Corticostriatal synaptic adaptations in Huntington's disease

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Abstract

Huntington's disease (HD) is a progressive neurodegenerative disorder that profoundly impairs corticostriatal information processing. While late stage pathology includes cell death, the appearance of motor symptoms parallels more subtle changes in neuronal function and synaptic integration. Because of the difficulty in modeling the disease and the complexity of the corticostriatal network, understanding the mechanisms driving pathology has been slow to develop. In recent years, advances in animal models and network analysis tools have begun to shed light on the circuit-specific deficits. These studies have revealed a progressive impairment of corticostriatal synaptic signaling in sub-populations of striatal neurons, turning classical excitotoxicity models of HD upside down. Disrupted brain derived neurotrophic factor signaling appears to be a key factor in this decline.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded polyglutamine repeat in the huntingtin gene [1–4]. HD patients are plagued by progressive motor dysfunction. Initially, patients manifest uncontrolled, choreic "dance-like" movements [4]. This hyperkinetic phase is followed by a hypokinetic phase where purposeful movement is difficult [5]. Cognitive dysfunction parallels the declining motor control.

Consistent with the motor symptoms, postmortem studies of HD brains have found the basal ganglia to be a major site of pathology, in spite of the widespread expression of mutant huntingtin (mHtt) [2,6–8]. The earliest neuronal pathology in the basal ganglia is in the caudate and putamen (collectively referred to the striatum in rodents). Less profound pathology also is found in the cerebral cortex and thalamus, both structures that innervate the striatum [4].

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The biphasic progression of symptoms in HD patients – and in many animal models – is consistent with the view that principal striatal GABAergic spiny projection neurons (SPNs) are not uniformly susceptible to mHtt [5,7]. Striatal SPNs can be divided into two roughly equally sized groups that differ along a number of dimensions, including peptide expression and axonal projection [9]. The first signs of pathology in HD patients are in one of these groups: indirect pathway SPNs (iSPNs) [7]; iSPNs anchor the basal ganglia network that suppresses contextually inappropriate movements. Later in the disease, direct pathway SPNs (dSPNs) that express substance P are affected [4]; dSPNs anchor the basal ganglia circuit that promotes contextually appropriate movements. Thus, HD neuropathology and symptoms align nicely with what is known about the functional circuitry of the striatum.

What is less clear is why SPNs should be particularly vulnerable to mHtt. A longstanding view posits that glutamate excitotoxicity is the culprit [10,11]. Support for this hypothesis comes primarily from the fact that intrastriatal injection of the glutamate receptor agonist quinolinic acid (an NMDAR agonist) mimics many characteristics of HD in rodents [12]. The proposition that NMDA receptors (NMDARs) drive neuronal loss in HD also is consistent with a large literature showing how this might happen [11,13]. However, more recent work has cast doubt on this theory. As outlined below, studies in animal models of HD suggest that there is a progressive loss of excitatory corticostriatal glutamatergic input to SPNs with advancing age, rather than a progressive growth of this input. In addition, there is evidence that the other major excitatory glutamatergic input to SPNs from the thalamus is also lost [14,15]. While these observations don't unequivocally kill the excitotoxicity hypothesis, they make it less plausible.

As the excitotoxicity hypothesis has fallen in favor, another hypothesis has risen to prominence. Several lines of study suggest that something goes awry with cortical trophic support for the striatum. Brain derived neurotrophic factor (BDNF) is synthesized by cortical pyramidal neurons innervating the striatum, transported to the striatum and released [16]. BDNF activation of TrkB receptors on SPNs is necessary to maintain normal dendritic and synaptic function [17–19]. The expression of mHtt can impair corticostriatal BDNF signaling, suggesting that SPNs 'wither' in HD.

In what follows, we briefly outline recent developments that have led to our current opinion about striatal excitatory synaptic dysfunction in HD. The review is not all inclusive and readers are referred to a number of other recent reviews that cover similar or complementary aspects of the expansive HD literature [20–24].

A plethora of genetic mouse models of HD - which one is best?

