Convergent pathogenic pathways in Alzheimer's and Huntington's diseases: shared targets for drug development

Dagmar E. Ehrnhoefer, Bibiana K. Y. Wong* and Michael R. Hayden**

Abstract | Neurodegenerative diseases, exemplified by Alzheimer's disease and Huntington's disease, are characterized by progressive neuropsychiatric dysfunction and loss of specific neuronal subtypes. Although there are differences in the exact sites of pathology, and the clinical profiles of these two conditions only partially overlap, considerable similarities in disease mechanisms and pathogenic pathways can be observed. These shared mechanisms raise the possibility of exploiting common therapeutic targets for drug development. As Huntington's disease has a monogenic cause, it is possible to accurately identify individuals who carry the Huntington's disease mutation but do not yet manifest symptoms. These individuals could act as a model for Alzheimer's disease to test therapeutic interventions that target shared pathogenic pathways.

Chorea
An abnormal involuntary movement such as an irregular, rapid, involuntary or excessive movement, which seems to randomly affect different parts of the body. A characteristic feature of Huntington's disease.

Dementia
A gradual decline in mental ability that affects intellectual skills such as memory, concentration and judgement. It is sometimes accompanied by emotional disturbances and changes in personality.

**Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, Child & Family Research Institute, University of British Columbia, 950 West 28th Avenue, Vancouver, British Columbia V5Z 4H4, Canada. Correspondence to M.R.H. e-mail: mrh@cmmt.ubc.ca*
doi:10.1038/nrd3556
Published online
21 October 2011

The rapidly growing aged population in industrialized countries, spurred by an increase in life expectancy, has led to an increased prevalence of late-onset neurodegenerative disorders, which imposes an enormous financial and social burden on health-care systems and society as a whole. For example, in 2010 the number of people over the age of 85 in the United States was 6 million, and this number is projected to quadruple by 2050 (REF. 1).

The clinical symptoms of neurodegenerative disorders such as Alzheimer's disease (AD) and Huntington's disease (HD) are progressive and debilitating. The hallmark of HD is motor disability that features chorea, whereas the main symptom of AD is dementia. Nevertheless, patients with HD and AD share many of the same clinical manifestations. These include behavioural and psychiatric disturbances (including depression and apathy) in the early stages of the diseases, as well as cognitive defects that result in forgetfulness, impaired judgement, disorientation and confusion. Cognitive deficits in patients with HD, however, are usually less severe than in AD; patients also exhibit difficulty in ambulation and eating at late stages of both diseases, which ultimately lead to death[1,2].

AD is genetically heterogeneous, and can be caused by one or more of several genes as well as environmental factors. Familial AD (FAD), which accounts for less than 1% of all AD cases, is caused by rare mutations in genes encoding amyloid precursor protein (APP), presenilin 1 (PSEN1) and PSEN2 (REFS 1,3). Numerous genes are associated with sporadic late-onset AD. The apolipoprotein E4 allele is the single strongest genetic risk factor for sporadic AD[4]. Cleavage of APP by β-secretase and the γ-secretase complex — which consists of PSEN1 or PSEN2, anterior pharynx defective 1, presenilin enhancer 2 and nicastrin — leads to the generation of the extracellular amyloid-β (Aβ) peptide. This peptide fragment is prone to aggregation and forms amyloid plaques that can be detected in the post-mortem brain samples of patients with AD[5,6]. In addition to amyloid plaques, neurofibrillary tangles made up of hyperphosphorylated aggregates of tau, a microtubule-associated protein, are also observed in post-mortem brain samples of patients with AD[5,6].

By contrast, HD is a monogenic disorder that occurs as a result of autosomal dominant inheritance and is caused by a CAG repeat that expands to 36 copies or more in the gene encoding the huntingtin (HTT) protein[2], resulting in an expansion of the polyglutamine tract. Furthermore, the length of the CAG tract is directly correlated with disease onset, with longer expansions leading to earlier onset of HD[2]. The enzymes β-secretase, γ-secretase and the Aβ peptide are well-validated therapeutic targets in AD[7], and mutant HTT is a promising target in HD[8,9]. However, these targets are not shared between AD and HD, and will therefore not be the focus of this Review.

At a neuropathological level, these two diseases are initially characterized by a specific loss of certain neuronal subtypes. In HD it is the medium spiny neurons in the striatum that undergo atrophy in early stages of the disease, whereas in AD large pyramidal neurons in the CA1 zone of the hippocampus as well as neurons in the basal forebrain and the entorhinal cortex are affected in early stages of the disease[10–12]. The process of neuronal dysfunction and death is progressive, and early changes are followed by a more widespread atrophy of the brain[10,13]. Considerable progress has been made in the elucidation of mechanisms that lead to neurodegeneration in AD and HD. There is evidence for the aberrant phosphorylation, palmitoylation and acetylation of disease-causing proteins, protein misfolding, a failure of the ubiquitin–proteasome system or autophagy to clear disease-causing proteins, as well as changes in NMDA (*N*-methyl-D-aspartate) receptor activity at the synapse. Additional mechanisms include alterations in levels of brain-derived neurotrophic factor (BDNF) and neuronal growth factor (NGF) as well as changes in levels of associated receptors and trafficking pathways, and increased activity of caspases in both disorders[5,6,9,14] (TABLE 1).

Although there are no treatments available that slow or halt neuronal degeneration and neuronal death, the analysis of disease-triggering pathways has led to the identification of common drug targets for AD and HD. These similarities have not been commonly appreciated by the HD or AD research communities, but we believe that an understanding of these similarities could lead to the development of drugs that could be used for both disorders. In this Review, we describe these shared pathways and therapeutic targets and rank them with target-validation scores based on a scale developed by the Cure Huntington's Disease Initiative (CHDI)[15] (TABLE 2), which we apply to both diseases for direct comparison (see the HD Research Crossroads website (registration required)). Potential therapeutic targets are hereby ranked by their degree of validation, from 1.0 (for a gene and/or protein that is linked to a disease-relevant biological mechanism) to 6.0 (if therapeutic modulation of the target demonstrates efficacy in a Phase III clinical trial). Although well-studied targets will automatically be ranked higher in this system than understudied targets, we believe that our ranking can identify common well-validated targets as well as knowledge gaps that warrant further studies.

In most cases it is unknown whether the modulation of targets will have a disease-modifying effect or whether it will only lead to the alleviation of symptoms, and the target-validation score does not discriminate between these possibilities. Long-term clinical studies will be necessary to clarify whether compounds will be disease-modifying, and we believe that these could initially be carried out in individuals carrying the genetic mutation that causes HD, as this population is well defined and alterations in the course of the disease can be determined at very early stages of the disease[16]. HD is the most common neurodegenerative disorder that has a purely genetic cause, whereas AD is the most common neurodegenerative disease overall[1,2]. As many of the pathways and targets described here are also implicated in other diseases — such as Parkinson's disease, dementia with Lewy bodies or ataxias — HD could serve as a general model for neurodegeneration, for which well-defined animal models are available for preclinical studies and end points for clinical trials are well established[16,17]. The Enroll-HD study that is currently underway will provide a registry of *HTT* mutation carriers worldwide, and may serve as a resource for recruiting patients into clinical trials (see the Enroll-HD website).

Targeting synaptic dysfunction

Excitotoxicity has been implicated as a cause of neuronal death in both HD and AD. The NMDA subtype of glutamate receptors is thought to be a major contributor to excitotoxic cell death because of its high permeability to calcium[18]. NMDA receptor (NMDAR) subunit 2A (NR2A; also known as GRIN2A) and NR2B (also known as GRIN2B) differ in their sensitivities to agonists and antagonists, their channel-gating properties, and in their localization. NR2A-containing NMDARs are generally found at the synapse, whereas NR2B-containing NMDARs are predominantly localized at extrasynaptic sites[18]. Enhanced activation of extrasynaptic NR2B-containing NMDARs is common in both HD and AD.

Aberrant extrasynaptic NMDAR activity. The presence of mutant HTT and APP alters the subcellular distribution of NMDARs[18,19]. In mouse models of both diseases, deficits in trafficking mechanisms increase levels of NR2B on the cell surface and decrease NR2B internalization[18]. Increased levels of NR2B on the cell surface result in enhanced NMDAR-mediated currents in mouse models of HD and AD[19]. Both wild-type HTT and tau, a neuronal protein that stabilizes microtubules, are involved in NR2B trafficking as well as the recruitment of kinases to NMDARs at the cell surface. Mutant HTT disrupts these processes, resulting in altered tyrosine phosphorylation of NR2B and enhanced NMDAR-mediated excitotoxicity[20]. Similarly, Aβ-induced NMDAR dysfunction is mediated by FYN, a tyrosine kinase that phosphorylates NR2B[21,22] and mediates its insertion into the plasma membrane[23] — thereby increasing the levels of NR2B on the cell surface.

The activation of extrasynaptic NR2B-containing NMDARs also leads to the dephosphorylation and inhibition of the signalling pathway mediated by cyclic AMP-responsive element-binding protein and peroxisome proliferator-activated receptor-γ co-activator 1α, which makes cells expressing mutant HTT more susceptible to cell death[24] (FIG. 1). Furthermore, enhanced activation of extrasynaptic NMDARs leads to excessive influx of calcium into the cell, which results in inappropriate activation of enzymes (such as calpains and other calcium-regulated enzymes) and mitochondrial dysfunction; this leads to apoptosis[18].

Activation of extrasynaptic NMDARs may also underlie the cognitive impairment that is observed in patients with HD and AD. Long-term potentiation (LTP), a measure of synaptic plasticity, is thought to be a

Microtubule
One of the principal components of the cytoskeleton. Microtubules are hollow, dynamic rod structures that participate in determining cell shape, cell locomotion and intracellular transport processes.

CAG repeat
A trinucleotide repeat of cytosine, adenine and guanine (CAG) that results in the expression of a chain of glutamines in the protein sequence.

Polyglutamine tract
The part of a protein that is entirely composed of the amino acid glutamine, resulting from a cytosine, adenine and guanine (CAG) repeat in the corresponding gene.

Medium spiny neurons
A type of GABA (γ-aminobutyric acid)-ergic inhibitory neurons that have a key role in movement initiation and control. They represent ~90% of the neurons in the striatum of the brain.

CA1 zone
Cornu ammonis area 1. An area of the hippocampus that is composed of densely packed pyramidal cells.

Entorhinal cortex
An area located in the medial temporal lobe of the brain. Neurons from this area project to the hippocampus. The entorhinal cortex is involved in memory formation, in particular spatial memory.

Ubiquitin–proteasome system
A major pathway for the intracellular degradation of proteins. Substrates are conjugated to the peptide ubiquitin and transported to the proteasome, an organelle that has proteolytic activity and breaks the polypeptide chain into single amino acids.

Neurotrophic factor
A peptide secreted by brain tissues to guide axonal growth that is responsible for neuronal growth, differentiation and survival.

Table 1 | **Pathogenic pathways that are involved in both AD and HD**

Pathways or processes	Pathogenic alterations in pathway and therapeutic modulation	Refs
Synaptic dysfunction	Increased levels of extrasynaptic NR2B-containing NMDARs	18,19
	Increased phosphorylation of NMDARs	20,22
	Defective LTP in affected neurons	25,26
	Increased calcium influx	18
	Defects in mitochondrial trafficking	18
	Mitochondrial fragmentation and dysfunction	18,97–99,142
	Alterations in microglial tryptophan metabolism lead to increased release of neurotoxic metabolites	5,14,35
Neurotrophic factor-related abnormalities	Reduced BDNF levels	39,40
	Reduced velocity and efficiency of axonal transport of BDNF	65,66
	Increased p75NTR levels and signalling	75,171
	Decreased TRK levels and signalling	75,171
	Increased GSK3β activity	66,172
	Altered ERK activity	173
	Increasing BDNF and NGF levels is beneficial in disease models	51–54
Apoptotic pathways	Increased caspase 6 activity	89,90
	Caspase 6-mediated cleavage of disease-causing proteins	89–92
	Preventing caspase-mediated cleavage of disease-causing proteins is beneficial in mouse models	93,94
Post-translational modifications	Palmitoylation of disease-causing proteins linked to aggregate formation	118,119
	Phosphorylation of disease-causing proteins reduces their cleavage by caspases	105,106
	HDAC inhibition is beneficial in disease models	69,125,126
Protein aggregation and clearance mechanisms	Misfolding and aggregation of disease-causing proteins	127
	Impairments in the ubiquitin–proteasome system	143,144
	Impaired autophagy	160
	Upregulation of autophagy is beneficial in disease models	152,154,155,157,161, 162,164,166,167
	Increased expression of beclin 1 is beneficial in disease models	154,159

AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase; GSK3β, glycogen synthase kinase 3β; HD, Huntington's disease; HDAC, histone deacetylase; LTP, long-term potentiation; NGF, nerve growth factor; NMDAR, *N*-methyl-D-aspartate receptor; NR2B, NMDA receptor subunit 2B; p75NTR, low-affinity nerve growth factor receptor; TRK, neurotrophic tyrosine kinase receptor.

Synaptic plasticity
A process involved in learning and memory, whereby synapses gauge the intensity of their response to an incoming signal. It occurs as a result of the modulation of the number or sensitivity of receptors at the synapse or changes in the quantity of neurotransmitters released.

