

Early Dysfunction of Neural Transmission and Cognitive Processing in Huntington's Disease

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1. Introduction

Huntington's disease (HD) is one of many deteriorative brain diseases, a class of disease in which neurons progressively die. In its final stages, HD robs patients of the dignity of their humanity; denying control of basic movements necessary for communication, facial expression and personal accomplishment. A means to test for the mutation has been available since 1993, when the Huntington's Disease Collaborative Research Group exposed the huntingtin gene and characterized the nature of the mutation process. Despite this, children of patients often avoid determining their genotype because such a diagnosis is currently merely bleak without hope of remedy, and because of legitimate fears of employment discrimination or difficulties maintaining health insurance given the legal definition of "pre-existing condition." In the absence of promising treatments or prospects for cures the devastating loss of muscular control during the final stages of disease progression is ominous. It is therefore not uncommon for HD patients to become aware of their own disease rather late into its progression when motor symptoms begin to emerge. As these movement symptoms arise they may be effectively masked by compensatory behavioral strategies. In time, however, these compensatory tactics fail to keep up with the advancing choreic movements which eventually dominate and negate purposeful motor control.

The regions of the brain that are most susceptible to neuron death in HD, in a manner that correlates with motoric symptom severity, are the cerebral cortex, and the caudate and putamen nuclei of the basal ganglia (Young et al., 1986; Halliday et al., 1998). At first glance, it may seem that halting or preventing progressive neuron death within these affected areas would provide an adequate therapeutic strategy for HD. While efforts to do this are indeed under way (see Mattson & Furukawa, 1996 or Mattson, 2000 for review; Leyva et al., 2010; Niatsetskaya et al., 2010), this approach has, in and of itself, proven insufficient. At best, efforts to block apoptosis-generating mechanisms in HD patients have delayed symptom onset at early stages, yet have failed to ward off motor symptom onset (*Vitamin E-related Antioxidant D- α -tocopherol* - Peyser et al., 1995; *Creatine* - Verbessem et al., 2003; *Coenzyme Q₁₀* - Huntington Study Group, 2001). Although higher dose studies are currently ongoing

with these compounds, it remains unclear whether enticing benefits observed *in vitro* (e.g. Wang et al., 2005; Hoffstrom et al., 2010), or with animal models (Ferrante et al., 2000; Dedeoglu et al. 2002; van Raamsdonk, 2005a) will manifest in human clinical trials (see Delanty & Dichter, 2000, or Wang et al., 2010 for broader reviews of treatment efforts). The physiological perspective represents a plausible theoretical viewpoint that may explain the rather disappointing clinical results of cell preservation efforts. Preventing neuronal death may perpetuate neurons, but are these preserved neurons in HD patients capable of carrying out their prescribed roles sufficiently, given their diseased state at the time of treatment? Efforts to merely prevent neuronal death by increasing ATP synthesis, antioxidants, or other anti-apoptosis remedies are unlikely to provide sufficient benefit to patients if neurons are already malfunctioning. Furthermore, if malfunctioning neurons that are maintained by treatments nevertheless fail to engage their appropriate roles, then their survival may be disruptive. It would seem that the key to rectifying HD will require not only maintaining neuron survival, but also their proper physiology. Beyond total cell counts, protected neurons must be able to respond appropriately to afferent signals, sensitivity modulations, and engage in or disengage from longer-term plastic changes in a normal manner. This chapter will focus on the functional disruptions of neural transmission and related cognitive processing at very early disease stages. Therefore, *presymptomatic HD* (pre-HD) will be defined as HD-related malfunctions arising prior to the emergence of diagnosable motor abnormalities described by Paulson (2008).

2. Primary or compensatory mechanisms?

Neurons, either as individual cells or as part of an integrated nervous system, continually attempt to compensate for disruptive influences and maintain a dynamic equilibrium. When signals become weak, receptor sensitivity is boosted to compensate. When energy utilization is high, extra synapses are created to maintain signals at reduced cost. These compensatory responses are known as *plasticity* and they are at work not only in response to damaging or disruptive influences but also to support learning and memory formations or the process of forgetting when information becomes less applicable (Lee et al., 2004; Fusi et al., 2007). Several famous neuroscientists offered early descriptions of the mechanisms underlying plasticity. Among these, the one who received the most recognition in this arena was Donald Hebb, who was a student of Karl Lashley and subsequently collaborated with Wilder Penfield (Brown & Milner, 2003). Hebb's main contribution was his theoretical description of a modifiable synapse that supports extended increases in synaptic strength when specific conditions are met; a process known as *long term potentiation* or LTP (Hinton, 2003; Milner, 2003). Recently, it has become popular to refer to a myriad of neuronal modification processes as "Hebbian" when they lead to either synaptic LTP or its opposite, *long term depression* or LTD (Massey & Bashir, 2007; McBain & Kauer, 2009).

It is evident that the activity of neurons during pre-HD stages is distorted. In addition, various affected brain systems attempt to compensate for the mutation-related malfunctions, particularly during these earlier stages. These simultaneous processes present a substantial challenge to neuroscientists attempting to unravel the neurophysiological mysteries of HD. To make things yet more challenging, compensations in one system may compromise another system. If researchers could localize and reverse primary malfunctions, it may be possible to control the spread of these potentially maladaptive compensatory adjustments.