Since the genetic locus of HD was identified in 1993 [1], a number of genetic models have been developed in mice. These models differ significantly in their genetic strategy, have different rates of progression and types of neuronal pathology (see reviews by [2,24,25]) (Fig. 1). The first models expressed an exon 1 fragment of mHtt with a large number (110–150) of CAG repeats (e.g., the R6/2 model) [26]. These mice are rapidly progressing, manifesting motor symptoms within a few weeks of birth and die prematurely. Subsequently, full length mHtt models were constructed with varying CAG repeat lengths (YAC72 (72

repeats), YAC128 (128 repeats) and BACHD (97 repeats). These models have slower disease progression with a clear dependence upon expansion length and gene dosage [27–29]. In the last few years, more biologically faithful knock-in models have been created (Q140, zQ175 lines). These models also manifest a slowly progressing pathology [30–32].

Do these models mimic the human disease? As discussed above, humans transition through a hyperkinetic (choreic) and then a hypokinetic state [5]. Biphasic behavioral changes like this are seen in many HD models, but not all. In particular, only some slowly progressing models manifest a hyperkinetic phase, whereas all have a hypokinetic phase. The short repeat fragment model (R6/1) and full-length YAC72, YAC128, Q94 and Q140 models have an early hyperkinetic phase before ultimately becoming hypokinetic [25,30]. Why BACHD and zQ175 models do not have this early phase is not clear [29,32]. The absence of a hyperkinetic phase in the zQ175 model is puzzling, as it was derived from Q140 model.

One possible explanation for the discrepancy is that mHtt does not affect brain circuits controlling movement sequentially, but rather affects them in parallel. If the rate of disease progression within each of these circuits is independently affected by the genetic approach used to introduce mHtt, then the duration of each motor phase could vary. The early hyperkinetic phase should be the most sensitive to this kind of parallel process. For example, let's suppose that the hyperkinetic phase is dependent upon reduced activity in the indirect pathway and the hypokinetic phase is dependent upon reduced activity in the direct pathway. A slower rate of progression in the direct pathway than the indirect pathway would yield the human pattern of staging. But if the rates of progression are similar is some models (e.g., BACHD), then the hyperkinetic phase would be absent.

Since no one mouse model perfectly recapitulates all aspects of the human HD condition, which model is the best? In principle, the heterozygous CAG140 and zQ175 models most accurately model the human condition as they place a single copy of full length mHtt in its native genomic locus; these models display a progressive behavioral phenotype and recapitulate many synaptic and anatomical pathologies present in more rapidly progressing models (Fig. 1). However, it must be acknowledged that the choice of the most appropriate model for a particular study will depend upon many factors.

Do SPNs get too much or too little excitatory input in HD?

For years, the pathology in HD was envisioned to be a consequence of glutamatergic excitotoxic damage to SPNs, as injection of NMDA receptor (NMDAR) agonists within the striatum produced a pattern of pathology resembling that found in HD brains [12]. But the ability of NMDAR agonists to phenocopy striatal changes does not mean that they mimic pathogenesis. Was there evidence that glutamatergic signaling in the striatum was altered in genetic models of HD? The first direct physiological evidence that something was changed came from the analysis of spontaneous excitatory events in ex vivo brain slices from the R6/2 HD mouse; in these studies, the frequency of spontaneous synaptic glutamate release onto SPNs increased and then decreased (Fig 1) [33]. Without knowing the identity of sampled SPNs (dSPNs or iSPNs) or the source of released glutamate, little can be inferred

about why this happened or what it might mean for the striatal circuitry, but what these studies do show is that glutamatergic signaling is changing in HD models.

Does the glutamatergic input to both iSPNs and dSPNs change? Recall that in humans, iSPNs appear to be the most vulnerable to the disease process. The loss of iSPN functional integrity has long been thought to be responsible for the hyperkinetic features of early stage HD, as iSPNs anchor the indirect pathway responsible for movement suppression [9,34]. More recent studies have begun to address this question by crossing HD genetic models with BAC transgenic mice in which dSPNs or iSPNs express green fluorescent protein (GFP) [35–37]. Using this strategy Levine's group suggested that the early increase in spontaneous glutamate EPSC frequency was specific to dSPNs, which would increase direct pathway excitability and promote hyperactivity. However, Andre et al. also showed that evoked glutamatergic responses were substantially larger in iSPNs in young HD models, but dSPN responses were normal [35]. These results suggest that early in the evolution of the disease, there is a complex set of pre- and post-synaptic changes taking place at SPN glutamatergic synapses, which might not map cleanly to the early and late motor symptoms of HD.