Morris water maze
An experiment that is used to assess spatial learning and memory in rodents. Rodents are placed in a circular pool of water, and by learning spatial markers they can identify the location of a hidden platform and escape from the water.

mechanism underlying learning and memory. In mouse models of AD and HD, neurons derived from affected brain regions have defective LTP[25,26]. Furthermore, the activation of extrasynaptic NMDARs in a mouse model of AD promotes β-secretase-mediated cleavage of APP, which results in increased levels of Aβ that are directly correlated with the severity of the cognitive deficit[27]. The presence of Aβ oligomers — early intermediates in the Aβ aggregation pathway — has in turn been associated with increased activation of extrasynaptic NMDARs, which could cause a feedback loop that leads to synaptic dysfunction[28]. However, the strongest evidence for the role of extrasynaptic NMDARs in cognitive impairment is the effectiveness of the NMDAR blocker memantine in rodent models of HD and AD as well as in patients with AD[24,29–31].

Therapeutic approaches. Inhibition of extrasynaptic NMDARs can be achieved using memantine. At a low dose (1 mg per kg, which is a human equivalent dose of 3 mg per m^2) memantine blocks extrasynaptic but not synaptic NMDAR activity in a mouse model of HD, whereas high doses of memantine (30 mg per kg, which is a human equivalent dose of 90 mg per m^2) inhibit both synaptic and extrasynaptic NMDAR activity (FIG. 1). A low dose of memantine rescues neuropathological and behavioural phenotypes as well as electrophysiological abnormalities in mouse models of HD. By contrast, administration of a high dose of memantine worsens these symptoms[24,29]. Similarly, the administration of a low dose of memantine in a mouse model of AD corrected defects in learning and memory tasks, such as performance in the Morris water maze test and passive avoidance learning[30].

Table 2 | **Target-validation scoring**

Score	Description
1.0	The gene or protein has been experimentally linked to a disease-relevant biological mechanism
2.0	The protein is associated with the disease and binds to a disease-causing protein; alternatively, the gene has an altered expression pattern in the disease, or the protein has an altered cellular distribution in the disease
2.5	The gene or protein has an altered pathway or functional activity in the disease
3.0	The gene or protein shows a causal relationship with the disease when it is manipulated genetically or pharmacologically in an *in vitro* or lower organism (non-rodent) model of the disease
3.5	When genetically manipulated, the gene modifies the disease phenotype in a rodent model of the disease or shows disease-like effects in a normal rodent; alternatively, the gene is identified as a genetic modifier of the disease phenotype in humans by a linkage analysis or association study
4.0	A therapeutically relevant drug or genetic intervention that is highly specific for the gene or protein target improves the disease phenotype in a rodent model of the disease
4.5	Manipulation of the gene or protein target improves the disease phenotype in a larger non-rodent mammalian model of the disease
5.0	A drug or gene therapy that is known to modulate the gene or protein target demonstrates a positive outcome in a Phase II clinical trial
6.0	A drug or gene therapy that is known to modulate the gene or protein target demonstrates efficacy in a Phase III clinical trial

Memantine treatment has also been tested in patients with AD, and is now approved by the US Food and Drug Administration for this indication (Namenda XR, Forest Laboratories). In clinical trials, patients with AD who received 28 mg of memantine (an extended-release formulation) for 24 weeks had a significantly reduced decline in cognitive symptoms in two measures of cognitive performance compared to patients receiving placebo. Longer studies are needed, however, to determine whether the effects of memantine are purely symptomatic or disease-modifying. Nevertheless, the improvements seen in patients with AD are encouraging, and NR2B-containing NMDARs are currently the best validated of the shared therapeutic targets between AD and HD, with target-validation scores of 6.0 and 4.0, respectively (See Supplementary information S1 (table)). In view of open-label studies in which memantine shows some potential therapeutic benefit in patients with HD, further clinical trials with memantine should be considered[32–34].

Non-neuronal contributions to excitotoxicity

Another striking similarity between AD and HD is the presence of activated microglia that act as markers of inflammation[5,14]. Microglia produce quinolinic acid, which is a metabolite of the tryptophan degradation pathway and a selective NMDAR agonist; it elicits symptoms that are similar to HD when it is injected into the striatum of rodents, and symptoms that are similar to AD when it is injected into the nucleus basalis of rodents[35]. Furthermore, a recent study has demonstrated that inhibiting kynurenine 3-monooxygenase, an enzyme involved in the metabolic pathway that generates quinolinic acid, can ameliorate excitotoxicity and disease phenotypes in mouse models of AD and HD[35].

Modulating neurotrophic factors and receptors

Neurotrophic factors, including NGF and BDNF, are secreted peptides that have prominent roles in neuronal development and health, as well as in the function of the regions of the brain that are most affected in patients with AD and HD[36]. NGF specifically binds to neurotrophic tyrosine kinase receptor type 1 (NTRK1; also known as TRKA) receptors, whereas BDNF recognizes NTRK2 (also known as TRKB) to activate downstream signalling pathways. In addition, both neurotrophic factors bind to the nerve growth factor receptor (NGFR; also known as p75NTR) with lower affinity, which is associated with pro-death signalling following neuronal injury[36] (FIG. 2). The unprocessed precursor forms of NGF and BDNF (pro-NGF and pro-BDNF, respectively) also bind to p75NTR, leading to apoptosis[36]. Alterations in the levels of NGF and BDNF, the levels and localization of cognate receptors and changes in the pathways activated by these neurotrophins have been implicated in the pathogenesis of HD and AD (FIG. 2; Supplementary information S1 (table)).

Increasing BDNF levels as a therapeutic approach. Reduced levels of BDNF have been observed in the striatum and hippocampus of patients suffering from HD and AD, respectively[37,38]. Polymorphisms in the *BDNF* gene have been positively associated with the age of onset of AD in some studies[39–41], although this association is controversial in some studies but not others[42–44]. Similarly, data on an association between *BDNF* polymorphisms and the age of onset in HD have also been conflicting[45,46].

The ability to increase BDNF levels through exercise is well documented[47]. Using transgenic mice harbouring mutations in *APP* and *PSEN1* genes (*APP*/*PSEN1*-transgenic mice), it has been shown recently that exercise increases BDNF levels and prevents a decline in spatial learning and memory through the improvement of LTP in the hippocampus[48]. The beneficial effects of BDNF overexpression using genetically modified mesenchymal stem cell transplantation, viral-mediated expression or intracranial injections of BDNF in different rodent models of HD and AD have validated BDNF as a therapeutic target and led to target-validation scores of 4.5 and 4.0 for AD and HD, respectively (Supplementary information S1 (table)). Overexpression of BDNF protects against neurotoxicity, prevents the loss of neurons, corrects motor dysfunction, improves procedural learning and corrects synaptic plasticity in mouse models of AD and HD[49–51]. Increasing BDNF levels in a non-human primate model of AD also improved hippocampal learning and ameliorated neuronal death with no observable adverse effects[52].

Pharmacological agents that are currently used or being investigated for other clinical applications, such as lithium or the ampakine CX929, can increase BDNF levels by increasing its expression and promoting its

Microglia
Resident macrophages of the central nervous system that initiate immune responses and inflammation in the brain.

Excitotoxicity
A pathological process that is mediated through excessive stimulation of NMDA (*N*-methyl-D-aspartate) receptors by glutamate or other agonists. Increased activation of these receptors leads to a massive influx of calcium, which activates pro-death signalling pathways.

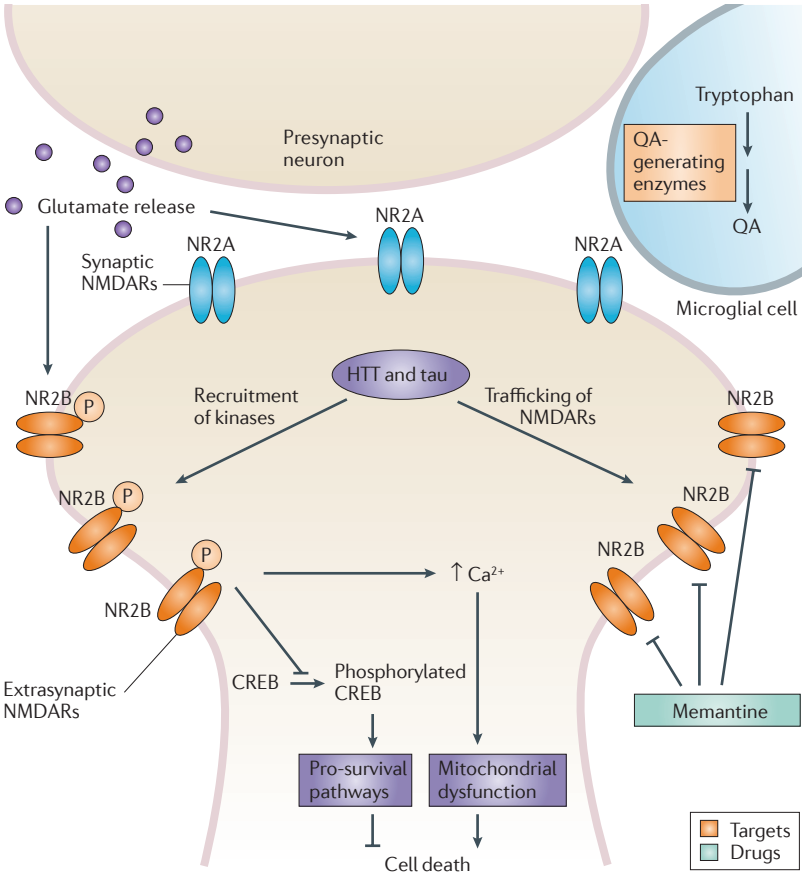

Figure 1 | **Therapeutic targets in the synaptic dysfunction pathway.** *N*-methyl-D-aspartate receptor (NMDAR) receptor signalling can be triggered by glutamate, which is released from the presynaptic neuron, or by the NMDAR agonist quinolinic acid (QA), which is a product of tryptophan metabolism in microglia. Although glutamate-mediated activation of synaptic NMDARs promotes neuronal survival, QA leads to excessive NMDAR activation and synaptic dysfunction. The levels of QA generation can be altered through inhibition of kynurenine 3-monooxygenase, an enzyme involved in tryptophan metabolism. An imbalance in levels of synaptic and extrasynaptic NMDARs is seen in both Huntington's disease and Alzheimer's disease. The huntingtin (HTT) protein and microtubule-associated protein tau are involved in regulating the trafficking of NMDAR subunit 2B (NR2B) to the extrasynaptic membrane. NR2B-containing NMDARs are hyperphosphorylated as mutant HTT and tau increase the recruitment of kinases to NR2B. An increase in the levels and phosphorylation of NR2B-containing NMDARs leads to an increase in extrasynaptic NMDA currents that triggers cell death through multiple pathways. Two major pathways leading to cell death in Huntington's disease and Alzheimer's disease are represented in this figure: inhibition of cyclic AMP-responsive element-binding protein (CREB) phosphorylation, which leads to inhibition of pro-survival pathways; and an increase in calcium influx, which leads to mitochondrial dysfunction.

trafficking, and improve phenotypes in animal models of HD and in patients suffering from AD[53,54]. A Phase II clinical trial studying the effect of lithium treatment in patients with AD is currently underway (ClinicalTrials.gov identifier: NCT00088387), and in a small cohort of patients lithium reduced the progression from mild cognitive impairment to AD[55]. In addition to increasing BDNF levels, lithium inhibits the hyperphosphorylation of tau mediated by glycogen synthase kinase 3β (GSK3β), and activates autophagy as well as pro-survival signalling mediated by cyclic AMP-responsive element-binding protein[56–59] (FIG. 2). Owing to these multiple effects, lithium is a suboptimal tool compound for investigating specific pathways but it remains a potential therapeutic for both AD and HD.

Trafficking defects in HD and AD: targeting microtubule-associated proteins. Striatal medium spiny neurons rely on the release of BDNF from innervating cortical neurons for their normal functioning and survival, which means that axonal trafficking of BDNF from the cell body of cortical neurons to the synapse is an important process in ensuring the survival and functioning of medium spiny neurons[60]. Defects in intracellular trafficking have been suggested as a cause for the reduced BDNF levels in the brains of patients with HD or AD[60,61]. Interestingly, polymorphisms in the *BDNF* gene that are associated with an increased risk of AD and reduced age of onset of HD impair the binding of pro-BDNF to huntingtin-associated protein 1 (HAP1), which is necessary for the intracellular trafficking of pro-BDNF[60,62]. These polymorphisms could therefore lead to reduced BDNF levels in both diseases (FIG. 2).

HTT and tau are predominantly found in the cytoplasm, where they colocalize with microtubules and vesicular structures and associate with proteins that are involved in intracellular trafficking[61,63]. Wild-type HTT interacts with HAP1, which in turn interacts with proteins that are essential for intracellular trafficking, such as kinesin and the p150 subunit of dynactin (DCTN1)[60,63]. Similarly, tau regulates axonal transport by inhibiting the motor activity of kinesin and dynein (FIG. 2; Supplementary information S1 (table))[63,64].

