

# Nature, nurture and neurology: gene–environment interactions in neurodegenerative disease

## FEBS Anniversary Prize Lecture delivered on 27 June 2004 at the 29th FEBS Congress in Warsaw

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### Keywords

Alzheimer; BDNF; environmental enrichment; Huntington; neurodegeneration

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(Received 21 January 2005, accepted 21 March 2005)

doi:10.1111/j.1742-4658.2005.04677.x

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.

### Introduction

Neurodegenerative disorders are a major cause of mortality and disability, and as a result of increasing life

spans represent one of the key medical research challenges of the 21st century. The last couple of decades have seen enormous advances in our understanding of molecular pathogenic mechanisms mediating disorders

### Abbreviations

A $\beta$ , amyloid- $\beta$  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-propionoxypiperidine; 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 Eε2ε3 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 claspings 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.

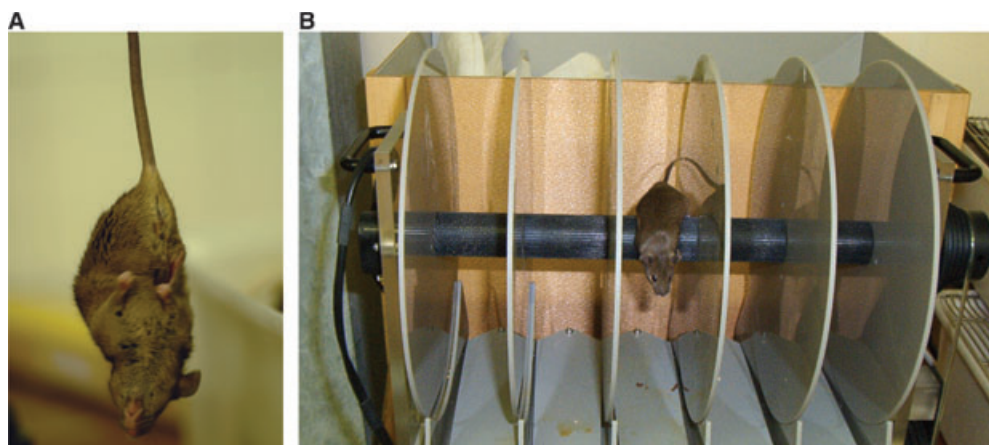
### Environmental enrichment in wild-type rodents affects behaviour, synaptic circuitry, and transcriptional regulation

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,



**Fig. 1.** R6/1 transgenic mice exhibit characteristic motor phenotypes. (A) Rear-paw claspings when briefly suspended by the tail is one classic sign of Huntington's disease (HD) symptoms in transgenic mice. (B) An accelerating rotarod is used to assess motor deficits in these mice, as loss of motor coordination will lead to a reduced time spent balancing on the rotarod (relative to wild-type littermates) as it accelerates.

hippocampal-dependent spatial memory in mice and rats is improved by enrichment [22–26]. The mediators of improved memory with enrichment remain unclear; however, morphological and chemical changes associated with enrichment have been discovered, which probably contribute to memory enhancement. Globally, enrichment generally decreases body weight because nonenriched animals are less active and eat more than their enriched counterparts, at least in rats [27]. Early experiments in rats showed that cortical weight and thickness, however, increase with enrichment [21]. This increase in cortical size could be caused either by enhanced dendritic branching and synaptogenesis (i.e. expanded volume of cortical neuropil) or increased neurogenesis. Support for the former theory came in the 1970s, largely from work by Greenough and colleagues. They performed experiments showing increases in dendritic branching, synaptic contact areas, and numbers of synapses per neuron in the occipital cortex of rats after exposure to an enriched environment [28]. Recent molecular evidence suggests that environmental enrichment may induce synaptogenesis in widely distributed brain regions, both cortical and subcortical [29].

As well as causing synaptogenesis, environmental enrichment can affect neurogenesis in the brain – even in adults. In the 1960s, Altman & Das reported neurogenesis in several areas of the adult mammalian brain, including the hippocampus [30]. However, the concept of adult neurogenesis was initially treated with a certain degree of skepticism (or ignored completely) until the 1990s when several technical developments allowed the characterization of new neurons in specific regions of the adult brain [31]. Environmental enrichment was found to increase hippocampal neurogenesis and promote the survival of newly generated neurons [26,28,32]. There are extensive ongoing investigations into molecular and cellular mechanisms of adult neurogenesis, as well as the function of the adult-born neurons [33].

Environmental enrichment also up-regulates the transcription of genes encoding neuronal proteins that are important for neuronal plasticity, learning, and memory [34]. Neurotrophins, in particular, are up-regulated by enrichment. In rats, brain-derived neurotrophic factor (BDNF) and nerve growth factor proteins are both up-regulated in the hippocampus following enrichment [32,35,36], and enrichment influences changes in the level of BDNF in response to stroke [37]. Although gene expression changes with enrichment have been most extensively studied in the hippocampus, neocortical changes are also observed. In the injured rat brain, cortical gene expression

changes in response to enrichment include increases of greater than threefold, indicating increased capacity for injury-associated plastic changes in the enriched cortex [38].