Nevertheless, these studies show that synaptic glutamate receptor function is not changing in a way that is consistent with an excitotoxicity model of HD. The 'out' here for the excitotoxicity model is that it does not specify that *synaptic* glutamate receptors are driving pathology. In the last decade it has become clear that while synaptic NMDARs promote neuronal viability, extrasynaptic NMDARs are coupled to signaling cascades that promote degeneration and death [11,38]. In a landmark paper, Milnerwood and Raymond demonstrated that the abundance of extrasynaptic GluN2B-containing NMDARs rises in HD SPNs [39]. Subsequently, they have shown that the insertion of extrasynaptic NMDARs is regulated by calpain- and striatal enriched protein tyrosine phosphatase (STEP) [40] in aged YAC128 mice (Fig. 2). Moreover, the elevation in extrasynaptic NMDARs appears to occur first in iSPNs [37], then ultimately spreads into both SPN types [41], establishing a parallel with the evolution of pathology in humans.

The proposition that there is a progressive engagement of extrasynaptic NMDARs driving pathology is also consistent with changes in astrocytic function seen in the HD models. Clearance of glutamate from the synaptic cleft is controlled by astrocytic uptake through transporters [42]. In symptomatic HD mice, astrocytic expression of glutamate transporter 1 (GLT1) is down-regulated [43]. In principle, this should lead to more robust engagement of extrasynaptic NMDARs (Fig. 2). In addition, recent work in aged R6/2 HD mice has shown that astrocytes down-regulate the expression of a key K^+ channel (Kir4.1), resulting in an elevation in extracellular K^+ concentration [44]. Elevating extracellular K^+ should depolarize SPNs and make it easier to remove the Mg^{2+} block of NMDARs. Thus, astrocytic dysfunction could potentiate the negative impact of rising extrasynaptic NMDARs (Fig. 2).

As plausible as this scenario seems, work in the last year has cast doubt on the proposition that extrasynaptic NMDARs are driving late stage striatal pathology in HD. Gladding et al (2014) found that while intrastriatal injection of quinolinate (an NMDAR agonist) induces neuronal death in young presymptomatic (6 week) YAC128 mice, the same injection into aged (1 year) YAC128 mice had little effect [45]. The resistance to NMDAR excitotoxicity

in the older HD mice appeared to be due to an attenuation of the ability of extrasynaptic NMDA receptors to activate pro-apoptotic p38 mitogen-activated protein kinase (p38 MAPK). In young mice, extrasynaptic NMDARs robustly engaged p38 MAPK, whereas in older HD mice, this linkage seemed to be attenuated. The change appeared to be dependent upon processing of STEP (Fig. 2).

Although this work suggests that NMDARs are not driving HD pathology, the issue is not resolved. Work by Perez-Otano et al. argues that striatal expression of GluN3A in very old (16 month) YAC128 mice is critical to late stage synaptic dysfunction and neurodegeneration [46]. Sorting out these seemingly discrepant findings is one of the challenges facing the field.

Is BDNF at the center of striatal dysfunction in HD?

There is a significant body of literature suggesting that mHtt impairs the ability of cortical pyramidal neurons to provide the striatum with needed BDNF, leading to striatal 'withering' [20,47,48]. There is no question that cortical BDNF expression and axonal transport can be impaired by mHtt. However, these studies have relied largely upon over-expression of mHtt in cell culture models, not in vivo or ex vivo approaches in mouse HD models. Those studies that have been done in mouse models that support this conclusion have focused upon BDNF mRNA abundance assays that have used less than optimal strategies for quantitation.

Another prickly issue with this model is that both dSPNs and iSPNs express the receptor for BDNF – TrkB receptors [49] – and receive overlapping cortical inputs [50]. How then, if non-cell autonomous factors are driving striatal HD pathology, does selective vulnerability come about?

