Introduction

Neurodegenerative disorders, such as Huntington’s, Alzheimer’s, and Parkinson’s diseases, affect millions of people worldwide and currently there are few effective treatments and no cures for these diseases. Transgenic mice expressing human transgenes for huntingtin, amyloid precursor protein, and other genes associated with familial forms of neurodegenerative disease in humans provide remarkable tools for studying neurodegeneration because they mimic many of the pathological and behavioural features of the human conditions. One of the recurring themes revealed by these various transgenic models is that different diseases may share similar molecular and cellular mechanisms of pathogenesis. Cellular mechanisms known to be disrupted at early stages in multiple neurodegenerative disorders include gene expression, protein interactions (manifesting as pathological protein aggregation and disrupted signaling), synaptic function and plasticity. Recent work in mouse models of Huntington’s disease has shown that enriching the environment of transgenic animals delays the onset and slows the progression of Huntington’s disease-associated motor and cognitive symptoms. Environmental enrichment is known to induce various molecular and cellular changes in specific brain regions of wild-type animals, including altered gene expression profiles, enhanced neurogenesis and synaptic plasticity. The promising effects of environmental stimulation, demonstrated recently in models of neurodegenerative disease, suggest that therapy based on the principles of environmental enrichment might benefit disease sufferers and provide insight into possible mechanisms of neurodegeneration and subsequent identification of novel therapeutic targets. Here, we review the studies of environmental enrichment relevant to some major neurodegenerative diseases and discuss their research and clinical implications.

Abbreviations

Aβ, amyloid-β peptide; AD, Alzheimer’s disease; apoE, apolipoprotein E; APP, amyloid precursor protein; arc, activity-regulated cytoskeleton-associated protein; BDNF, brain-derived neurotrophic factor; DARPP-32, dopamine and cAMP regulated phosphoprotein, 32 kDa; HD, Huntington’s disease; MPTP, 1-methyl-4-phenyl-4-propionoxy-piperidine; PD, Parkinson’s disease; PS, presenilin.
with predominantly genetic causes, such as Huntington’s disease (HD) and other trinucleotide repeat expansion disorders, as well as those occurring in both familial and nonfamilial forms, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD). The recent discovery that the onset and progression of the autosomal dominant disease, HD, which was once thought to be the epitome of genetic determinism, can be modified by environmental factors, has focused new attention on the crucial area of gene–environment interactions. While understanding gene mutations and molecular mediators of pathogenesis is a key step in the development of novel therapeutics for these currently incurable diseases, we also need to understand in detail the environmental modulators for each disorder in order to inform drug development as well as to guide the advancement of preventative medicine and occupational therapies via evidence-based environmental interventions. This review will focus on the neurodegenerative disorders HD, AD and PD, and experimental data from mouse models in particular. However, the general concepts illustrated and hypotheses generated are likely to be relevant to many other disorders.

**Genetic and epigenetic contributors to HD**

HD is an autosomal dominant neurodegenerative disorder, with onset usually in midlife (30–45 years), first described by George Huntington in 1872. Patients with HD exhibit a devastating triad of symptoms, often beginning with psychiatric problems, such as depression and mood swings, as well as cognitive symptoms, including diminished short-term memory and concentration. As the disease progresses, the movement disorder sets in, including overt symptoms such as chorea, characterized by writhing involuntary movements of the head, trunk, and limbs. The ability to walk, speak, and swallow deteriorates, and death follows usually 10–20 years after disease onset [1]. Neuropathological hallmarks of HD at postmortem include dramatic loss of neurons and associated molecular markers in the striatum and cerebral cortex (although other brain areas can also be affected) and the formation of inclusions of aggregated protein in neuronal nuclei and neuropil [2,3].