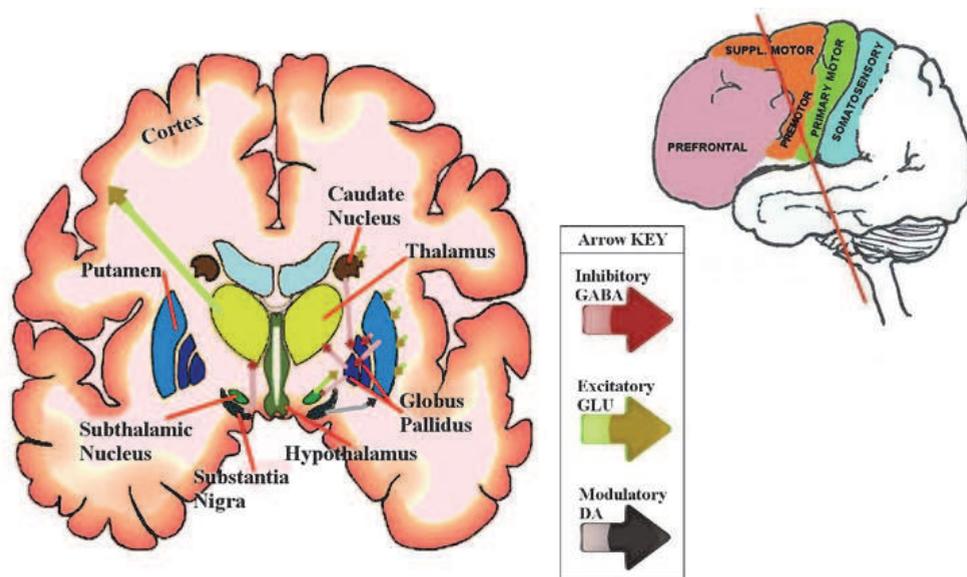


Fig. 1. Basal Ganglia Circuitry. The input regions (caudate, putamen, subthalamic nucleus) are generally conceptualized as receiving converging excitatory input from the cortex. Within these regions, modulatory DA input arising from the substantia nigra tailors the responses of the majority efferent MSNs. The subthalamic nucleus contributes excitatory input to the globus pallidus while the centromedian and intralaminar nuclei of the thalamus send excitatory input to the caudate and putamen. The caudate and putamen contribute sequential inhibitory signals through the globus pallidus and the substantia nigra reticulata, converging inhibitory signals on the thalamus. These converging inhibitory signals modulate thalamic relay neurons which return excitatory signals into the frontal cortex based on amassed inhibition or disinhibition. The thalamocortical targets are mostly the supplementary motor and premotor areas for movement, but other cortico-basal ganglia-cortical loops interact with other regions of prefrontal cortex involved in behavior planning. Slightly modified version of basal ganglia image reprinted with permission Courtesy of the Dana Foundation, Copyright 2007, all rights reserved.

To fully understand pre-HD, it is necessary to provide background about the cerebral circuitry where malfunctions begin to appear. HD is primarily a disorder of the basal ganglia, so we'll begin by describing the primary associated nuclei and connections of this system. The key associated neurotransmitters are glutamate (GLU), gamma aminobutyric acid (GABA), acetylcholine (ACh), adenosine (ADN), nitric oxide (NO), dopamine (DA), serotonin (5-HT), endocannabinoids, and various cotransmitter neuropeptides. As diagrammed in Figure 1, the basal ganglia are generally conceptualized first by orienting to the primary input regions, the *caudate* and *putamen* nuclei (these are indistinct in experimental animals and referred to as a combined "striatum"). The whole of the cortical mantle, along with centromedian and intralaminar thalamic nuclei, send excitatory GLU projections to these structures where they converge on both the GABAergic *medium spiny*

neurons (MSNs) and local interneurons containing GABA, ACh, or NO, along with various neuropeptides. Following local integration, the MSNs project to the globus pallidus or the substantia nigra reticulata, which both harbor GABAergic neurons that feed forward to the thalamus where they modulate thalamic relay neurons that feed back to the cortex. DA originates from the substantia nigra compacta, releasing the highest levels of this neurotransmitter into the caudate and putamen where it modulates local MSN activity, along with 5-HT originating from the dorsal raphe nucleus. Thalamic relay neurons that close the “motor loop” feed back to the supplementary and premotor cortices, while those that close the “cognitive loop” feed back to the prefrontal cortex (see Middleton & Strick, 2000, for explanation of loops).

Given the high convergence of axon terminals, and associated astrocytes (see Pascual et al., 2005), releasing so many different neurotransmitters (GLU, GABA, NO, DA, 5-HT, ADN) onto MSNs, the complexity of their modulation seems to present a wide window for error in ordinary conditions. Additionally, if these modulatory inputs begin to send inappropriate signals (as will be discussed below) it is surprising that this system continues to process movement signals for as long as it does before motor symptoms begin. Striatal MSNs represent the majority (approximately 90%) of neurons in the striatum responsible for relaying processed information to subsequent basal ganglia stations. Since striatal MSNs are most notably vulnerable in HD, it will be important to place these neurons into proper context.

Figure 2 depicts a model striatal MSN with a subset of notable afferent influences. These neurons are influenced by nitric oxide arising from GABA interneurons that synapse on dendritic spine necks (Kubota & Kawaguchi, 2000), by ACh arising from cholinergic interneurons that are generally understood to be the “tonically active” striatal neurons (Wilson et al., 1990), and by adenosine (ADN) arising from both local neurons and astrocytes in a nonsynaptic but activity-dependent manner (Delaney & Geiger, 1998; Pascual et al., 2005; Pajski & Venton, 2010). Also, recent findings have elevated endocannabinoids to a prominent position in striatal synaptic processing, as these compounds tend to be released by MSNs in response to GLU and DA stimulation and provide feedback to CB1 receptors located on GLU-releasing axon terminals (Matyas et al., 2006; Uchigashima et al., 2007; Lovinger, 2010).

The history of basal ganglia exploration was profoundly influenced for many years by the pioneering work of Charles Gerfen, who was the first to expose distinctions between two prominent circuitry pathways emanating from the rat striatum: the *striatonigral* and the *striatopallidal* pathways (Gerfen & Young, 1988; Gerfen, 1992a). Thus, striatal MSNs were understood to send efferent axons from the striatum *either* to the substantia nigra pars reticulata (includes internal pallidum in humans) *or* the external globus pallidus, but not both. Within this seminal work, Gerfen and others delineated several important distinctions between these two GABAergic efferent pathways, such as differential neuropeptide expression, DA receptor expression (Gerfen, 1992b), and more recently, differential muscarinic receptor expression (Acquas & DiChiara, 2002). These data have been foundational to many speculations regarding the function of the basal ganglia and its role in selecting behavioral actions.

When the functions of the basal ganglia are evaluated in humans, it is likely that our anatomical connections are more like primates than rats or mice. Therefore, while it is tempting to speculate that the different pathways, often referred to as *direct* (striatonigral) and *indirect* (striatopallidal) pathways may be distinctly impacted within rodent HD models, it would seem less likely that such distinctions remain in the human condition. Nevertheless, the sensitivities of MSNs to modulation and plasticity within the striatum (caudate and putamen for humans) are likely to bear considerable resemblance to responses and mechanisms exposed in rodents.