Recent work using very different approaches argues that there are corticostriatal BDNF signaling deficits in HD models, but that these deficits are in the postsynaptic response to BDNF, not its delivery, release or binding to TrkBRs [37,51]. In 6 month old BACHD and heterozygous zQ175 knock-in mice (before striatal cell loss) neither cortical nor striatal BDNF mRNA or protein was abnormal. Neither was striatal TrkBR expression or activation of TrkBRs by stimulation of corticostriatal axons. However, TrkBR activation of Akt – a key signaling kinase in prosurvival pathways – was impaired [37].

To pinpoint why this was the case, a functional assay for TrkBR signaling was developed using the fact that corticostriatal long term potentiation (LTP) requires SPN TrkBR signaling (Fig 2) [18]. This led to the conclusion that TrkBR signaling through phosphoinositide-3 kinase (PI3K) was blunted specifically in HD iSPNs due to up-regulation of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) [37]. It also was found that p75 neurotrophic factor receptor (p75NTR) signaling was necessary for PTEN-mediated attenuation of TrkBR signaling. Why PTEN is up-regulated initially in iSPNs remains to be determined (Fig 2) [37], but one intriguing possibility is that D2 receptors, which are expressed by iSPNs and not dSPNs, are involved, as D2 receptors have been shown to elevate the engagement of several downstream targets of p75NTRs [52]. Whether this turns

out to be the mechanism or not, these studies support the proposition that neuronal phenotype is a determinant of the staging of HD pathology.

A deficit in iSPN TrkBR signaling and LTP induction is consistent with the progressive attenuation of corticostriatal glutamatergic signaling described in HD models (Fig. 1). While the earliest deficits in striatal TrkBR signaling have been found in iSPNs, it is likely that as the disease progresses, this deficit will spread to dSPNs. It is of some note that HD patients have a lower incidence of cancer and PTEN (the proximal culprit in impaired TrkBR signaling) is a tumor suppressor [53]; this suggests that mHtt might ultimately induce PTEN up-regulation broadly. Not only might this lead to impaired TrkBR signaling in dSPNs, but the deficit should appear in cortical pyramidal neurons and neurons in other regions of the brain.

An important implication of these findings is that delivery of small molecule TrkBR agonists is unlikely to be effective in HD. Rather, targeting p75NTR signaling should be more effective as well as less burdened by side-effects, as this receptor is developmentally downregulated and has a restricted tissue distribution.

It also should be remembered that the cerebral cortex and striatum form part of a richly connected network involved in movement and thought control [9]. It is impossible to affect one component of this network without affecting other components (Fig 3) [54]. For example, expression of mHtt in a discrete cortical neuron populations induces pathology in neighboring neurons [55]. Since BDNF production and release are activity dependent [56,57], deficits in corticostriatal signaling are very likely to ultimately lead to deficits in BDNF signaling within other components of the circuit, most importantly the cerebral cortex [47,58].

Does GABAergic input to SPNs change?

For some time it has been thought that GABAergic input to SPNs increased in HD models, nominally compensating for their increased intrinsic excitability [59]. This conclusion was based upon a reported increase in the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) in a random sample of SPNs in symptomatic R6/2, YAC128 and CAG140 HD models [60]. Subsequent work in BAC-eGFP transgenic mice found that the increase occurred first in dSPNs and then later in iSPNs [61].

The trouble with measurements of sIPSCs is that they are heterogeneous. This is particularly problematic in the striatum where the GABAergic circuitry is very complex. SPNs have GABAergic synapses arising from other SPNs and a heterogeneous group of interneurons (there are at least 3 classes). Because spontaneous IPSCs are a mixture of miniature IPSCs (whose frequency depends upon terminal release probability) and spike-drivien IPSCs, there is no way of knowing which circuit elements are driving changes in sIPSC frequency or why.