The velocity and efficiency of the transport of BDNF-containing vesicles are reduced in the presence of mutant HTT and PSEN1, as well as hyperphosphorylated tau[60,61]. In neuronal cultures and post-mortem extracts of brain tissue taken from patients with HD, mutant HTT binds to HAP1 with increased affinity, which in turn disrupts the binding of HAP1 to kinesin and weakens the HAP1–DCTN1 interaction, thereby reducing the efficiency and velocity of the transport of BDNF-containing vesicles[60]. Interestingly, HAP1 deficiency also affects kinesin-dependent transport of APP, which suggests that HAP1 may have a role in the pathogenesis of AD[65]. Mutations in *PSEN1* that are associated with FAD deregulate GSK3β, leading to hyperphosphorylation of tau and its detachment from microtubules, which results in cytoskeletal collapse and deficits in axonal transport — both of which contribute to the pathogenesis of AD[61,66,67] (FIG. 2).

Although there are currently no therapies available that can ameliorate trafficking deficits to increase BDNF levels, the BDNF trafficking pathway has many potential therapeutic targets — such as HAP1, kinesin, dynein and/or DCTN1 and microtubules — that could be modified for the treatment of HD and AD.

Inhibitors of histone deacetylases (HDACs), which are currently being used as cancer therapeutics[68], influence axonal transport through increased acetylation of α-tubulin, which enhances its binding to kinesin[4,69]. Therefore, the effects of HDAC inhibitors

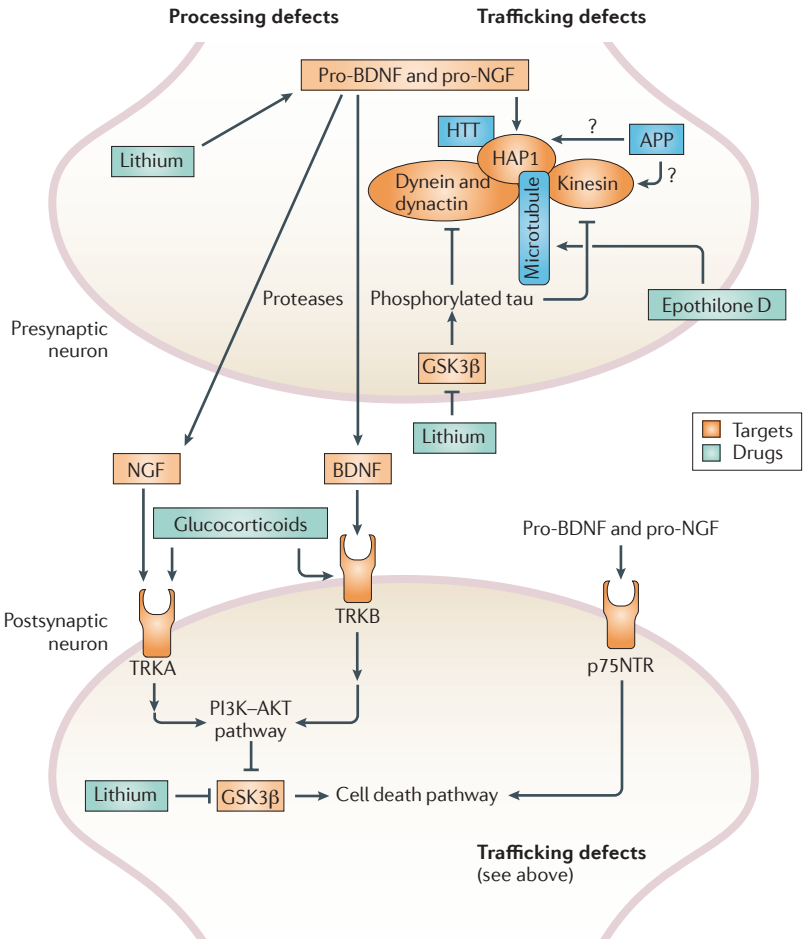

Figure 2 | **Therapeutic targets in the neurotrophin pathway.** Levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are reduced in both Huntington's disease (HD) and in Alzheimer's disease (AD). Presynaptically, the huntingtin (HTT) protein, amyloid precursor protein (APP) and microtubule-associated protein tau influence trafficking mechanisms by interacting with huntingtin-associated protein 1 (HAP1), kinesin, and dynein or dynactin, which influences the binding of HAP1, kinesin and dynein or dynactin to microtubules. The unprocessed precursor forms of BDNF and NGF — pro-BDNF and pro-NGF, respectively — are processed by unknown proteases to generate mature BDNF and NGF. Furthermore, levels of neurotrophic tyrosine kinase receptor type 1 (TRKA) and TRKB are decreased in AD and HD, respectively. Signalling through TRK receptors is reduced, thereby increasing glycogen synthase kinase 3β (GSK3β) activity and enhancing cell death pathways. Increased levels of low-affinity nerve growth factor receptor (p75NTR) and signalling mediated by pro-BDNF and pro-NGF also triggers cell death. Therapeutics that have been examined to target this pathway include epothilone D, BDNF, NGF, glucocorticoids and lithium. PI3K, phosphoinositide 3-kinase.

on kinesin- and/or dynein-mediated axonal transport deserve greater investigation as a potential therapy for HD. The modulation of HAP1 binding to mutant HTT would probably be harder to achieve, as the strengthening of a protein–protein interaction is generally not considered to be a druggable intervention. However, drugs that bind and/or stabilize microtubules — such as paclitaxel and epothilones, which are currently used as a form of cancer therapy[70–72] — could be tested in mouse or rodent models of HD and AD to validate therapeutic targets in axonal transport pathways more effectively (Supplementary information S1 (table)). Epothilone D, a microtubule-binding agent from the epothilone natural product family, has been shown to penetrate the blood–brain barrier and increase microtubule stability in the central nervous system of tau transgenic mice[71]. The identification and evaluation of agents that bind microtubules is therefore a promising area of research for the treatment of neurodegenerative disorders that have impaired axonal transport, such as HD and AD.

Increasing NGF is beneficial. A reduction in the levels of mature NGF is observed in the basal forebrain of aged animals and in rodent models of AD, as well as in patients with AD[73]. However, the levels of NGF in patients with HD have not been reported. Nevertheless, the overexpression of NGF in model systems of HD and AD has beneficial effects that are similar to BDNF overexpression. Rat models of AD and mouse models of HD that are transplanted with NGF-loaded microspheres in the forebrain show significant improvements in learning and memory tasks, and improved survival of cholinergic neurons[74,75]. Intrastriatal transplantation of genetically engineered mesenchymal stem cells expressing NGF and the administration of an amplifier of NGF into transgenic mouse models of HD slows neurodegeneration and rescues behavioural deficits[50].

Therapeutic clinical trials assessing the effects of increasing NGF levels in patients with AD are underway. In a Phase I clinical study, the implantation of modified fibroblasts expressing human NGF in the basal forebrain of patients with AD resulted in a decrease in the rate of cognitive decline[76]. Currently, therapeutic options that are less invasive are being explored, including the intranasal delivery of recombinant NGF, which rescued behavioural and neuropathological defects in a mouse model of AD[77]. NGF — like BDNF — is therefore a highly validated target for AD and HD, with target-validation scores of 4.5 and 4.0, respectively (Supplementary information S1 (table)).

Activating TRK and reducing p75NTR signalling as a therapeutic strategy. In animal models of AD and HD as well as in patients suffering from these diseases, p75NTR levels are increased. In patients and animal models of AD there is a decrease in TRKA levels, and in patients and animal models of HD there is a decrease in TRKB levels[73,78]. Neurotrophin-mediated cell death that occurs through the activation of p75NTR is mediated through caspase 6 activity[79], and this enzyme has emerged as a therapeutic target for both AD and HD in several studies (described below and in Supplementary information S1 (table)).

Neurotrophin signalling through TRK receptors activates pro-survival pathways, such as the phosphoinositide 3-kinase (PI3K)–AKT signalling pathway. However, reduced signalling through TRK receptors results in increased GSK3β activity, which has been implicated in the prevention of LTP, the induction of microglia-mediated inflammation and the promotion of neuronal death in animal models of AD and HD[57,80]. In AD increased GSK3β signalling also increases tau phosphorylation and Aβ production, whereas in HD increased GSK3β activity enhances the toxicity of mutant HTT[57,80].

Caspase 6
A member of the cysteine-aspartic protease (caspase) family that has essential roles in programmed cell death (apoptosis).

Reduced NGF signalling also results in the increased production and intracellular aggregation of Aβ peptides, which is mediated through increased transcription of APP and increased processing of APP by β-secretase and γ-secretases[81]. The pathogenic effects of altered TRK and p75NTR signalling in HD, however, are not well characterized (Supplementary information S1 (table)).

Glucocorticoids have protective effects in the central nervous system, and this protection is dependent on an increase in TRK receptor activity[82]. Glucocorticoid treatment may therefore be beneficial in HD and AD, but this remains to be demonstrated using relevant disease models, as TRK receptors currently have low target-validation scores (FIG. 2; Supplementary information S1 (table)).

Targeting apoptotic pathways

The caspase family of proteases are best known for their roles in apoptotic cell death, where they are activated either by extrinsic signals mediated through death receptors or intrinsic pathways initiated by DNA or mitochondrial damage[83]. Both pathways culminate in the activation of one or more members of the so-called executioner caspase subfamily (caspase 3, caspase 7 and caspase 6), which cleave cytoskeletal proteins as well as pro-survival and anti-apoptotic factors and thereby induce cell death[83]. However, in addition to this classical role, caspases are involved in non-apoptotic processes[84]. In the brain in particular, activation of the executioner caspases has been observed in events associated with learning and memory, such as synaptic plasticity and LTP, as well as in the developmental pruning of axons[85–88]. These findings challenge the view that caspases are only the final executioners of cell death, and suggest that these enzymes may have a role upstream of the signalling pathways that are implicated in neurodegeneration, where they could mediate early neuronal dysfunction.

Preventing caspase 6 cleavage is beneficial in AD and HD. Caspase 6 has been shown to be activated in brain tissue samples taken from pre-symptomatic individuals carrying the *HTT* mutation and in individuals with only mild cognitive impairment (which can progress into AD), which supports the idea that caspase activation is an early event in the pathogenesis of neurodegenerative diseases[89,90]. These findings are paralleled by results that show aberrant cleavage of caspase 6 substrates in brain tissue samples taken from patients with HD or AD[90–92]. Interestingly, the disease-causing proteins mutant HTT, tau and APP are substrates for caspase 6, and the abrogation of mutant HTT or APP cleavage in mouse models has a protective effect — leading to a dramatic improvement in the disease phenotype[93,94].

Therapeutic approaches. Although the findings discussed above make caspase 6 an interesting and well-validated target in the apoptotic pathway of both diseases (Supplementary information S2 (table)), it may not be easily tractable by small-molecule inhibitors. The inhibition of executioner caspases by compounds such as IDN-6,556, compound 34 or M867 may also cause some liabilities, including carcinogenic side effects[95,96]. An alternative would be to inhibit activators of caspase 6. However, the exact mechanism underlying aberrant caspase activation in AD and HD is not fully understood. It could occur through the activation of initiator caspases such as caspase 9, or via death or neurotrophic receptors such as death receptor 6 (also known as tumour necrosis factor superfamily member 1), p75NTR, TRKB or TRKA. As described above, alterations in these receptors occur in HD and AD, and neuronal death mediated through p75NTR in a seizure model is dependent on the downstream activation of caspase 6 (REF. 79) (FIG. 3).

The intrinsic apoptotic pathway is another well-described paradigm for caspase activation, and it can be triggered by endoplasmic reticulum stress, protein misfolding (see below), as well as DNA and mitochondrial damage or oxidative stress[83]. Mutant HTT and Aβ can directly alter mitochondrial function in HD and AD. HTT can be found on the mitochondrial membrane[97], and in the presence of mutant HTT oligomers the expression levels of proteins involved in mitochondrial fusion and fission are altered in mouse models of HD. These changes in the levels of protein expression may be responsible for decreased mitochondrial function by causing structural abnormalities in — and defective trafficking of — mitochondria in HD[97]. In AD, Aβ is accumulated in mitochondria — especially synaptic mitochondria — in an age-dependent manner[98,99], which enhances the permeability of the mitochondrial permeability transition pore and causes the generation of reactive oxygen species[99]. Clinical trials of antioxidants that might ameliorate oxidative stress, as well as DNA and mitochondrial damage, have not yielded conclusive results in patients with AD or HD[100,101]. However, a better understanding of endogenous antioxidant levels in patients before and after treatment might help to stratify potential responders from non-responders[100].

Caspases can also be activated by disturbances in developmental and synaptic plasticity signals such as axonal pruning or LTP[85–88,102]. In these non-apoptotic paradigms, caspase activation is usually contained in a well-defined subcellular compartment such as the synapse, and the active executioner caspases are kept under tight control either by endogenous inhibitor proteins or through degradation by the proteasome[88,103]. This ensures that the activation of enzymes — such as caspase 3 — that are usually highly efficient at amplifying the cell death cascade remains locally contained and does not trigger the death of the cell. Under pathological conditions, toxic proteins or fragments thereof (such as mutant HTT and Aβ) can cause proteasomal dysfunction, which might lead to impaired degradation and thus accumulation of active caspase 6 and caspase 3 (REF. 103). The resulting increase in caspase activity could then lead to an amplification of the apoptotic cascade and induce cell death, even though the initial caspase-activating signal was meant to only trigger non-apoptotic functions.