In 1983, Gusella and colleagues found a polymorphic DNA marker genetically linked to the HD gene on chromosome 4p16.3 [4]. After a decade of work, an international team identified the mutation causing HD: an expanded CAG repeat in the gene encoding a protein that came to be known as huntingtin [5]. Normal individuals have 10–34 CAG repeats in this gene. Individuals with more than 39 repeats develop HD, whilst in people with 35–39 repeats the disease is variably penetrant [6]. The expanded CAG repeat in HD translates into an expanded polyglutamine tract in the N-terminal region of the huntingtin protein. Repeat length correlates with age of onset and accounts for 50–70% of variance in onset [7]; however, patients with identical repeat lengths can often exhibit initial symptoms at different ages, implicating genetic and environmental modifiers in regulating disease onset. Siblingship accounts for 11–19% of the additional variance in age of onset [8] – evidence for familial modifiers independent of CAG repeat length. Several genes influencing age of onset have been identified, including a polymorphism in an allele for a noncoding TAA repeat in the GluR6 kainate receptor [9,10], apolipoprotein E ε2ε3 genotype [11], and a polymorphism in a polyglutamine tract in the transcription factor CA150 [12]. Environmental influences also affect HD progression and age of onset; these will be discussed below.

There are at least eight other neurodegenerative diseases caused by CAG repeat expansions, encoding polyglutamine tracts in different proteins, suggesting that these diseases may involve overlapping molecular mechanisms of pathogenesis involving toxic gain-of-function of the mutant proteins [13]. For unknown reasons, which cannot be attributed to the expression patterns of the disease genes, the majority of these CAG repeat expansion neurodegenerative diseases are spinocerebellar ataxias (SCA1, 2, 3, 6, 7, 17), except for HD, dentatorubralpallidolusian atrophy and spinobulbar muscular atrophy (or Kennedy’s disease). While HD will be the only trinucleotide repeat disorder to be discussed in detail in this review, it is expected that insights into CAG/glutamine repeat mediated pathogenesis, and associated environmental modulators, in HD will have relevance to other members of this major family of neurodegenerative disorders.

Determination of the genetic cause of HD allowed the development of numerous transgenic animal models of the disease. These crucial in vivo models make it possible to study early pathogenesis, protein aggregation, and neurodegeneration, and to test possible therapeutics. HD models have been developed in species as diverse as yeast, worms, mice, and rats [1]. The first successful transgenic mouse models of HD, called the R6 lines, were developed in the mid-1990s. These mice, which express the promoter and exon 1 of the human huntingtin gene containing an expanded CAG repeat (115 to > 150 repeats), develop neuropathology as well as motor and cognitive symptoms similar to those seen in clinical HD [14]. Early neuro-
pathological investigations of these mice led to the discovery of intracellular inclusions [15], formed via pathological protein aggregation, which have subsequently been found in the brains of patients with HD [3] and other polyglutamine diseases and may represent a common neurodegenerative mechanism. The R6 mice also exhibit reduced brain and body weight similar to human HD [14,16]. Furthermore, they have striatal and cortical atrophy without extensive cell death [17], allowing detailed examination of mechanisms mediating neuronal dysfunction, which appears to be sufficient to induce disease symptoms.

Progressive behavioural deficits of the early onset (long CAG repeat) R6/2 line of mice are well characterized. They exhibit a rear-paw clasping motor phenotype when suspended by the tail and develop deficiencies of locomotive behaviour and motor skill, assessed using tests such as the accelerating rotarod [16,18–20] (Fig. 1). Consistent with clinical findings, it appears that the onset of cognitive abnormalities, such as spatial memory deficits in the Morris water-maze, precede motor symptoms [18,20]. The R6/1 line of transgenic mice have a shorter CAG repeat than the R6/2 line and consequently have later symptom onset. This R6/1 model was used in the original experiments exploring the effects of environmental enrichment on HD mouse models, which will be discussed below.

Environmental enrichment in wild-type rodents affects behaviour, synaptic circuitry, and transcriptional regulation

While an enormous amount of research in the past decade, harnessing the power of genomics and transgenic technology, has focused on how individual genes contribute to brain development, function, and behaviour in standard-housed laboratory animals, much less work has involved the examination of gene–environment interactions, despite the fact that virtually all medical disorders involve both genetic and environmental factors. The vast majority of the many thousands of different mouse lines around the world are housed in ‘standard’ cages, with bedding on the floor and unlimited access to food (usually pellets) and water. In order to enrich the housing conditions of laboratory animals, and thus enhance the quantity and complexity of environmental stimulation, various objects of different shapes, sizes and composition can be added to the home cages, or the animals can be regularly removed and placed in environmental enrichment chambers. Mice and rats, which are by far the most commonly used animals in biomedical research, are innately curious and exploratory (in the absence of anxiogenic stimuli) and will actively explore and interact with these enriched environments.