Recent work using another approach has challenged the general notion that GABAergic inhibition of SPNs is increased in HD models. Dvorzhak et al. found that in both R6/2 and zQ175 models, GABAergic responses evoked by minimal local stimulation were reduced in

SPNs [62]. The reduction was attributable to an up-regulation in mGluR5 mediated endocannabinoid (eCb) production, resulting in presynaptic CB1 receptor activation and suppression of GABA release. Although the identity of the presynaptic axons was not determined, it is not unreasonable to make the conjecture that they were collaterals from neighboring GABAergic SPNs given the strong CB1R mediated suppression of GABA release [63]. Consistent with this interpretation, Cepeda et al. [36] found that collateral connectivity between SPNs was attenuated in the R6/2 model. In this same study, the authors found that optogenetic activation of fast-spiking interneurons (FSIs) evoked larger responses in HD SPNs. Stimulation of another major interneuron input to SPNs – from PLTSIs – yielded similar amplitude responses, but the spontaneous activity of these interneurons was elevated in HD brain slices. Taken together, these studies suggest that GABAergic input to SPNs from interneurons is elevated in the HD striatum, whereas that arising from collaterals is diminished.

As both FSIs and PLTSIs appear to be part of a corticostriatal feedforward inhibitory circuit [64], the changes described could serve to limit the duration of the striatal response to cortical glutamatergic excitation. In contrast, collateral feedback between SPNs would be expected to limit the spatial dimensions of the cortically evoked striatal activity. That said, there are some fundamental unknowns in this equation. One is that it is far from clear whether it is appropriate to characterize $GABA_A$ receptors as inhibitory. At rest, Kir2 K^+ channels dominate the SPN conductance profile (though there is evidence their somatic density may be reduced in HD SPNs [65]), holding the membrane potential in a 'down' state near the K^+ equilibrium potential (~ -90 mV). Although it has not been determined rigorously in adult SPNs, the Cl^- reversal potential is sure to be more depolarized than this, probably in the range of -65 to -70 mV [66]. Thus, GABAergic input is very likely to be depolarizing to quiescent SPNs. The shunting effect of open $GABA_A$ receptors could counter-balance this effect to some extent when there is temporally coincident excitatory input [67]. But this effect is short-lived and because the local depolarizing effect of GABA should globally collapse the electrotonic structure of SPNs, glutamatergic inputs that trail the GABAergic input should be amplified. This could bring NMDA receptors into a voltage range where Mg^{2+} block is less potent. Sorting how these interactions occur in SPN dendrites still faces technical hurdles but advances like multi-color opsins [68] should make profitable study feasible soon.

Another unresolved issue is the impact of tonic, extrasynaptic $GABA_A$ receptor currents in the HD models. Recent data suggest they may be decreased in R6/2 iSPNs [36]. Tonic currents are prominent in SPNs [69,70] and help set the membrane potential and input resistance of dendrites – key determinants of synaptic integration. Neurogliaform GABAergic interneurons, which have not been examined in HD models to date, appear to exert a strong influence on these receptors [71]. Also, if there is astrocytic dysfunction in HD, GABA could easily 'overflow' from synaptic sites to these receptors.

Are there other plastic changes in HD?

Although recent studies provide a rich working framework for understanding how mHtt alters the moment-to-moment activity in the corticostriatal network, there are fundamental

questions about long-term plasticity of synapses that remain unanswered. For example, is corticostriatal LTP the only form of synaptic plasticity altered in the HD striatum? This seems unlikely. The best understood form of synaptic depression at both cortical glutamatergic and intrastriatal GABAergic synapses requires postsynaptic group I metabotropic glutamate receptor (mGluR) mediated production of endocannabinoids (eCBs), which then diffuse to the presynaptic terminal, bind to presynaptic CB1 receptors (CB1Rs), and reduce neurotransmitter release probability [72–74]. One of the earliest molecular changes in HD patients is a decrease in CB1R expression in both the striatum and cortex [75,76]. It is unknown if corticostriatal synaptic depression is altered in HD, but recent work showed that genetically correcting CB1R down-regulation in SPNs rescues axospinous (largely corticostriatal) synapse loss in HD mice [77]. Why would elevating SPN CB1R expression increase glutamatergic axospinous synapses? Perhaps the effect is indirect. Much of the intrastriatal GABAergic input to SPNs comes from recurrent collateral synapses [64]. Suppression of SPN collateral GABA release might engage homeostatic mechanisms to increase glutamatergic innervation (leading to more spines). This makes sense if GABAergic synapses were excitatory. As mentioned above, this is not so far-fetched since SPNs rest about 20 mV more hyperpolarized than the Cl$^-$ reversal potential (GABA$_A$ receptors are Cl$^-$ permeable channels) [66]. In this scenario, suppression of GABAergic signaling could lead to SPN hypoexcitability, triggering homeostatic up-regulation of glutamatergic synapses [78].