Further studies are needed to obtain a better understanding of the mechanisms involved in apoptotic pathways in AD and HD, and to more effectively validate therapeutic targets that are further upstream in the signalling cascade.

Apoptotic cell death
Also known as programmed cell death. A mechanism of removing superfluous or damaged cells without eliciting an inflammatory response. It occurs during development and following chronic or acute cell and tissue damage.

Developmental pruning
A change in neuronal structure during development that removes unnecessary neurons or neuronal connections.

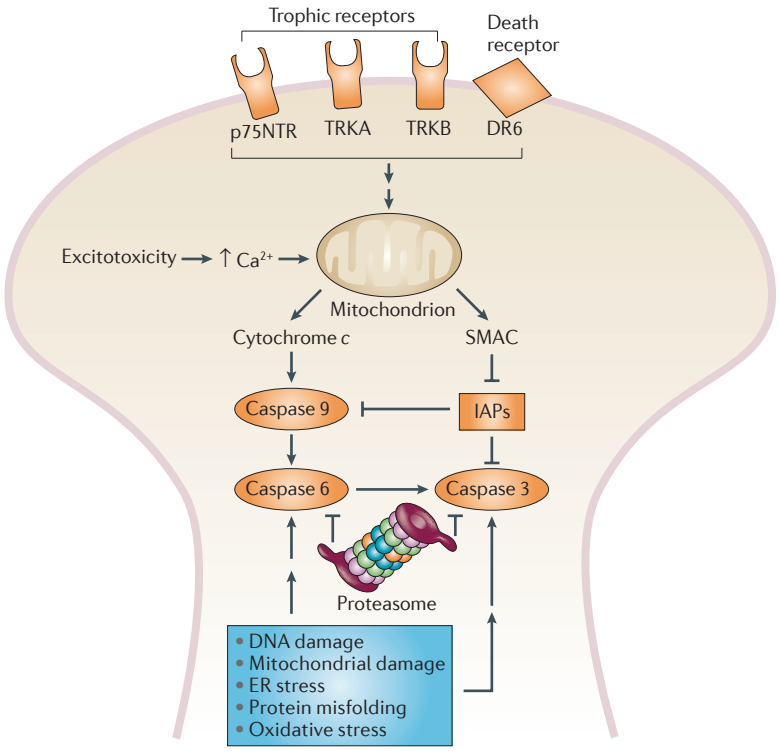

Figure 3 | **Therapeutic targets in the apoptotic pathway.** The aberrant activation of caspase 6 that is seen in animal models and in patients with either Huntington's disease (HD) or Alzheimer's disease (AD) could be mediated through multiple pathways. Excitotoxicity leads to an excessive influx of calcium, which can depolarize mitochondrial membranes and lead to caspase activation. Aberrant signalling through trophic receptors or death receptors (such as death receptor 6 (DR6)) can result in the release of cytochrome c and second mitochondria-derived activator of caspase (SMAC) from mitochondria, which activate caspase 9 and inhibit the apoptosis regulator B cell lymphoma 2 as well as inhibitor of apoptosis proteins (IAPs). These events lead to a subsequent activation of caspase 6, either by blocking inhibitory pathways and/or through direct activation of caspase 9. Furthermore, caspase 6 and caspase 3 could be activated through the intrinsic pathway, as evidence for DNA and mitochondrial damage, endoplasmic reticulum (ER) stress, protein misfolding and oxidative stress has been observed in patients with AD or HD, as well as in animal models. Degradation of caspase 6 through the proteasome reduces its activity. p75NTR, low-affinity nerve growth factor receptor; TRKA, neurotrophic tyrosine kinase receptor 1.

Targeting post-translational modifications

Although the proteolytic cleavage of mutant HTT and APP is a post-translational modification that is involved the pathogenesis of both disorders, additional reversible post-translational modifications of mutant HTT, Aβ and tau have been described[6,9,104]. These additional modifications lead to considerable overlap between potential therapeutic strategies targeting AD and HD, as discussed below.

Kinases and phosphatases. Both mutant HTT and APP are phosphorylated at multiple sites. Phosphorylation at specific amino acid residues (Ser421 for mutant HTT and Thr668 for APP) reduces the amount of caspase-mediated cleavage at adjacent sites as well as the toxicity that is associated with this process[105,106]. Mutant HTT is phosphorylated at Ser421 by AKT, and its dephosphorylation depends on the protein phosphatases PP1 and PP2A[107,108], whereas APP is phosphorylated by cyclin-dependent kinase 5 and GSK3β in neurons[104] (Supplementary information S3 (table)). GSK3β is also the major kinase that phosphorylates tau in AD, which leads to the formation of insoluble tau aggregates (known as tau tangles) and the subsequent disruption of the microtubule system[67]. The phosphatases that are responsible for the dephosphorylation of APP or tau have not yet been discovered.

Therapeutic strategies. Inhibition of GSK3β using lithium has a protective effect in mouse models of AD. This protection has been partly attributed to a decrease in tau hyperphosphorylation and improved BDNF trafficking (as described above) as well as a reduction in APP cleavage and Aβ accumulation, as the GSK3α isoform has been implicated in the processing of APP by γ-secretase[67,109]. Lithium treatment is also beneficial in mouse models of HD[57,110], and levels of GSK3β are increased before the onset of disease symptoms[111]. The treatment of primary neurons derived from mouse models of HD with GSK3β inhibitors reduces neuronal death[111] (Supplementary information S3 (table)).

Sodium valproate, which is widely used as a mood stabilizer and anti-epileptic drug, has promising neuroprotective effects in several mouse models of AD[112]. It inhibits GSK3β, but has additional effects by acting as a transcriptional modulator (through the inhibition of HDACs) and by reducing excitotoxicity[110,113]. Although sodium valproate might not be suitable for the management of agitation in dementia[114], longer-term studies are necessary to ascertain its neuroprotective effects.

Inhibition of PP1 and PP2A is a possible strategy to boost the phosphorylation of mutant HTT in HD and thus reduce its toxicity[108]. As illustrated by the low target-validation score of phosphatases (Supplementary information S3 (table)), further studies are needed before phosphatase inhibition can be pursued as a therapeutic option. Notably, the identity of the regulatory subunits of PP1 and PP2A that mediate HTT dephosphorylation remains unknown. The inhibition of these regulatory subunits might be a more successful strategy than the development of active-site inhibitors, as the active phosphatase subunits are considerably promiscuous in terms of substrate specificity[115]. Conversely, upregulation of AKT activity could be achieved through modulation of the insulin-like growth factor 1 and PI3K signalling pathway upstream of AKT[107]. This pathway has also emerged as a target in the upregulation of autophagy in AD and HD.

Palmitoylation: palmitoyl transferases and thioesterases as targets. Palmitoylation[116–119], a post-translational modification that attaches a single palmitate moiety to a cysteine residue, is important in synaptic transmission and neuronal plasticity[120]. In AD the palmitoylation of β-secretase reduces the shedding of the ectodomain of the protease, which in turn reduces the formation of Aβ[119]. The HTT protein itself is palmitoylated by the palmitoyl transferases huntingtin-interacting protein 14 (HIP14; also known as ZDHHC17) and the related

Post-translational modification
A biochemical change made to a protein after the synthesis of the polypeptide chain is complete. This can include the attachment of lipids, carbohydrates, other small chemical entities (such as phosphate or acetate groups) or peptides (such as ubiquitin or small ubiquitin-related modifier), as well as the proteolytic cleavage of precursor proteins into functional fragments.

protein HIP14L (also known as ZDHHC13)[117], and acts as a cofactor for the palmitoylation of other HIP14 substrates[121]. The interaction of mutant HTT with HIP14 is reduced in a mouse model of HD[118]. The resulting decrease in the palmitoylation of several synaptic substrates could lead to the phenotype that is observed in HD[121] (Supplementary information S3 (table)). Furthermore, the ablation of HIP14 in a mouse model leads to a phenotype similar to HD[122].

An increase in palmitoyl transferase activity or thioesterase inhibition could therefore be beneficial by reducing Aβ generation in AD and by normalizing the aberrant palmitoylation of numerous synaptic substrates in HD. However, because of the lack of information on the palmitoyl transferase (or transferases) involved in β-secretase palmitoylation and the thioesterases involved in the depalmitoylation of HTT or β-secretase, further studies are warranted before targeted therapies to correct palmitoylation defects can be developed.

Aberrant protein acetylation and HDACs. Both AD and HD are associated with transcriptional dysregulation that is linked to altered histone acetylation, and defective axonal transport that is due to a lack of tubulin acetylation[69,123]. These defects could account for several of the disease phenotypes that are associated with AD and HD, such as the altered expression and transport of neurotrophic factors[124], and might therefore be upstream events in the pathogenic pathways of both disorders.

As a therapeutic strategy to increase acetylation, the inhibition of HDACs by compounds such as phenyl butyrate, trichostatin A or suberoylanilide hydroxamic acid (also known as vorinostat) (Zolinza, Merck) has a protective effect in cellular and animal models of AD and HD[69,125,126] (Supplementary information S3 (table)). HDAC inhibitors such as suberoylanilide hydroxamic acid or valproic acid are currently in Phase II/III clinical trials for different types of cancer (ClinicalTrials.gov identifiers: NCT00128102; NCT01386398; NCT00773747; NCT00262834; and NCT00977132), which — together with the high degree of target validation for HDACs — makes them good candidates for clinical trials in neurodegenerative diseases.

Protein aggregation and clearance mechanisms

Protein aggregation is a neuropathological hallmark of AD and HD that has been recognized for many decades. In HD this involves the deposition of intracellular and intranuclear aggregates of mutant HTT, whereas in AD it involves the accumulation of extracellular Aβ plaques and intracellular tau tangles[127]. The accumulation of misfolded proteins that have amyloid characteristics (a tertiary structure that is rich in β-sheets and can be visualized by staining with dyes such as Congo red and thioflavin S) is thought to result from improper folding of the mutant proteins as well as insufficient clearance mechanisms[128]. Endogenous chaperones, in particular the heat shock proteins, prevent the misfolding and aggregation of mutant HTT, tau and Aβ[129], and their overexpression is protective against neurotoxic insults such as excitotoxicity[130] (Supplementary information S4 (table)).

Targeting protein misfolding directly and/or through chaperones. Screening campaigns have led to the identification of several compounds that directly interfere with the misfolding and aggregation of Aβ, mutant HTT and tau in cell-free systems, as well as compounds that modulate the activity of heat shock proteins and other chaperones[131–137] (FIG. 4). However, for both classes of compounds the translation of therapeutic efficacy into mouse models has been difficult.

Geldanamycin, a compound that is highly efficient in the upregulation of chaperone proteins and can thus reduce amyloid formation in cell culture, has the drawback of having substantial toxicity and low blood–brain barrier penetration. Another example is epigallocatechin-3-gallate, a compound that has a beneficial effect in patients suffering from systemic amyloidosis by reducing the amount of aggregated protein in tissues such as the heart[138]. It stabilizes the non-toxic forms of both mutant HTT and Aβ (which have a low β-sheet content)[133,134], and although some studies report beneficial effects of this compound in animal models of AD[139], its delivery into the central nervous system is difficult[140]. Lack of translation of the effects seen in cell culture into mouse models has also been attributed to the high drug–amyloid protein ratios that need to be achieved to directly modulate protein aggregation.

A major limitation of the development of inhibitors of protein aggregation is an incomplete understanding of the protein misfolding and aggregation pathway. Although early studies focused on preventing the formation of large amyloid aggregates, it is now clear that misfolding events that occur at an early stage in the amyloidogenic process lead to the generation of monomers or small oligomers that can mediate neurotoxicity and degradation[141,142]. Owing to the difficulties associated with detecting these smaller toxic monomers or oligomers, the exact mechanism of action for many aggregation inhibitors — such as the benzothiazoles, C2-8 or triazines — remains unknown. Moreover, although they prevent the formation of large Aβ plaques and mutant HTT aggregates[131,132,135], these inhibitors might not interfere with the initial misfolding steps and thus they will not have a substantial impact on the pathogenesis of AD and HD (FIG. 4).

Proof of the therapeutic benefits of inhibitors of protein aggregation through studies in mammalian models of AD and HD is therefore necessary to increase their target-validation score (Supplementary information S4 (table)). Such studies would also ascertain whether the prevention of protein aggregation alone is sufficient to slow down the pathogenesis of AD and HD.