The effects of environmental enrichment on the brains of wild-type animals have been studied since the 1960s when Rosenzweig, Bennett, and colleagues showed that rats exposed to enriching experiences had measurable changes in neuroanatomy and neurochemistry [21]. Subsequent work has detailed how environmental enrichment changes the brain and how these concepts can be used in humans to promote successful ageing, recovery from brain damage, and the delay of symptoms of degenerative disease.

A range of behavioural tests indicate that environmental enrichment enhances memory function in learning tasks, even in ageing animals. In particular,
In the injured rat brain, cortical gene expression changes in response to enrichment include increases of greater than threefold, with increased capacity for injury-associated plastic changes in the enriched cortex [38].

Environmental enrichment also causes molecular changes in the developing brain. Enriching animals from birth accelerates development of the visual system at the molecular, behavioural, and electrophysiological levels. Earlier eye opening and accelerated development of visual acuity with enrichment is accompanied by increased expression of BDNF and glutamic acid decarboxylase and earlier cAMP response element-mediated gene expression [39–41]. Behavioural and molecular deficits induced by lead exposure in young rats are reversed by enrichment, even when it starts after exposure occurs. Specifically, N-methyl-D-aspartate (NMDA) receptor subunit NR1 deficits are rescued and BDNF is up-regulated in the hippocampus with enrichment in lead-exposed animals [42].

As discussed above, enrichment induces numerous gene expression changes, but the underlying causes of these gene expression changes remain elusive. Up-regulation of immediate early genes with enrichment may lead to the observed gene expression changes and anatomical changes. Two candidate genes, encoding activity-regulated cytoskeleton-associated protein and nerve growth factor induced-A, are up-regulated in the neocortex, hippocampus, and striatum of enriched animals [43,44].

Environmental stimulation can be analyzed according to its different components that could have differential contributions to its effects on gene expression, neuronal morphology and function, as well as behaviour. Mice interact with their environment and each other, providing motor, sensory, social, and other cognitive stimulation (i.e. spatial map formation, learning, and memory). Socially housed animals perform better in the water-maze than those housed singly [25], indicating the importance of social interaction as an environmental factor. Physical activity has also been shown to enhance spatial learning in rodents and reduce oxidative stress in old rats [28,45]. Voluntary exercise in the form of wheel running increases hippocampal neurogenesis, up-regulates the expression of BDNF, and improves spatial learning [46–48].

Enriched environments ameliorate the HD phenotype in transgenic mouse models

In the R6/1 mouse model of HD, we found that home cage environmental enrichment (Fig. 2) delays the onset of motor symptoms and prevents associated cerebral atrophy [49]. In this initial study, we observed...
that nonenriched (standard-housed) HD mice begin to fail the static rod test (i.e. they could not turn around on a suspended rod to return to safety) at around 60 days of age. Enriched HD mice were able to complete this task up to 100 days of age, a dramatic delay in symptom onset. Similarly, the enriched HD mice developed the rear-paw clasping phenotype, indicative of HD-associated motor deficits, much later than nonenriched HD mice. Onset of the clasping phenotype in nonenriched R6\(^{1/2}\) mice occurs at around 10 weeks of age, when over half of the mice tested display the phenotype. Over half of the enriched mice clasped after 20 weeks of age, indicating a 10 week delay in clasping onset [49]. The density of ubiquitin-positive intracellular inclusions counted in striatum by using light microscopy was not significantly affected by home-cage enrichment at 5 months of age, nor was the decrease in striatal volume changed. However, the cerebral volume loss around the striatum (consisting predominantly of neocortex) was ameliorated by environmental enrichment [49]. Furthermore, there is evidence that environmental enrichment can lead to a reduced diameter of protein aggregates in the cortex, as visualized by using electron microscopy [50] and light microscopy (TL Spires, JH Cha and AJ Hannan, unpublished observation).