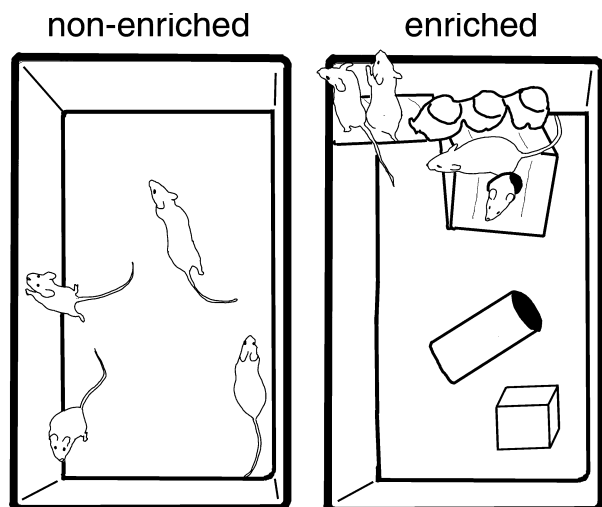
Environmental enrichment also causes molecular changes in the developing brain. Enriching animals from birth accelerates development of the visual system at the molecular, behavioural, and electrophysiological levels. Earlier eye opening and accelerated development of visual acuity with enrichment is 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



**Fig. 2.** Home-cage environmental enrichment consists of adding novel objects of different shapes, sizes and composition (e.g. paper, plastic and wood) to the mouse cage, and changing them regularly, to provide a complex environment in which levels of sensory, cognitive and motor stimulation are enhanced relative to standard housing.

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 clasp phenotype, indicative of HD-associated motor deficits, much later than nonenriched HD mice. Onset of the clasp phenotype in nonenriched R6/1 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 clasp 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).

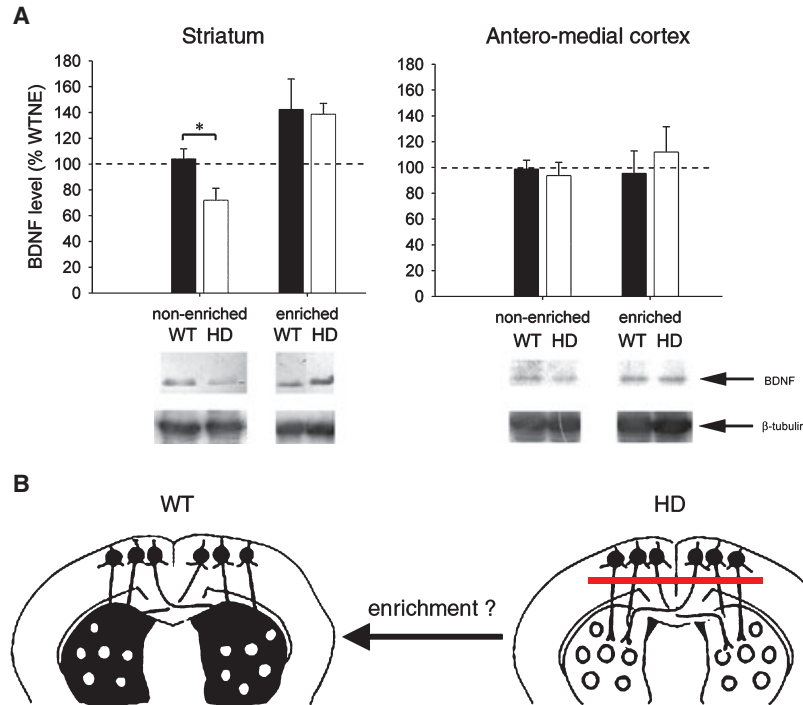
The delay of onset and progression of symptoms with environmental enrichment was also confirmed in the more severe (early onset) R6/2 mouse model of

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 clasp 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 clasp 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



**Fig. 3.** Striatal brain-derived neurotrophic factor (BDNF) protein deficits in R6/1 Huntington's disease (HD) mice are rescued by environmental enrichment (A), while there is no effect of enrichment on BDNF levels in anterior cortex. As most striatal BDNF is anterogradely transported from cortical neurons, this indicates a deficit in cortico-striatal axonal transport that is rescued by enrichment (B).

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 deficit [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  $\beta$  peptide ( $A\beta$ ) [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  $A\beta$  [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)  $\epsilon 4$  allele increases the risk of contracting AD [103,104], while the  $\epsilon 2$  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  $\epsilon 4$  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  $A\beta$  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> × PS1ΔE9) 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

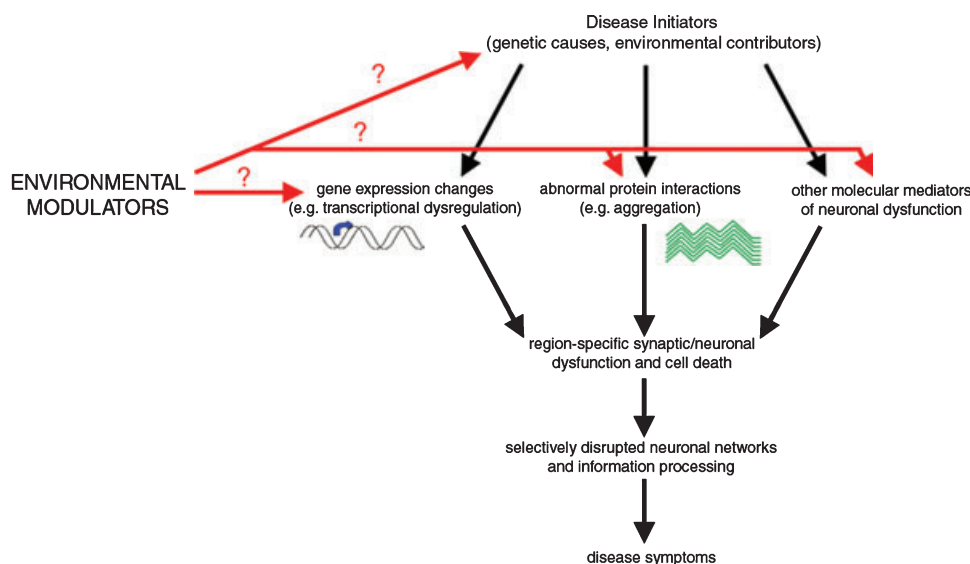
In summary, evidence from mouse models of HD and AD indicate that environmental enrichment can modulate disease onset and severity (Table 1)

**Table 1.** Enrichment rescues neurodegenerative phenotypes in transgenic mouse models. Aβ, amyloid-β peptide; AD, Alzheimer's disease; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; DARPP-32, dopamine and cAMP regulated phosphoprotein, 32 kDa; HD, Huntington's disease.

Model	Phenotype	Effect of enrichment	Reference
HD (R6/1)	Rear-paw claspings	Delayed onset	[49]
HD (R6/1)	Rotarod deficit	Amelioration	[57]
HD (R6/1)	Peristriatal cerebral volume loss	Amelioration	[49]
HD (R6/1)	Striatal volume loss	No effect at 5 months	[49]
HD (R6/1)	Striatal BDNF deficit	Amelioration	[57]
HD (R6/1)	Hippocampal BDNF deficit	Amelioration	[57]
HD (R6/1)	Striatal DARPP-32 deficit	No effect at 5 months	[57]
HD (R6/1)	Cortical DARPP-32 deficit	Amelioration	[57]
HD (R6/1)	Decreased dendritic spine density and length	No effect at 5 months	[77]
HD (R6/1)	Protein aggregate formation	Decreased diameter	[50]
HD (R6/2)	Rotarod deficit	Amelioration	[51]
HD (R6/2)	Peristriatal cerebral volume loss	Amelioration	[51]
HD (N171-82Q)	Rotarod deficit	Amelioration	[52]
HD (N171-82Q)	Shortened lifespan	No effect	[52]
HD (N171-82Q)	Weight loss	Amelioration	[52]
AD (APP <sub>Swe</sub> )	Spatial cognitive deficit	Cognitive improvement	[128]
AD (APP <sub>Swe</sub> × PS1ΔE9)	Increased Aβ levels accelerated amyloid deposition	Amelioration	[132]

**Table 2.** Environmental influences on neurodegenerative disease. AD, Alzheimer's disease; HD, Huntington's disease; PD, Parkinson's disease.

Disease	Environmental factor	Associated effects	Reference(s)
HD	Remotivation therapy	Improve function in patients	[53]
HD	Differing environments of monozygotic twins and HD kindred	Differing age of onset and clinical symptoms	[54,55]
AD	Head trauma	Increased risk of developing sporadic AD	[108–110]
AD	High level of education	Decreased risk of developing sporadic AD	[114]
AD	Cognitively stimulating activities	Decreased risk of developing sporadic AD	[113,115,116]
AD	Vitamins E, B6, B12; folate	Decreased risk of developing sporadic AD	[122]
AD	High calorie intake	Increased risk of developing sporadic AD	[125,127]
AD	Cognitive-motor stimulation	Cognitive stabilization and mood improvement in patients	[133]
PD	Smoking	Decreased risk of developing typical PD	[141]
PD	Caffeine consumption	Decreased risk of developing PD (men)	[140]
PD	Pesticide exposure	Increased risk of developing PD	[143]

**Fig. 4.** Evidence from several diseases indicates that environmental modulators may affect several common neurodegenerative pathways and their associated molecular mediators.

[49,51,52,57,128]. 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 overlaid. 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

This review is dedicated to the memory of Christopher Job, a brilliant young scientist. The work was supported by NIH grant NIA 5 T32 AG00277 and an Alzheimer Association pioneer award, and the Australian National Health and Medical Research Council. AJH would like to thank C. Hannan for comments on the manuscript as well as past and present members of his laboratory for useful discussions.

## References

- Bates G, Harper P & Jones L (2002) *Huntington's Disease*, 3rd edn. Oxford University Press, Oxford.
- Glass M, Dragunow M & Faull RL (2000) The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA (A) receptor alterations in the human basal ganglia in Huntington's disease. *Neuroscience* **97**, 505–519.
- DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP & Aronin N (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science* **277**, 1990–1993.
- Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY *et al.* (1983) A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* **306**, 234–238.
- Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* **72**, 971–983.
- Young AB (2003) Huntingtin in health and disease. *J Clin Invest* **111**, 299–302.
- Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, Starr E, Squitieri F, Lin B, Kalchman MA *et al.* (1993) The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet* **4**, 398–403.
- Rosenblatt A, Brinkman RR, Liang KY, Almqvist EW, Margolis RL, Huang CY, Sherr M, Franz ML, Abbott MH, Hayden MR *et al.* (2001) Familial influence on age of onset among siblings with Huntington disease. *Am J Med Genet* **105**, 399–403.
- MacDonald ME, Vonsattel JP, Shrinidhi J, Couropmitree NN, Cupples LA, Bird ED, Gusella JF & Myers RH (1999) Evidence for the GluR6 gene associated with younger onset age of Huntington's disease. *Neurology* **53**, 1330–1332.
- Rubinsztein DC, Leggo J, Chiano M, Dodge A, Norbury G, Rosser E & Craufurd D (1997) Genotypes at the GluR6 kainate receptor locus are associated with variation in the age of onset of Huntington disease. *Proc Natl Acad Sci USA* **94**, 3872–3876.
- Kehoe P, Krawczak M, Harper PS, Owen MJ & Jones AL (1999) Age of onset in Huntington disease: sex specific influence of apolipoprotein E genotype and normal CAG repeat length. *J Med Genet* **36**, 108–111.
- Holbert S, D Nghien I, Kiechle T, Rosenblatt A, Wellington C, Hayden MR, Margolis RL, Ross CA, Dausset J, Ferrante RJ *et al.* (2001) The Gln-Ala repeat transcriptional activator CA150 interacts with huntingtin: neuropathologic and genetic evidence for a role in Huntington's disease pathogenesis. *Proc Natl Acad Sci USA* **98**, 1811–1816.
- van Dellen A & Hannan AJ (2004) Genetic and environmental factors in the pathogenesis of Huntington's disease. *Neurogenetics* **5**, 9–17.
- Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trotter Y, Lehrach H, Davies SW *et al.* (1996) Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* **87**, 493–506.
- Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE, Mangiarini L & Bates GP (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* **90**, 537–548.
- Dunnett SB, Carter RJ, Watts C, Torres EM, Mahal A, Mangiarini L, Bates G & Morton AJ (1998) Striatal transplantation in a transgenic mouse model of Huntington's disease. *Exp Neurol* **154**, 31–40.
- Sathasivam K, Hobbs C, Mangiarini L, Mahal A, Turmaine M, Doherty P, Davies SW & Bates GP

- (1999) Transgenic models of Huntington's disease. *Philos Trans R Soc Lond B Biol Sci* **354**, 963–969.
- 18 Lione LA, Carter RJ, Hunt MJ, Bates GP, Morton AJ & Dunnett SB (1999) Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. *J Neurosci* **19**, 10428–10437.
  - 19 Carter RJ, Lione LA, Humby T, Mangiarini L, Mahal A, Bates GP, Dunnett SB & Morton AJ (1999) Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. *J Neurosci* **19**, 3248–3257.
  - 20 Murphy KP, Carter RJ, Lione LA, Mangiarini L, Mahal A, Bates GP, Dunnett SB & Morton AJ (2000) Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation. *J Neurosci* **20**, 5115–5123.
  - 21 Bennett DA, Diamond MC, Krech D & Rosenzweig MR (1964) Chemical and anatomical plasticity of brain. *Science* **146**, 610–619.
  - 22 Frick KM, Stearns NA, Pan JY & Berger-Sweeney J (2003) Effects of environmental enrichment on spatial memory and neurochemistry in middle-aged mice. *Learn Mem* **10**, 187–198.
  - 23 Frick KM & Fernandez SM (2003) Enrichment enhances spatial memory and increases synaptophysin levels in aged female mice. *Neurobiol Aging* **24**, 615–626.
  - 24 Duffy SN, Craddock KJ, Abel T & Nguyen PV (2001) Environmental enrichment modifies the PKA-dependence of hippocampal LTP and improves hippocampus-dependent memory. *Learn Mem* **8**, 26–34.
  - 25 Williams BM, Luo Y, Ward C, Redd K, Gibson R, Kuczaj SA & McCoy JG (2001) Environmental enrichment: effects on spatial memory and hippocampal CREB immunoreactivity. *Physiol Behav* **73**, 649–658.
  - 26 Kempermann G, Kuhn HG & Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. *Nature* **386**, 493–495.
  - 27 Fiala B, Snow FM & Greenough WT (1977) 'Impoverished' rats weigh more than 'enriched' rats because they eat more. *Devel Psychobiol* **10**, 537–541.
  - 28 Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF & Greenough WT (2002) Exercise, experience and the aging brain. *Neurobiol Aging* **23**, 941–955.
  - 29 Nithianantharajah J, Levis H & Murphy M (2004) Environmental enrichment results in cortical and subcortical changes in levels of synaptophysin and PSD-95 proteins. *Neurobiol Learn Mem* **81**, 200–210.
  - 30 Altman J & Das GD (1965) Post-natal origin of micro-neurons in the rat brain. *Nature* **207**, 953–956.
  - 31 Gould E & Gross CG (2002) Neurogenesis in adult mammals: some progress and problems. *J Neurosci* **22**, 619–623.
  - 32 Young DH, Lawlor PA, Leone P, Dragunow M & During MJ (1999) Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuro-protective. *Nat Med* **5**, 448–453.
  - 33 Kempermann G, Wiskott L & Gage FH (2004) Functional significance of adult neurogenesis. *Curr Opin Neurobiol* **14**, 186–191.
  - 34 Rampon C, Jiang CH, Dong H, Tang YP, Lockhart DJ, Schultz PG, Tsien JZ & Hu Y (2000) Effects of environmental enrichment on gene expression in the brain. *Proc Natl Acad Sci USA* **97**, 12880–12884.
  - 35 Falkenberg T, Mohammed AK, Henriksson B, Persson H, Winblad B & Lindfors N (1992) Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. *Neurosci Lett* **138**, 153–156.
  - 36 Pham TM, Ickes B, Albeck D, Soderstrom S, Granholm AC & Mohammed AH (1999) Changes in brain nerve growth factor levels and nerve growth factor receptors in rats exposed to environmental enrichment for one year. *Neuroscience* **94**, 279–286.
  - 37 Zhao LR, Risedal A, Wojcik A, Hejzlar J, Johansson BB & Kokaia Z (2001) Enriched environment influences brain-derived neurotrophic factor levels in rat forebrain after focal stroke. *Neurosci Lett* **305**, 169–172.
  - 38 Keyvani K, Sachser N, Witte OW & Paulus W (2004) Gene expression profiling in the intact and injured brain following environmental enrichment. *J Neuro-pathol Exp Neurol* **63**, 598–609.
  - 39 Sale A, Putignano E, Cancedda L, Landi S, Cirulli F, Berardi N & Maffei L (2004) Enriched environment and acceleration of visual system development. *Neuro-pharmacology* **47**, 649–660.
  - 40 Cancedda L, Putignano E, Sale A, Viegi A, Berardi N & Maffei L (2004) Acceleration of visual system development by environmental enrichment. *J Neurosci* **24**, 4840–4848.
  - 41 Bartoletti A, Medini P, Berardi N & Maffei L (2004) Environmental enrichment prevents effects of dark-rearing in the rat visual cortex. *Nat Neurosci* **7**, 215–216.
  - 42 Guilarte TR, Toscano CD, McGlothan JL & Weaver SA (2003) Environmental enrichment reverses cognitive and molecular deficits induced by developmental lead exposure. *Ann Neurol* **53**, 50–56.
  - 43 Pinaud R, Penner MR, Robertson HA & Currie RW (2001) Upregulation of the immediate early gene arc in the brains of rats exposed to environmental enrichment: implications for molecular plasticity. *Brain Res Mol Brain Res* **91**, 50–56.
  - 44 Pinaud R, Tremere LA, Penner MR, Hess FF, Robertson HA & Currie RW (2002) Complexity of sensory environment drives the expression of candidate-plasticity gene, nerve growth factor induced-A. *Neuroscience* **112**, 573–582.

- 45 Goto S, Radak Z, Nyakas C, Chung HY, Naito H, Takahashi R, Nakamoto H & Abea R (2004) Regular exercise: an effective means to reduce oxidative stress in old rats. *Ann N Y Acad Sci* **1019**, 471–474.
- 46 Kitamura T, Mishina M & Sugiyama H (2003) Enhancement of neurogenesis by running wheel exercises is suppressed in mice lacking NMDA receptor epsilon 1 subunit. *Neurosci Res* **47**, 55–63.
- 47 Rhodes JS, van Praag H, Jeffrey S, Girard I, Mitchell GS, Garland T & Gage FH (2003) Exercise increases hippocampal neurogenesis to high levels but does not improve spatial learning in mice bred for increased voluntary wheel running. *Behav Neurosci* **117**, 1006–1016.
- 48 Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH & Christie BR (2004) Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats *in vivo*. *Neuroscience* **124**, 71–79.
- 49 van Dellen A, Blakemore C, Deacon R, York D & Hannan AJ (2000) Delaying the onset of Huntington's in mice. *Nature* **404**, 721–722.
- 50 Spires TL, Varshney N, Grote H, van Dellen A, Blakemore C & Hannan AJ (2002) Effects of environmental enrichment on disease symptoms, gene expression and protein aggregation in Huntington's disease mice. *Soc Neurosci Abstr* **28**, 388.13.
- 51 Hockly E, Cordery PM, Woodman B, Mahal A, van Dellen A, Blakemore C, Lewis CM, Hannan AJ & Bates GP (2002) Environmental enrichment slows disease progression in R6/2 Huntington's disease mice. *Ann Neurol* **51**, 235–242.
- 52 Schilling G, Savonenko AV, Coonfield ML, Morton JL, Vorovich E, Gale A, Neslon C, Chan N, Eaton M, Fromholt D *et al.* (2004) Environmental, pharmacological, and genetic modulation of the HD phenotype in transgenic mice. *Exp Neurol* **187**, 137–149.
- 53 Sullivan FR, Bird ED, Alpay M & Cha JH (2001) Remotivation therapy and Huntington's disease. *J Neurosci Nurs* **33**, 136–142.
- 54 Georgiou N, Bradshaw JL, Chiu E, Tudor A, O'Gorman L & Phillips JG (1999) Differential clinical and motor control function in a pair of monozygotic twins with Huntington's disease. *Mov Disord* **14**, 320–325.
- 55 Wexler NS, Lorimer J, Porter J, Gomez F, Moskowitz C, Shackell E, Marder K, Penchaszadeh G, Roberts SA, Gayan J *et al.* (2004) Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci USA* **101**, 3498–3503.
- 56 van Dellen A, Deacon R, York D, Blakemore C & Hannan AJ (2001) Anterior cingulate cortical transplantation in transgenic Huntington's disease mice. *Brain Res Bull* **56**, 313–318.
- 57 Spires TL, Grote HE, Varshney NK, Cordery PM, Van Dellen A, Blakemore C & Hannan AJ (2004) Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *J Neurosci* **24**, 2270–2276.
- 58 Altar CA, Cai N, Bliven T, Juhasz M, Conner JM, Acheson AL, Lindsay RM & Wiegand SJ (1997) Anterograde transport of brain-derived neurotrophic factor and its role in the brain. *Nature* **389**, 856–860.
- 59 Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR *et al.* (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* **293**, 493–498.
- 60 Ferrer I, Goutan E, Marin C, Rey MJ & Ribalta T (2000) Brain-derived neurotrophic factor in Huntington disease. *Brain Res* **866**, 257–261.
- 61 Luthi-Carter R, Hanson SA, Strand AD, Bergstrom DA, Chun W, Peters NL, Woods AM, Chan EY, Kooperberg C, Krainc D *et al.* (2002) Dysregulation of gene expression in the R6/2 model of polyglutamine disease: parallel changes in muscle and brain. *Hum Mol Genet* **11**, 1911–1926.
- 62 Duan W, Guo Z, Jiang H, Ware M, Li XJ & Mattson MP (2003) Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. *Proc Natl Acad Sci USA* **100**, 2911–2916.
- 63 Clifford JJ, Drago J, Natoli AL, Wong JY, Kinsella A, Waddington JL & Vaddadi KS (2002) Essential fatty acids given from conception prevent topographies of motor deficit in a transgenic model of Huntington's disease. *Neuroscience* **109**, 81–88.
- 64 Lee J, Duan W, Long JM, Ingram DK & Mattson MP (2000) Dietary restriction increases the number of newly generated neural cells, and induces BDNF expression, in the dentate gyrus of rats. *J Mol Neurosci* **15**, 99–108.
- 65 Barnabe-Heider F & Miller FD (2003) Endogenously produced neurotrophins regulate survival and differentiation of cortical progenitors via distinct signaling pathways. *J Neurosci* **23**, 5149–5160.
- 66 Lazic SE, Grote H, Armstrong RJ, Blakemore C, Hannan AJ, van Dellen A & Barker RA (2004) Decreased hippocampal cell proliferation in R6/1 Huntington's mice. *Neuroreport* **15**, 811–813.
- 67 van Praag H, Kempermann G & Gage FH (2000) Neural consequences of environmental enrichment. *Nat Rev Neurosci* **1**, 191–198.
- 68 Grote HE, Howard ML, van Dellen A, Blakemore C & Hannan AJ (2005) The serotonin reuptake inhibitor fluoxetine rescues cognitive and affective deficits in a transgenic mouse model of Huntington's disease. *Proc Aust Neurosci Soc* **16**, 131.

- 69 Curtis MA, Penney EB, Pearson AG, van Roon-Mom WM, Butterworth NJ, Dragunow M, Connor B & Faull RL (2003) Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. *Proc Natl Acad Sci USA* **100**, 9023–9027.
- 70 Luthi-Carter R, Strand A, Peters NL, Solano SM, Hollingsworth ZR, Menon AS, Frey AS, Spektor BS, Penney EB, Schilling G *et al.* (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. *Hum Mol Genet* **9**, 1259–1271.
- 71 Chan EY, Luthi-Carter R, Strand A, Solano SM, Hanson SA, DeJohn MM, Kooperberg C, Chase KO, DiFiglia M, Young AB *et al.* (2002) Increased huntingtin protein length reduces the number of polyglutamine-induced gene expression changes in mouse models of Huntington's disease. *Hum Mol Genet* **11**, 1939–1951.
- 72 Cha JH, Kosinski CM, Kerner JA, Alsdorf SA, Mangiarini L, Davies SW, Penney JB, Bates GP & Young AB (1998) Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human huntington disease gene. *Proc Natl Acad Sci USA* **95**, 6480–6485.
- 73 van Dellen A, Welch J, Dixon RM, Cordery P, York D, Styles P, Blakemore C & Hannan AJ (2000) *N*-Acetylaspartate and DARPP-32 levels decrease in the corpus striatum of Huntington's disease mice. *Neuroreport* **11**, 3751–3757.
- 74 Glass M, van Dellen A, Blakemore C, Hannan AJ & Faull RL (2004) Delayed onset of Huntington's disease in mice in an enriched environment correlates with delayed loss of cannabinoid CB1 receptors. *Neuroscience* **123**, 207–212.
- 75 Hannan AJ (2004) Huntington's disease: which drugs might help patients? *IDrugs* **7**, 351–358.
- 76 Hannan AJ (2004) Molecular mediators, environmental modulators and experience-dependent synaptic dysfunction in Huntington's disease. *Acta Biochim Pol* **51**, 415–430.
- 77 Spires TL, Grote HE, Garry S, Cordery PM, Van Dellen A, Blakemore C & Hannan AJ (2004) Dendritic spine pathology and deficits in experience-dependent dendritic plasticity in R6/1 Huntington's disease transgenic mice. *Eur J Neurosci* **19**, 2799–2807.
- 78 Levine MS, Klapstein GJ, Koppel A, Gruen E, Cepeda C, Vargas ME, Jokel ES, Carpenter EM, Zanjani H, Hurst RS *et al.* (1999) Enhanced sensitivity to *N*-methyl-D-aspartate receptor activation in transgenic and knockin mouse models of Huntington's disease. *J Neurosci Res* **58**, 515–532.
- 79 Laforet GA, Sapp E, Chase K, McIntyre C, Boyce FM, Campbell M, Cadigan BA, Warzecki L, Tagle DA, Reddy PH *et al.* (2001) Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. *J Neurosci* **21**, 9112–9123.
- 80 Cepeda C, Ariano MA, Calvert CR, Flores-Hernandez J, Chandler SH, Leavitt BR, Hayden MR & Levine MS (2001) NMDA receptor function in mouse models of Huntington disease. *J Neurosci Res* **66**, 525–539.
- 81 Cepeda C, Hurst RS, Calvert CR, Hernandez-Echeagaray E, Nguyen OK, Jocoy E, Christian LJ, Ariano MA & Levine MS (2003) Transient and progressive electrophysiological alterations in the corticostriatal pathway in a mouse model of Huntington's disease. *J Neurosci* **23**, 961–969.
- 82 Mazarakis NK, Cybulska-Klosowicz A, Grote H, Pang T, Van Dellen A, Kossut M, Blakemore C & Hannan AJ (2005) Experience-dependent cortical plasticity and sensory discrimination deficits in presymptomatic Huntington's disease mice. *J Neurosci* **25**, 3059–3066.
- 83 Cybulska-Klosowicz A, Mazarakis NK, Van Dellen A, Kossut M, Blakemore C, Hannan AJ & Kossut M (2004) Impaired learning-dependent cortical plasticity in Huntington's disease transgenic mice. *Neurobiol Dis* **17**, 427–434.
- 84 Hebert LE, Scherr PA, Bienias JL, Bennett DA & Evans DA (2003) Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* **60**, 1119–1122.
- 85 Citron M, Oltersdorf T, Haass C, McConlogue L, Hung AY, Seubert P, Vigo-Pelfrey C, Lieberburg I & Selkoe DJ (1992) Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. *Nature* **360**, 672–674.
- 86 Alzheimer A (1907) Ubereine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiatr – Gerichtl Med* **64**, 146–148.
- 87 Spires TL & Hyman BT (2004) Neuronal structure is altered by amyloid plaques. *Rev Neurosci* **15**, 267–278.
- 88 Glenner GG & Wong CW (1984) Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* **120**, 885–890.
- 89 Small DH, Mok SS & Bornstein JC (2001) Alzheimer's disease and Abeta toxicity: from top to bottom. *Nat Rev Neurosci* **2**, 595–598.
- 90 Kang J, Lemaire HG, Unterbeck A, Salbaum JM, Masters CL, Grzeschik KH, Multhaup G, Beyreuther K & Muller-Hill B (1987) The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature* **325**, 733–736.
- 91 Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L *et al.* (1991) Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* **349**, 704–706.
- 92 Naruse S, Igarashi S, Kobayashi H, Aoki K, Inuzuka T, Kaneko K, Shimizu T, Iihara K, Kojima T,

- Miyatake T *et al.* (1991) Mis-sense mutation Val-Ile in exon 17 of amyloid precursor protein gene in Japanese familial Alzheimer's disease. *Lancet* **337**, 978-979.
- 93 De Strooper B (2003) Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex. *Neuron* **38**, 9-12.
- 94 Selkoe DJ (1999) Biology of beta-amyloid precursor protein and the mechanism of Alzheimer disease. In *Alzheimer Disease* (Terry RD, Katzman R, Bick KL & Sisoda SS, eds), pp. 293-310, Lippincott Williams & Wilkins, Philadelphia.
- 95 Alzheimer's Disease Collaborative Group (1995) The structure of the presenilin 1 (S182) gene and identification of six novel mutations in early onset AD families. *Nat Genet* **11**, 219-222.
- 96 Levy-Lahad E, Wijsman EM, Nemens E, Anderson L, Goddard KA, Weber JL, Bird TD & Schellenberg GD (1995) A familial Alzheimer's disease locus on chromosome 1. *Science* **269**, 970-973.
- 97 Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T *et al.* (1995) Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* **376**, 775-778.
- 98 Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K *et al.* (1995) Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* **375**, 754-760.
- 99 St George-Hyslop P, Haines J, Rogaev E, Mortilla M, Vaula G, Pericak-Vance M, Foncin JF, Montesi M, Bruni A, Sorbi S *et al.* (1992) Genetic evidence for a novel familial Alzheimer's disease locus on chromosome 14. *Nat Genet* **2**, 330-334.
- 100 Kidd M (1963) Paired helical filaments in electron microscopy in Alzheimer's disease. *Nature* **197**, 192-193.
- 101 Brion JP, Couck AM, Passareiro E & Flament-Durand J (1985) Neurofibrillary tangles of Alzheimer's disease: an immunohistochemical study. *J Submicrosc Cytol* **17**, 89-96.
- 102 Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ & Gilman S (1997) Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. *Ann Neurol* **41**, 706-715.
- 103 Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL & Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.
- 104 Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ *et al.* (1993) Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43**, 1467-1472.
- 105 Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, Rimmler JB, Locke PA, Conneally PM, Schmechel KE *et al.* (1994) Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet* **7**, 180-184.
- 106 Phinney AL, Horne P, Yang J, Janus C, Bergeron C & Westaway D (2003) Mouse models of Alzheimer's disease: the long and filamentous road. *Neurol Res* **25**, 590-600.
- 107 Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TV, Hyman BT *et al.* (1999) Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nat Neurosci* **2**, 271-276.
- 108 Mortimer JA, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Rocca WA *et al.* (1991) Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol* **20**, S28-S35.
- 109 Rasmuson DX, Brandt J, Martin DB & Folstein MF (1995) Head injury as a risk factor in Alzheimer's disease. *Brain Inj* **9**, 213-219.
- 110 Uryu K, Laurer H, McIntosh T, Pratico D, Martinez D, Leight S, Lee VM & Trojanowski JQ (2002) Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis. *J Neurosci* **22**, 446-454.
- 111 Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, Chun M, Tycko B & Shelanski M (1995) Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. *Neurology* **45**, 555-557.
- 112 Laurin D, Verreault R, Lindsay J, MacPherson K & Rockwood K (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* **58**, 498-504.
- 113 Scarmeas N, Levy G, Tang MX, Manly J & Stern Y (2001) Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology* **57**, 2236-2242.
- 114 Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D & Mayeux R (1994) Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* **271**, 1004-1010.
- 115 Wilson RS, Bennett DA, Bienias JL, Aggarwal NT, Mendes de Leon CF, Morris MC, Schneider JA & Evans DA (2002) Cognitive activity and incident AD in a population-based sample of older persons. *Neurology* **59**, 1910-1914.

- 116 Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA & Bennett DA (2002) Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* **287**, 742–748.
- 117 Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, Petot GJ & Debanne SM (2001) Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc Natl Acad Sci USA* **98**, 3440–3445.
- 118 Scarmeas N & Stern Y (2004) Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep* **4**, 374–380.
- 119 Luchsinger JA & Mayeux R (2004) Dietary factors and Alzheimer's disease. *Lancet Neurol* **3**, 579–587.
- 120 Standridge JB (2004) Pharmacotherapeutic approaches to the prevention of Alzheimer's disease. *Am J Geriatr Pharmacother* **2**, 119–132.
- 121 Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N & Schneider J (2003) Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol* **60**, 940–946.
- 122 Mattson MP (2003) Gene–diet interactions in brain aging and neurodegenerative disorders. *Ann Intern Med* **139**, 441–444.
- 123 Berman K & Brodaty H (2004) Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs* **18**, 807–825.
- 124 McDowell I (2001) Alzheimer's disease: insights from epidemiology. *Aging (Milano)* **13**, 143–162.
- 125 Luchsinger JA, Tang MX, Shea S & Mayeux R (2002) Caloric intake and the risk of Alzheimer disease. *Arch Neurol* **59**, 1258–1263.
- 126 Breteler MM (2000) Vascular risk factors for Alzheimer's disease: An epidemiologic perspective. *Neurobiol Aging* **21**, 153–160.
- 127 Miller LJ & Chacko R (2004) The role of cholesterol and statins in Alzheimer's disease. *Ann Pharmacother* **38**, 91–98.
- 128 Arendash GW, Garcia MF, Costa DA, Cracchiolo JR, Wefes IM & Potter H (2004) Environmental enrichment improves cognitive function in aged Alzheimer's transgenic mice despite stable [beta]-amyloid deposition. *Neuroreport* **15**, 1751–1754.
- 129 Cracchiolo JR, Costa DA, Arendash GW, Bales KR, Paul SM & Potter H (2004) Environmental enrichment in Alzheimer's transgenic mice protects against widespread cognitive impairment without affecting A $\beta$  deposition. *Soc Neurosci Abstr* **30**, 830.11.
- 130 Jankowsky JL, Xu G, Fromholt D, Gonzales V & Borchelt DR (2003) Environmental enrichment exacerbates amyloid plaque formation in a transgenic mouse model of Alzheimer disease. *J Neuropathol Exp Neurol* **62**, 1220–1227.
- 131 Levi O, Jongen-Relo AL, Feldon J, Roses AD & Michaelson DM (2003) ApoE4 impairs hippocampal plasticity isoform-specifically and blocks the environmental stimulation of synaptogenesis and memory. *Neurobiol Dis* **13**, 273–282.
- 132 Lazarov O, Robinson J, Tang Y-P, Hairston IS, Korade-Mirnic Z, Lee VM-Y, Hersh LB, Sapolsky RM, Mirnic K & Sidodia SS (2005) Environmental enrichment reduces A $\beta$  levels and amyloid deposition in transgenic mice. *Cell* **120**, 101–113.
- 133 Olazarán J, Muniz R, Reisberg B, Pena-Casanova J, delSer T, Cruz-Jentoft AJ, Serrano P, Navarro E, Garcia de la Rocha ML, Frank A *et al.* (2004) Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. *Neurology* **63**, 2348–2353.
- 134 Le Couteur DG, Muller M, Yang MC, Mellick GD & McLean AJ (2002) Age–environment and gene–environment interactions in the pathogenesis of Parkinson's disease. *Rev Environ Health* **17**, 51–64.
- 135 Huang Y, Cheung L, Rowe D & Halliday G (2004) Genetic contributions to Parkinson's disease. *Brain Res Brain Res Rev* **46**, 44–70.
- 136 Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R & Langston JW (1999) Parkinson disease in twins: an etiologic study. *JAMA* **281**, 341–346.
- 137 Paolini M, Sapone A & Gonzalez FJ (2004) Parkinson's disease, pesticides and individual vulnerability. *Trends Pharmacol Sci* **25**, 124–129.
- 138 Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV & Greenamyre JT (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nature Neurosci* **3**, 1301–1306.
- 139 Dauer W & Przedborski S (2003) Parkinson's Disease: mechanisms and models. *Neuron* **39**, 889–909.
- 140 Ascherio A & Chen H (2003) Caffeinated clues from epidemiology of Parkinson's disease. *Neurology* **61**, 51S–54.
- 141 Morens DM, Grandinetti A, Reed D, White LR & Ross GW (1995) Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue? *Neurology* **45**, 1041–1051.
- 142 Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV & Greenamyre JT (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci* **3**, 1301–1306.
- 143 Priyadarshi A, Khuder SA, Schaub EA & Shrivastava S (2000) A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology* **21**, 435–440.
- 144 Mayeux R (2003) Epidemiology of neurodegeneration. *Annu Rev Neurosci* **26**, 81–104.