Increasing the clearance of misfolded proteins: the ubiquitin–proteasome system as a target. Intracellular aggregates of mutant HTT and tau contain high levels of ubiquitin; this led to the hypothesis that the proteasomal degradation of ubiquitylated proteins could be impaired in HD and AD, and that this might lead to the accumulation of amyloid aggregates[143,144]. There is conflicting evidence for an impairment of the ubiquitin–proteasome system in HD and AD. A time-lapse study

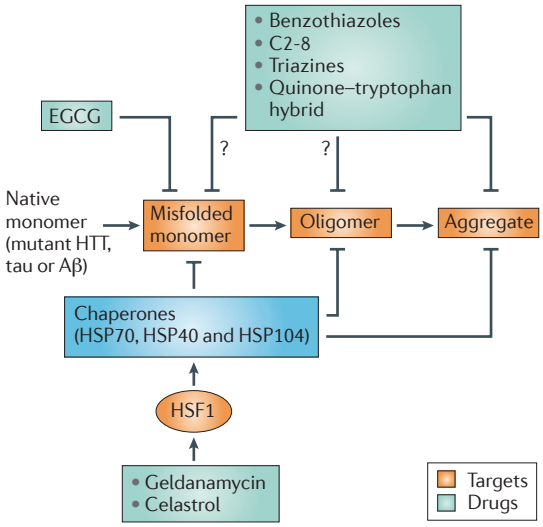

Figure 4 | **Therapeutic targets in the protein misfolding pathway.** The disease-causing proteins mutant huntingtin (HTT), microtubule-associated protein tau and amyloid-β (Aβ) undergo misfolding and aggregation, which is a multistep process involving misfolded monomers, oligomers and large aggregate structures. Endogenous chaperone proteins from the heat shock protein (HSP) family can inhibit aggregation and probably interfere with protein misfolding and aggregation at different steps of the protein misfolding and aggregation pathway. HSPs (such as HSP70, HSP40 and HSP104) can be transcriptionally upregulated through heat shock factor protein 1 (HSF1), which in turn is activated by compounds such as celastrol or geldanamycin that reduce protein aggregation and toxicity in cell cultures and in *Drosophila melanogaster* models of Alzheimer's disease and Huntington's disease. Chemical compounds that directly interfere with the aggregation cascade are often identified as inhibitors of aggregate formation and, with the exception of epigallocatechin-3-gallate (EGCG), the precise step at which they interfere with the aggregation cascade is unknown.

of single neurons expressing mutant HTT showed that the ubiquitin–proteasome system is impaired before the formation of visible aggregates. However, the function of the ubiquitin–proteasome system normalizes at later time points in the presence of aggregates[145]. Recent studies further show that the ubiquitin–proteasome system has an important function in the degradation of signalling molecules at the synapse, and contributes to synaptic plasticity[146]. As synaptic dysfunction occurs at an early stage in the pathogenesis of neurodegenerative diseases, it is possible that localized impairment of the ubiquitin–proteasome system has an important role in the accumulation of misfolded proteins, even if the overall function of the ubiquitin–proteasome system at other subcellular localizations remains intact[147].

Although the ubiquitin–proteasome system is a popular target in cancer, where its activity is reduced by compounds such as bortezomib (Velcade, Millennium Pharmaceuticals)[148], upregulation of proteasomal degradation by a small molecule has only recently been reported[149]. It will be interesting to follow the further development of such compounds and monitor their effects in rodent models of HD and AD, as they are valuable tools for additional validation of the ubiquitin–proteasome system as a therapeutic target.

Lysosomal proteases as therapeutic targets. Macroautophagy is also an important pathway for the elimination of toxic or misfolded proteins. Protein degradation in the autophagic pathway takes place following the fusion of the autophagosome with lysosomes, and these vesicles are known sites of pathology in AD and HD (FIG. 5). Aβ can be generated from APP in autophagic vesicles via its cleavage by γ-secretase, and these vesicles accumulate in dystrophic neurites in patients with AD as well as in mouse models[150]. PSEN1 is not only an essential part of the γ-secretase complex in lysosomes but also necessary for maintaining an acidic pH in these vesicles, which in turn is required to guarantee the degradation of protein cargo[151]. *PSEN1* mutations that are linked to FAD impair this function, leading to the accumulation of vesicles containing Aβ[151].

After the fusion of the autophagosome with the lysosome, proteases of the cathepsin family break down cargo proteins (FIG. 5). The genetic deletion of an endogenous inhibitor of cathepsins — cystatin B — ameliorates the memory deficits and decreases Aβ aggregate load in a mouse model of AD[152], which indicates that lysosomal proteases are able to clear disease-causing proteins in AD and that their upregulation should have a beneficial effect (Supplementary information S4 (table)). It was proposed that the expression of mutant HTT in HD impairs vesicular transport from the Golgi to the lysosomes and thus leads to a reduction in the levels of lysosomal cathepsins[153] (FIG. 5), which would result in inefficient autophagy in HD. Cystatin B knockdown in mouse models of HD and studies with cathepsin inhibitors in animal models of AD and HD could help to further confirm and validate these therapeutic targets.

Targeting the PI3K and BECN1 pathway. The beclin 1 (BECN1)–PI3K complex influences autophagy through the modulation of autophagosome formation, maturation and degradation[154] (FIG. 5). In a mouse model of AD the loss of BECN1 leads to the accumulation of Aβ plaques and lysosomes, as well as neuronal loss[154]. A reduction in the levels of BECN1 leads to the accumulation of mutant HTT and reduces the viability of a mouse model of HD[155]. The autophagic response initiated by the exposure of cultured cells to Aβ is mediated by PI3K[156], and a similar induction of autophagy through PI3K activity occurs in cell-culture models of HD[157]. Conversly, blocking autophagy through the pharmacological inhibition of PI3K activity by 3-methyladenine increases the levels of mutant HTT and reduces the viability of cells expressing mutant HTT[158].

Preservation or upregulation of the function of PI3K and BECN1, which normally declines with age[155], is therefore a promising strategy for increasing the degradation of mutant HTT and Aβ (Supplementary information S4 (table)), although pharmacological agents that could achieve this effect are currently not available. However, *BECN1* gene transfer has been used

Macroautophagy
The second major degradation pathway that can be used to degrade proteins, protein aggregates and entire organelles. Substrates are engulfed by vesicles (autophagosomes) that later fuse with lysosomal vesicles that have proteolytic activity. Degradation occurs in the final autophagolysosome.

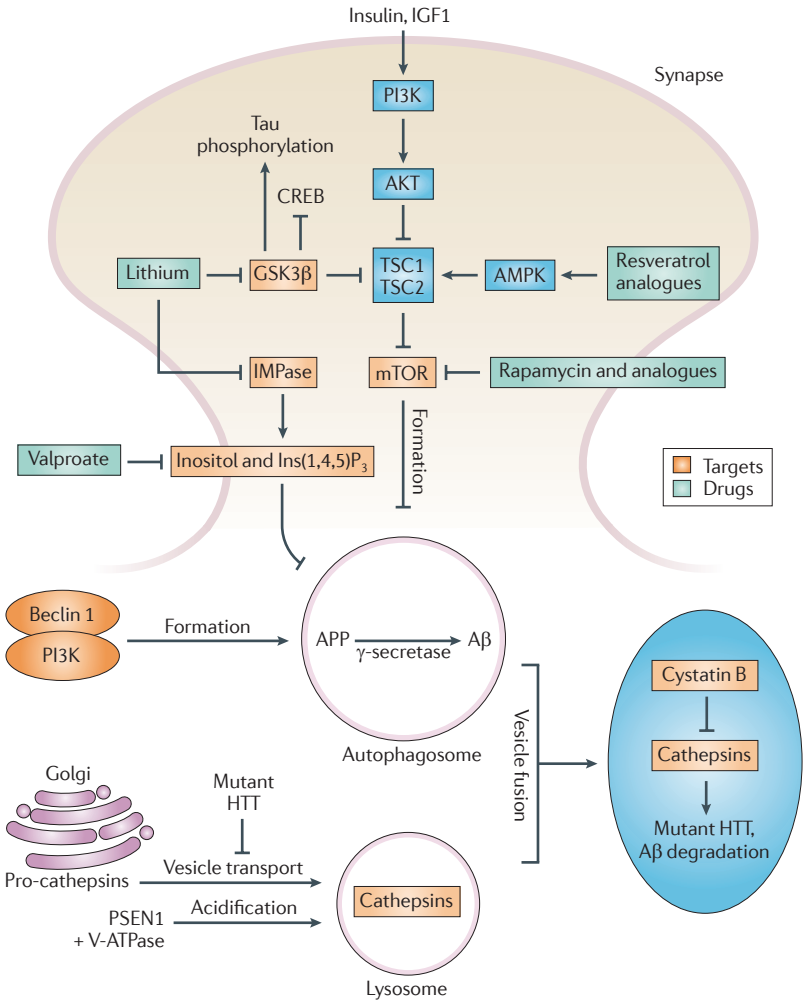

Figure 5 | **Therapeutic targets in the autophagy pathway.** Upregulation of autophagy is an efficient way to clear disease-causing proteins in Alzheimer's disease (AD) and Huntington's disease (HD), and therapeutic interventions have been tested against several targets. The balance between inhibition of autophagy by AKT and its activation by AMP-activated protein kinase (AMPK) is shifted using resveratrol analogues, which increase AMPK activity. Inhibition of glycogen synthase kinase 3β (GSK3β) using lithium prevents excessive phosphorylation of microtubule-associated protein tau and allows pro-survival cyclic AMP-responsive element-binding protein (CREB) signalling; this consequently results in increased autophagy through inhibition of the inositol monophosphatase (IMPase) pathway. Inhibition of mammalian target of rapamycin (mTOR) with rapamycin and analogue compounds lifts the block on autophagosome formation, and these compounds are beneficial in mouse models of both AD and HD. An mTOR-independent pathway that activates autophagy can be triggered by treatment with valproate, and this pathway leads to a decrease in inositol and inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$) levels. The beclin 1–phosphoinositide 3-kinase (PI3K) complex promotes autophagosome formation, and the loss or inhibition of either protein is detrimental in mouse and cell-culture models of AD and HD. Autophagosomes not only engulf aggregates of disease-causing proteins that are present in the cytoplasm but also generate Aβ through γ-secretase-mediated cleavage of APP. Upon fusion with the lysosome, the autophagosome becomes acidic, and lysosomal proteases such as the cathepsins degrade the disease-causing proteins. Genetic deletion of the endogenous cathepsin inhibitor cystatin B is beneficial in a mouse model of AD. Furthermore, mutant huntingtin (HTT) interferes with lysosome function by impairing vesicle transport from the Golgi, resulting in a decrease in levels of proteases in the lysosome. Presenilin 1 (*PSEN1*) deletion or mutations interfere with the acidification of the lysosome, thus reducing the activity of lysosomal proteases and rendering autophagy-mediated protein degradation less efficient. APP, amyloid precursor protein; IGF1, insulin-like growth factor 1; TSC1, tuberous sclerosis 1; V-ATPase, vacuolar ATPase.

successfully to activate autophagy in a mouse model of Parkinson's disease; similar strategies could therefore be tested in models of AD and HD[159].

Targeting mTOR to modulate autophagy. Mammalian target of rapamycin (mTOR) negatively regulates autophagy through the phosphorylation of its target proteins UNC51-like kinase 1 and autophagy-related protein 13 (REF. 160), which prevents the formation of autophagosomes[160] (FIG. 5). The mTOR inhibitors rapamycin (also known as sirolimus) (Rapamune; Pfizer) and its analogues everolimus (Afinitor; Novartis) and temsirolimus (Torisel, Pfizer) increase the autophagic clearance of mutant HTT and Aβ. This has been associated with decreased toxicity in cellular models and the rescue of different disease phenotypes in animal models of AD and HD[161,162] (Supplementary information S4 (table)). These drugs are approved for the prevention of organ transplant rejection and for the treatment of different forms of cancer, and preclinical trials have been carried out for several autoimmune and infectious diseases (reviewed in REF. 163). However, haematological side effects are common and often lead to the termination of treatment[163], so the long-term use of these drugs for HD or AD is unlikely.

An additional pathway for the induction of autophagy has been described, which is independent of mTOR activity and mediated through the inhibition of inositol monophosphatase and the subsequent reduction in inositol or inositol-1,4,5-trisphosphate levels[164]. This inhibition can be therapeutically achieved using lithium or valproate, and has been shown to be beneficial in *Drosophila melanogaster* and zebrafish models of HD[164] (FIG. 5). Lithium has additional effects on neurotrophic factors and tau phosphorylation, and although an initial short-term clinical trial in patients with AD did not result in altered levels of phosphorylated tau[165], a potential disease-modifying effect has been shown in a longer-term study[55]. Moreoever, the so-called small-molecule enhancers of rapamycin are a series of compounds that induce autophagy in neurons independently of mTOR[166], and were protective in a *Drosophila melanogaster* model of HD through an effect that was also independent or downstream of mTOR[167].

In summary, the autophagic pathway contains several well-validated targets (with target-validation scores of 3.0 or higher) that are involved in the pathogenesis of AD and HD. Although the inhibition of mTOR has been studied in great detail, the application of currently available compounds that inhibit autophagy is hampered by severe side effects. If no alternative compounds can be developed, other avenues such as the stabilization of BECN1 could be pursued to increase the autophagic clearance of disease-causing proteins in AD and HD.

