seemingly a lesser extent in axons and terminals (Vonsattel and DiFiglia, 1998). Ko *et al.* (2001) recently suggested, based on studies using antibodies directed against different epitopes of wild-type Htt, that Htt may play diverse roles in cellular function. Presumably as a reflection of this diversity, they found that different epitopes of huntingtin are immunohistochemically detectable in different subcellular compartments, implying differential processing or folding of Htt for its role in the different compartments. Among its functions, huntingtin appears to be a cell membrane-associated scaffolding protein involved in vesicular trafficking (DiFiglia *et al.*, 1995; Qin *et al.*, 2004; Sharp *et al.*, 1995; Velier *et al.*, 1998; Wood *et al.*, 1996). Immunolabeling and immunoprecipitation studies indicate that huntingtin may also be involved in the endosomal-lysosomal protein degradation pathway (DiFiglia *et al.*, 1995; Gutekunst *et al.*, 1995; Sapp *et al.*, 1997; Sharp *et al.*, 1995; Velier *et al.*, 1998; Vonsattel and DiFiglia, 1998; Wood *et al.*, 1996). Nuclear localization of full-length wild-type Htt has also been reported (Atwal *et al.*, 2007; Dorsman *et al.*, 1999; Wilkinson *et al.*, 1999).

Neuropathological studies suggest that the pathogenic HD gain of function could be the formation of ubiquitinated aggregates of the N-terminal fragment of mutated huntingtin, which is thought to occur due to enhanced cleavage and aggregation of the polyglutamine rich part of the mutant huntingtin N-terminus (DiFiglia *et al.*, 1997; Gutekunst *et al.*, 1999; Li and Li, 1998; Maat-Schieman *et al.*, 1999; Martindale *et al.*, 1998; Sieradzan *et al.*, 1999; Vonsattel, 2008). Aggregates of mutant protein are observed in neocortex, entorhinal cortex, subiculum, hippocampal pyramidal neurons, and striatum, more so in advanced and/or juvenile onset HD (Fig. 3). Aggregates are, however, rare in globus pallidus, substantia nigra, and cerebellum. Some aggregates in HD brain possess an amyloid-like structure, suggesting parallels in aggregate formation with other amyloid-associated diseases such as Alzheimer's and prion diseases (McGowan *et al.*, 2000). Both cytoplasmic and intranuclear aggregation have been observed in HD brain, the latter termed neuronal intranuclear inclusions, or NIIs (Kuemmerle *et al.*, 1999). While considerable attention has been given to the possibility that these aggregates are themselves pathogenic (Davies *et al.*, 1997; DiFiglia *et al.*, 1997; Kim and Tanzi, 1998; Saudou *et al.*, 1998; Sisodia, 1998), the means by which they might lead to neuronal death remains uncertain (Cha *et al.*, 1998; Hackham *et al.*, 1998a,b; Sisodia, 1998). Mutant huntingtin aggregates may, in part, be pathogenic by their capacity to incorporate and thus sequester vital proteins such as the transcription factor TATA-binding protein (van Roon-Mom *et al.*, 2002). The possibility that the aggregates may, at least in part, act by inactivating both mutant and normal huntingtin has been raised by recent evidence showing that the aggregates which form in HD can sequester normal-length polyglutamine-containing proteins, including Htt and CREB-binding protein, both of which promote BDNF production (Cattaneo *et al.*, 2001; Narain *et al.*, 1999; Nucifora *et al.*, 2001; Ona *et al.*, 1999; Preisinger *et al.*, 1999; Shieh *et al.*, 1998; Tao *et al.*, 1998; Wheeler *et al.*, 2000). Neuropathological studies, however, show that formation of NIIs in HD victims is not prominent in cerebral cortex until advanced stages of HD and is never

prominent in striatum (1–4% of neurons) at any stage (DiFiglia *et al.*, 1997; Gutekunst *et al.*, 1999; Kuemmerle *et al.*, 1999; Sapp *et al.*, 1999). In fact, the striatal neurons that do possess NIIs tend to be interneurons, which survive well in HD, rather than projection neurons (Kuemmerle *et al.*, 1999). This brings into question if NIIs are pathogenic. Neuropil aggregates (found in spines, dendrites, and axons) are far more common in HD cortex and striatum than NIIs, and thus may be pathogenic by interfering with neuronal function, particularly corticostriatal communication (DiFiglia *et al.*, 1997; Gutekunst *et al.*, 1999; Kuemmerle *et al.*, 1999; Sapp *et al.*, 1999). Regardless of the motor versus mood symptoms, there is a consistently higher number of aggregates in the superior frontal gyrus than in the motor cortex, suggesting a consistent regional difference in aggregate density that thus does not account for differing symptomatology between cases (van Roon-Mom *et al.*, 2006).