3. Presymptomatic neurotransmitter release

Collective explorations of neurotransmitter release using *in vivo* microdialysis or voltammetry-related techniques can provide useful insights into neuronal malfunctions predating motor symptom expression in HD. Investigations into whether neurons are stimulated sufficiently to release, whether neurotransmitter availability/storage in vesicles provides sufficient quantities upon release, and whether neurotransmitters are removed appropriately to terminate the postsynaptic response, have all indicated that different neurotransmitter systems can exhibit unique malfunctions. Because of the common associations between the excitatory neurotransmitter GLU, excitotoxicity, and apoptosis in the HD brain, the glutamatergic striatal afferents were the first system to be investigated for early stage HD-associated problems using available rodent models (Greenamyre, 1986). A full account of all rodent HD models is beyond the scope of this chapter, but a brief description is pertinent to make a key point. The transgenic rodent (rat or mouse) has become a popular model of HD, and perhaps the most popular to date would be the R6/2 mouse that harbors exon 1 of the human mutated huntingtin gene with approximately 150 CAG repeats, exhibiting symptoms by 8 weeks (Carter et al., 1999). This is to be distinguished from the *knock-in* 150 mice (KI-150) that harbor full-length mutant but murine-based huntingtin genes inserted into the genome in a manner that replaces the endogenous gene but maintains endogenous expression control. These KI-150 mice take up to 80 weeks to exhibit symptoms despite harboring a similar number of CAG repeats (Heng et al., 2007). The key point here would be that when expression control presumably minimizes protein creation, symptom severity is dampened providing greater windows for exploring presymptomatic stages.

As previously indicated (Figure 2), striatal MSNs are heavily innervated by glutamatergic afferents arising from the cortex (corticostriatal) and the thalamus (thalamostriatal). The convergence of this input represents the primary excitatory drive for all striatal neurons, with the majority of glutamatergic synapses targeting the tips of dendritic spines. Striatal neurons recorded in slice preparations (Berretta, 2008; Stern et al., 1998; Wilson & Kawaguchi, 1996) and stationary awake animals (Sandstrom & Rebec, 2003; Wilson, 1993, 2004) are mostly silent. In turn, bursts of activity arise in intact animals during bouts of movement, and are believed to be generated by correlated surges among glutamatergic afferents (Wilson, 2004). Evidence indicates that striatal MSNs are stimulated by increased amounts of GLU beginning at presymptomatic stages, both because synaptic transport mechanisms begin to fail (Estrada-Sanchez et al., 2009; Brustovetsky et al., 2004; Behrens et al., 2002; Lievens et al., 2001), and as a result of altered control of glutamate release (authors' observations; Estrada-Sanchez et al., 2009; Nicnicocail et al., 2001). In fact, findings of

increased resistance to excitotoxicity in the presymptomatic R6/2 mouse suggest early compensations occur to diminish GLU sensitivity somewhat (Qian et al., 2011; Estrada-Sanchez et al., 2010; Hansson et al., 1999). Furthermore, treatments that decrease glutamate transporter expression enhance glutamate-related neurotoxicity (Estrada-Sanchez et al., 2010). Conversely, boosting the expression of astrocyte-based GLT-1 glutamate transporter using an antibiotic drug called ceftriaxone, which increases glutamate reuptake in R6/2 mice, not only diminished motor-symptom expression, such as paw claspings and ballistic twitching, but also seemed to improve cognitive processing, as indicated in plus-maze activity (Sari et al., 2010; Miller et al., 2008a). These deficits in GLU control seem to extend into the frontal cortex as well (Hassel et al., 2008; Behrens et al., 2002) which would be expected to distort information processing more profoundly in both motor and cognitive domains by affecting both primary and downstream targets.

Microdialysis is a technique commonly used to measure extracellular release of neurotransmitters and is a versatile technique in that it can measure several different neurotransmitter substances at once. The basic technique requires pumping a solution that closely approximates cerebrospinal fluid across a small semi-permeable membrane-enclosed probe tip that is placed inside the brain region of interest. Via diffusion, neurotransmitter substances released will enter the semi-permeable membrane tip, pass into an output line, and accumulate in collection vials. The contents of these vials are then analyzed for neurotransmitter content using high performance liquid chromatography (HPLC) and the levels of neurotransmitter measured represent snapshots of release activity that took place during the experiment. Collections can be taken at intervals throughout the experiment to indicate the changes that take place over time.

Our laboratory has investigated release activity in, perhaps, the most valid model of pre-HD, the KI-150 mouse. As described previously, this knock-in model provides a wide window of presymptomatic development. They also lack even subtle motor symptoms until at least 14 weeks of age. With this model, we found disrupted GLU release control at the earliest age ever observed, prior to the onset of cognitive deficits. We performed a within-subject set of experiments that began following weaning with multi-stage training of an operant task during the next 3 weeks, from 6-9 weeks of age. Training culminated in a task that required animals to alternate bar-pressing between two levers in an operant box (Med Associates, St. Albans, VT) in a left-right-left-right-left sequence. The reward was a sucrose pellet for each successful sequence accomplished. Once trained, 9-10 week old animals were then challenged to adopt the reverse sequence (right-left-right-left-right); a challenge intended to test behavioral flexibility after habitual behavior had been established.

In vivo microdialysis was performed during this challenge, and during a task-free period that followed, in order to measure neurotransmitter changes elicited within the mouse striatum. After two recovery days, these same animals were then subject to a second microdialysis experiment, during which high-level (80mM, normally 2.9mM) potassium-containing artificial cerebrospinal fluid was pumped across the membrane. This technique is a popular method, used to generate local excitation of neurons and terminals within the region of interest (Nicniocaill et al., 2001; Tossman et al., 1986). Potassium typically flows through neuronal membranes easily, and when it is provided extracellularly this depolarizes the local neurons and afferent axons. Although no statistically significant genotype distinction was found in operant-stimulated GLU levels, potassium-stimulated

GLU was significantly increased among the homozygote mice, by comparison to the remaining genotypes (see Figure 3).

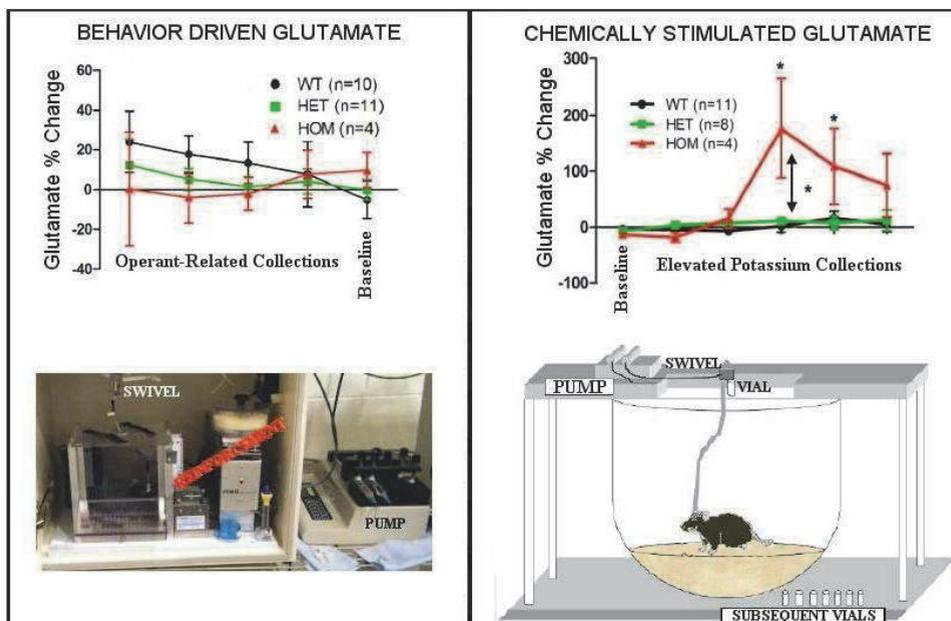


Fig. 3. Glutamate Microdialysis with Knock-In Mice. Two sequential microdialysis sessions were performed with freely-moving KI-150 mice. In the first session, measurements of GLU were taken during operant behavior, while these measures were taken in the second session during elevated potassium stimulation. GLU levels measured in the first session were not significant, while a significant difference was found between homozygote mice and both their heterozygote and wild-type littermates in response to striatal potassium stimulation. The homozygote animals averaged 160% increases in glutamate during potassium stimulation (from 2.9-mM to 80-mM) while no increases in GLU responses to behavioral stimulation were observed. These groups showed no genotype distinctions in the number of reinforcers earned when required to reverse their bar-pressing pattern. No genotype-related movement deficits were exhibited by these animals as measured by open field activity or grip strength measures, indicating they were presymptomatic. At this early age (10-11 weeks) these knock-in animals showed no signs of motoric pathology in the hallmark longitudinal study that used far more extensive batteries of tests to thoroughly assess deficit onset (Heng et al., 2007).

The data depicted in Figure 3 also relates to a common theme with neurochemical measurements in the context of deteriorative disease: deficits in release control often require stimulation to reveal an existing abnormality. This relates to the compensatory mechanisms previously described. In our experiments for example, it would seem that engaging in operant bar-pressing behavior for food reward was not sufficient to expose an underlying problem with glutamate control, while the 80 millimolar elevated potassium concentrations in the extracellular fluid apparently was. Within the striatum, it seems the large majority of

synaptic GLU removal, post-release, is accomplished by transporters expressed by astrocytes (Lee & Pow, 2010). Energy is required for astrocytes to accomplish GLU transport (Azarias et al., 2011), and a corresponding decline in the astrocytic expression of GLU transporters seems to reach a point where the striatum can no longer keep up with the behavior-related surges of GLU necessary to generate striatal bursting activity (Wilson, 2004). It seems this occurs despite observations that astrocytes initially proliferate in HD, perhaps as a compensatory strategy (Faideau et al., 2010). It is also relevant to pre-HD that developmental changes seem to take place between youth and later adulthood regarding astrocytic participation in GLU clearance. Apparently astrocytes adopt a greater role in this clearance at later ages, when HD symptoms are more profound (Thomas et al., 2011a).

Another neurotransmitter that appears to become disrupted in early HD is dopamine (DA). The deficit in DA release is not as profound in HD as it is in Parkinson's disease (PD), which is known to result primarily from the deterioration of DA-producing neurons. Whenever a neurotransmitter system is dampened, it produces functional loss, either within the same system (movement-related), or within an alternate system that also depends on that neurotransmitter (cognitive or strategic). Evidence from animal models indicates that the capacity to release DA is substantially reduced in the context of both huntingtin mutations (Ortiz et al., 2010, 2011; Tang et al., 2007; Johnson et al., 2006, 2007; Yohrling et al., 2003), and the mitochondria-compromising neurotoxin, 3-nitropropionic acid (3-NP), also used to model HD (Kraft et al., 2009). These 3-NP findings suggest that compromised DA may arise in part from a cellular energy deficit. Yohrling and colleagues (2003) also looked at loss of tyrosine hydroxylase, the rate limiting enzyme in DA production, in the substantia nigra of postmortem HD brains and found over 30% loss, which would functionally compromise DA availability. Therefore, ironically, despite the implications of DA overactivity that may arise from the clinical effectiveness of dampening this neurotransmitter with currently FDA-approved drugs such as tetrabenazine (Guay, 2010; de Tommaso et al., 2011), animal research indicates DA function is, in fact *reduced*, even prior to motor symptom expression (Ortiz et al., 2010, 2011; Johnson et al., 2006; Bibb et al., 2000).

When DA is compromised its modulatory effect is diminished, resulting in abnormal synaptic plasticity in the striatum and also in the frontal cortex, which is known to receive less dopaminergic innervation than the striatum (Cummings et al., 2006). This altered modulatory influence may contribute to the cognitive, strategic, or behavioral-flexibility-type symptoms that arise early in HD (Walker et al., 2008; Montoya et al., 2006; Paulsen & Conybeare, 2005; van Raamsdonk et al., 2005b; Nieoullon, 2002). From this presumption follow expected speculations as to whether stimulating the DA system may provide certain functional benefits. This approach has been attempted with R6/2 mice using methamphetamine in combination with levodopa treatment, which would be expected to promote both dopamine availability and release. However, while short-term improvement of some motor symptoms were found, animals treated with this regimen eventually exhibited increased problems on the rotarod, indicating loss of movement coordination as well as a shortened life-spans (Hickey et al., 2002).

It is important to recognize a distinct but equally important concept that has emerged from DA exploration: DA transmission aggravates oxidative processes that promote neuronal death in the context of the huntingtin mutation (Deyts et al., 2009; Charvin et al., 2005). Thus, interfering with DA transmission may be a rational choice for treatment, since it

would serve to slow deteriorative processes, despite the repercussions for plasticity. In fact, direct research with two neuroleptics: haloperidol (Charvin et al., 2008) and tetrabenazine (Wang et al., 2010), demonstrated a neuroprotective effect on huntington mutation-bearing striatal neurons in isolation. Conversely, stimulation with DA receptor agonists tends to promote neuronal death (Tang et al., 2007). Furthermore, Paoletti and colleagues (2008) compared striatal cells from mouse models, harboring either 7 or 111 CAG repeats in their huntingtin genes, for vulnerability to DA and NMDA glutamate receptor stimulation. They found that the cells with 111 CAG repeats in huntingtin were killed more readily by stimulation with D1 DA receptor agonists, and cell vulnerability was enhanced when this stimulation was combined with NMDA receptor stimulation.

Thus, the presymptomatic rise in extracellular glutamate would be expected to enhance the destructive potential of DA. The Paoletti (2008) study also found that this combination of stimuli leads to intracellular molecular events that activate apoptotic or programmed cell death genes in a manner similar to what occurs in the brains of HD patients. If indeed this is the case in HD patients, treatment strategies may pose a Faustian bargain: *“Would you be willing to compromise your cognitive function in order to delay the loss of movement control?”* Such a dichotomous choice is not necessarily inevitable, but a DA-blocking treatment should not be offered without exploring the consequences. Ideally, a treatment will emerge that balances both the sensitivities to, and the need for, DA transmission.

Even in the absence of DA-compromising medication, the earliest cognitive decline exhibited by HD patients is in set shifting, where subjects must abandon attention to one strategy for another, also referred to as behavioral flexibility (Lawrence et al., 1996; Ho et al., 2003). In fact, direct correlations have been found between pre-HD patients' success with tasks requiring this sort of strategic flexibility and DA activity or control, as measured by positron emission tomography (PET) receptor or transporter binding assessment (Bäckman et al., 1997; Lawrence et al., 1998b). These correlations of pre-HD DA activity and cognitive flexibility are evaluated with tasks such as the Tower of Hanoi and Wisconsin Card Sort.

PET scan-related binding studies using radiolabeled raclopride (a D2 receptor antagonist) also reveal DA receptor malfunctions in pre-HD in both the striatum and the cortex that correlate with cognitive deficits (Pavese et al., 2003, 2010; van Oostrom et al., 2009). Unfortunately, it is practically impossible to distinguish binding to presynaptic versus postsynaptic DA D2 receptors in these regions using PET technology. However, reductions in presynaptic D2 receptors may well suggest either decreased dopaminergic terminals or decreased autoreceptor expression, both of which would distort DA release. The aforementioned study that found a correlation between performance on the Tower of Hanoi task and DA function assessed binding to DA transporters that are largely expressed on DA terminals (Bäckman et al., 1997), suggesting at least some of the reductions in D2 binding may result from terminal loss. Thus, it appears clear that suppressing DA in HD is simultaneously neuroprotective, and yet, more disruptive to cognitive processing; representing a dilemma that will need to be resolved in future treatment efforts.

4. Presymptomatic neuronal activity and plasticity dysfunction

In the context of pre-HD, when abnormal synaptic GLU levels linger for prolonged periods and a diminished DA modulation exists, MSNs must adapt to maintain normal function. To

picture the various converging synaptic influences surrounding MSNs, refer back to Figure 2. In the context of the dramatic modulatory influences present at the MSN synapse, a new appreciation of spike-timing dependent plasticity has been developed that describes different ramifications when signals arrive before or after action potentials in the striatum. The known response patterns were recently reviewed by Fino and Venance (2010), who describe an impressive precision in the sensitivities to input timing exhibited by striatal neurons.

Apparently, striatal neurons exhibit differences in long-term reactions to input (as dramatic as LTP versus LTD) that depend upon whether modulatory inputs arrive before or after action potentials. Impressively, these responses can be realized with subthreshold membrane currents. Of course, GABA release at the terminal regions of MSNs (internal/external globus pallidus, substantia nigra reticulata) necessitates action potential generation. *In vitro* findings indicate that membrane currents occurring before thresholds are reached can influence the direction of subsequent responses. Given that experiments performed with freely-moving animals typically assess action potentials without appreciating sub-threshold activity, a great deal of information may be processed by striatal neurons that is likely to be missed in those experiments that typically rely on extracellular recording (Kiyatkin & Rebec, 1996). This subthreshold activity that can contribute timed depolarizations is nevertheless important for establishing extended response tendencies.

As mentioned, striatal neurons tend to exhibit low spontaneous action potential generation in healthy awake animals in the absence of spontaneous behavior (Sandstrom & Rebec, 2003). Therefore, the large majority of modulatory influences are likely to occur at subthreshold membrane potentials. This expands the potential for disruptive malfunctions resulting from the huntingtin mutation as even minor disruptions to transmitter release will distort pre-threshold synaptic currents.

Given the initial increases in GLU that may surge to higher endogenous levels, it makes sense that there seems to be a presymptomatic sensitivity to NMDA and quinolinic acid (a potent NMDA receptor agonist) among MSNs from YAC128 mice, a popular model with extended pre-HD periods (Graham et al., 2009). Later, at symptomatic stages, these same mice show resistance to quinolinic acid-induced excitotoxicity. This later-stage resistance to GLU excitotoxicity has also been observed in other HD mouse models (Starling et al., 2005; Zeron et al., 2002; Levine et al., 1999). Although this may represent a gradual decrease in sensitivity to GLU stimulation, recordings of striatal neuronal activity demonstrate hyperactivity in symptomatic transgenic R6/2 mice (Rebec et al., 2006) indicating corticostriatal malfunction. In fact, this study treated R6/2 mice with high amounts of systemic ascorbate which seemed to ameliorate the observed deficiency of endogenous striatal ascorbate, and subsequently reduced striatal hyperactivity. This effect suggests that the ascorbate contributes substantially to GLU uptake transport, and can help diminish detrimental excitatory drive when present.

Changes in responses to NMDA stimulation and AMPA stimulation among cortical neurons also takes place in the R6/2 model, and these are more easily seen when neurons are observed in isolation (André et al., 2006). This may be a general type of response that occurs when control of GLU levels or activity is compromised, whereby neurons decrease sensitivity to accommodate the increased basal GLU levels. Interestingly, striatal neuron hyperactivity is not a common feature of all HD mouse models, as the R6/2 mouse shows this but the knock-in 140 (KI-140) mouse does not (Miller et al., 2008b). Also, striatal

hyperactivity is not observed in the transgenic rat model (51-CAG; Miller et al., 2010). However, the capacity to generate coordinated afferent bursts into the striatum, as measured by coordination of firing patterns between pairs of striatal neurons, was disrupted in all these models (Miller et al., 2011). It is likely that this disrupted cortical input originates from aberrant activity within the cortex (Dorner et al., 2009), which was also evidenced in terms of a lack of synchrony between pairs of neurons in the prefrontal cortex of both R6/2 and KI-140 mice (Walker et al., 2008).

It is important to note that these demonstrations of changes in cortical and striatal activity were shown in symptomatic animals. The contributions of cortical disruptions to the time course of behavioral deficit expression make sense when considering the presymptomatic loss of GLU regulation. Cummings and colleagues (2009) found that cortical activity became disrupted with larger and more frequent excitatory postsynaptic potentials in several animal models including the R6/2, YAC128, and KI-140 lines, largely in the presymptomatic stages. In addition, more frequent inhibitory postsynaptic potentials within the striatum could easily disrupt the coordination of cortical input to the striatum. Laforet and colleagues (2001) evaluated the pathological cortical and striatal alterations that precede HD symptoms in both humans and animal models and concluded the contributions of cortical malfunction must be critical.

Human data indicate that cortical metabolic dysfunction occurs among HD patients before brain-scan indications of pathology manifest in the striatum (Rosas et al., 2005; Paulsen et al., 2004; Sax et al., 1996). Combined with evidence that knock-in mouse models with lower CAG repeat numbers lack both cortical neuronal changes and later behavioral changes (Wheeler et al., 2000), while longer repeat containing knock-in models exhibit moderate cortical involvement and moderate behavioral changes (Lin et al., 2001), these data strongly implicate early cortical malfunctions preceding striatal malfunctions and perhaps contributing to their development. Research with restricted expression models, where mutated huntingtin is expressed only in striatal MSNs, show striatal NMDA sensitivities, but these animals do not seem to develop behavioral deficits in the normal progression. This suggests cortical expression of huntingtin mutations are also necessary for pathology (Gu et al., 2007; although see Thomas et al., 2011b).

A related complication that has commanded recent attention is the increased stimulation of extrasynaptic NMDA receptors (expressed outside the postsynaptic zone), arising in pre-HD. Stimulation of these extrasynaptic NMDA receptors seems to elevate apoptotic cascades, while synaptic NMDA stimulation serves to prevent this and maintain neuronal health (Milnerwood et al., 2010; Okamoto et al., 2009; Li et al., 2004). Apparently, the majority of extrasynaptic NMDA receptors in the striatum contain the NR2B subunit that seems to confer a disruptive influence on both MSN survival (Okamoto et al., 2009) and neuronal responses and plasticity, including a tendency to decrease CREB signaling (Milnerwood et al., 2010; Leveille et al., 2008; Hardingham et al., 2002). With the lack of synergy between cortical inputs, increasing chaotic nature of cortical impulses, and the diminished control of the GLU released via transporter malfunctions, it is not surprising that GLU spill-over into extrasynaptic domains increases as HD pathology advances.

MSNs normally exhibit hyperpolarized membrane potentials and decreased input resistances, both of which reduce their tendency to produce action potentials in response to sporadic and temporally uncoordinated input. This leads to their relative silence in healthy

animals in the absence of movement. Findings from electrophysiological explorations of both presymptomatic and symptomatic R6/2 mouse striatal slices show both increased input resistance when stimulated directly and decreased paired-pulse facilitation when stimulated indirectly and repetitively via the cortex (Klapstein et al., 2001). It seems that decreased inwardly rectifying potassium channel expression may account for a corresponding depolarization of the resting membrane potential that occurs in MSNs of these mice, but neither of these are observed during the presymptomatic stage (Ariano et al., 2005). These combined data therefore also suggest that cortical neuronal malfunctions may precede striatal changes.

The most direct demonstration of presymptomatic cortical contributions during the development of HD in an animal model (R6/2 and R6/1 mice; Cepeda, 2003) indicated a progressive decrease in spontaneous currents in striatal neurons, along with increased generation of large synaptic current events that occur prior to symptom expression. This decreased spontaneous current generation is counter-intuitive, given the data described above that indicated reuptake transport control over GLU release is lost in pre-HD mouse models (as early as 10-11 weeks, among KI-150 mice; Figure 3). Nonetheless, a consequence of increased input resistance among MSNs in HD would be increased excitability, and a decreased rheobase (current intensity necessary to reach action potential) expressed in MSNs of pre-HD mice (Klapstein et al., 2001).

Interestingly, a recent series of elegant experiments were performed with pre-HD 51-CAG rats in which *in vivo* electrophysiological measures (taken while animals were under pentobarbital anesthesia) correlated with operant-task deficits in time appreciation (Höhn et al., 2011). The major electrophysiological finding in that study was an increased theta-burst generated LTD among homozygote rats, as demonstrated by before-and-after input-output curves, *despite the lack of any changes in paired-pulse facilitation*. It remains unclear why increased plasticity within the striatum would be responsible for the observed correlated behavioral deficit among homozygote rats in time appreciation. This presymptomatic deficit was exposed by challenging rats to recognize differences in the duration of signals and to respond differentially to short and long signals. The ability to discern differences in the length of these signals could be made more challenging by shortening the long signal, and homozygote rats exhibited more difficulty when this was done than wild type rats.

This sort of compromised appreciation of elapsed time also seems to present among pre-HD patients (Rowe et al., 2010; Paulsen et al., 2008; Beste et al., 2007). In fact, in an extensive review, Matell and Meck (2004) support the hypothesis that a primary role of the basal ganglia depends on the timing of coincident cortical inputs, and subsequent integration that occurs on MSNs, to generate conscious appreciation of time. Their modeling of expected oscillations in striatal neurons, should the cortical input become increasingly varied, seems to predict what was found to occur in actual oscillations recorded in an HD mouse model by Cepeda and colleagues (2003). The lack of synergy in cortical activity, chaotic nature of cortical impulses, diminished GLU control, and disruptions in plasticity, based on extrasynaptic NMDA stimulation, could easily underlie this sort of behavioral disruption.

Generalizations of DA effects on neurons in both the striatum and cortex are more useful in appreciating the changes likely to become relevant during pre-HD. DA has been shown to elicit an increased signal-to-noise ratio when applied in the context of recording from single striatal neurons at the time of stimulation by GLU iontophoresis in freely-moving rats

(Kiyatkin & Rebec, 1996). It is interesting that convergent stimulation of striatal neurons, arising during motor activity, was enhanced by DA iontophoresis, while spontaneous activity unrelated to movement was usually suppressed (Pierce & Rebec, 1995). From this perspective, DA seemed to promote behavior-related striatal activity and diminish the spontaneous activity generally not seen in intact rats that sit quietly, while otherwise awake (Sandstrom & Rebec, 2003). Increases in MSN input resistance, along with increased sensitivities of NMDA receptors and malfunctioning cortical input may lead to increased spontaneous striatal activity in freely-moving symptomatic R6/2 mice (Rebec et al., 2006), as well as reduced coordination of striatal activity (Miller et al., 2011).

One rather mysterious finding presented clearly and convincingly in a review by Fino and Venance (2010), is that LTP can be induced by pairings of corticostriatal input activity to MSN impulses in the order of *post-pre*, while LTD tends to result from pairings of the same activities in the order of *pre-post* (see also Fino et al., 2005). Even more intriguing would be the implications of sub-threshold EPSPs on later firing tendencies seeming to follow the same rules (Fino & Venance, 2010). It is challenging to justify these findings with what might be expected if striatal learning is accomplished by promoting the sensitivity of neurons commonly activated by corticostriatal input in the typical manner. It would seem that in circumstances involving spontaneous activity that is present prior to coordinated efforts of corticostriatal terminals converging on MSNs, the order of action potentials would emphasize *post-pre* relations, while the reverse (*pre-post*) would be the natural order of activity across these terminals, subsequently causing striatal action potentials. If the natural order leads to depression of MSN sensitivity (*pre-post*), while neurons abnormally active before coordinated inputs from corticostriatal terminals become more sensitive (*post-pre*), this would decrease the sensitivity of synapses that function properly and increase the sensitivity of those that do not. DA, which is not likely to be present in quantities as high as those found *in vivo* in the slices of these experiments, seems to do the opposite, promoting activity arising from coordinated corticostriatal input (behavior related), and diminishing unrelated activity (Pierce et al., 1995). If the capacity to release DA declines during pre-HD, it is therefore easy to imagine that both disrupted plasticity and increased noise in striatal transmission could corrupt contributions of the basal ganglia in behavior processing.

Investigations of DA receptors indicate a selective initial, presymptomatic vulnerability of either D2 receptor expression or D2 expressing striatal neurons in human HD patients, followed by progressive loss of D1 receptors at the intermediate and late stages of the disease (Glass et al., 2000). This pattern does not seem to occur in animal models, which seem to diminish both D1 and D2 dopamine receptors more readily (Cha et al., 1998). As has been suggested, DA also participates in inducing pathological responses among striatal neurons which are manifested in electrophysiological explorations of neurons in several mouse models of HD (André et al., 2011). Experiments with HD mouse models have revealed that during pre-HD, specific neurons that can be distinguished as expressing *either* D1 or D2 receptors exhibit abnormal NMDA-related plasticity more exclusively among the D1 expressing neurons, and that this seems to be normalized by reducing DA presence. As these same mice seem to exhibit deficiencies in DA signaling (Bibb et al., 2000), and the recent experiments demonstrating plasticity disruptions were performed in slices where maintenance of endogenous-like levels of extracellular dopamine is dubious, it may be premature to promote DA suppression as a therapeutic strategy, even though it is currently the only FDA-approved treatment for HD.

5. Presymptomatic cognitive dysfunction

The area where problems begin to appear in pre-HD is not in engaging in a chosen behavior, but rather in making the original decision about the best behavior to select. This is especially evident when an individual is faced with an array of seemingly relevant information. Given that there are often multiple strategies to effective problem-solving, choosing the best strategy depends on processing varied input, referencing past experience, and creative thinking. Patients, themselves, often do not recognize their own cognitive limitations; since most daily tasks do not involve being challenged to constantly switch strategies in order to keep up with changing scenarios. In fact, an interesting recent study, involving both pre-HD patients and their regular companions, explored the general perception of apathy, disinhibition, and executive dysfunction, using a modified version of the Frontal System Behavior Scale (FrSBe, Grace & Malloy, 2001). This study demonstrated that even the more severe diagnosis-predicting perceptions of problems were not as readily recognized by patients as they were by their companions (Duff et al., 2010). The lack of awareness that surrounds these early cognitive symptoms can complicate their exploration, evaluation, and intervention development.

As HD develops, there is a progressive decline in internal time assessment, attention, executive function, and short-term memory (Rowe et al., 2010; Beste et al., 2007; Bourne et al., 2006; Paulsen & Conybeare, 2005; Ho et al., 2003). These early cognitive declines arise in pre-HD expressed by patients (Rowe et al., 2010; Ho et al., 2003; Lemiere et al., 2002; Snowden et al., 2001; Kirkwood et al., 2000) and animal models (Höhn et al., 2011; Trueman et al., 2007, 2008; van Raamsdonk et al., 2005b). The diminished appreciation of elapsed time recently shown in HD animal models (Höhn et al., 2011) seems to recapitulate similar problems exhibited by HD patients, who present difficulties when they are required to maintain consistent self-pacing (Rowe et al., 2010).

The most commonly referenced aspect of cognitive decline exhibited in early HD is executive function, manifested as cognitive inflexibility. This cognitive inflexibility, defined as an inability to coordinate the most effective strategic response, or adaptation to apparent changes in circumstances, is related to expressions of apathy that are not easily perceived by preclinical patients but are recognized by their regular companions (Duff et al., 2010). It is easy to imagine that when circumstances become complex and patients become overloaded, frustration and disappointment lead to irritation or apathy, which can be difficult for companions (Quarrell, 2008; Bourne et al., 2006). Assessments of cognitive inflexibility in pre-HD typically requires the use of specialized tasks, such as the Wisconsin Card Sorting and Tower of London tasks (Brandt et al., 2008), whereby patients are challenged to routinely shift strategies, depending on circumstances. Complicated and multifaceted tasks are otherwise rare, and, as such, pre-HD patients are typically able to cope in their day-to-day functions.

Associating difficulties with cognitive flexibility with the known malfunctions of the basal ganglia in pre-HD can be complex. It is perhaps helpful to employ a simplified version of the information-processing circuit, which would proceed as follows (see Figure 1): (1) the whole cortical mantle including both sensations and emotions converge into the striatum (caudate and putamen in humans) which then proceeds to internally process signals within the basal ganglia way-stations, converting the original signals into a modulatory feedback that is directed back towards the frontal cortex where "executive functions" (strategic

behavior decisions) are performed; (2) as the strategies are chosen, the frontal cortex attempts to hold the relevant information in short-term memory and adjusts the plan according to all available appreciated circumstances until finally feeding it forward to primary motor cortex; (3) from there the final decision is generated and sent to lower motor systems to be engaged, but these commands can still be vetoed even after initial movements begin by engaging antagonist muscles (e.g. when a batter starts a swing in baseball only to stop before committing when it becomes clear the ball will fly wide).

Pre-HD patients, when examined with functional magnetic resonance imaging, show metabolic malfunctions in the striatum (Kuwert et al., 1993), the frontal cortex (Wolf et al., 2007), and even the thalamus, all of which are interconnected (Feigin et al., 2007). The degree to which these alterations are evident depends on the cognitive load at the time of measurement (Wolf et al., 2008). To demonstrate this, Wolf and colleagues (2008) challenged pre-HD patients with a working memory task which would be expected to activate the prefrontal cortices (Kane & Engle, 2002). As the working memory load was increased, pre-HD patients presented decreased correlations in activity between the frontal cortices and their striatal activities, similar to the above-described findings of decreased coordination of cortical activity in experimental animals (Cummings et al., 2009; Walker et al., 2008). Similarly, in animal models of pre-HD, cortical neuron control seems to be diminished, largely by the lack of sufficient local inhibition, resulting in uncoordinated activity patterns (Cummings et al., 2009). Cortical neuropathology, and even some minor tissue deterioration observed in terms of thinning, clearly begins to arise during pre-HD (Kipps et al., 2005), as well as at the very beginning of symptom expression (Beglinger et al., 2005), correlating with apparent cognitive difficulties.