Efficient clinical trials through predictive testing

The design of clinical trials for patents with AD has often been criticized for only including patients in late stages of the disease, in whom substantial neurodegeneration has already occurred, or for including patients who

Table 3 | **Comparison of target-validation scores for top targets in AD and HD**

Target	Target-validation score for AD	Target-validation score for HD
NR2B-containing NMDA recepors	6.0	4.0
Brain derived neurotrophic factor	4.5	4.0
Nerve growth factor	4.5	4.0
Histone deacteylases	4.0	4.0
Kynurenine 3-monooxygenase	4.0	4.0
Huntingtin-associated protein 1	2.5	3.5
Caspase 6	3.5	3.5
Caspase 9	3.5	2.5
B cell lymphoma 2	3.5	3.5
Glycogen synthase kinase 3β	3.5	3.0
Heat shock proteins	3.5	3.5
Cystatin B	3.5	Not characterized
Cathepsins	3.5	2.0
Beclin 1	3.5	3.0
Mamalian target of rapamycin	3.5	3.5
Inhibitor of apoptosis proteins	2.0	3.0
Huntingtin-interacting protein 14	Not characterized	3.0
Misfolded proteins (such as mutant huntingtin, amyloid-β or tau)	3.0	3.0
Phosphoinositide 3-kinase	2.0	3.0

AD, Alzheimer's disease; HD, Huntington's disease; NMDA, *N*-methyl-D-aspartate; NR2B, NMDA receptor subunit 2B.

suffer from other forms of dementia instead of AD[168]. There has been substantial progress in the development of biomarkers to reliably diagnose early-stage AD and monitor disease progression. Although levels of total tau, phosphorylated tau and Aβ in the cerebrospinal fluid yield reasonable sensitivity (95%) and specificity (83%)[169], these measures still show considerable variability and so the accurate identification of patients with early-stage AD is difficult[170].

The monogenic cause of HD, however, makes it possible to determine the effect of therapeutic interventions on the onset of disease symptoms in patients who do not yet show substantial neuronal loss. In HD a more homogeneous disease phenotype, better-defined clinical end points and longitudinal markers of disease progression that are currently being established allow the disease-modifying effects of therapeutics to be assessed in a time frame of 1–2 years[16]. In our opinion, compounds that show efficacy in patients with HD could be prioritized for clinical trials in patients with AD, whereas drugs that do not show efficacy in patients with HD could be given lower priority. However, the development of reliable biomarkers that are correlated with early stages of the disease remains a challenge to conducting clinical trials for AD. Currently, therapeutic interventions are being tested in patients with mild cognitive impairment, and their progression to clinically manifest AD is being monitored[55]. Therapeutics that have been beneficial in clinical trials of patients with HD would provide proof of concept that the targeted pathway can be modulated, and could similarly be assessed.

Despite the numerous common therapeutic targets that have been identified for AD and HD, it is unknown why the phenotype of both diseases is different, with different brain areas affected, different sets of proteins misfolded and accumulated, as well as different clinical symptoms observed. The most obvious explanation is the difference in underlying genetic mutations: the aetiology of HD is defined by the expression of the mutant HTT protein, whereas AD is largely of unknown aetiology or — in rare cases — caused by mutations in *APP*, *PSEN1* or *PSEN2*. Differences in the expression patterns of these crucial proteins — including HTT — as well as alterations in protein–protein interactions could account for the susceptibility of distinct neuronal subpopulations to degeneration and death, which are in turn correlated with the major clinical symptoms of chorea in HD or dementia in AD. Although mutant *HTT, APP*, *PSEN1* and *PSEN2* are therapeutic targets in their own right, the dysfunction of these proteins triggers the activation of pathogenic pathways that are shared between AD and HD and that constitute promising therapeutic targets. We believe that the modulation of these targets is likely to be possible using the same therapeutic strategy for both diseases (TABLE 3), and that these interventions will also result in similar side effects for both patient subpopulations.

Overall, the convergence of pathways that are shared between AD and HD should encourage greater interaction between scientists from both AD and HD research communities, as lessons learned from one disorder may have an impact on the other disorder.

1. Alzheimer's Association, Thies, W. & Bleiler, L. 2011 Alzheimer's disease facts and figures. *Alzheimers Dement.* **7**, 208–244 (2011).
2. Novak, M. J. & Tabrizi, S. J. Huntington's disease. *BMJ* **340**, c3109 (2010).
3. Mihaescu, R. *et al.* Translational research in genomics of Alzheimer's disease: a review of current practice and future perspectives. *J. Alzheimers Dis.* **20**, 967–980 (2010).
4. Zetzsche, T., Rujescu, D., Hardy, J. & Hampel, H. Advances and perspectives from genetic research: development of biological markers in Alzheimer's disease. *Expert Rev. Mol. Diagn.* **10**, 667–690 (2010).
5. Bi, X. Alzheimer disease: update on basic mechanisms. *J. Am. Osteopath. Assoc.* **110**, S3–S9 (2010).
6. Crews, L. & Masliah, E. Molecular mechanisms of neurodegeneration in Alzheimer's disease. *Hum. Mol. Genet.* **19**, R12–R20 (2010).
7. Karran, E., Mercken, M. & De Strooper, B. The amyloid cascade hypothesis for Alzherimer's disease: an appraisal for the development of therapeutics. *Nature Rev. Drug Discov.* **10**, 698–712 (2011).
8. Southwell, A. L. & Patterson, P. H. Gene therapy in mouse models of huntington disease. *Neuroscientist* **17**, 153–162 (2011).
9. Ehrnhoefer, D. E., Sutton, L. & Hayden, M. R. Small changes, big impact: posttranslational modifications and function of huntingtin in huntington disease. *Neuroscientist* 10 Feb 2011 (doi:10.1177/1073858410390378).
10. Albin, R. L. *et al.* Abnormalities of striatal projection neurons and *N*-methyl-D-aspartate receptors in presymptomatic Huntington's disease. *N. Engl. J. Med.* **322**, 1293–1298 (1990).
11. Price, J. L. *et al.* Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. *Arch. Neurol.* **58**, 1395–1402 (2001).
12. Tagliavini, F. & Pilleri, G. Neuronal counts in basal nucleus of Meynert in Alzheimer disease and in simple senile dementia. *Lancet* **1**, 469–470 (1983).
13. Mouton, P. R., Martin, L. J., Calhoun, M. E., Dal Forno, G. & Price, D. L. Cognitive decline strongly correlates with cortical atrophy in Alzheimer's dementia. *Neurobiol. Aging* **19**, 371–377 (1998).
14. Zuccato, C., Valenza, M. & Cattaneo, E. Molecular mechanisms and potential therapeutical targets in Huntington's disease. *Physiol. Rev.* **90**, 905–981 (2010).
This is a comprehensive review of the molecular mechanisms and therapeutic targets that are involved in HD.
15. Kwak, S. P., Wang, J. K. T. & Howland, D. S. in *Neurobiology of Huntington's Disease: Applications to Drug Discovery* (eds Lo, D. C. & Hughes, R. E.) 85–120 (CRC, Boca Raton, Florida, 2011).
16. Tabrizi, S. J. *et al.* Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol.* **10**, 31–42 (2011).
This is a detailed study on the feasibility of clinical trials in patients without (or with very early) manifest symptoms of HD, including clearly defined end points and power calculations used in statistical comparisons.
17. Ehrnhoefer, D. E., Butland, S. L., Pouladi, M. A. & Hayden, M. R. Mouse models of Huntington disease: variations on a theme. *Dis. Model. Mech.* **2**, 123–129 (2009).
18. Fernandes, H. B. & Raymond, L. A. in *Biology of the NMDA receptor (Frontiers in Neuroscience)* Ch.2 (ed. Van Dongen, A. M.) 17–40 (CRC, Boca Raton, 2009).
19. Hoe, H. S. *et al.* The effects of amyloid precursor protein on postsynaptic composition and activity. *J. Biol. Chem.* **284**, 8495–8506 (2009).
20. Song, C., Zhang, Y., Parsons, C. G. & Liu, Y. F. Expression of polyglutamine-expanded huntingtin induces tyrosine phosphorylation of *N*-methyl-D-aspartate receptors. *J. Biol. Chem.* **278**, 33364–33369 (2003).
21. Roberson, E. D. *et al.* Amyloid-β/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. *J. Neurosci.* **31**, 700–711 (2011).
22. Ittner, L. M. *et al.* Dendritic function of tau mediates amyloid-β toxicity in Alzheimer's disease mouse models. *Cell* **142**, 387–397 (2010).
23. Hu, J. L., Liu, G., Li, Y. C., Gao, W. J. & Huang, Y. Q. Dopamine D1 receptor-mediated NMDA receptor insertion depends on Fyn but not Src kinase pathway in prefrontal cortical neurons. *Mol. Brain* **3**, 20 (2010).
24. Okamoto, S. *et al.* Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. *Nature Med.* **15**, 1407–1413 (2009).
This is a detailed analysis of the mechanism of action of memantine, and a demonstration of its beneficial effects in a mouse model of HD.
25. Sydow, A. *et al.* Tau-induced defects in synaptic plasticity, learning, and memory are reversible in transgenic mice after switching off the toxic Tau mutant. *J. Neurosci.* **31**, 2511–2525 (2011).
26. Kung, V. W., Hassam, R., Morton, A. J. & Jones, S. Dopamine-dependent long term potentiation in the dorsal striatum is reduced in the R6/2 mouse model of Huntington's disease. *Neuroscience* **146**, 1571–1580 (2007).
27. Bordji, K., Becerril-Ortega, J., Nicole, O. & Buisson, A. Activation of extrasynaptic, but not synaptic, NMDA receptors modifies amyloid precursor protein expression pattern and increases amyloid-β production. *J. Neurosci.* **30**, 15927–15942 (2010).
28. Li, S. *et al.* Soluble Aβ oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. *J. Neurosci.* **31**, 6627–6638 (2011).
29. Milnerwood, A. J. *et al.* Early increase in extrasynaptic NMDA receptor signaling and expression contributes to phenotype onset in Huntington's disease mice. *Neuron* **65**, 178–190 (2010).
30. Filali, M., Lalonde, R. & Rivest, S. Subchronic memantine administration on spatial learning, exploratory activity, and nest-building in an APP/PS1 mouse model of Alzheimer's disease. *Neuropharmacology* **60**, 930–936 (2011).
31. Schulz, J. B. *et al.* Sustained effects of once-daily memantine treatment on cognition and functional communication skills in patients with moderate to severe Alzheimer's disease: results of a 16-week open-label trial. *J. Alzheimers Dis.* **25**, 463–475 (2011).
32. Beister, A. *et al.* The *N*-methyl-D-aspartate antagonist memantine retards progression of Huntington's disease. *J. Neural Transm. Suppl.* **68**, 117–122 (2004).
33. Hjermind, L. E., Law, I., Jonch, A., Stokholm, J. & Nielsen, J. E. Huntington's disease: effect of memantine on FDG–PET brain metabolism? *J. Neuropsychiatry Clin. Neurosci.* **23**, 206–210 (2011).
34. Ondo, W. G., Mejia, N. I. & Hunter, C. B. A pilot study of the clinical efficacy and safety of memantine for Huntington's disease. *Parkinsonism Relat. Disord.* **13**, 453–454 (2007).
35. Zwilling, D. *et al.* Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration. *Cell* **145**, 863–874 (2011).
This study provides proof of concept for the beneficial effects of the therapeutic modulation of the pathway that generates quinolinic acid in mouse models of AD and HD.
36. Hennigan, A., O'Callaghan, R. M. & Kelly, A. M. Neurotrophins and their receptors: roles in plasticity, neurodegeneration and neuroprotection. *Biochem. Soc. Trans.* **35**, 424–427 (2007).
37. Ferrer, I., Goutan, E., Marin, C., Rey, M. J. & Ribalta, T. Brain-derived neurotrophic factor in Huntington disease. *Brain Res.* **866**, 257–261 (2000).
38. Connor, B. *et al.* Brain-derived neurotrophic factor is reduced in Alzheimer's disease. *Brain Res. Mol. Brain Res.* **49**, 71–81 (1997).
39. Voineskos, A. N. *et al.* The brain-derived neurotrophic factor Val66Met polymorphism and prediction of neural risk for Alzheimer disease. *Arch. Gen. Psychiatry* **68**, 198–206 (2011).
40. Bian, J. T., Zhang, J. W., Zhang, Z. X. & Zhao, H. L. Association analysis of brain-derived neurotrophic factor (*BDNF*) gene 196 A/G polymorphism with Alzheimer's disease (AD) in mainland Chinese. *Neurosci. Lett.* **387**, 11–16 (2005).
41. Ventriglia, M. *et al.* Association between the BDNF 196 A/G polymorphism and sporadic Alzheimer's disease. *Mol. Psychiatry* **7**, 136–137 (2002).
42. Desai, P., Nebes, R., DeKosky, S. T. & Kamboh, M. I. Investigation of the effect of brain-derived neurotrophic factor (BDNF) polymorphisms on the risk of late-onset Alzheimer's disease (AD) and quantitative measures of AD progression. *Neurosci. Lett.* **379**, 229–234 (2005).
43. Bagnoli, S. *et al.* Brain-derived neurotrophic factor genetic variants are not susceptibility factors to Alzheimer's disease in Italy. *Ann. Neurol.* **55**, 447–448 (2004).
44. Combarros, O., Infante, J., Llorca, J. & Berciano, J. Polymorphism at codon 66 of the brain-derived neurotrophic factor gene is not associated with sporadic Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* **18**, 55–58 (2004).
45. Alberch, J. *et al.* Association between BDNF Val66Met polymorphism and age at onset in Huntington disease. *Neurology* **65**, 964–965 (2005).
46. Kishikawa, S. *et al.* Brain-derived neurotrophic factor does not influence age at neurologic onset of Huntington's disease. *Neurobiol. Dis.* **24**, 280–285 (2006).
47. Neeper, S. A., Gomez-Pinilla, F., Choi, J. & Cotman, C. Exercise and brain neurotrophins. *Nature* **373**, 109 (1995).
48. Liu, H. L., Zhao, G., Cai, K., Zhao, H. H. & Shi, L. D. Treadmill exercise prevents decline in spatial learning and memory in APP/PS1 transgenic mice through improvement of hippocampal long-term potentiation. *Behav. Brain Res.* **218**, 308–314 (2011).
49. Arancibia, S. *et al.* Protective effect of BDNF against β-amyloid induced neurotoxicity *in vitro* and *in vivo* in rats. *Neurobiol. Dis.* **31**, 316–326 (2008).
50. Dey, N. D. *et al.* Genetically engineered mesenchymal stem cells reduce behavioral deficits in the YAC 128 mouse model of Huntington's disease. *Behav. Brain Res.* **214**, 193–200 (2010).
51. Blurton-Jones, M. *et al.* Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc. Natl Acad. Sci. USA* **106**, 13594–13599 (2009).
52. Nagahara, A. H. *et al.* Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nature Med.* **15**, 331–337 (2009).
This study demonstrates the therapeutic effects of BDNF in six animal models of AD, including mouse models and non-human primate models.
53. Simmons, D. A. *et al.* Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. *Proc. Natl Acad. Sci. USA* **106**, 4906–4911 (2009).
54. Leyhe, T. *et al.* Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease. *J. Alzheimers Dis.* **16**, 649–656 (2009).
55. Forlenza, O. V. *et al.* Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. *Br. J. Psychiatry* **198**, 351–356 (2011).
56. Toledo, E. M. & Inestrosa, N. C. Activation of *Wnt* signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1ΔE9 mouse model of Alzheimer's disease. *Mol. Psychiatry* **15**, 272–285 (2010).
57. Carmichael, J., Sugars, K. L., Bao, Y. P. & Rubinsztein, D. C. Glycogen synthase kinase-3β inhibitors prevent cellular polyglutamine toxicity caused by the Huntington's disease mutation. *J. Biol. Chem.* **277**, 33791–33798 (2002).
58. Rockenstein, E. *et al.* Neuroprotective effects of regulators of the glycogen synthase kinase-3β signaling pathway in a transgenic model of Alzheimer's disease are associated with reduced amyloid precursor protein phosphorylation. *J. Neurosci.* **27**, 1981–1991 (2007).
59. Quiroz, J. A., Machado-Vieira, R., Zarate, C. A. Jr & Manji, H. K. Novel insights into lithium's mechanism of action: neurotrophic and neuroprotective effects. *Neuropsychobiology* **62**, 50–60 (2010).
60. Gauthier, L. R. *et al.* Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell* **118**, 127–138 (2004).
61. Peethumnongsin, E. *et al.* Convergence of presenilin- and tau-mediated pathways on axonal trafficking and neuronal function. *J. Neurosci.* **30**, 13409–13418 (2010).
62. Wu, L. L., Fan, Y., Li, S., Li, X. J. & Zhou, X. F. Huntingtin-associated protein-1 interacts with pro-brain-derived neurotrophic factor and mediates its transport and release. *J. Biol. Chem.* **285**, 5614–5623 (2010).
63. Harjes, P. & Wanker, E. E. The hunt for huntingtin function: interaction partners tell many different stories. *Trends Biochem. Sci.* **28**, 425–433 (2003).
64. Dixit, R., Ross, J. L., Goldman, Y. E. & Holzbaur, E. L. Differential regulation of dynein and kinesin motor proteins by tau. *Science* **319**, 1086–1089 (2008).