X. HD Brain Pathology and the Vonsattel Grading System

Neuropathological and imaging studies reinforce the view that brain abnormalities in HD develop well before evident symptoms, are progressive, and eventually involve the entire brain to a greater or lesser extent, resulting in about 25% brain weight loss in advanced HD (Halliday *et al.*, 1998; Sharp and Ross, 1996). Nonetheless, the most prominent neuropathology in HD occurs within the striatal part of the basal ganglia, in which gross atrophy is accompanied by extensive neuronal loss and astrogliosis, both of which become more severe as the disease progresses, with the atrophy leading to great enlargement of the lateral ventricles (Fig. 4). At least some of these dying neurons show nuclear fragmentation and marker expression characteristic of apoptotic cell death (Thomas *et al.*, 1995; Vis *et al.*, 2005). Reactive astrocytes are increased in HD striatum and show increased coupling by gap junctions, which may provide increased spatial buffering in an attempt to maintain a beneficial environment for neurons (Vis *et al.*, 1998). Striatal pathology in both caudate and putamen is more prominent caudally than rostrally in early disease, and striatal degeneration proceeds, for unknown reasons, in a dorsomedial to ventrolateral direction (Roos *et al.*, 1985; Vonsattel, 2008). Caudate atrophy as detected by MRI or CT has been shown to be correlated with CAG repeats and with a worsening of the UHDRS motor score (Culjkovic *et al.*, 1999; Jech *et al.*, 2007). Marked neuronal loss and shrinkage is also seen in deep layers of the cerebral cortex. Other regions, including globus pallidus, hippocampus, amygdala, thalamus, subthalamic nucleus, substantia nigra, and cerebellum, show varying degrees of atrophy and/or neuronal loss, depending on disease stage (Rosas *et al.*, 2003). The neuron loss is reflected in regional brain atrophy. For example, late in disease, volumetric losses of the following magnitudes are observed: 20% in cortex, 30% in cerebral white matter, 60% in striatum, 55% in globus pallidus, and 30% in thalamus (de la Monte *et al.*, 1988; Lange *et al.*, 1976; Heinsen *et al.*, 1994). Caudate shrinkage is significant already 10 years from estimated disease onset, while putamen and globus pallidus shrinkage is not significant until 3 years before estimated disease onset (Aylward *et al.*, 1996). Gene expression analysis of caudate, cerebellum, prefrontal association cortex, and primary motor cortex shows the greatest number and magnitude of differentially expressed mRNAs in caudate, followed by motor cortex, then cerebellum, with no detected changes in prefrontal cortex (Hodges *et al.*, 2006). Thus, caudate is most affected in HD, and cerebral cortex is not uniform in its response in HD. Note that caudate volume loss, overall brain volume loss, and white matter

disorganization are manifest early in HD, and these HD brain abnormalities precede overt signs of disease (Aylward *et al.*, 1994; Kassubek *et al.*, 2004c; Paulsen *et al.*, 2006; Squitieri *et al.*, 2009; Reading *et al.*, 2005; Rosas *et al.*, 2005).

A system for grading HD neuropathological severity has been developed based on macroscopic and microscopic criteria related to striatal morphology (Fig. 5) (Vonsattel *et al.*, 1985). This system recognizes five Grades (0–4) designated in the ascending order of severity, with the grades correlating closely with the degree of clinical disability. There are no evident gross, and few microscopic abnormalities in premanifest HD striatum (Grade 0, also termed presymptomatic). The microscopic abnormalities that can be present involve increased abundance of oligodendrocytes and neurons with nuclear aggregates in the tail of caudate, and some neuron loss in head of caudate (Gómez-Tortosa *et al.*, 2001; Vonsattel, 2008). Grade 1 cases have abnormalities that can be detected microscopically in striatum (50% neuron loss in head of caudate) but gross atrophy is not evident, as the ventricular profile of the caudate maintains its normal convex appearance. The Grade 1 changes involve neuron loss and gliosis in the medial paraventricular portions of the caudate, in the tail of the caudate, and in the dorsal part of the putamen. In Grade 2, striatal atrophy is present, but the ventricular profile of the caudate remains convex, but less so than in normal brain. The lateral half of the striatum shows relative preservation in Grades 1–2. In Grade 3, striatal atrophy is more severe, and the ventricular profile of the caudate is flat. In Grade 4, 95% of caudate neurons are lost, striatal atrophy is severe, and the ventricular surface of the caudate is concave. Astrocytes are greatly increased above normal in HD Grades 2–4. This grading system has come to be widely used in neuropathological studies of HD that seek to describe changes as disease progresses.

XI. Basal Ganglia Pathology in HD

The major site of pathology in HD is the basal ganglia, which consists of striatal and pallidal subdivisions. The striatum consists of two major neuron types, projection neurons and interneurons, while globus pallidus consist mainly of projection neurons. We will detail how HD affects these various neuronal populations below. Of note, striatal neuron loss in HD largely involves projection neurons, with most striatal interneuron types highly resistant to HD.

A. Striatum—Projection Neurons

Striatal projection neurons are all GABAergic and can be subdivided into four major types based on their primary projection target: (1) those projecting only or mainly to the external segment of globus pallidus (GPe), which are typically rich in enkephalin (ENK) and poor in or devoid of substance P (SP), and located in the striatal matrix compartment; (2) those projecting mainly to the internal segment of globus pallidus (GPi), which are rich in SP and dynorphin (DYN) but poor in ENK, and located in the striatal matrix compartment; (3) those projecting mainly to the substantia nigra pars reticulata (SNr), which are also rich in SP and DYN, and typically poor in ENK, and located in the striatal matrix compartment; and (4) those projecting to the substantia nigra pars compacta (SNc), which also are rich in SP and DYN, and typically poor in ENK, and largely localized to the striatal patch compartment (Beckstead and Cruz, 1986; Feger and Crossman, 1984; Kawaguchi *et al.*, 1990; Parent *et*

al., 1989, 1995; Reiner and Anderson, 1990; Reiner *et al.*, 1999; Wu *et al.*, 2000). Because these striatal neurons are GABAergic, they all express the enzymes that convert glutamate to GABA, namely the 65kD and 67kD forms of glutamic acid decarboxylase (GAD). The perikarya of striato-GPe neurons and their terminals in GPe are also enriched in D2 dopamine and A2a adenosine receptors (Fink *et al.*, 1992; Le Moine and Bloch, 1995; Schiffmann *et al.*, 1991). In turn, the perikarya of striato-GPi neurons and their terminals in GPi are enriched in D1 dopamine receptors, as are the perikarya of striatonigral neurons and their terminals in substantia nigra (Fink *et al.*, 1992; Le Moine and Bloch, 1995; Schiffmann *et al.*, 1991). All striatal projection neuron perikarya and terminals also possess cannabinoid receptors (Glass *et al.*, 1997; Herkenham *et al.*, 1991; Mailleux and Vanderhaeghen, 1992). These various neurochemical traits provide markers by which the progressive effect of HD on these projection neuron populations can be characterized, either by studying the loss of terminals in the target areas or by studying loss of the perikarya. These four neuronal types play different roles in movement control, and it is thus valuable to characterize how HD affects them to better understand HD pathophysiology. As summarized below, the overall data indicate that while striatal projection neurons as a class are highly vulnerable in HD, and as a result projection neurons markers are lost from striatum as disease progresses (Goto *et al.*, 1989; Seto-Ohshima *et al.*, 1988), projection neuron types do exhibit differences in susceptibility. Notably, striato-GPe and striato-nigral neurons are lost more rapidly in HD than are striato-GPi neurons.