The delay of onset and progression of symptoms with environmental enrichment was also confirmed in the more severe (early onset) R6/2 mouse model of HD [51] and, more recently, in N171-82Q transgenic HD mice [52]. This suggests that these findings of gene–environment interactions in HD are robust, and can be demonstrated in multiple animal models.

These exciting data in HD mouse models suggested that therapy based on the principles of environmental enrichment might also benefit humans with HD. Indeed support for the beneficial effects of environmental stimulation in humans was provided by subsequent research, which highlighted six case studies of remotivation therapy that led to improved physical, mental and social functioning in patients with HD by providing a more fertile, stimulating environment [53]. A study which compared a genetically verified pair of monozygotic twins with identical CAG repeat lengths in the huntingtin gene also suggested a possible role for environmental factors in clinical HD [54]. A recent study, involving a large number of Venezuelan kindreds and rigorous assessment of symptom onset, has also implicated environmental factors in modulating the age of onset in clinical HD [55]. However, the nature of these environmental modulators remains unknown, and will require extensive epidemiological studies of the type described below for Alzheimer’s disease.

Another interesting issue raised by the original experiments involving enrichment of R6/1 HD mice was the contribution of the cortex to the effects of the environment on symptoms [49]. As striatal volume and inclusion density were unaffected, despite dramatic behavioural benefits, and peristriatal cerebral volume loss was prevented by enrichment, we hypothesized that the cortex might be crucially involved in mediating the effects of enrichment and might play a larger role in the neuropathological progression of HD than previously believed. In support of this idea, unilateral transplantation of wild-type donor cortex into R6/1 HD anterior cortex after resection of the native cortex resulted in a delay in onset of the hind-limb clasping motor phenotype [56].

To further investigate how enriching the home-cage environment of R6/1 HD mice ameliorates the behavioural phenotype, we measured the levels of specific proteins in the striatum, hippocampus, and cortex of enriched and nonenriched mice [57]. In this study, the mice were examined at 5 months of age, a point when 100% of nonenriched HD mice exhibit the clasping phenotype and fail the static rod test, while only half of enriched HD mice clasp and 20% fail the rod test. To confirm the beneficial effects of enrichment in the cohort of mice tested for protein levels, an accelerating rotarod test was used. Nonenriched HD mice could only remain on the accelerating rotarod for half as
long as control mice, and environmental enrichment completely rescued this deficit. At this age, environmental enrichment rescued striatal and hippocampal BDNF protein deficits in HD mice [57]. Antero-medial cortical levels of BDNF protein were unaffected. As most of the BDNF protein present in the striatum is transported from cortical neurons [58], we hypothesized that cortico-striatal transport may be disrupted in HD and that enrichment rescues this phenomenon (Fig. 3). BDNF is an extremely important neurotrophin, known to regulate synaptic plasticity, neurogenesis and neuronal survival.

BDNF expression is also down-regulated in clinical HD [59,60] and in the R6/2 mouse model [61]. Rescuing levels of this important neurotrophin may underlie some of the behavioral benefits of enrichment. Interestingly, dietary restriction in HD transgenic mice also increases BDNF levels in the striatum and cortex and slows disease progression, and essential fatty acids administered from conception onwards also ameliorate motor deficits in HD mice [62,63]. The beneficial effects of both dietary restriction and enrichment may be partially mediated by the BDNF regulation of adult neurogenesis [64,65], although the role of BDNF in synaptic plasticity and other aspects of neuronal function is also likely to contribute to these environmentally mediated effects.

The recent finding that hippocampal cell proliferation is decreased in R6/1 HD mice [66], combined with the known effects of enrichment on neurogenesis [67], suggests that this may be one avenue whereby the therapeutic effects of environmental stimulation are mediated. This hypothesis is strengthened by the recent demonstration that pharmacological rescue of hippocampal neurogenesis deficits in HD mice is associated with the amelioration of cognitive disorders [68]. The relevance of this work to the clinical setting is emphasized by the recent finding of altered neurogenesis in the brains of patients with HD at postmortem examination [69].