While the Wolf (2008) study found a disconnect between activity in the cortex and striatum in tasks requiring working memory, complex planning tasks, that are more related to executive function and cognitive flexibility, also challenge pre-HD patients. Two extensive studies demonstrated that testing pre-HD patients just prior to motoric symptom expression, using tests such as the Wisconsin Card Sorting task, resulted in greater difficulties than both mutation-free and pre-HD subjects who were further from motor symptom expression (Brandt et al., 2008; Snowden et al., 2002). In the first of these studies (Snowden et al., 2002), the data indicated that working memory malfunctions may arise earlier in the disease progression than problems with executive function. Further explorations of executive function suggest that DA plays a pivotal role within both the prefrontal cortex and the striatum. Tests of behavioral flexibility using rats in operant chambers demonstrated that pharmacological manipulations of DA receptor activity, within either the prefrontal cortex (Winter et al., 2009) or the ventral striatum (Haluk & Floresco, 2009) during ongoing behavior, disrupts the animals' capacities to switch patterns of behavior to obtain more reinforcers.

Interesting experiments performed to track the activity of DA-producing neurons in behaving monkeys, suggest that DA neuron activity depends more on the reward-predicting value of cues than on rewards themselves (Waelti et al., 2001). The general tendency when recording from DA neurons, in either the ventral tegmental area (VTA) or substantia nigra pars compacta (SNpc), is that phasic firing increases initially occur at the time of reward delivery, but in time become associated with stimuli that predict reward rather than the rewards themselves. As this change occurs (when they no longer indicate

only the reward) this likely promotes changes in striatal or frontal cortex DA levels that increase via acquired associations with the predictive aspect of cues, which themselves would suggest appropriate behavior strategies.

Given the previously-described enhancements to the coordinated signals and diminishments to uncoordinated signals revealed in studies using DA iontophoresis in intact animals (Kiyatkin & Rebec, 1996; Pierce & Rebec, 1995), these phasic increases in firing would allow DA signals to enhance the neuronal responses in targeted areas by eliminating background noise in a normally-functioning system. Thus, intact DA modulations should be expected to enhance recognition of faulty or maladaptive behavior patterns or at least promote cortically coordinated patterns. Perhaps for this reason, unmedicated Parkinson's patients who are tested early in their disease progression (as DA diminishes well before movement deficits emerge in PD) exhibit impairment in "set-shifting" tasks that require cognitive flexibility (Owen et al., 1992). The previously described declines in presymptomatic DA release capacity exposed in HD animal models (Ortiz et al., 2010, 2011) would predict a DA-related deficit in behavioral flexibility in HD patients. Such deficits were found by Lawrence and his colleagues (1998b), who showed that pre-HD mutation carriers were impaired on cognitive tests in a manner that correlated with DA receptor binding levels measured by PET scans. A positive correlation was found across HD patients and control subjects between success on the Tower of Hanoi task and DA transporter binding (Bächman, 1997). The bottom line of these findings were that HD patients had lower DAT binding, which predicts lower release capacities, as these transporters are expressed on DA neuron terminals in the caudate and putamen (reduced release capacity = reduced success). Set-shifting deficits exhibited by pre-HD patients (Lawrence et al., 1998a) are also likely to depend upon early DA malfunctions.

Another pre-HD difficulty exhibited involves the appreciation of emotion. The area of social emotion appreciation that is most affected by HD was originally believed to be disgust recognition (Hennenlotter et al., 2004; Sprengelmeyer et al., 2006). However, in a more recent study (Johnson et al., 2007), the deficits in emotional processing were broadened to involve the recognition of all negative emotions (i.e., anger, disgust, fear, and sadness). These emotion perception issues are intimately connected to cognitive flexibility, as the same population of DA neurons shown to fire in accordance to reward-predictability (Waelti et al., 2001), also project throughout the limbic system, including the amygdala and prefrontal cortex (Salgado-Pineda et al., 2005) which provide critical support for perception of emotion. The critically important role emotion plays in cognitive processing is well documented (see Damasio, 1996, 1999) and its role in the disruptive cognitive processing observed in pre-HD patients provides a fertile area of research that promises to deliver further insights into the etiology and potential treatments for early stage HD.

6. Conclusions

Despite the discovery of the gene primarily responsible for HD, it is fair to say that our understanding of its etiology is largely preliminary. This is because the gene and corresponding protein seem to be incredibly complex and involved in multiple aspects of neuronal physiology. Delineating HD-related neurophysiological deficits will necessitate appreciation of events that occur before neuronal death and the onset of motoric symptoms. Determining the primary, pre-compensatory malfunctions will likely suggest treatment

strategies that can target and alleviate these without becoming entangled in compensation cascades. Furthermore, coordination and normalization of neuronal activity in key brain regions such as the frontal cortex, caudate, and putamen would seem to require restoration of healthy GLU management. Experiments with ceftriaxone show promise in that regard along with other efforts to boost GLU reuptake.

The DA system in HD represents a greater puzzle since there are clearly pros and cons to the currently FDA approved strategies that mostly diminish DA in the earlier stages of HD, which may alleviate emerging motor symptoms but may also aggravate cognitive dysfunction. As such, it is important to consider the cognitive domain in the context of neuronal activity and transmission deficits, since these circuits seem to show changes before motoric disruptions emerge. If sensitivity to DA or NMDA transmission could be diminished, these systems could be normalized far more effectively. Attempts to decipher the dynamic transmission interactions and elucidate the role of mutant huntingtin should continue in parallel to testing potential treatments in animal models of HD.

In this chapter, we have identified several key sources of physiological disruptions and integrated them into a theoretical framework to help explain the early expressions of cognitive malfunction in this disease. Isolating the physiological disruptions underlying pre-HD is critical for devising more effective treatments. Until it becomes possible to repair damaged or mutated genes, the most effective therapies will be those that help relevant neuron populations resume their normal roles and compensate for the extensive dysfunction driven by abnormal huntingtin protein physiology.

It is likely that both the preliminary malfunctions, such as cognitive decline and the later-stage loss of movement control depend upon similar physiological alterations within the same neuronal populations. However, potential treatments given during earlier stages of HD should be more efficacious as they will benefit from greater neuron numbers that would be available prior to widespread neuron death. As such, investigations into the early pre-HD may provide the greatest hope of effectively slowing the progress of this devastating disease.

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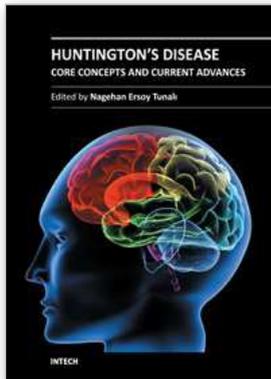
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Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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