Immunohistochemical studies have indicated that ENK/GAD+ terminals in GPe and SP/GAD+ terminals in the substantia nigra are lost sooner in HD progression than are SP/GAD+ terminals in GPi (Figs. 6–8). For example, depletion of ENK+ immunostaining from GPe has been noted in premanifest HD (Albin *et al.*, 1990b, 1992; Hedreen and Folstein, 1995), and striatal PPE expression appears reduced in premanifest HD (Albin *et al.*, 1991; Augood *et al.*, 1996, 1997). By Grade 1, ENK/GAD+ fibers in GPe are reduced to about 35% of control abundance and SP/GAD+ fibers in SNc and SNr are reduced to about 30% and 50%, respectively, of control abundance (Allen *et al.*, 2009; Deng *et al.*, 2004; Sapp *et al.*, 1995). By contrast, the loss of striatal terminals in GPi is much less in Grade 1, with SP/GAD+ fibers being 70–80% of control abundance (Deng *et al.*, 2004; Sapp *et al.*, 1995). The loss of striato-GPe and striato-nigral projections remains greater than the loss of striato-GPi projections through Grades 2 and 3 (Albin *et al.*, 1990a; Allen *et al.*, 2009; Deng *et al.*, 2004; Reiner *et al.*, 1988; Sapp *et al.*, 1995). For example, in Grade 2, striatal terminals in GPe are at 25% of normal abundance (Deng *et al.*, 2004; Sapp *et al.*, 1995), and in SNc and SNr are at about 35% of normal abundance (Deng *et al.*, 2004). By contrast immunolabeled striatal terminals in GPi are at 60% of their normal abundance (Deng *et al.*, 2004; Sapp *et al.*, 1995). In Grade 3 HD, immunolabeled striatal fibers in GPe, SNc, and SNr are at 20% of normal abundance, but in GPi are at 50% of normal abundance (Deng *et al.*, 2004). By Grade 4 of HD, however, profound loss in all projection systems is apparent (Albin *et al.*, 1990a; Reiner *et al.*, 1988), with striato-GPe and striato-GPi projections at about 5% of normal, and striato-SNc and SNr projections at 10% of normal (Deng *et al.*, 2004). Thus, striato-GPe and striatonigral neurons appear to be lost more rapidly than striato-GPi neurons during HD progression. DTI confirms massive loss of striatal projections in HD, indicating the immunolabeling changes reflect real fiber loss and not just

staining loss (Douaud *et al.*, 2009). Direct support for this premise at the perikaryal level has come from *in situ* hybridization histochemistry for SP and ENK mRNA in HD striatum (Albin *et al.*, 1991; Richfield *et al.*, 1995a, 1995b), and from binding of D1 and D2 dopamine (Glass *et al.*, 2000) and A2a adenosine receptors (Glass *et al.*, 2000) in HD striatum. For example, the loss of the SP+ projection to nigra and the loss of the ENK+ projection to GPe, with the relative preservation of the SP+ projection to GPi, predict that SP+ neuron survival should be better than ENK neuron survival in HD striatum. In fact, neurons expressing mRNA for the SP precursor (i.e., preprotachykinin or PPT) are more abundant in striatum during Grades 1–3 HD than are neurons expressing mRNA for the ENK precursor PPE (Richfield *et al.*, 1995a, 1995b).

These findings for striato-GPe and striato-GPi projections in HD are also compatible with the radioimmunoassay (RIA) study of Seizinger *et al.* (1986), who reported that dynorphin (DYN), which is co-localized with SP in striatal terminals in GPi (Reiner *et al.*, 1999), was undiminished in GPi in HD victims. By contrast, the PPE-derived neuropeptide MERGL was only half its normal abundance in GPe in the HD brains they studied. Biochemical studies have also shown that GABA and GAD are more greatly decreased in GPe than in GPi in symptomatic HD (Ellison *et al.*, 1987; Spokes, 1980; Storey and Beal, 1993). Since striato-GPi and striato-GPe projection neurons are both GABAergic (Reiner and Anderson, 1990), these results too indicate a preferential loss among striatopallidal neurons of those projecting to GPe. One prior biochemical study has suggested that GABA is diminished in GPe in premanifest HD while GABA in GPi remains normal (Reynolds and Pearson, 1990).

Biochemical studies of SP, DYN, GABA, or GAD also indicate that striatal input to nigra is severely depleted in HD (Buck *et al.*, 1981; Beal *et al.*, 1988; Ellison *et al.*, 1987; Emson *et al.*, 1980; Gale *et al.*, 1977; Kanazawa *et al.*, 1977, 1979; Seizinger *et al.*, 1986; Spokes, 1980; Spokes *et al.*, 1980; Storey and Beal, 1993). Of note, Seizinger *et al.* (1986) found that DYN in nigra and MERGL in GPe were halved in HD victims, but DYN in GPi was undiminished. The possibility that the striatal projection to SNc is differently affected in HD than that to SNr has been of interest because they arise from different striatal neuron types, and because Hedreen and Folstein (1995) reported that striosomal neurons, whose principal projection target is pars compacta (Gerfen, 1992), are already affected at Grade 0. Judging whether the SP+ fiber loss is greater for SNc than for SNr is difficult, however, because many dopaminergic neurons of SNc in primates are dispersed within the SNr territory, making it ambiguous to precisely define the boundaries of SNc (Arsenault *et al.*, 1988; Hökfelt *et al.*, 1984). Not surprisingly, the available immunolabeling data do not unambiguously support the notion that presymptomatic HD is characterized by loss in the striato-SNc projection but not in the striato-SNr projection (Deng *et al.*, 2004). Similarly, by RIA Beal *et al.* (1988) observed extensive loss of SP from both SNr and SNc by Grade 1, followed by further loss in subsequent grades, with no clear differences between them at any grade. Other biochemical studies have reported varied results, however, with some observing greater loss of SP or GABA from SNr than SNc (Buck *et al.*, 1981; Ellison *et al.*, 1987; Emson *et al.*, 1980; Kanazawa *et al.*, 1977), and others the opposite (Gale *et al.*, 1977). One study that distinguished HD cases as choreic (early to mid-HD) versus rigid (late HD) reported greater loss of GAD from SNr than SNc in both (Spokes, 1980). Tippet *et al.*

(2007) have reported that preferential striosomal loss (i.e., striato-SNc neuron loss) is not invariably a trait of early HD but does appear associated with mood abnormality when it does occur.

The major findings in HD obtained using neuropeptides or GAD as markers have been confirmed by studies using additional markers of striatal neurons and their terminals. For example, Grade 0 HD has been found to be characterized by loss of cannabinoid, D2 and A2a receptor binding from striatum and by a large increase in GABAA binding in GPe (Glass *et al.*, 2000). These findings are consistent with a preferential loss of ENK+ input to GPe at Grade 0. The absence of reductions in D1 receptor binding in striatum or in GPi at Grade 0 (Glass *et al.*, 2000) suggests that striatal SP+ neurons in general and those projecting to GPi, in particular, are largely unaffected in premanifest HD. The occurrence of reduced D1 receptor binding in SNr at Grade 0 (Glass *et al.*, 2000) and reduced striatal message for D1 receptors and PPT at Grade 0, however, suggest that defects not yet evident at the peptide level or the level of GABA/GAD production are present in presymptomatic HD in striato-SNr projection neurons.

Grade 1 HD is characterized by about 90% loss of striatal D2 dopamine and A2a adenosine receptors (localized to ENK+ neurons), 75% loss of striatal cannabinoid receptors, 50% loss of striatal D1 receptors, near complete depletion of D2 and A2a adenosine receptors from GPe, continued upregulation of GABAA receptor binding in GPe, complete preservation of D1 receptors in GPi, greater preservation of cannabinoid receptors in GPi than GPe or SNr, and 20% loss of D1 receptors from SNr (Allen *et al.*, 2009; Glass *et al.*, 2000; Richfield and Herkenham, 1994; Walker *et al.*, 1984). These findings are consistent with relative preservation of the striato-GPi projection at Grade 1 concomitant with considerable loss in the striato-GPe and striatonigral projections. Grade 2 is characterized by 80–95% loss of striatal cannabinoid, D2 dopamine and A2a adenosine receptors, 50% loss of striatal D1 receptors, near complete depletion of D2 and A2a adenosine receptors from GPe, 66% loss of D1 receptors from GPi, 69% loss of D1 receptors from SNr, and greater preservation of cannabinoid receptors in GPi than GPe (Allen *et al.*, 2009; Glass *et al.*, 2000; Richfield and Herkenham, 1994). These findings are consistent with greater preservation of the striato-GPi than the striato-GPe projection at Grade 2, although the finding by Glass *et al.* (2000) of comparable preservation of D1 receptors in GPi and SNr at Grade 2 is inconsistent with greater vulnerability of the latter. At Grade 3, striatum and GPe are nearly devoid of cannabinoid, D2 and A2a receptors, but about 30% of striatal D1 receptors remain, and GPi cannabinoid receptor levels still exceed those in GPe (Allen *et al.*, 2009; Glass *et al.*, 2000; Richfield and Herkenham, 1994). Both GPi and SNr are, however, greatly depleted of D1 receptors by Grade 3, and substantial upregulation of GABAA receptors is evident in GPi (Allen *et al.*, 2009; Glass *et al.*, 2000). These findings too are consistent with greater preservation of the striato-GPi projection than the striato-GPe at Grade 3, but with significant loss of input to GPi. The data of Waeber and Palacios (1989) on 5HT-1 receptors in Grade 3 HD pallidum are also consistent with this conclusion. By Grade 4, these various receptor markers, as well as such intracellular signaling markers as calcineurin, are all greatly reduced in striatum and its targets (Goto *et al.*, 1989b; Glass *et al.*, 2000; Richfield and Herkenham, 1994). This is consistent with near total loss in all striatal projection

systems by Grade 4, as well as the neuropathological evidence of severe striatal neuron loss by this grade (Vonsattel *et al.*, 1985).

The attributes that make striato-GPi neurons more resistant than striato-GPe and striatonigral neurons is not known, although considerable attention has focused on the role of glutamate receptor subunit configuration, free radical defenses, calcium sequestering, and anti-apoptotic mechanisms (Beal *et al.*, 1991; Calabresi *et al.*, 1998; Chen *et al.*, 1996, 1998; DiFiglia, 1990; Figueredo-Cardenas *et al.*, 1998; Gervais *et al.*, 2002; Hackham *et al.*, 2000; Hedreen and Folstein, 1995; Huang *et al.*, 1995; Medina *et al.*, 1996; Zeron *et al.*, 2002). Regardless, of their basis, the differential loss explains the progression of HD symptoms (Fig. 9). The early loss of striato-GPe and perhaps striato-SNc neurons accounts for the chorea seen commonly in early HD, according to the now standard direct-indirect pathway model of basal ganglia function (Albin *et al.*, 1989; Crossman, 1987; Deng *et al.*, 2004; Hedreen and Folstein, 1995). Given that each type of striatal projection neuron is organized into microzones that interweave with other types within striatum (Flaherty and Graybiel, 1993; Gimenez-Amaya and Graybiel, 1991), the preferential loss of some types of striatal projection neurons in early HD may be why diverse striatal projection neuron markers show patchy loss from striatum (Augood *et al.*, 1996, 1997; Glass *et al.*, 2000; Goto *et al.*, 1989a; Richfield *et al.*, 1991, 1995; Richfield and Herkenham, 1994). Loss of striato-SNr neurons by Grade 1 may cause the saccade abnormalities in early HD since SNr plays a role in saccadic eye movements (Hikosaka, 1989). By Grade 3, considerable loss of striato-GPi neurons appears to occur, and this loss may contribute to the bradykinesia that develops late in HD, while the near complete loss of this projection system by Grade 4 is likely to explain the akinesia in terminal Grade 4 HD (Albin *et al.*, 1989). The functional implications of striato-SNc neuron loss are uncertain, but Tippet *et al.* (2007) indicate that loss of these neurons is associated with mood abnormalities in HD patients. Although differential loss is evident for the four main striatal projection systems, imaging studies assessing brain volume, glucose metabolism, or receptors on striatal projection neurons or their terminals emphasize that neither the striatum itself nor any striatal projection neuron type is completely normal even in premanifest HD (Antonini *et al.*, 1996; Augood *et al.*, 1996, 1997; Aylward *et al.*, 1994, 1996; Glass *et al.*, 2000; Grafton *et al.*, 1992; Kuwert *et al.*, 1993; Weeks *et al.*, 1996).

B. Striatum – Interneurons

Striatal interneurons include (1) very large aspiny cholinergic neurons (Bennett *et al.*, 2000; Kawaguchi *et al.*, 1995); (2) large aspiny neurons that contain GABA and parvalbumin (PARV) (Kawaguchi *et al.*, 1995; Kita *et al.*, 1990); (3) medium-sized aspiny neurons that contain GABA, somatostatin (SS), neuropeptide Y (NPY), and nitric oxide synthase (NOS) (Figueredo-Cardenas *et al.*, 1996a; Kawaguchi *et al.*, 1995); (4) medium-sized aspiny neurons that contain GABA and calretinin (CALR) (Bennett and Bolam, 1993; Cicchetti *et al.*, 2000; Figueredo-Cardenas *et al.*, 1996b; Kawaguchi *et al.*, 1995; Kubota *et al.*, 1993). While the roles of the SS+ and CALR+ interneurons are uncertain, cholinergic and PARV+ interneurons are known to modulate striatal projection neurons (Kawaguchi, 1993; Kawaguchi *et al.*, 1995; Kita *et al.*, 1990; Koos and Tepper, 1999). Cholinergic neurons mediate reward-related (i.e., dopamine-release related) alterations in projection neuron

firing, while PARV+ interneurons inhibit striatal projection neurons in a feed-forward manner as part of the process of switching from one movement to the next in a sequence (Berke, 2008; Gage *et al.*, 2010). Cholinergic, SS + , and medium-sized calretinerergic striatal interneurons are resistant in HD and survive even late into the disease (Fig. 10) (Albin *et al.*, 1990a; Beal *et al.*, 1986, 1991; Cicchetti and Parent, 1996; Cicchetti *et al.*, 2000; Dawbarn *et al.*, 1985; Ferrante *et al.*, 1985, 1986, 1987a, Ferrante *et al.*, 1987b; Hawker and Lang, 1990; Kowall *et al.*, 1987; Massouh *et al.*, 2008; Norris *et al.*, 1996; Richfield *et al.*, 1995; Sapp *et al.*, 1995). Existing published data, although limited, suggest that PARV+ interneurons may be lost from the striatum as HD progresses (Ferrer *et al.*, 1994; Harrington and Kowall, 1991). This loss may contribute to the worsening motor dysfunction evident as HD progresses. Although SS+ neuron abundance does not decline in HD striatum, expression of NOS and SS in these neurons is progressively diminished (Norris *et al.*, 1996). Similarly, the preservation of cholinergic interneurons in HD striatum is nonetheless accompanied by diminished expression of such cholinergic neuron markers as choline acetyltransferase (Aquilonius *et al.*, 1975; Massouh *et al.*, 2008) and the vesicular acetylcholine transporter (Smith *et al.*, 2006).

C. Globus Pallidus

In HD, significant progressive atrophy occurs in GPe and GPi, with greater atrophy and gliosis in GPe than GPi (Halliday *et al.*, 1998; Douaud *et al.*, 2006; Roos, 1986; Vonsattel, 2008; Vonsattel and DiFiglia, 1998). The atrophy and gliosis are evident by Grade 3, and prominent by Grade 4 (50%). The shrinkage appears to be due to both neuron loss and loss of striatal input (Lange *et al.*, 1976). Of interest, pallidal shrinkage seems more diagnostic of symptom onset than does striatal shrinkage since imaging studies show that striatal shrinkage occurs well before symptoms are manifest, but pallidal shrinkage more immediately precedes symptom appearance (Aylward *et al.*, 1996). The pathophysiological contribution of these pallidal changes is uncertain. In principle, preferential loss of GPe neurons would disinhibit the subthalamic nucleus and contribute to akinesia and possibly rigidity.

XII. Other Telencephalic Areas in HD

A. Cerebral Cortex

Cerebral cortex undergoes cell loss, gliosis, and shrinkage in HD, but less so and more slowly than does striatum (Byers *et al.*, 1983; Cudkowicz and Kowall, 1990; De La Monte *et al.*, 1988; Passani *et al.*, 1997; Selemon *et al.*, 2004; Vonsattel *et al.*, 1985). The loss occurs mainly in Layers 3, 5, and 6, is evident over Grades 2–4, and is prominent in Grade 4 (Sotrel *et al.*, 1991). For example, Hedreen *et al.* (1991) noted 57% loss in Layer 6 and 71% loss in Layer 5 in Grade 4 HD. The cortical neuron loss appears to involve the pyramidal projection neurons of cerebral cortex, but not interneurons (MacDonald and Halliday, 2002). For example, neither nNOS nor somatostatin mRNA are significantly decreased in the sensorimotor cortex in HD (Norris *et al.*, 1996), indicating survival of this interneuron class in HD cortex. MRI and fMRI studies show that the cortical thinning is related to disease progress and to CAG repeat length (Kassubek *et al.*, 2004b; Jech *et al.*, 2007), and seems to yield loss of input to striatum (Klöppel *et al.*, 2008; Wolf *et al.*, 2008).

Differences in regional neuron loss and thinning in cerebral cortex occur in HD, and have been described by various authors. Primary motor and premotor cortices both consistently show 40–50% pyramidal neuron loss in late HD (MacDonald and Halliday, 2002). On the other hand, Selemon *et al.* (2004) reported that prefrontal cortex area 9 showed neuron loss but not prefrontal cortex area 46, but both showed shrinkage. Sotrel *et al.* (1993) reported that surviving pyramidal neurons of Layers 3 and 5 in prefrontal cortex showed dendritic augmentation, reflecting perhaps compensation for the loss of other neurons from those layers. MRI and CT imaging studies show results similar to these, revealing that the sensorimotor, insular, and opercular cortices show the most thinning, while frontal and temporal cortices show relatively less (Douaud *et al.*, 2006; Kassubek *et al.*, 2004b; Mühlau *et al.*, 2007; Rosas *et al.*, 2003), with thinning in these areas manifest even before overt HD motor symptoms and associated with decline in cognitive function as measured by the UHDRS (Rosas *et al.*, 2005). Heterogeneity in HD in motor versus mood symptoms appears in part attributable to regional variation in cortical neuron loss since a significant association between motor dysfunction and neuronal loss in primary motor cortex is seen in HD, as well as between mood disturbance and neuronal loss in anterior cingulate cortex (Thu *et al.*, 2010). Braak and Braak (1992) reported loss of entorhinal cortex neurons in advanced HD, suggesting a basis for memory deficits in late HD.

Functional alterations in neurotransmitter release also occur for neurons of cerebral cortex, and may underlie HD symptoms. For example, a loss of various presynaptic proteins, such as the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein, synaptosome-associated protein 25 (SNAP 25), and the vesicle docking and recycling protein rabphilin 3a, occurs in frontal cortex in HD Grades 1–4 (Morton *et al.*, 2001; Smith *et al.*, 2007). These losses are not due to a general loss of synapses in HD cortex (Smith *et al.*, 2007). Similarly, Zucker *et al.* (2010) showed that Layer 5 motor cortex neurons in HD make less Lin7 homolog b (Lin7b, also known as *veli-2* and *mals2*), which is a scaffold protein implicated in synaptic plasticity and neurite outgrowth. These types of changes could impair synaptic function within cortex and between cortex and striatum. In HD, uptake of glutamate was found to be reduced by 43% in prefrontal cortex, with the defect increasing in severity with CAG repeat expansion; impairment of glutamate uptake may contribute to neuronal dysfunction and pathogenesis in HD (Hassel *et al.*, 2008).

B. Amygdala

The amygdala comprises pallial and subpallial subdivisions. Significant amygdala shrinkage has been reported in HD, based on MRI and CT (Douaud *et al.*, 2006; Rosas *et al.*, 2003), and Kipps *et al.* (2007) reported declining emotion recognition in others with amygdala volume loss in HD, possibly contributing to HD affective symptoms. Zech *et al.* (1986) reported that the central nucleus of the subpallial amygdala in one choreiform HD case was markedly shrunken, with considerable attenuation of immunolabeling for VIP, ENK, neurotensin, and NPY.

XIII. Brainstem Areas in HD

A. Thalamus

Thalamus and the subthalamic nucleus undergo shrinkage and cell loss in HD (Byers *et al.*, 1973; Douaud *et al.*, 2006; Mann *et al.*, 1993; Vonsattel *et al.*, 1985). The centre median, for example, shows evident neuronal loss and astrogliosis by Grade 3 (Vonsattel, 2008), and together the centromedian/parafascicular nucleus complex shows about a 25% volume loss and 50% neuron loss in advanced HD (Heinsen *et al.*, 1996), while only 15% neuron and volume loss is seen in mediodorsal nucleus (Heinsen *et al.*, 1999). Up to 25% volume loss is observed in subthalamic nucleus by Grade 4 (Lange *et al.*, 1976). It is uncertain if this reflects neuron loss or loss of GPe input. Ventrobasal thalamus also shows atrophy (Dom *et al.*, 1976). Imaging studies indicate that thalamic nuclei projecting to frontal cortex and/or striatum (dorsomedial, centre median, parafascicular, and ventrobasal) undergo considerable atrophy in HD, and their atrophy is associated with affective symptoms (Kassubek *et al.*, 2004a).

B. Hypothalamus

Many of the nonmotor symptoms of HD, such as weight loss, sleep abnormalities, hypometabolism, and muscle atrophy are unexplained. Given the central role of hypothalamus in these functions, attention has recently focused on the impact of HD on hypothalamus. Studies using voxel-based morphometry of MR images or CT have shown hypothalamic atrophy in early HD patients (Douaud *et al.*, 2006; Kassubek *et al.*, 2004a,b), and significant hypothalamic atrophy (as reflected in ventricular expansion) is evident even 10 years before estimated symptom onset (Soneson *et al.*, 2010). Among specific nuclei, atrophy of the lateral tuberal nucleus (Kremer *et al.*, 1990), reflecting loss of somatostatinergic neurons (Timmers *et al.*, 1996), has been seen in HD. Notably with regard to sleep disorders in HD, a 28% loss and a 27% atrophy of neurons expressing the neuropeptide orexin has been noted in the lateral hypothalamic area of HD patients (Petersén *et al.*, 2005). The lateral hypothalamus contains neuronal populations important for regulation of sleep and wakefulness, and feeding (DiLeone *et al.*, 2003). As loss of orexinergic neurons is associated with narcolepsy and obesity (Kok *et al.*, 2003), their loss in HD is unlikely to be involved in HD-related weight loss but may be contributory to the sleep defects. Given that the somatostatin and orexin cell populations are small, and atrophy of the hypothalamus is prominent in HD, diverse hypothalamic populations are likely to be affected in HD. Since oxytocin and vasopressin neurons were decreased by 45% and 24%, respectively, in advanced HD, it seems likely that paraventricular and supraoptic nucleus loss contributes to HD hypothalamic shrinkage (Gabery *et al.*, 2010). The numbers of NPY neurons (many of which are involved in feeding suppression) is, however, unchanged (Gabery *et al.*, 2010). Detailed characterization of hypothalamic neuropathology in HD, its progression, and its relation to the nonmotor symptoms of HD is still, however, limited.

C. Substantia Nigra

Substantia nigra undergoes cell loss and shrinkage in HD, but less so than does striatum (Byers *et al.*, 1983; Cudkowicz and Kowall, 1990; De La Monte *et al.*, 1988; Sharp and Ross, 1996; Vonsattel *et al.*, 1985). Shrinkage of substantia nigra as detected by CT has also

been reported, which could stem from both striatal input loss and nigral neuron death (Douaud *et al.*, 2006). Loss of both SNr GABAergic neurons, and SNc dopaminergic neurons is evident in HD (Vonsattel, 2008), and Oyanagi *et al.* (1989) have reported 40% loss in both populations. Yohrling *et al.* (2003) reported that in Grade 4 HD tyrosine hydroxylase expression by dopaminergic neurons, as detected by *in situ* hybridization, was decreased by 46% per surviving dopaminergic neuron. Moreover, the dopaminergic neurons were 33% smaller than normal. Neuron counts were not, however, performed to assess dopaminergic neuron loss in that study. Consistent with the reduced tyrosine hydroxylase expression, Yohrling *et al.* (2003) additionally found that tyrosine hydroxylase protein in the nigra was reduced by 32%. They attributed the reduced tyrosine hydroxylase expression to an effect of mutant huntingtin on the tyrosine hydroxylase promoter. As would be predicted from loss of nigral dopaminergic neurons and reduced tyrosine hydroxylase expression, terminals containing tyrosine hydroxylase appear to be reduced in abundance in advanced HD striatum (Ferrante and Kowall, 1987). Dopamine and its metabolite HVA, and VMAT2 have also been reported to be reduced in HD striatum by some authors (Bohnen *et al.*, 1986; Bohnen *et al.*, 2000; Kish *et al.*, 1987; Reynolds and Garrett, 1986). Loss of dopamine input could contribute to akinesia in HD, as it does in Parkinson's disease.

D. Cerebellum

Volumetric loss and sporadic Purkinje cell loss is evident in HD Grades 3 and 4, notably in juvenile onset victims (Castaigne *et al.*, 1976; Hattori *et al.*, 1984; Jeste *et al.*, 1984; Rodda, 1981; Vonsattel, 2008). Amino acid and neuropeptide neurotransmitter levels, and GABA receptor levels appear to be largely normal in HD cerebellum (Beal *et al.*, 1988; Kish *et al.*, 1983).

E. Brainstem

Significant loss of neurons from diverse brainstem regions and overall brainstem shrinkage has also been reported in HD (Hattori *et al.*, 1984). For example, Koeppen (1989) reported about 30% loss from the midline pontine region controlling saccades, and linked this loss to saccadic defects in HD.

XIV. HD and Neurogenesis

In response to striatal injury, the subventricular zone (SVZ) of the caudate increases the production of progenitor cells that migrate toward the site of the injury where they can differentiate into mature neurons and glia as part of a restorative process (Curtis *et al.*, 2007). Curtis *et al.* (2003) showed an increase in cell proliferation in the SVZ in HD caudate, progressive with HD grade and CAG repeat, using the cell cycle marker proliferating cell nuclear antigen (PCNA). Proliferating cells were shown to express the neuronal marker beta III-tubulin or the glial cell marker GFAP, demonstrating generation of neurons and glial cells in the SVZ of HD caudate. The SVZ of HD caudate is 2.8-fold thicker than normal at Grade 2/3, with thickness increasing with grade. An increase in glial cells is mainly responsible for the large increase, but neuroblasts and progenitor cells are also increased in abundance (Curtis *et al.*, 2005a,b).

XV. Neuroinflammatory Neuropathology in HD

Microglial activation and the associated neuroinflammation appear to be a prominent pathological feature of HD, evident from early in the disease process (Tai *et al.*, 2007). For example, activated microglia are greatly increased in abundance in HD cortex, striatum, and globus pallidus, and their abundance increases with grade and neuron loss (Pavese *et al.*, 2006; Sapp *et al.*, 2001a). Similarly, the expression of the neuroinflammation mediators, CCL2 and IL-10, is increased specifically in the striatum in HD, presumably in activated microglia, but not in cortex or cerebellum (Silvestroni *et al.*, 2009). By contrast, an upregulation of the neuroinflammation mediators IL-6, IL-8, and MMP9 is seen in cortex and the cerebellum. The activated microglia may be neurotrophic and act to combat the HD pathogenic process, or their sustained activation may exacerbate the HD injury process (Möller, 2010).

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Fig. 1.

Image A shows the location of the Huntington's disease gene in band 4p16.3 of chromosome 4 (Adapted from Figure 1 of Gusella *et al.*, 1994). Image B illustrates the huntingtin protein, showing that it contains a polyglutamine region (polyQ) and a proline-rich domain (PRD) at its N-terminus, and 10 HEAT repeats clustered in three domains in the N-terminal half of the protein (Adapted from Figs. 1 and 2 of Harjes and Wanker, 2003). Numbers indicate amino acids. Image C shows a graph depicting the relationship between CAG repeat and Huntington's disease age of onset. Note the overall significant negative correlation between HD onset and the expanded repeat length ($n = 609$, $r^2 = 0.65$, $p = 0.0001$). Nonetheless, the relationship is more complex than this. For example, while there is a strong correlation between CAG repeat and age of onset for adult-onset cases (>20 years) over the 35-55 repeat range, in the case of juvenile (<20 years) onset increasing CAG does not notably advance age of onset highlighted (by dark and pale shading). Moreover, this is also true for the few HD cases found with repeats >200 CAG (not shown in graph). The textured box highlights anomalous adult onset cases with expansion beyond the 60 CAG typically associated with juvenile onset (Adapted from Fig. 4 of Squitieri *et al.*, 2006). (For color version of this figure, the reader is referred to the web version of this book.)

Fig. 2.

Immunofluorescence labeling for huntingtin (*Ht*) in the rat striatum viewed with CLSM. Two low-magnification fields (*A*, *B*) and two high-magnification fields (*C*, *D*) show that scattered large neurons intensely labeled for huntingtin and numerous medium-sized neurons moderately labeled for huntingtin are present in striatum. Magnification in *A* is as in *B*; magnification in *C* is as in *D*. Images *E* and *F* show immunofluorescence labeling for huntingtin in the lower layers of rat cerebral cortex, at increasingly higher magnification. Both fields show intense labeling of pyramidal neurons in Layer 5 of cortex. All images are from Fusco *et al.* (1999).

Fig. 3.

Images showing immunolabeling for huntingtin in HD brain, revealing aggregates of mutant huntingtin in neuronal nuclei, termed intranuclear inclusions (NIIs). Image A shows the presence of numerous NIIs in cerebral cortex of juvenile HD victim at low magnification. Images B and C show immunolabeled NIIs in individual cortical pyramidal neurons in the same juvenile HD victim, using Nomarski optics to highlight the NIIs. The nucleolus in each cell is unlabeled. These images are adapted from A-C of Fig. 1 from DiFiglia *et al.* (1997).

Fig. 4.

Coronal slices through human telencephalon, showing a normal brain on the right and an advanced HD brain (Grade 4) on the left. Note the profound shrinkage of cortex and caudate and the resulting ventricular expansion in the HD brain. Image courtesy of the Harvard Brain Tissue Resource Center. (For color version of this figure, the reader is referred to the web version of this book.)

Fig. 5. Schematic illustrations of caudate at HD Grades 0 through 4 according to the Vonsattel et al grading scale. Note that the ventricular profile of the caudate is diagnostic for classification, and the extent of caudate neuron loss distinguishes normal from HD, and Grade 0 versus Grade 1 HD. This illustration is adapted from Fig. 2 of Vonsattel *et al.* (1985).

Fig. 6.

Images of immunohistochemically labeled sections showing GPi, GPe, and substantia nigra in control, Grade 1 HD, and Grade 3 HD cases, immunostained for SP in the case of GPi and the nigra and for ENK in the case of GPe. In the control, SP+ fibers abound in GPi, ENK+ fibers abound in GPe, and SP+ fibers abound in the nigra. In Grade 1 HD, ENK+ fibers in GPe and SP+ fibers in the nigra are depleted, while SP+ fibers in GPi remain abundant. The contrast is even more evident in the Grade 3 specimen, where ENK+ fibers are markedly depleted in the atrophied GPe and SP+ fibers in the nigra are sparse and patchy, but SP+ fibers in GPi are still quite prominent. This illustration is Fig. 5 from Deng *et al.* (2004).

Fig. 7.

High-power images showing SP+ fibers in GPi (B, D, F) and ENK+ fibers (A, C, D) in GPe. In the control case, abundant woolly fibers can be seen in both GPi and GPe. In Grade 1, loss of ENK+ fibers in GPe is apparent, while the SP+ fibers in GPi are indistinguishable from that in control. In Grade 3, ENK+ woolly fibers are completely absent, while the SP+ fibers in GPi are relatively preserved, although a decrease in terminal density is apparent. This illustration is Fig. 6 from Deng *et al.* (2004).

Fig. 8.

Low-power images showing GAD+ staining in both GPi and GPe of control, Grade 1 HD, and Grade 3 HD cases. Note the greater loss of GAD+ woolly fibers from GPe than from GPi. This illustration is Fig. 7 from Deng *et al.* (2004).

Fig. 9.

Schematic illustration of the preferential loss of ENK+ striato-GPe neurons compared to SP + striato-GPi neurons during the progression of HD, and the relation of this differential loss to HD symptoms. In brief, the early loss of striato-GPe neurons, which suppress unwanted movements, explain the early appearance of chorea in HD, while the later loss of the striato-GPi neurons, which promote desired movement, explain the appearance of akinesia as a later symptom. (For color version of this figure, the reader is referred to the web version of this book.)

Fig. 10.

Camera lucida reconstructions of the distributions of neuropeptide Y-immunoreactive (NPY +) neurons at comparable levels of the basal ganglia, of a normal individual (A), a choreic Grade 3HD case (B), and a rigid Grade 4 HD case (C). Although the number of NPY+ perikarya in putamen is similar, shrinkage of the putamen greatly elevates the packing density of these neurons in Grades 3 and 4 HD. Note also the progressive shrinkage of GPe and GPi in the HD cases. GPe = external globus pallidus; GPi = internal globus pallidus. This illustration is Fig. 2 from Albin *et al.* (1990a).