65. McGuire, J. R., Rong, J., Li, S. H. & Li, X. J. Interaction of Huntingtin-associated protein-1 with kinesin light chain: implications in intracellular trafficking in neurons. *J. Biol. Chem.* **281**, 3552–3559 (2006).
66. Lazarov, O. *et al.* Impairments in fast axonal transport and motor neuron deficits in transgenic mice expressing familial Alzheimer's disease-linked mutant presenilin 1. *J. Neurosci.* **27**, 7011–7020 (2007).
67. Sereno, L. *et al.* A novel GSK-3β inhibitor reduces Alzheimer's pathology and rescues neuronal loss *in vivo*. *Neurobiol. Dis.* **35**, 359–367 (2009).
68. Marks, P. A. The clinical development of histone deacetylase inhibitors as targeted anticancer drugs. *Expert Opin. Investig. Drugs* **19**, 1049–1066 (2010).
69. Dompierre, J. P. *et al.* Histone deacetylase 6 inhibition compensates for the transport deficit in Huntington's disease by increasing tubulin acetylation. *J. Neurosci.* **27**, 3571–3583 (2007).
70. Butler, D., Bendiske, J., Michaelis, M. L., Karanian, D. A. & Bahr, B. A. Microtubule-stabilizing agent prevents protein accumulation-induced loss of synaptic markers. *Eur. J. Pharmacol.* **562**, 20–27 (2007).
71. Brunden, K.R. *et al.* Epothilone D improves microtubule density, axonal integrity, and cognition in a transgenic mouse model of tauopathy. *J. Neurosci.* **30**, 13861–13866 (2010).
72. Iwase, H. *et al.* A Phase II multi-center study of triple therapy with paclitaxel, S-1 and cisplatin in patients with advanced gastric cancer. *Oncology* **80**, 76–83 (2011).
73. Schulte-Herbruggen, O., Jockers-Scherubl, M. C. & Hellweg, R. Neurotrophins: from pathophysiology to treatment in Alzheimer's disease. *Curr. Alzheimer Res.* **5**, 38–44 (2008).
74. Gu, H., Long, D., Song, C. & Li, X. Recombinant human NGF-loaded microspheres promote survival of basal forebrain cholinergic neurons and improve memory impairments of spatial learning in the rat model of Alzheimer's disease with fimbria-fornix lesion. *Neurosci. Lett.* **453**, 204–209 (2009).
75. Menei, P. *et al.* Intracerebral implantation of NGF-releasing biodegradable microspheres protects striatum against excitotoxic damage. *Exp. Neurol.* **161**, 259–272 (2000).
76. Tuszynski, M. H. *et al.* A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nature Med.* **11**, 551–555 (2005).
This is a report on the first clinical trial of growth factor therapy in a human neurodegenerative disease.
77. Covaceuszach, S. *et al.* Development of a non invasive NGF-based therapy for Alzheimer's disease. *Curr. Alzheimer Res.* **6**, 158–170 (2009).
78. Zuccato, C. *et al.* Systematic assessment of BDNF and its receptor levels in human cortices affected by Huntington's disease. *Brain Pathol.* **18**, 225–238 (2008).
79. Troy, C. M., Friedman, J. E. & Friedman, W. J. Mechanisms of p75-mediated death of hippocampal neurons. Role of caspases. *J. Biol. Chem.* **277**, 34295–34302 (2002).
80. Peineau, S. *et al.* LTP inhibits LTD in the hippocampus via regulation of GSK3β. *Neuron* **53**, 703–717 (2007).
81. Fombonne, J., Rabizadeh, S., Banwait, S., Mehlen, P. & Bredesen, D. E. Selective vulnerability in Alzheimer's disease: amyloid precursor protein and p75(NTR) interaction. *Ann. Neurol.* **65**, 294–303 (2009).
82. Jeanneteau, F., Garabedian, M. J. & Chao, M. V. Activation of Trk neurotrophin receptors by glucocorticoids provides a neuroprotective effect. *Proc. Natl Acad. Sci. USA* **105**, 4862–4867 (2008).
83. Moffitt, K. L., Martin, S. L. & Walker, B. From sentencing to execution — the processes of apoptosis. *J. Pharm. Pharmacol.* **62**, 547–562 (2010).
84. Feinstein-Rotkopf, Y. & Arama, E. Can't live without them, can live with them: roles of caspases during vital cellular processes. *Apoptosis* **14**, 980–995 (2009).
85. Nikolaev, A., McLaughlin, T., O'Leary, D. D. & Tessier-Lavigne, M. APP binds DR6 to trigger axon pruning and neuron death via distinct caspases. *Nature* **457**, 981–989 (2009).
This study shows that APP-mediated axon pruning and neuronal death result from caspase 6 and caspase 3 activity, respectively.
86. Park, K. J., Grosso, C. A., Aubert, I., Kaplan, D. R. & Miller, F. D. p75NTR-dependent, myelin-mediated axonal degeneration regulates neural connectivity in the adult brain. *Nature Neurosci.* **13**, 559–566 (2010).
87. Schoenmann, Z. *et al.* Axonal degeneration is regulated by the apoptotic machinery or a NAD^+-sensitive pathway in insects and mammals. *J. Neurosci.* **30**, 6375–6386 (2010).
88. Li, Z. *et al.* Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. *Cell* **141**, 859–871 (2010).
89. Albrecht, S. *et al.* Activation of caspase-6 in aging and mild cognitive impairment. *Am. J. Pathol.* **170**, 1200–1209 (2007).
90. Graham, R. K. *et al.* Cleavage at the 586 amino acid caspase-6 site in mutant huntingtin influences caspase-6 activation *in vivo*. *J. Neurosci.* **30**, 15019–15029 (2010).
91. Guo, H. *et al.* Active caspase-6 and caspase-6-cleaved tau in neuropil threads, neuritic plaques, and neurofibrillary tangles of Alzheimer's disease. *Am. J. Pathol.* **165**, 523–531 (2004).
92. Halawani, D. *et al.* Identification of caspase-6-mediated processing of the valosin containing protein (p97) in Alzheimer's disease: a novel link to dysfunction in ubiquitin proteasome system-mediated protein degradation. *J. Neurosci.* **30**, 6132–6142 (2010).
93. Galvan, V. *et al.* Reversal of Alzheimer's-like pathology and behavior in human APP transgenic mice by mutation of Asp664. *Proc. Natl Acad. Sci. USA* **103**, 7130–7135 (2006).
This study shows that AD-like symptoms in a mouse model can be reversed by preventing the caspase-mediated cleavage of APP.
94. Graham, R. K. *et al.* Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. *Cell* **125**, 1179–1191 (2006).
This study shows that similarly to AD, HD-like symptoms in a mouse model are prevented by making mutant HTT resistant to cleavage by caspase 6.
95. Ghavami, S. *et al.* Apoptosis and cancer: mutations within caspase genes. *J. Med. Genet.* **46**, 497–510 (2009).
96. Philchenkov, A., Zavelevich, M., Kroczak, T. J. & Los, M. Caspases and cancer: mechanisms of inactivation and new treatment modalities. *Exp. Oncol.* **26**, 82–97 (2004).
97. Shirendeb, U. *et al.* Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington's disease: implications for selective neuronal damage. *Hum. Mol. Genet.* **20**, 1438–1455 (2011).
98. Du, H. *et al.* Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. *Proc. Natl Acad. Sci. USA* **107**, 18670–18675 (2010).
99. Pagani, L. & Eckert, A. Amyloid-β interaction with mitochondria. *Int. J. Alzheimers Dis.* **2011**, 925050 (2011).
100. Pratico, D. Evidence of oxidative stress in Alzheimer's disease brain and antioxidant therapy: lights and shadows. *Ann. NY Acad. Sci.* **1147**, 70–78 (2008).
101. Stack, E. C., Matson, W. R. & Ferrante, R. J. Evidence of oxidant damage in Huntington's disease: translational strategies using antioxidants. *Ann. NY Acad. Sci.* **1147**, 79–92 (2008).
102. Jo, J. *et al.* $A\beta_{1-42}$ inhibition of LTP is mediated by a signaling pathway involving caspase-3, Akt1 and GSK-3β. *Nature Neurosci.* **14**, 545–547 (2011).
103. Gray, D. C., Mahrus, S. & Wells, J. A. Activation of specific apoptotic caspases with an engineered small-molecule-activated protease. *Cell* **142**, 637–646 (2010).
104. Schettini, G., Govoni, S., Racchi, M. & Rodriguez, G. Phosphorylation of APP-CTF-AICD domains and interaction with adaptor proteins: signal transduction and/or transcriptional role — relevance for Alzheimer pathology. *J. Neurochem.* **115**, 1299–1308 (2010).
105. Taru, H., Yoshikawa, K. & Suzuki, T. Suppression of the caspase cleavage of β-amyloid precursor protein by its cytoplasmic phosphorylation. *FEBS Lett.* **567**, 248–252 (2004).
106. Warby, S. C. *et al.* Phosphorylation of huntingtin reduces the accumulation of its nuclear fragments. *Mol. Cell Neurosci.* **40**, 121–127 (2009).
107. Humbert, S. *et al.* The IGF-1/Akt pathway is neuroprotective in Huntington's disease and involves Huntingtin phosphorylation by Akt. *Dev. Cell* **2**, 831–837 (2002).
108. Metzler, M. *et al.* Phosphorylation of huntingtin at Ser^{421} in YAC128 neurons is associated with protection of YAC128 neurons from NMDA-mediated excitotoxicity and is modulated by PP1 and PP2A. *J. Neurosci.* **30**, 14318–14329 (2010).
109. Phiel, C. J., Wilson, C. A., Lee, V. M. & Klein, P. S. GSK-3α regulates production of Alzheimer's disease amyloid-β peptides. *Nature* **423**, 435–439 (2003).
110. Chiu, C. T., Liu, G., Leeds, P. & Chuang, D. M. Combined treatment with the mood stabilizers lithium and valproate produces multiple beneficial effects in transgenic mouse models of huntington's disease. *Neuropsychopharmacology* 27 Jul 2011 (doi:10.1038/npp.2011.128).
111. Valencia, A. *et al.* Mutant huntingtin and glycogen synthase kinase 3-β accumulate in neuronal lipid rafts of a presymptomatic knock-in mouse model of Huntington's disease. *J. Neurosci. Res.* **88**, 179–190 (2010).
112. Qing, H. *et al.* Valproic acid inhibits Aβ production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models. *J. Exp. Med.* **205**, 2781–2789 (2008).
113. Gottlicher, M. Valproic acid: an old drug newly discovered as inhibitor of histone deacetylases. *Ann. Hematol.* **83** (Suppl. 1), 91–92 (2004).
114. Herrmann, N., Lanctot, K. L., Rothenburg, L. S. & Eryavec, G. A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* **23**, 116–119 (2007).
115. Fardilha, M., Esteves, S. L., Korrodi-Gregorio, L., da Cruz e Silva, O. A. & da Cruz e Silva, F. F. The physiological relevance of protein phosphatase 1 and its interacting proteins to health and disease. *Curr. Med. Chem.* **17**, 3996–4017 (2010).
116. Cheng, H. *et al.* *S*-palmitoylation of γ-secretase subunits nicastrin and APH-1. *J. Biol. Chem.* **284**, 1373–1384 (2009).
117. Huang, K. *et al.* Neuronal palmitoyl acyl transferases exhibit distinct substrate specificity. *FASEB J.* **23**, 2605–2615 (2009).
118. Yanai, A. *et al.* Palmitoylation of huntingtin by HIP14 is essential for its trafficking and function. *Nature Neurosci.* **9**, 824–831 (2006).
119. Benjannet, S. *et al.* Post-translational processing of β-secretase (β-amyloid-converting enzyme) and its ectodomain shedding. The pro- and transmembrane/cytosolic domains affect its cellular activity and amyloid-β production. *J. Biol. Chem.* **276**, 10879–10887 (2001).
120. Fukata, Y. & Fukata, M. Protein palmitoylation in neuronal development and synaptic plasticity. *Nature Rev. Neurosci.* **11**, 161–175 (2010).
121. Huang, K. *et al.* Wild-type HTT modulates the enzymatic activity of the neuronal palmitoyl transferase HIP14. *Hum. Mol. Genet.* **20**, 3356–3365 (2011).
122. Singaraja, R. R. *et al.* Altered palmitoylation and neuropathological deficits in mice lacking HIP14. *Hum. Mol. Genet.* **20**, 3899–3909 (2011).
123. Robakis, N. K. An Alzheimer's disease hypothesis based on transcriptional dysregulation. *Amyloid* **10**, 80–85 (2003).
124. Hathorn, T., Snyder-Keller, A. & Messer, A. Nicotinamide improves motor deficits and upregulates PGC-1α and *BDNF* gene expression in a mouse model of Huntington's disease. *Neurobiol. Dis.* **41**, 43–50 (2011).
125. Hockly, E. *et al.* Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. *Proc. Natl Acad. Sci. USA* **100**, 2041–2046 (2003).
126. Ricobaraza, A. *et al.* Phenylbutyrate ameliorates cognitive deficit and reduces tau pathology in an Alzheimer's disease mouse model. *Neuropsychopharmacology* **34**, 1721–1732 (2009).
127. Ross, C. A. & Poirier, M. A. Protein aggregation and neurodegenerative disease. *Nature Med.* **10**, S10–S17 (2004).
128. Greenwald, J. & Riek, R. Biology of amyloid: structure, function, and regulation. *Structure* **18**, 1244–1260 (2010).
129. Perrin, V. *et al.* Neuroprotection by Hsp104 and Hsp27 in lentiviral-based rat models of Huntington's disease. *Mol. Ther.* **15**, 903–911 (2007).
130. Dedeoglu, A., Ferrante, R. J., Andreassen, O. A., Dillmann, W. H. & Beal, M. F. Mice overexpressing 70-kDa heat shock protein show increased resistance to malonate and 3-nitropropionic acid. *Exp. Neurol.* **176**, 262–265 (2002).
131. Heiser, V. *et al.* Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: implications for Huntington's disease therapy. *Proc. Natl Acad. Sci. USA* **97**, 6739–6744 (2000).