Dopamine and cAMP-regulated phosphoprotein, 32 kDa (DARPP-32) is a key regulator of intracellular signaling and neurotransmitter receptor modulation in striatal and cortical neurons expressing dopamine receptors. Enrichment also rescued cortical and striatal DARPP-32 deficits in HD mice [57], suggesting that the down-regulation of DARPP-32 is causatively associated with pathogenesis and that the molecular rescue of this signaling pathway may contribute to the beneficial effects of environmental enrichment.

Transcriptional dysregulation is widespread in HD and mouse models of the disease resulting in deficits of neurotransmission and synaptic signaling [2,61,70–73]. Environmental enrichment rescues the deficits of BDNF and DARPP-32, as outlined above, as well as of cannabinoid CB1 receptors [57,74], which may underlie some of the observed behavioural benefits [13]. We are currently exploring other gene–environment
interactions in HD, in the hope of using environmental manipulations as powerful tools to dissect cause and effect in disease pathogenesis.

The search for molecular and cellular changes associated with the environmental stimulation of transgenic and wild-type mice is ongoing, and may lead to the development of ‘enviromimetics’ – novel neuroprotective therapeutics which mimic or enhance the beneficial effects of specific environmental stimuli [75,76]. It is anticipated that such enviromimetics may have therapeutic efficacy, not only in HD, but also in other neurodegenerative diseases in which comparable gene–environment interactions occur.

Morphological changes in neurons are associated with HD and are replicated in mouse models of the disease. Environmental enrichment could act, as seen in wild-type animals, to increase synaptogenesis or dendritic branching, which would also affect behaviour. A Golgi study of striatal and cortical neurons showed no gross morphological differences between R6/1 HD and wild-type control brains in soma and dendrite anatomy. As expected, HD mice have a decreased dendritic spine density compared to wild-type mice [77]. Environmental enrichment slightly increased spine density in wild-type animals, but did not rescue the HD-associated defect [77], indicating abnormalities in experience-dependent plasticity in the HD mice. In support of this idea, there is in vitro evidence of electrophysiological abnormalities in brain slices from several mouse models of HD [20,78–81]. Furthermore, in vivo deficits of cortical plasticity have recently been demonstrated in the barrel cortex (which processes somatosensory information from the whiskers) of motor presymptomatic R6/1 HD mice and correlated with somatosensory discrimination learning deficits [82,83].

Environmental enrichment may also be beneficial in AD

AD, another neurodegenerative disorder, affects over 12 million people worldwide and is the leading cause of dementia [84,85]. Patients with AD suffer memory loss, cognitive decline, and eventually psychiatric problems. Neuropathological characteristics of AD, first described by Alois Alzheimer, include senile plaques, neurofibrillary tangles, and dramatic atrophy of vulnerable brain regions [86]. Neuronal morphology is also altered during the progression of AD. Synapses and dendritic spines are lost, dendritic trees degenerate, aberrant sprouting occurs, and dystrophic neurites form [87]. As seen in HD, there is evidence that environmental factors influence the onset and progression of this devastating disorder.

Senile plaques are extracellular lesions that consist mainly of fibrillar amyloid β peptide (Aβ) [88], a toxic peptide which is produced from the cleavage of amyloid precursor protein (APP) [89,90]. Mutations in the gene coding for APP have been linked to rare familial forms of AD [91,92]. Similarly, mutations in presenilins (PS) 1 and 2, which participate in the cleavage of APP to form Aβ [93,94], are also associated with familial AD [95–99]. Neurofibrillary tangles consist of intracellular paired helical filaments of hyperphosphorylated tau protein [100,101]. No tau mutations have been associated with AD; however, mutations in the tau gene are associated with frontotemporal dementia and the formation of neurofibrillary tangles [102]. Genetic risk factors also contribute to nonfamilial, or sporadic, AD. Inheritance of the apolipoprotein E (apoE) e4 allele increases the risk of contracting AD [103,104], while the e2 allele appears protective [105]. The APP, PS, apoE and tau mutations associated with the formation of plaques and neurofibrillary tangles have been used to develop transgenic animal models of AD and tauopathy, which exhibit impaired memory and learning as they age [106,107]. These models allow, among other things, the exploration of the interactions of the environment with neurodegenerative pathology.

Environmental factors appear to play a role in the risk of developing AD and interact with genetic risk factors. Head trauma or traumatic brain injury account for 2–20% of AD cases [108–110], and the apoE e4 genotype exacerbates the increased risk [111]. Epidemiologic evidence from large cohorts of ageing participants indicates that a higher level of education, a higher level of occupational attainment, participation in cognitively stimulating activities, and participation in leisure activities all reduce the risk of developing sporadic AD [112–117]. The cognitive reserve hypothesis holds that these enriched lifestyles may result in more efficient cognitive networks, thus providing a cognitive reserve that delays the onset of the clinical manifestations of dementia [118].

Several studies also indicate that diet can have a protective effect against AD [119]. Intake of omega-3 fatty acids from fish, vitamins E, B6, B12, and folate, and a moderate intake of red wine, are all associated with a reduced risk of developing sporadic AD [120–124]. Conversely, high calorie intake, and risk factors for vascular disease and stroke, increase AD risk [125,126], and statins, which lower cholesterol levels, appear protective [127].

In an APP-expressing mouse model of AD, long-term environmental enrichment was found to result in global improvement in cognitive function, without a reduction in Aβ deposition [128]. A report by the same
group indicated that enrichment did not ameliorate the APP-associated changes in dendritic branching [129], similarly to our results in HD mice [77]. However, environmental enrichment studies of other mouse models suggest that the gene–environment interactions observed may be dependent on the exact nature of transgenes and experimental paradigms used [130,131], and there is ongoing debate as to which transgenic mouse models of AD are most accurate. A recent study has found that the environmental enrichment of a double mutant line (APP<sub>swe</sub> × PS1<sup>D</sup>E9) leads to reduced Aβ levels and amyloid deposition [132].

A recent study in patients with mild cognitive impairment and AD explored the effects of enrichment on patients by providing a cognitive-motor program twice a week, for 3.5 h each session [133]. This program, which emphasized cognition, provided transitory cognitive stabilization and long-term mood benefits to the participants.

**PD: more environmental than genetic?**

We shall touch only briefly on gene–environment interactions in PD, as the complexities of epidemiology [134] and the limitations of the current animal models of PD, make interpretation of causative factors difficult. Nevertheless, enormous progress has been made in identifying genetic factors contributing to PD in recent years [135]. Low concordance for clinical disease in monozygotic twins indicates environmental influences on PD [136], and the finding that accidental exposure of humans to the drug MPTP (1-methyl-4-phenyl-4-propionoxypiperidine) causes a Parkinson-like syndrome, spurred much research into the environmental contributors to PD [137]. The environmental factors that have been found to be associated with PD in epidemiological studies include neurotoxins, although it is not yet clear why dopaminergic neurons of the substantia nigra should be particularly vulnerable in this disease, nor why intuitively detrimental activities such as smoking (and perhaps other addictive behaviors) might be associated with a lower incidence of the disease. Animal models of PD have been developed by the injection of neurotoxins, such as 6-hydroxydopamine, paraquat, MPTP, and rotenone – all of which appear to inhibit mitochondrial complex I, thus inducing neurodegeneration [138,139]. Several environmental factors are associated with PD risk in epidemiological studies. Caffeine consumption is associated with a reduced risk of PD in men [140], and cigarette smoking is associated with a reduced risk of PD in both men and women [141], although it is not clear whether these actions are protective or whether people predisposed to PD have an aversion to habit-forming behaviours. Pesticide exposure strongly associates with higher risk for PD [142,143].

**Conclusions**

In summary, evidence from mouse models of HD and AD indicate that environmental enrichment can modulate disease onset and severity (Table 1).

<table>
<thead>
<tr>
<th>Model</th>
<th>Phenotype</th>
<th>Effect of enrichment</th>
<th>Reference</th>
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<tbody>
<tr>
<td>HD (R6/1)</td>
<td>Rear-paw clasping</td>
<td>Delayed onset</td>
<td>[49]</td>
</tr>
<tr>
<td>HD (R6/1)</td>
<td>Rotarod deficit</td>
<td>Amelioration</td>
<td>[57]</td>
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<tr>
<td>HD (R6/1)</td>
<td>Peristriatal cerebral volume loss</td>
<td>Amelioration</td>
<td>[49]</td>
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<td>HD (R6/1)</td>
<td>Striatal volume loss</td>
<td>No effect at 5 months</td>
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<td>HD (R6/1)</td>
<td>Striatal BDNF deficit</td>
<td>Amelioration</td>
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<td>HD (R6/1)</td>
<td>Hippocampal BDNF deficit</td>
<td>Amelioration</td>
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<td>HD (R6/1)</td>
<td>Striatal DARPP-32 deficit</td>
<td>No effect at 5 months</td>
<td>[57]</td>
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<tr>
<td>HD (R6/1)</td>
<td>Cortical DARPP-32 deficit</td>
<td>Amelioration</td>
<td>[57]</td>
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<tr>
<td>HD (R6/1)</td>
<td>Decreased dendritic spine density and length</td>
<td>No effect at 5 months</td>
<td>[77]</td>
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<tr>
<td>HD (R6/1)</td>
<td>Protein aggregate formation</td>
<td>Decreased diameter</td>
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<td>HD (R6/2)</td>
<td>Rotarod deficit</td>
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<td>HD (R6/2)</td>
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<td>Amelioration</td>
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<td>HD (N171-82Q)</td>
<td>Rotarod deficit</td>
<td>Amelioration</td>
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<td>HD (N171-82Q)</td>
<td>Shortened lifespan</td>
<td>No effect</td>
<td>[52]</td>
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<td>HD (N171-82Q)</td>
<td>Weight loss</td>
<td>Amelioration</td>
<td>[52]</td>
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<tr>
<td>AD (APP&lt;sub&gt;swe&lt;/sub&gt;)</td>
<td>Spatial cognitive deficit</td>
<td>Cognitive improvement</td>
<td>[128]</td>
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<tr>
<td>AD (APP&lt;sub&gt;swe&lt;/sub&gt; × PS1ΔE9)</td>
<td>Increased Aβ levels accelerated amyloid deposition</td>
<td>Amelioration</td>
<td>[132]</td>
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The striking behavioural benefits in HD mice are mediated, at least in part, by environmental rescue of cortical volume loss [49], specific protein deficits [57] and neurogenesis deficits [66,68]. Evidence from HD patients undergoing remotivation therapy, studies of large kindreds with HD, and evidence from monozygotic twins with HD, also indicate the powerful effects of environmental factors on this autosomal dominant disorder [53–55]. Epidemiologic studies in AD and PD, more prevalent neurodegenerative diseases with both genetic and environmental contributors, also show that in these diseases environmental factors such as education, cognitive stimulation, leisure activities, diet, and smoking can modify disease risk (Table 2). Furthermore, cognitive-motor stimulation can provide benefits to patients with AD [133]. The similar effects of environmental factors on several diseases indicate that environmental modulators act on common pathways in neurodegenerative disease, such as transcriptional dysregulation and abnormal protein interactions (Fig. 4).

It is clear from the evidence described in this review and clinical epidemiology [144], that the understanding of gene–environment interactions is not only important in HD, AD and PD, but also in a range of other neurodegenerative disorders, including non-Alzheimer dementias, motor neuron disease and spinocerebellar ataxias. Genetic and environmental factors, and their complex interplay, must also be responsible for the variability in brain ageing and associated cognitive...
decline in all human populations, forming a template on which specific disease gene mutations and environmental risk factors are overlayed. The use of genetically accurate animal models and appropriate environmental manipulations will allow us to experimentally explore gene–environment interactions in the healthy and diseased states, and the associated relationships between brain function and behavior.

In the short term, research on environmental enrichment of mouse models, epidemiologic studies, and small studies modifying the environment of AD and HD patients, all indicate that individuals who are genetically susceptible and sufferers of these devastating neurodegenerative conditions could benefit from mental, physical, and social stimulation. In the longer term, these studies provide insight into brain plasticity during the disease process and open avenues of research towards preventative strategies, treatments and cures.

Acknowledgements

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References

Gene–environment interactions in neurodegenerative disease

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