Finally, though striatal glutamatergic hypoexcitability is a common theme among late stage HD models, it is far from certain that this hypoexcitability is entirely synaptic in origin. For example, dendritic morphology and ion channel composition exquisitely shape how SPNs integrate glutamatergic inputs [79,80]. Alterations in either of these parameters might diminish the response to activation of glutamatergic synapses. In fact, the near universal increase in SPN input resistance (Fig. 1) [21] might reflect an intrinsic homeostatic adaptation of this sort. Although SPN dendrites are too small to directly record, two photon laser scanning microscopy, optogenetics and two photon uncaging techniques make these regions accessible to investigation [79,80]. These approaches should make the role of intrinsic mechanisms in HD pathogenesis clearer in the near future.

Concluding Remarks

The development of new mouse models and tools for analyzing brain networks and synapses has led to fundamental new insights into the mechanisms driving HD pathogenesis. This is most evident in our understanding of how mHtt affects the corticostriatal network. In the last few years, the field has moved from thinking that striatal pathology in HD was driven by excitotoxic mechanisms to the view that, if anything, it is a hypoexcitability disorder driven by impaired corticostriatal signaling. Although there remain fundamental gaps in our understanding of synaptic dysfunction in HD, the tools at our disposal should accelerate progress toward filling these gaps. With that understanding should come the first generation of effective therapies for HD.

Acknowledgments

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• Special Interest

•• Outstanding Interest

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Highlights

1. Advances in genetic mouse models and tools to probe neural circuits have led to new insights about pathogenic mechanisms in Huntington's disease (HD).

2. Recent work suggests that there is a progressive decline in corticostriatal glutamatergic signaling in HD.

3. The progressive decline in corticostriatal glutamatergic signaling appears to be driven by both cell-autonomous and network mechanisms.

4. Deficits in brain derived neurotrophic factor signaling have emerged as a major factor in synaptic pathogenesis and the death of striatal neurons in HD.
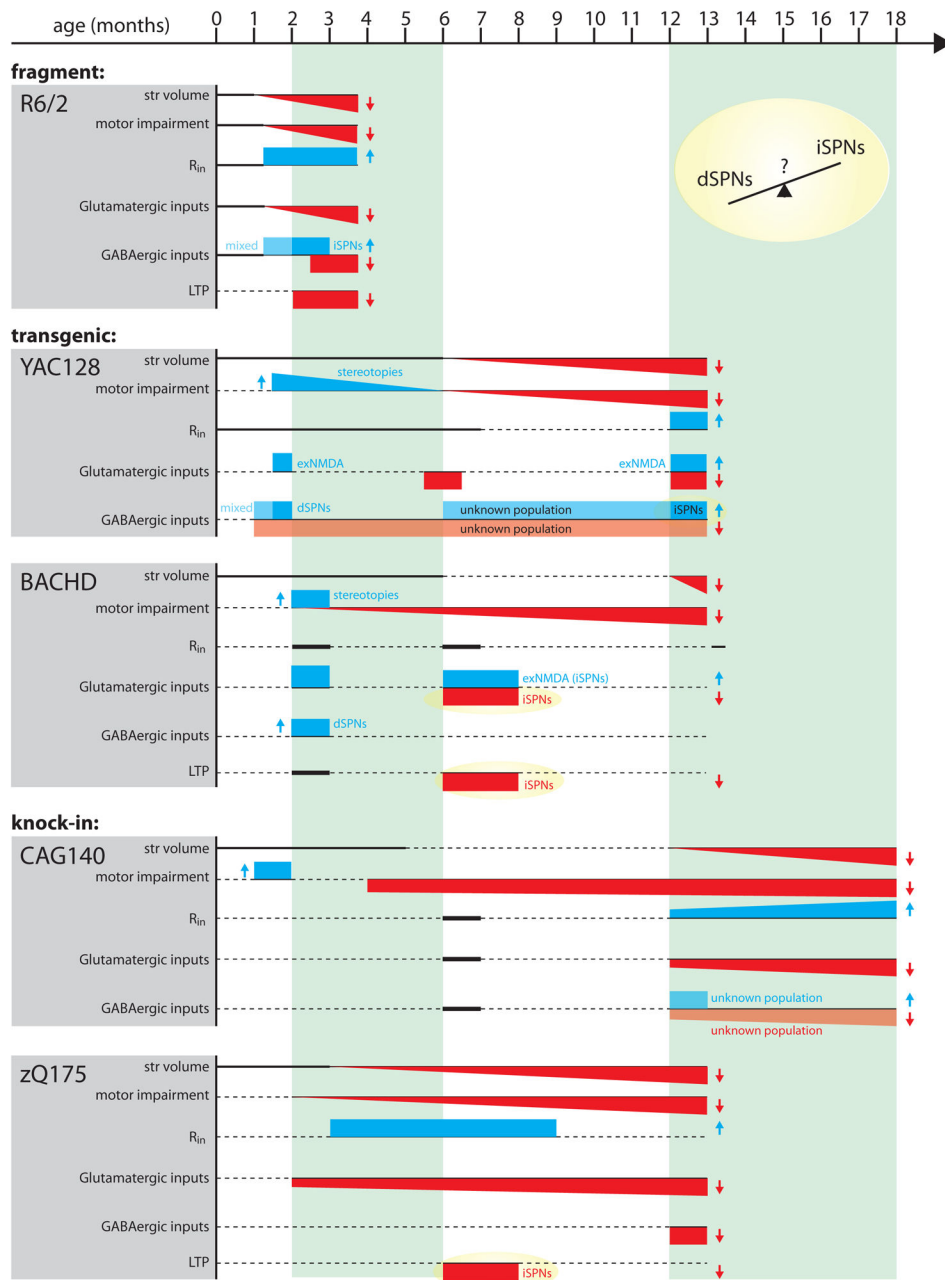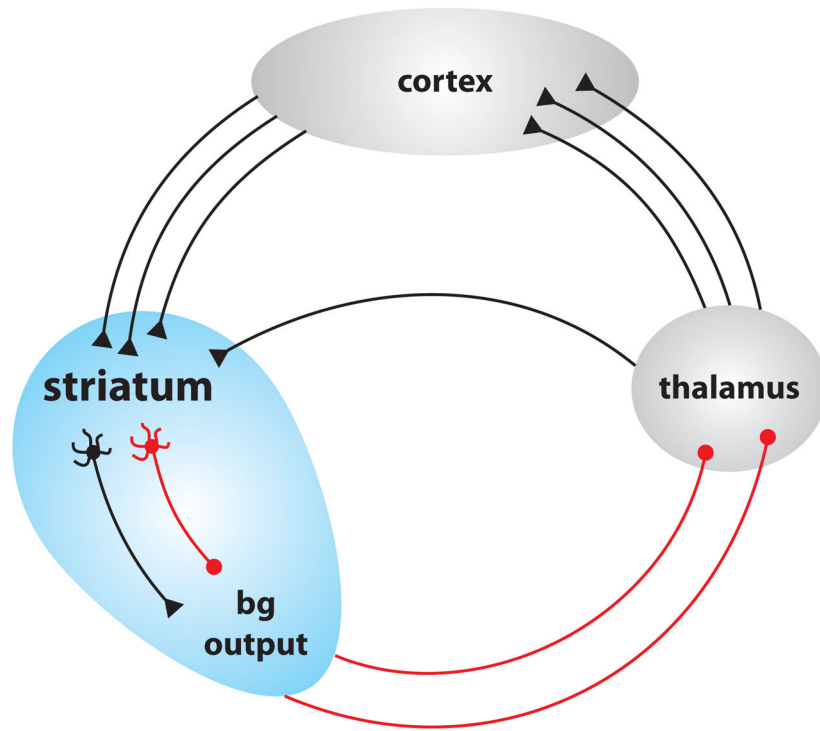
Figure 1.
Representation of disease progression in 5 genetic mouse models of HD. Parameters include striatal volume (a measure of frank cell loss), motor impairments (if not specified, based on rotorod performance and open field locomotor activity), input resistance (R_{in}), glutamatergic inputs (studies measuring both spontaneous and evoked glutamatergic events are included; exNMDA refers to extrasynaptic NMDA receptor engagement), GABAergic inputs (studies measuring both spontaneous and evoked GABAergic events are included) and LTP (long term potentiation). Unless otherwise noted, physiological changes are from mixed populations of iSPNs and dSPNs. Rectangles represent binned time points. Angled lines

represent progressive alterations. Red-filled downward directed shapes and blue-filled upward directed shapes represent decreases and increases, respectively. Lightened colors represent unidentified SPN populations. Thick solid horizontal lines indicate no change was observed. Dashed horizontal lines indicate data at the corresponding time points were not reported in the referenced studies. Data compiled from [2,29,31–33,35,39,41,59,81–84].
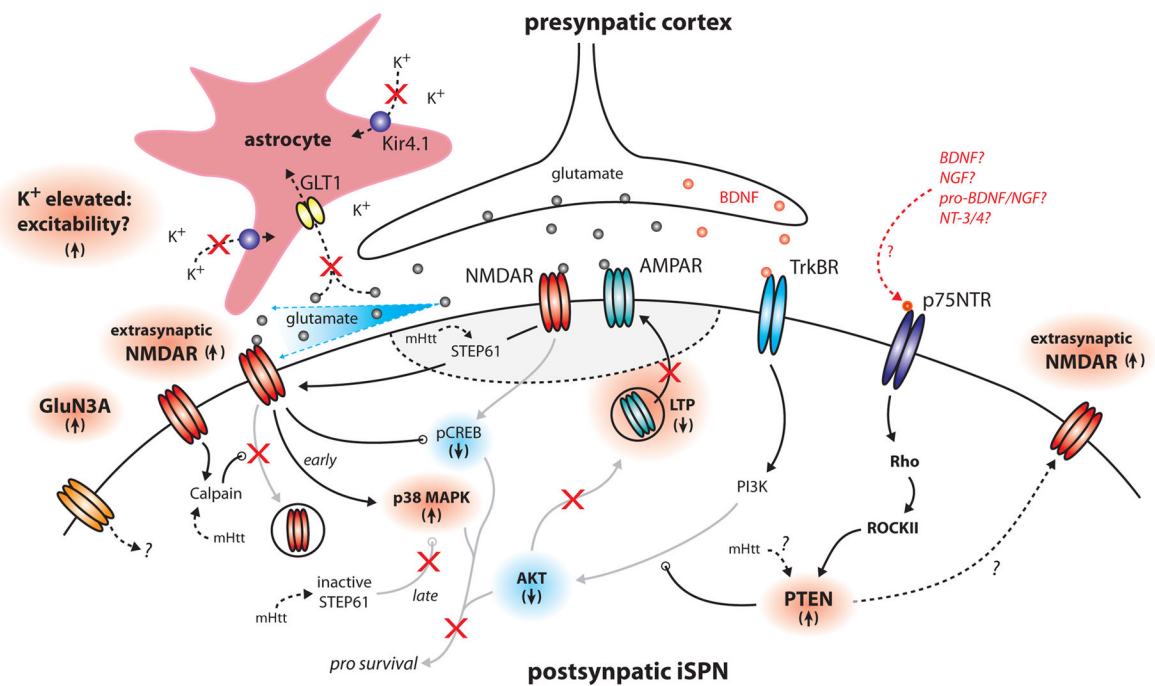
Figure 2.
Schematic diagram of alterations in iSPNs leading to attenuated LTP, NMDA receptor signaling and cell death. STEP61, striatal enriched protein tyrosine phosphatase 61; pCREB, phosphorylated cyclic adenosine monophoshate response element; Rho, Rho A small GTPase; ROCKII, Rho-associated, coiled-coil containing protein kinase II; NGF, nerve growth factor; pro-NGF, pro-nerve growth factor; pro-BDNF, pro-brain derived neurotrophic factor; NT-3/4, neurotropic 3/neurotrophic 4 [37,39,40,43–46].

Figure 3.
Schematic representation of the basal ganglia-thalamus-cortex feedback loop.