132. Zhang, X. *et al.* A potent small molecule inhibits polyglutamine aggregation in Huntington's disease neurons and suppresses neurodegeneration *in vivo*. *Proc. Natl Acad. Sci. USA* **102**, 892–897 (2005).
133. Ehrnhoefer, D. E. *et al.* EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers. *Nature Struct. Mol. Biol.* **15**, 558–566 (2008).
134. Ehrnhoefer, D. E. *et al.* Green tea (–)-epigallocatechin-gallate modulates early events in huntingtin misfolding and reduces toxicity in Huntington's disease models. *Hum. Mol. Genet.* **15**, 2743–2751 (2006).
135. Scherzer-Attali, R. *et al.* Complete phenotypic recovery of an Alzheimer's disease model by a quinone-tryptophan hybrid aggregation inhibitor. *PLoS ONE* **5**, e11101 (2010).
136. Hamaguchi, T., Ono, K. & Yamada, M. Anti-amyloidogenic therapies: strategies for prevention and treatment of Alzheimer's disease. *Cell. Mol. Life Sci.* **63**, 1538–1552 (2006).
137. Pickhardt, M. *et al. N*-phenylamine derivatives as aggregation inhibitors in cell models of tauopathy. *Curr. Alzheimer Res.* **4**, 397–402 (2007).
138. Mereles, D., Buss, S. J., Hardt, S. E., Hunstein, W. & Katus, H. A. Effects of the main green tea polyphenol epigallocatechin-3-gallate on cardiac involvement in patients with AL amyloidosis. *Clin. Res. Cardiol.* **99**, 483–490 (2010).
139. Rezai-Zadeh, K. *et al.* Green tea epigallocatechin-3-gallate (EGCG) reduces β-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice. *Brain Res.* **1214**, 177–187 (2008).
140. Smith, A. *et al.* Nanolipidic particles improve the bioavailability and α-secretase inducing ability of epigallocatechin-3-gallate (EGCG) for the treatment of Alzheimer's disease. *Int. J. Pharm.* **389**, 207–212 (2010).
141. Arrasate, M., Mitra, S., Schweitzer, E. S., Segal, M. R. & Finkbeiner, S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* **431**, 805–810 (2004).
142. Umeda, T. *et al.* Intraneuronal amyloid β oligomers cause cell death via endoplasmic reticulum stress, endosomal/lysosomal leakage, and mitochondrial dysfunction *in vivo*. *J. Neurosci. Res.* **89**, 1031–1042 (2011).
143. Davies, J. E., Sarkar, S. & Rubinsztein, D. C. The ubiquitin proteasome system in Huntington's disease and the spinocerebellar ataxias. *BMC Biochem.* **8** (Suppl. 1), 2 (2007).
144. Oddo, S. The ubiquitin-proteasome system in Alzheimer's disease. *J. Cell. Mol. Med.* **12**, 363–373 (2008).
145. Mitra, S., Tsvetkov, A. S. & Finkbeiner, S. Single neuron ubiquitin-proteasome dynamics accompanying inclusion body formation in huntington disease. *J. Biol. Chem.* **284**, 4398–4403 (2009).
146. Bingol, B. & Sheng, M. Deconstruction for reconstruction: the role of proteolysis in neural plasticity and disease. *Neuron* **69**, 22–32 (2011).
147. Wang, J. *et al.* Impaired ubiquitin–proteasome system activity in the synapses of Huntington's disease mice. *J. Cell Biol.* **180**, 1177–1189 (2008).
148. Bedford, L., Lowe, J., Dick, L. R., Mayer, R. J. & Brownell, J. E. Ubiquitin-like protein conjugation and the ubiquitin–proteasome system as drug targets. *Nature Rev. Drug Discov.* **10**, 29–46 (2011).
149. Lee, B. H. *et al.* Enhancement of proteasome activity by a small-molecule inhibitor of USP14. *Nature* **467**, 179–184 (2010).
150. Yu, W. H. *et al.* Macroautophagy — a novel β-amyloid peptide-generating pathway activated in Alzheimer's disease. *J. Cell Biol.* **171**, 87–98 (2005).
151. Lee, J. H. *et al.* Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell* **141**, 1146–1158 (2010).
152. Yang, D. S. *et al.* Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits. *Brain* **134**, 258–277 (2011).
153. del Toro, D. *et al.* Mutant huntingtin impairs post-Golgi trafficking to lysosomes by delocalizing optineurin/Rab8 complex from the Golgi apparatus. *Mol. Biol. Cell* **20**, 1478–1492 (2009).
154. Jaeger, P. A. & Wyss-Coray, T. Beclin 1 complex in autophagy and Alzheimer disease. *Arch. Neurol.* **67**, 1181–1184 (2010).
155. Shibata, M. *et al.* Regulation of intracellular accumulation of mutant Huntingtin by Beclin 1. *J. Biol. Chem.* **281**, 14474–14485 (2006).
156. Lipinski, M. M. *et al.* Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **107**, 14164–14169 (2010).
157. Yamamoto, A., Cremona, M. L. & Rothman, J. E. Autophagy-mediated clearance of huntingtin aggregates triggered by the insulin-signaling pathway. *J. Cell Biol.* **172**, 719–731 (2006).
158. Qin, Z. H. *et al.* Autophagy regulates the processing of amino terminal huntingtin fragments. *Hum. Mol. Genet.* **12**, 3231–3244 (2003).
159. Spencer, B. *et al.* Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in α-synuclein models of Parkinson's and Lewy body diseases. *J. Neurosci.* **29**, 13578–13588 (2009).
160. Wong, E. & Cuervo, A. M. Autophagy gone awry in neurodegenerative diseases. *Nature Neurosci.* **13**, 805–811 (2010).
This is a detailed review on the dysfunction of autophagic pathways in neurodegeneration.
161. Ravikumar, B. *et al.* Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nature Genet.* **36**, 585–595 (2004).
162. Spilman, P. *et al.* Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-β levels in a mouse model of Alzheimer's disease. *PLoS ONE* **5**, e9979 (2010).
163. Sofroniadou, S. & Goldsmith, D. Mammalian target of rapamycin (mTOR) inhibitors: potential uses and a review of haematological adverse effects. *Drug Saf.* **34**, 97–115 (2011).
164. Williams, A. *et al.* Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. *Nature Chem. Biol.* **4**, 295–305 (2008).
165. Hampel, H. *et al.* Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicenter 10-week study. *J. Clin. Psychiatry* **70**, 922–931 (2009).
166. Tsvetkov, A. S. *et al.* A small-molecule scaffold induces autophagy in primary neurons and protects against toxicity in a Huntington disease model. *Proc. Natl Acad. Sci. USA* **107**, 16982–16987 (2010).
167. Floto, R. A. *et al.* Small molecule enhancers of rapamycin-induced TOR inhibition promote autophagy, reduce toxicity in Huntington's disease models and enhance killing of mycobacteria by macrophages. *Autophagy* **3**, 620–622 (2007).
168. Petersen, R. C. Early diagnosis of Alzheimer's disease: is MCI too late? *Curr. Alzheimer Res.* **6**, 324–330 (2009).
169. Hansson, O. *et al.* Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol.* **5**, 228–234 (2006).
170. Ballard, C. *et al.* Alzheimer's disease. *Lancet* **377**, 1019–1031 (2011).
171. Calissano, P., Matrone, C. & Amadoro, G. Nerve growth factor as a paradigm of neurotrophins related to Alzheimer's disease. *Dev. Neurobiol.* **70**, 372–383 (2010).
172. Murer, M. G. *et al.* An immunohistochemical study of the distribution of brain-derived neurotrophic factor in the adult human brain, with particular reference to Alzheimer's disease. *Neuroscience* **88**, 1015–1032 (1999).
173. Colucci-D'Amato, L., Perrone-Capano, C. & di Porzio, U. Chronic activation of ERK and neurodegenerative diseases. *Bioessays* **25**, 1085–1095 (2003).

Acknowledgements
The authors would like to thank W. Song and B. Leavitt for their comments on this article.

Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
Michael Hayden's homepage: http://www.cmmt.ubc.ca/research/investigators/hayden/lab
ClinicalTrials.gov: http://clinicaltrials.gov.
Enroll-HD website: http://www.enroll-hd.org.
FDA approval review, Center for Drug Evaluation and Research (Application number 22-525): http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525Orig1s000MedR.pdf.
HD Research Crossroads website: http://www.hdresearchcrossroads.org.

SUPPLEMENTARY INFORMATION
See online article: S1 (table) | S2 (table) | S3 (table) | S4 (table)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF