NATURE|Vol 443|19 October 2006|doi:10.1038/nature05289

A network dysfunction perspective on neurodegenerative diseases

Jorge J. Palop[1], Jeannie Chin[1] & Lennart Mucke[1]

Patients with Alzheimer's disease or other neurodegenerative disorders show remarkable fluctuations in neurological functions, even during the same day. These fluctuations cannot be caused by sudden loss or gain of nerve cells. Instead, it is likely that they reflect variations in the activity of neural networks and, perhaps, chronic intoxication by abnormal proteins that the brain is temporarily able to overcome. These ideas have far-reaching therapeutic implications.

The prevalence of neurodegenerative diseases is increasing rapidly[1]. Although the speed of research has increased, clinical trials have yielded mostly disappointing results. Are we missing something critical? Are there untested therapeutic entry points that deserve consideration? We propose that reversible network dysfunction may be such an entry point (Figs 1, 2). Although progressive neuronal loss is a hallmark of neurodegenerative disorders (see page 796), some neurological impairment may reflect dysfunction rather than loss of neurons. Abnormal protein assemblies seem to trigger vicious cycles of aberrant neuronal activity and compensatory alterations in neurotransmitter receptors and related signalling pathways that lead to synaptic deficits, disintegration of neural networks, and, ultimately, failure of neurological functions. At least in animal models, some pathogenic cascades can be prevented or reversed by removing abnormal proteins or pharmacologically modulating neuronal activities, interestingly without obvious effects on neuronal number. Enhancing neuronal plasticity might help the remaining neural circuits to compensate for lost or broken circuits and improve overall network performance and neurological function. Improving network activity may also help to prevent the inexorable loss of neuronal processes and cell bodies that occurs in Alzheimer's disease (AD) and other neurodegenerative disorders.

Functional fluctuations and neurological decline

Most clinicians and family members caring for people with neurodegenerative disorders are well aware of the striking fluctuations in functional abilities that these patients experience, often within the same day and covering a surprising range of functional (dis)abilities. The extent of these fluctuations is illustrated by the following caregiver descriptions of patients' best and worst performances within the same day[2]. One carer stated that although at times the patient "was nonsensical, confused, and mumbled incoherently," at other times, "she was almost as she was." And the wife of another patient reported that at one point, "he kept looking for the exit, couldn't find the bedroom or the bathroom and had trouble recognizing me," whereas, at another, "he was alert, opened the door, and greeted me after work. He knew me and seemed pleased to see me." Surprisingly, relatively few studies have systematically investigated this fascinating phenomenon. The few methods available to analyse these fluctuations inclue a scale for clinicans (Clinician Assessment of Fluctuation) and a scale for non-clinicians (One Day Fluctuation Assessment Scale). Results of these scales correlate significantly with each other as well as with neuropsychological and electrophysiological measures[3,4].

Many fluctuations recorded in AD relate to memory, whereas fluctuations in dementia with Lewy bodies (DLB) affect a wider range of functions and tend to be more extreme[2,4]. Fluctuating cognition with pronounced variations in attention and alertness are so characteristic of DLB that they have been made a core feature in the clinical diagnosis of this condition[5]. Why fluctuations are more severe in DLB than AD is not known. It is also not clear whether and to what extent these fluctuations overlap mechanistically with delirium, which occurs at increased frequency in people with dementias, even in the absence of other medical problems[6].

Underlying mechanisms

Because the progressive neurological decline seen in neurodegenerative disorders is associated with neuronal loss, the peak performance of patients at any disease stage may be capped by the loss of neurons. However, the extent to which neurological deficits in such conditions relate directly to neuronal loss is controversial[7–11]. Moreover, similar functional impairments can be caused by processes that do not involve significant neuronal loss[12,13].

It is unlikely that changes in neuronal number account for rapid and reversible fluctuations in neurological functions. Such fluctuations probably reflect complex adjustments in molecules, signalling cascades, synaptic modifications, neuronal activities and network interactions.

Transgenic mouse models expressing abnormal proteins associated with AD, DLB, Parkinson's disease (PD), Huntington's disease (HD) and tauopathies such as frontotemporal dementia (FTD) develop distinct disease-related neurological impairments (Box 1). In transgenic mice,

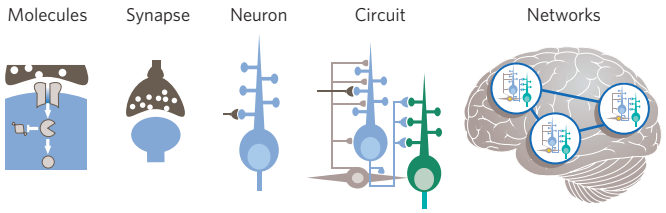


Figure 1 | Neurodegenerative disorders affect neural activities at many levels. Neurodegenerative disorders can disrupt molecular pathways, synapses, neuronal subpopulations and local circuits in specific brain regions, as well as higher-order neural networks. Abnormal network activities may result in a vicious cycle, further impairing the integrity and functions of neurons and synapses, for example, through aberrant excitation or inhibition.

[1]Gladstone Institute of Neurological Disease and Department of Neurology, University of California, San Francisco, California 94158, USA.

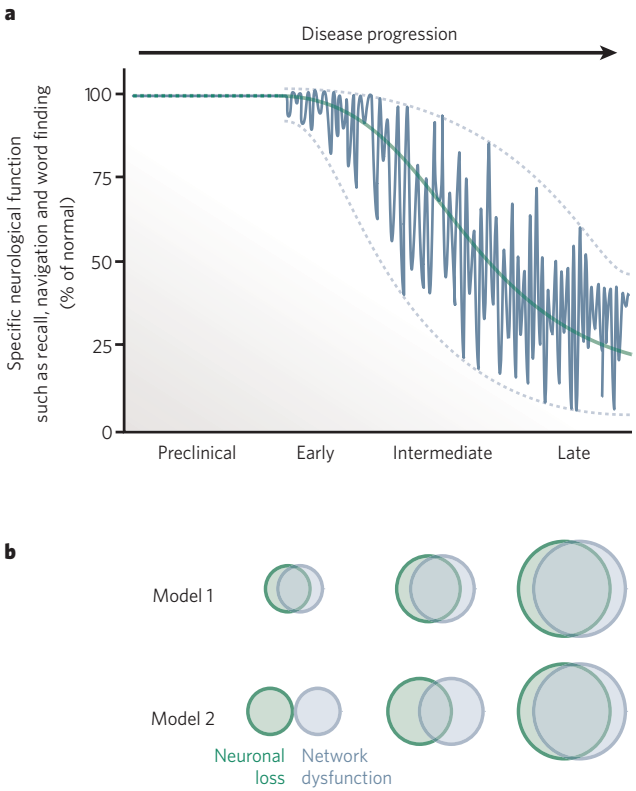


Figure 2 | Functional fluctuations in neurodegenerative disorders may represent fruitful entry points for mechanistic investigations and clinical trials. a, Hypothetical diagram contrasting the relatively rapid functional fluctuations (grey) with the more gradual and prolonged overall neurological decline (green). Understanding the mechanisms that separate the peaks from the troughs of fluctuation might allow the development of drugs to optimize performance and minimize disability at different stages of these conditions. The efficacy of such drugs could be assessed much more rapidly than that of drugs aimed at the gradual decline. If there is mechanistic overlap between the fluctuations and the gradual decline, drugs aimed at the fluctuations may also stall disease progression. **b**, The interdependence between network dysfunction and neuronal loss in neurodegenerative disorders remains to be determined. It could be extensive from the start (model 1) or increase as the diseases progress (model 2).

the elimination of abnormal proteins can reverse neurological deficits without changing neuronal number (Box 1). Thus, some neurological impairments that are associated with neurodegenerative conditions might be caused by neuronal dysfunction rather than neuronal loss. This concept is less radical than it might seem at first glance, given that effective neural plasticity allows the brain to cope surprisingly well with even striking neuronal losses[14,15].

Many factors might influence what different people can accomplish with their surviving neurons at different stages of their illness. These include the functional state of neurons in affected areas[16], the extent to which alternative neural networks can compensate for lost ones[17,18], whether people are able to use specific learning strategies to overcome deficits[19,20], genetic factors such as apolipoprotein-E isoforms[21], and comorbidities such as vascular disease[22]. Several, if not all, of these modulators represent potential targets for therapeutic intervention.

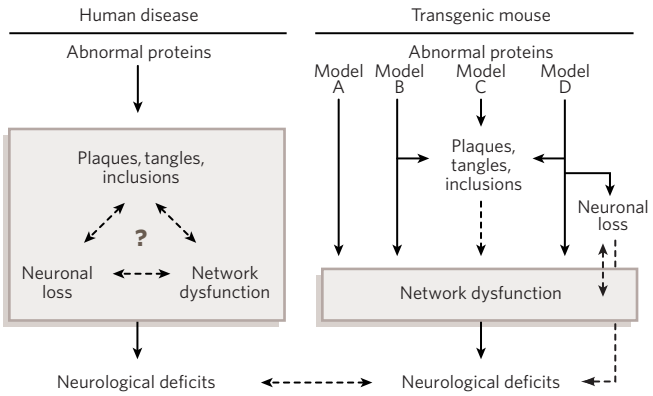
Even in the absence of disease, neural systems are characterized by extensive 'degeneracy' — in other words, the ability of structurally different elements to perform the same function or yield the same output[23,24]. The degeneracy of nervous-system design may help to explain why so many neurons in the substantia nigra can die before they are missed at the clinical level, and why most neurodegenerative diseases progress so gradually. The complexity of compensatory mechanisms is well illustrated by the multi-level adjustments that occur in the cortical–basal-ganglia–thalamocortical network at different stages of PD and in related animal models[16,25]. Progressive failure of these compensatory mechanisms might contribute to the prominent daily fluctuations in the effectiveness (known as the on–off phenomenon) of the drug L-DOPA (L-3,4-dihydroxyphenylalanine) that are often seen in advanced PD.

Thus, within the boundaries set by neuronal loss, the remainder of the nervous system has a notable, albeit variable, capacity to maintain neurological functions. Tremendous benefits might be reaped from therapeutic interventions that maximize a patient's opportunity for optimal performance — shifting the focus from neurons that are lost to those that survive.

From synaptic dysfunction to network failure

Neural plasticity is highly adaptive during both health and disease. It allows animals to interact effectively with their environment and to cope better with neural injuries. A major component of neural plasticity is

Box 1 | Insights from neurodegenerative disease models



In neurodegenerative disorders, the accumulation of abnormal proteins (see page 774), network dysfunction and neurological deficits are associated with pathological hallmarks (plaques, tangles and inclusion bodies) and neuronal loss. Transgenic mouse models can be used to test specific hypotheses about the relationships among these features (see panel, above). The studies highlighted in the table below most strongly support models B and D, demonstrating that some neuronal dysfunction and neurological deficits caused by the abnormal protein assemblies can be independent of plaques, tangles, inclusions and neuronal loss. They also illustrate that reducing the production, enhancing the removal, or neutralizing the actions of abnormal protein assemblies effectively reverses neurological deficits.

Diseases/models	Associated neurological deficits	Prevented or reversed by
Alzheimer's disease		
APP transgenic mice[72]	Learning/memory	Active immunization with Aβ peptides[73,74]
		Intraperitoneal injection of anti-Aβ antibody[75,76]
Huntington's disease		
Huntingtin transgenic mice[36,37]	Locomotor	Downregulation of transgene expression[77,78]
Lewy body diseases including DLB and PD		
α-Synuclein transgenic mice[36]	Locomotor	Active immunization with α-synuclein peptide[79]
Parkin-knockout mice[36]	Locomotor	None known
Tauopathies		
Tau transgenic mice[80]	Learning/memory	Downregulation of transgene expression[81]

APP, amyloid precursor protein.

Box 2 | Mechanisms of neuronal dysfunction in AD models

Normally, neurons are hardy, long-lived cells that adapt swiftly to molecular alterations in their immediate environment and to changes in the activity of the networks they connect with. A common feature of neurodegenerative diseases is the insidious tendency of abnormal protein assemblies to disable mechanisms underlying this remarkable plasticity. Experimental models have helped to identify several molecules that may be involved in this pathogenic process. Although these examples focus on AD and Aβ, mechanisms of neural plasticity are also disrupted in HD and related conditions.

The list below provides details on the structures, molecules and processes that have been implicated in the pathogenesis of AD.

Activity-regulated gene expression

- Immediate-early genes including those encoding Fos and activity-regulated cytoskeletal protein[45,47,82–84]

Cell-surface receptors

- Integrins and cell-adhesion molecules[32,40,85]
- Metabotropic glumate receptors[86]
- Nicotinic acetylcholine receptors[40,82,87,88]
- *N*-methyl-D-aspartate (NMDA) receptors[47,67,87]

Neurotransmitter release

- Synaptic vesicle cycling or exocytosis[89]

Signalling cascades

- Kinase pathways including the mitogen-activated protein kinase superfamily, cyclin-dependent kinase 5 and tyrosine kinases[40,67,82,90–92]
- Phosphatases such as calcineurin and striatal-enriched phosphatase[67,82,87]
- Scaffolding molecules that regulate signalling at the postsynaptic density[93,94]

Synaptic integrity

- Presynaptic terminals[95,96]
- Postsynaptic dendritic spines[97]

Synaptic transmission and plasticity

- Basal synaptic transmission[95,98]
- Long-term potentiation[26,99,100]
- Paired-pulse modification[26]

found in synapses, which are actively strengthened and weakened by complex processes to form the dynamic neural circuits and higher-order networks that store memories, give rise to thoughts and harbour the very essence of who we are. Notably, the abnormal proteins that are suspected of causing neurodegenerative disorders impair the integrity or function of presynaptic terminals and postsynaptic specializations[21,26,27] (Boxes 1, 2). Many mechanisms may be involved, including excitotoxicity[28,29], inflammation[30], oxidative stress[31] and other processes[27,32–34].

In AD, synaptic loss exceeds neuronal loss, and depletion of synapses and synaptic proteins correlates better with cognitive decline than does the abundance of plaques or tangles; comparable findings have also been made in other neurodegenerative conditions[16,35–37].

Chronic alterations in synaptic plasticity and neurotransmission can affect activity-dependent signalling and gene expression, resulting in the disintegration of neural networks and, ultimately, the failure of neural functions (Box 2; Figs 1, 3). Conversely, environmental stimulation, which increases synaptic plasticity, can both delay and decrease pathological alterations, at least in mouse models[37,38].

Although neural plasticity may account, at least in part, for the fact that neurodegenerative disorders typically do not become apparent until old age, these disorders might affect plasticity itself[39]. By eroding the nervous system's main coping mechanism, this 'degeneration of degeneracy' may be a particularly insidious aspect of these conditions, reminiscent of viruses that paralyse the immune mechanisms that the host would use to fend them off.

The lipid carrier apolipoprotein E (apoE) modulates neural plasticity and susceptibility to the most common neurodegenerative disorders. Diverse neural injuries elicit effective plasticity responses with the protective apoE2 and apoE3 isoforms, but not with apoE4, which increases the risk and accelerates the onset of AD, PD and other neurological conditions[21].

Mechanisms that promote or disrupt neural plasticity might be attractive therapeutic targets. However, predicting the potential value of such targets becomes increasingly difficult as one moves away from the most proximal genetic or environmental triggers and down the branching molecular cascades that connect these triggers to neurological decline. A better understanding of the complexities encountered along this path might facilitate the development of more effective treatments.

Complexities in space and time

The same molecular process or drug activity can have very different functional consequences in different cell types. Although this might seem trivial, it is easy to underestimate its importance. For example, amyloid-β (Aβ) binds various cell-surface molecules, including neurotransmitter receptors[40]. The network consequences of this depend on whether Aβ activates or blocks the receptors, and on the cell type on which the receptors are expressed in relevant regions of the AD brain. Overstimulation of a neurotransmitter receptor on excitatory principal cells might result in excitotoxicity, whereas stimulation of a similar receptor on inhibitory interneurons could shut the network down. Overstimulation of such receptors on both types of cell might ignite an ongoing battle between excitatory and inhibitory activities and destabilize the network.

The situation is made still more complex by the expression and modulation of receptors on synaptic versus extrasynaptic sites on the same neuron. The fact that ageing and neurodegenerative disorders can both alter the distribution of neurotransmitter receptors and other molecules makes it even harder to predict the outcome of drug treatments in these diseases. The clinical relevance of these considerations is highlighted by current questions about the wisdom of blocking *N*-methyl-D-aspartate (NMDA) receptors in AD, which is the main effect of the latest drug approved for the treatment of this illness[41].

Neural networks contain a variety of glial cells with which neurons have complex reciprocal interactions. Notably, abnormal proteins can impair neurons indirectly through pathogenic glial loops involving the production of neurotoxic factors by microglia[42,43] or the impairment of astroglial support functions[44].

Complexities can also arise at the level of network interactions (Fig. 3a, b). The radiological, electrophysiological and molecular mapping of neuronal activities across brain regions is beginning to define the functional topology of neurodegenerative disorders, which extends well beyond the areas showing typical pathological alterations[18,45,46].

Discrepancies between neuropathological and functional alterations are perhaps not surprising, because some structural alterations may have little functional consequence, some functional alterations may have no detectable structural correlates, and alterations in one brain region can indirectly affect neuronal functions in other regions through efferent or reciprocal connections. For example, although granule cells in the dentate gyrus typically resist neurodegeneration in AD, they can show considerable Aβ-dependent molecular and functional alterations, possibly reflecting changes in the entorhinal cortex and basal forebrain, from which granule cells receive afferent inputs[45,47,48]. Thus, the differential vulnerability of neuronal populations to functional impairments is probably determined by both cell-autonomous effects of pathogenic factors and alterations in the activity of the networks in which the vulnerable neurons participate.

Pathogenic processes almost always trigger compensatory mechanisms (Fig. 3). The recognition of an abnormality as a compensatory change, as opposed to a (co)pathogenic one, is crucial, because treatments aimed at its reversal might worsen rather than ameliorate the disease. A particularly pertinent example is the recent demonstration

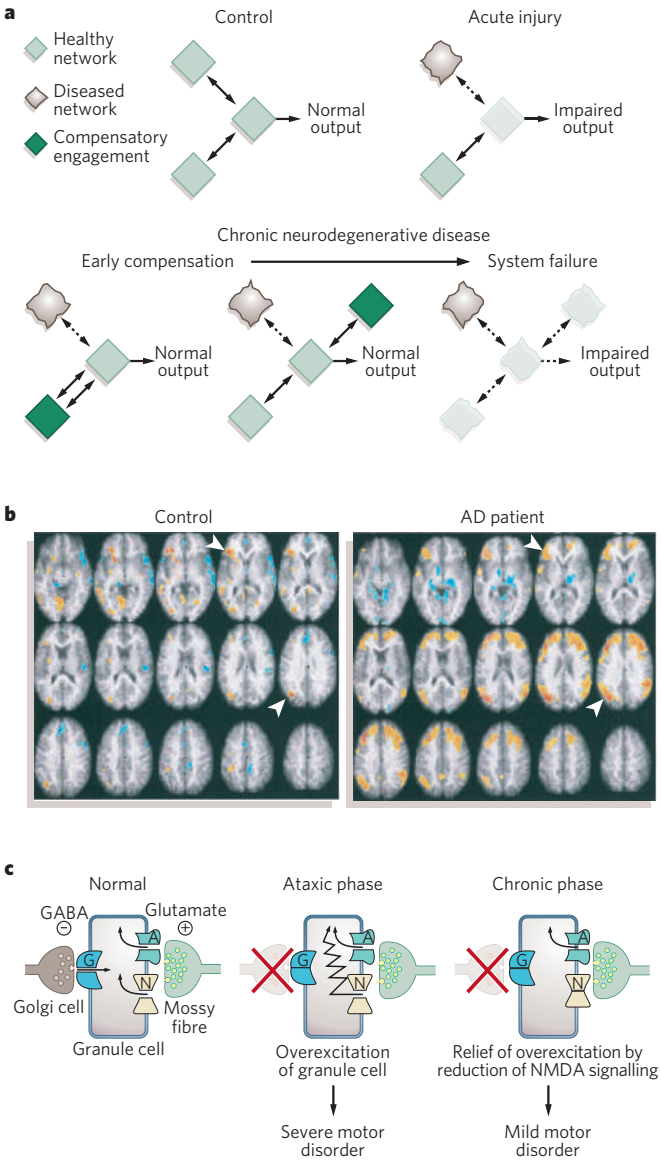


Figure 3 | Neural plasticity counteracts neurodegenerative disorders at multiple levels. a, In the healthy brain, activities in different regions (squares) are balanced for optimal overall network performance. Acute injuries to a specific brain region can destabilize the network, upset the activity in other brain regions, and result in neurological deficits. The chronicity of neurodegenerative diseases allows the brain to engage compensatory mechanisms — for example, increasing neuronal activity in undamaged brain regions that normally participate in affected functions and drawing brain regions into the network that are usually involved in other functions. Over time, however, these compensatory mechanisms can fail, and some may even become co-pathogenic, for example, through the excessive stimulation or inhibition of vulnerable neuronal populations. **b**, Positron emission tomography images from a control subject (left) and a patient with early AD (right), illustrating the activation of additional brain regions in the AD case in response to a semantic and an episodic memory task[69]. Whereas controls demonstrated fairly lateralized left-side activity in prefrontal and temporal cortices, AD patients engaged a network involving the bilateral dorsolateral prefrontal and posterior cortices (arrows). Importantly, *de novo* engagement of these networks in AD patients correlated with better performance on memory tasks (pseudocolour indicates brain areas with significant positive correlation with high performance), suggesting that such recruitment of additional areas represents a compensatory mechanism. Comparable activation patterns have also been observed with functional magnetic resonance imaging[70]. Equally pertinent to our network perspective is the demonstration that cognitive decline in AD is associated with a progressive inability to suppress the activation of task-irrelevant brain regions during visual navigation[46]. (Image reproduced, with permission, from ref. 69.) **c**, A particularly instructive example of injury-responsive neural adaptation has been described by Watanabe and colleagues[51]. γ-Aminobutyric acid (GABA)-containing inhibitory interneurons in the cerebellum of mice were ablated through an immunotoxin approach. Before and after this manipulation, the investigators determined the time it took for mice to fall off a rotating rod as a measure of coordination. An acute phase of ataxia (incoordination) was followed by a chronic recovery phase during which the lesioned mice were able to stay on the rod if it rotated slowly but not if it rotated rapidly. The images provide an interpretation of results obtained in a detailed analysis of synaptic functions during the different stages of neurological impairment. Elimination of inhibitory interneurons resulted in network dysfunction and ataxia through the unopposed overstimulation of NMDA receptors by glutamate. Network activity was then improved, but not fully normalized, by the compensatory reduction of functional NMDA receptors and the adaptation of synaptic transmission, preventing further overexcitation of cerebellar granule cells. (Adapted, with permission, from ref. 71.) A, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor; G, GABA type A receptor; N, NMDA receptor.

that inclusion-body formation in HD does not harm but rather protects neurons against the mutant huntingtin protein[49].

Some compensatory mechanisms may result in cell survival at the cost of network failure[45]. Vulnerability of excitatory neurons to Aβ might depend on the amount of inhibitory activity present in a given circuit (known as the circuit buffer)[47,50]. The compromising nature of injury-responsive synaptic adaptations has been shown elegantly in the neuronal network of the cerebellar cortex[51] (Fig. 3c). This study demonstrates that neural plasticity can result in a significant, albeit partial, recovery of neurological function after destruction of an important neuronal population.

Last, but not least, neurodegenerative diseases are chronic, but not static. For example, choline-acetyltransferase activity in the hippocampus is increased in mild cognitive impairment (MCI), which may precede or represent early AD, but is decreased in later stages of the disease[52], raising questions about the best timing for cholinergic-replacement therapy in AD[53]. Radiological imaging studies in patients with MCI have identified hyperactivation of hippocampal and neocortical regions that become hypoactive and atrophic with the progression to AD[54]. Similarly, neuronal activity in the globus pallidus seems to be increased during early stages and decreased in advanced stages of PD[25].

To facilitate the development of better treatments for neurodegenerative disorders, these intricacies will have to be confronted with diligence and courage.

Therapeutic implications

From a therapeutic perspective, it is crucial to determine whether the early increases in neural activity are compensatory or pathogenic mechanisms, and to differentiate progression of the original pathogenic process from the emergence of co-pathogens and the age-related failure of compensatory mechanisms (Fig. 3a). If the original trigger of disease must persist for the disease to progress, treatments aimed at the trigger might be effective throughout the course of the disease. If, however, the trigger acts in a 'hit-and-run' event[55], setting in motion a self-perpetuating cascade, different stages of disease may require distinct therapeutic interventions.

Although early prevention of neuronal loss is clearly an important objective, it is also important to recognize that a proportion of the deficits associated with neurodegenerative disorders might reflect reversible network dysfunction. The therapeutic implications of such dysfunction can be illustrated with reference to epilepsy. Most cases of epilepsy are of unknown and probably multifactorial origin[56]. Although available antiepileptic drugs are not typically categorized as 'disease modifying', they can make an enormous difference in the lives of epileptic patients. Uncontrolled seizures are associated with neurological decline, neuronal loss and premature mortality[57,58], and antiepileptic drugs reasonably control seizures in many patients[56].

Might improvements in network activities in neurodegenerative disorders have similar benefits? At the very least, optimizing the plasticity

of remaining neural networks could allow patients to function as well as possible within the limits of lost neural structures. In the best case, normalization of network activities could help to prevent progressive loss of neurons, because both excessive and inadequate neuronal stimulation can contribute to neurodegeneration.

What will it take to normalize neural plasticity and network activity in neurodegenerative disorders? Although some treatments seem to improve the function of remaining neural circuits, their effect is limited and none seems capable of a permanent functional rescue[34,59,60]. This disappointing result is somewhat surprising, as the treatments were based on sound rationales relating to the degeneration of particular neuronal populations and well-established deficiencies or imbalances in specific neurotransmitter systems. Perhaps the strategies target too few of the most critical derangements, or the derangements are too advanced or dynamic for standard regimens[61]. Multidisciplinary studies are needed to better define the dysfunction in key networks in different neurodegenerative diseases and related animal models.

Interestingly, several neurodegenerative disorders, including AD, DLB and HD, are associated with an increased incidence of seizures[62–64]. Transgenic mice whose neurons express human amyloid precursor proteins or mutant huntingtin are also prone to epileptic activity[65,66], and Aβ toxicity in some cell-culture models can be inhibited with anticonvulsants[28]. These and other observations[29,34] suggest that the relationship between neurodegenerative disorders and epilepsy should be further explored, particularly during early stages of disease and in susceptible subpopulations.

Drugs aimed at neurotransmitter receptors might fail because related signalling pathways are disrupted by abnormal protein assemblies, creating a downstream block that cannot be overcome by upstream modulation. Encouragingly, experimental models are helping to unravel the molecular cascades through which abnormal protein assemblies might cause this disruption (Box 2). Evidence from AD and HD models has implicated abnormal proteins in the disruption of glutamatergic neurotransmission and calcium signalling[29,33,34,45,47,67]. Further work is needed to determine whether the therapeutic modulation of affected pathways (Box 2) can improve network activities and neurological functions in neurodegenerative conditions and enhance the efficacy of available treatments.

At present, diverse efforts are being directed at the elimination of the abnormal protein assemblies themselves, and with good reason[27,68]. Reducing the production, enhancing the removal or neutralizing the actions of these assemblies may improve neuronal survival. If the functional decline in neurodegenerative diseases is caused primarily by the gradual loss of neurons, it may take years to detect benefits of these disease-modifying interventions — a daunting prospect that may discourage the development of better drugs for AD and related conditions. However, if the pathogenic proteins actively interfere with synaptic functions and related signalling cascades, lowering their levels or inhibiting their actions might have more immediate effects that could become apparent within weeks or even days (Fig. 2). This hypothesis is supported by results obtained in various experimental models (Box 1).

If future studies confirm the pathogenic importance of reversible network dysfunction in neurodegenerative disorders, it may become possible to shorten clinical-trial periods and to evaluate a greater diversity of therapeutic compounds. This could accelerate the pace of drug validation and offer obvious cost savings. It might also facilitate the identification of effective combinations of drugs with distinct modes of action. Although such regimens are difficult to assess in clinical trials, they have proved useful in other multifactorial diseases (such as epilepsy, hypertension and cancer) and will probably also be required for the effective treatment of neurodegenerative disorders. ■

1. Cowan, W. M. & Kandel, E. R. Prospects for neurology and psychiatry. *J. Am. Med. Assoc.* **285,** 594–600 (2001).
2. Bradshaw, J., Saling, M., Hopwood, M., Anderson, V. & Brodtmann, A. Fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease is qualitatively distinct. *J. Neurol. Neurosurg. Psychiatry* **75,** 382–387 (2004).
3. Walker, M. P. *et al.* The clinician assessment of fluctuation and the one day fluctuation assessment scale. Two methods to assess fluctuating confusion in dementia. *Br. J. Psychiatry* **177,** 252–256 (2000).
4. Walker, M. P. *et al.* Quantifying fluctuation in dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. *Neurology* **54,** 1616–1625 (2000).
5. McKeith, I. G. *et al.* Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* **65,** 1863–1872 (2005).
6. Robertsson, B., Blennow, K., Gottfries, C. G. & Wallin, A. Delirium in dementia. *Int. J. Geriatr. Psychiatry* **13,** 49–56 (1998).
7. Terry, R. D. *et al.* Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann. Neurol.* **30,** 572–580 (1991).
8. Morrison, J. H. & Hof, P. R. Life and death of neurons in the aging brain. *Science* **278,** 412–419 (1997).
9. Kordower, J. H. *et al.* Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. *Ann. Neurol.* **49,** 202–213 (2001).
10. Price, J. L. *et al.* Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. *Arch. Neurol.* **58,** 1395–1402 (2001).
11. Greffard, S. *et al.* Motor score of the Unified Parkinson Disease Rating Scale as a good predictor of Lewy body-associated neuronal loss in the substantia nigra. *Arch. Neurol.* **63,** 584–588 (2006).
12. Blanchet, P. J. Antipsychotic drug-induced movement disorders. *Can. J. Neurol. Sci.* **30** (Suppl. 1), S101–S107 (2003).
13. Martino, D. & Giovannoni, G. Antibasal ganglia antibodies and their relevance to movement disorders. *Curr. Opin. Neurol.* **17,** 425–432 (2004).
14. Lewin, R. Is your brain really necessary? *Science* **210,** 1232–1234 (1980).
15. Chen, R., Cohen, L. G. & Hallett, M. Nervous system reorganization following injury. *Neuroscience* **111,** 761–773 (2002).
16. Bezard, E., Gross, C. E. & Brotchie, J. M. Presymptomatic compensation in Parkinson's disease is not dopamine-mediated. *Trends Neurosci.* **26,** 215–221 (2003).
17. Stern, Y. What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* **8,** 448–460 (2002).
18. Buckner, R. L. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* **44,** 195–208 (2004).
19. Iaria, G., Petrides, M., Dagher, A., Pike, B. & Bohbot, V. D. Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *J. Neurosci.* **23,** 5945–5952 (2003).
20. Maguire, E. A., Valentine, E. R., Wilding, J. M. & Kapur, N. Routes to remembering: the brains behind superior memory. *Nature Neurosci.* **6,** 90–95 (2003).
21. Mahley, R. W., Weisgraber, K. H. & Huang, Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **103,** 5644–5651 (2006).
22. Zlokovic, B. V. Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci.* **28,** 202–208 (2005).
23. Prinz, A. A., Bucher, D. & Marder, E. Similar network activity from disparate circuit parameters. *Nature Neurosci.* **7,** 1345–1352 (2004).
24. Edelman, G. M. & Gally, J. A. Degeneracy and complexity in biological systems. *Proc. Natl Acad. Sci. USA* **98,** 13763–13768 (2001).
25. Whone, A. L., Moore, R. Y., Piccini, P. P. & Brooks, D. J. Plasticity of the nigropallidal pathway in Parkinson's disease. *Ann. Neurol.* **53,** 206–213 (2003).
26. Walsh, D. M. & Selkoe, D. J. Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron* **44,** 181–193 (2004).
27. Muchowski, P. J. & Wacker, J. L. Modulation of neurodegeneration by molecular chaperones. *Nature Rev. Neurosci.* **6,** 11–22 (2005).
28. Mark, R. J., Ashford, J. W., Goodman, Y. & Mattson, M. P. Anticonvulsants attenuate amyloid β-peptide neurotoxicity, Ca^{2+} deregulation, and cytoskeletal pathology. *Neurobiol. Aging* **16,** 187–198 (1995).
29. Hynd, M. R., Scott, H. L. & Dodd, P. R. Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. *Neurochem. Int.* **45,** 583–595 (2004).
30. Wyss-Coray, T. & Mucke, L. Inflammation in neurodegenerative disease — a double-edged sword. *Neuron* **35,** 419–432 (2002).
31. Beal, M. F. Mitochondria take center stage in aging and neurodegeneration. *Ann. Neurol.* **58,** 495–505 (2005).
32. Small, D. H., Mok, S. S. & Bornstein, J. C. Alzheimer's disease and Aβ toxicity: from top to bottom. *Nature Rev. Neurosci.* **2,** 595–598 (2001).
33. Mattson, M. P. Pathways towards and away from Alzheimer's disease. *Nature* **430,** 631–639 (2004).
34. Handley, O. J., Naji, J. J., Dunnett, S. B. & Rosser, A. E. Pharmaceutical, cellular and genetic therapies for Huntington's disease. *Clin. Sci. (Lond.)* **110,** 73–88 (2006).
35. Honer, W. G. Pathology of presynaptic proteins in Alzheimer's disease: more than simple loss of terminals. *Neurobiol. Aging* **24,** 1047–1062 (2003).
36. Levine, M. S., Cepeda, C., Hickey, M. A., Fleming, S. M. & Chesselet, M. F. Genetic mouse models of Huntington's and Parkinson's diseases: illuminating but imperfect. *Trends Neurosci.* **27,** 691–697 (2004).
37. van Dellen, A., Grote, H. E. & Hannan, A. J. Gene–environment interactions, neuronal dysfunction and pathological plasticity in Huntington's disease. *Clin. Exp. Pharmacol. Physiol.* **32,** 1007–1019 (2005).
38. Lazarov, O. *et al.* Environmental enrichment reduces Aβ levels and amyloid deposition in transgenic mice. *Cell* **120,** 701–713 (2005).
39. Mesulam, M. M. Neuroplasticity failure in Alzheimer's disease: bridging the gap between plaques and tangles. *Neuron* **24,** 521–529 (1999).
40. Verdier, Y., Zarandi, M. & Penke, B. Amyloid β-peptide interactions with neuronal and glial cell plasma membrane: binding sites and implications for Alzheimer's disease. *J. Pept. Sci.* **10,** 229–248 (2004).
41. Schmitt, H. P. Pouring oil into the fire? On the conundrum of the beneficial effects of NMDA receptor antagonists in Alzheimer disease. *Psychopharmacology (Berl.)* **179,** 151–153 (2005).
42. Chen, J. *et al.* SIRT1 protects against microglia-dependent amyloid-β toxicity through inhibiting NF-κB signaling. *J. Biol. Chem.* **280,** 40364–40374 (2005).
43. Giorgini, F., Guidetti, P., Nguyen, Q., Bennett, S. C. & Muchowski, P. J. A genomic screen in yeast implicates kynurenine 3-monooxygenase as a therapeutic target for Huntington disease. *Nature Genet.* **37,** 526–531 (2005).

44. Eddleston, M. P. & Mucke, L. Molecular profile of reactive astrocytes — implications for their role in neurologic disease. *Neuroscience* **54,** 15–36 (1993).
45. Palop, J. J. *et al.* Neuronal depletion of calcium-dependent proteins in the dentate gyrus is tightly linked to Alzheimer's disease-related cognitive deficits. *Proc. Natl Acad. Sci. USA* **100,** 9572–9577 (2003).
46. Drzezga, A. *et al.* Impaired cross-modal inhibition in Alzheimer disease. *PLoS Med.* **2,** 986–995 (2005).
47. Palop, J. J. *et al.* Vulnerability of dentate granule cells to disruption of Arc expression in human amyloid precursor protein transgenic mice. *J. Neurosci.* **25,** 9686–9693 (2005).
48. Colom, L. V. Septal networks: relevance to theta rhythm, epilepsy and Alzheimer's disease. *J. Neurochem.* **96,** 609–623 (2006).
49. 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).
50. Graf, R. A. & Kater, S. B. Inhibitory neuronal activity can compensate for adverse effects of β-amyloid in hippocampal neurons. *Brain Res.* **786,** 115–121 (1998).
51. Watanabe, D. *et al.* Ablation of cerebellar Golgi cells disrupts synaptic integration involving GABA inhibition and NMDA receptor activation in motor coordination. *Cell* **95,** 17–27 (1998).
52. DeKosky, S. T. *et al.* Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. *Ann. Neurol.* **51,** 145–155 (2002).
53. Small, D. H. Do acetylcholinesterase inhibitors boost synaptic scaling in Alzheimer's disease? *Trends Neurosci.* **27,** 245–249 (2004).
54. Dickerson, B. C. *et al.* Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* **65,** 404–411 (2005).
55. Oldstone, M. B. Molecular mimicry, microbial infection, and autoimmune disease: evolution of the concept. *Curr. Top. Microbiol. Immunol.* **296,** 1–17 (2005).
56. Duncan, J. S., Sander, J. W., Sisodiya, S. M. & Walker, M. C. Adult epilepsy. *Lancet* **367,** 1087–1100 (2006).
57. Thompson, P. J. & Duncan, J. S. Cognitive decline in severe intractable epilepsy. *Epilepsia* **46,** 1780–1787 (2005).
58. Forsgren, L. *et al.* Mortality of epilepsy in developed countries: a review. *Epilepsia* **46** (Suppl. 11)**,** 18–27 (2005).
59. Schapira, A. H. Present and future drug treatment for Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* **76,** 1472–1478 (2005).
60. Lleo, A., Greenberg, S. M. & Growdon, J. H. Current pharmacotherapy for Alzheimer's disease. *Annu. Rev. Med.* **57,** 513–533 (2006).
61. Gsell, W., Jungkunz, G. & Riederer, P. Functional neurochemistry of Alzheimer's disease. *Curr. Pharm. Des.* **10,** 265–293 (2004).
62. Nance, M. A. & Myers, R. H. Juvenile onset Huntington's disease — clinical and research perspectives. *Ment. Retard. Dev. Disabil. Res. Rev.* **7,** 153–157 (2001).
63. Weiner, M. F. *et al.* Can Alzheimer's disease and dementias with Lewy bodies be distinguished clinically? *J. Geriatr. Psychiatry Neurol.* **16,** 245–250 (2003).
64. Amatniek, J. C. *et al.* Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia* **47,** 867–872 (2006).
65. Mangiarini, L. *et al.* Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* **87,** 493–506 (1996).
66. Del Vecchio, R. A., Gold, L. H., Novick, S. J., Wong, G. & Hyde, L. A. Increased seizure threshold and severity in young transgenic CRND8 mice. *Neurosci. Lett.* **367,** 164–167 (2004).
67. Xie, C. W. Calcium-regulated signaling pathways: role in amyloid β-induced synaptic dysfunction. *Neuromolecular Med.* **6,** 53–64 (2004).
68. Selkoe, D. J. & Schenk, D. Alzheimer's disease: molecular understanding predicts amyloid-based therapeutics. *Annu. Rev. Pharmacol. Toxicol.* **43,** 545–584 (2003).
69. Grady, C. L. *et al.* Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *J. Neurosci.* **23,** 986–993 (2003).
70. Pariente, J. *et al.* Alzheimer's patients engage an alternative network during a memory task. *Ann. Neurol.* **58,** 870–879 (2005).
71. Nakanishi, S. Synaptic mechanisms of the cerebellar cortical network. *Trends Neurosci.* **28,** 93–100 (2005).
72. Kobayashi, D. T. & Chen, K. S. Behavioral phenotypes of amyloid-based genetically modified mouse models of Alzheimer's Disease. *Genes Brain Behav.* **4,** 173–196 (2005).
73. Janus, C. *et al.* Aβ peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. *Nature* **408,** 979–982 (2000).
74. Morgan, D. *et al.* Aβ peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. *Nature* **408,** 982–985 (2000).
75. Dodart, J. C. *et al.* Immunization reverses memory deficits without reducing brain Aβ burden in Alzheimer's disease model. *Nature Neurosci.* **5,** 452–457 (2002).
76. Kotilinek, L. A. *et al.* Reversible memory loss in a mouse transgenic model of Alzheimer's disease. *J. Neurosci.* **22,** 6331–6335 (2002).
77. Yamamoto, A., Lucas, J. J. & Hen, R. Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell* **101,** 57–66 (2000).
78. Martin-Aparicio, E. *et al.* Proteasomal-dependent aggregate reversal and absence of cell death in a conditional mouse model of Huntington's disease. *J. Neurosci.* **21,** 8772–8781 (2001).
79. Masliah, E. *et al.* Effects of α-synuclein immunization in a mouse model of Parkinson's disease. *Neuron* **46,** 857–868 (2005).
80. Brandt, R., Hundelt, M. & Shahani, N. Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochim. Biophys. Acta* **1739,** 331–354 (2005).
81. Santacruz, K. *et al.* Tau suppression in a neurodegenerative mouse model improves memory function. *Science* **309,** 476–481 (2005).
82. Chin, J. *et al.* Fyn kinase induces synaptic and cognitive impairments in a transgenic mouse model of Alzheimer's disease. *J. Neurosci.* **25,** 9694–9703 (2005).
83. Dickey, C. A. *et al.* Selectively reduced expression of synaptic plasticity-related genes in amyloid precursor protein + presenilin-1 transgenic mice. *J. Neurosci.* **23,** 5219–5226 (2003).
84. Lacor, P. N. *et al.* Synaptic targeting by Alzheimer's-related amyloid β oligomers. *J. Neurosci.* **24,** 10191–10200 (2004).
85. Cotman, C. W., Hailer, N. P., Pfister, K. K., Soltesz, I. & Schachner, M. Cell adhesion molecules in neural plasticity and pathology: similar mechanisms, distinct organizations? *Prog. Neurobiol.* **55,** 659–669 (1998).
86. Wang, Q., Walsh, D. M., Rowan, M. J., Selkoe, D. J. & Anwyl, R. Block of long-term potentiation by naturally secreted and synthetic amyloid β-peptide in hippocampal slices is mediated via activation of the kinases c-Jun N-terminal kinase, cyclin-dependent kinase 5, and p38 mitogen-activated protein kinase as well as metabotropic glutamate receptor type 5. *J. Neurosci.* **24,** 3370–3378 (2004).
87. Snyder, E. M. *et al.* Regulation of NMDA receptor trafficking by amyloid-β. *Nature Neurosci.* **8,** 1051–1058 (2005).
88. Oddo, S. & LaFerla, F. M. The role of nicotinic acetylcholine receptors in Alzheimer's disease. *J. Physiol. (Paris)* **99,** 172–179 (2006).
89. Kelly, B. L., Vassar, R. & Ferreira, A. β-amyloid-induced dynamin 1 depletion in hippocampal neurons. A potential mechanism for early cognitive decline in Alzheimer disease. *J. Biol. Chem.* **280,** 31746–31753 (2005).
90. Haddad, J. J. Mitogen-activated protein kinases and the evolution of Alzheimer's: a revolutionary neurogenetic axis for therapeutic intervention? *Prog. Neurobiol.* **73,** 359–377 (2004).
91. Lee, G. Tau and src family tyrosine kinases. *Biochim. Biophys. Acta* **1739,** 323–330 (2005).
92. Giese, K. P., Ris, L. & Plattner, F. Is there a role of the cyclin-dependent kinase 5 activator p25 in Alzheimer's disease? *Neuroreport* **16,** 1725–1730 (2005).
93. Roselli, F. *et al.* Soluble β-amyloid$_{1-40}$ induces NMDA-dependent degradation of postsynaptic density-95 at glutamatergic synapses. *J. Neurosci.* **25,** 11061–11070 (2005).
94. Almeida, C.G. *et al.* Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. *Neurobiol. Dis.* **20,** 187–198 (2005).
95. Hsia, A. *et al.* Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. *Proc. Natl Acad. Sci. USA* **96,** 3228–3233 (1999).
96. Mucke, L. *et al.* High-level neuronal expression of Aβ$_{1-42}$ in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *J. Neurosci.* **20,** 4050–4058 (2000).
97. Moolman, D. L., Vitolo, O. V., Vonsattel, J. P. & Shelanski, M. L. Dendrite and dendritic spine alterations in Alzheimer models. *J. Neurocytol.* **33,** 377–387 (2004).
98. Kamenetz, F. *et al.* APP processing and synaptic function. *Neuron* **37,** 925–937 (2003).
99. Chapman, P. F. *et al.* Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nature Neurosci.* **2,** 271–276 (1999).
100. Walsh, D. M. *et al.* Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation *in vivo*. *Nature* **416,** 535–539 (2002).

Acknowledgments We thank S. Finkbeiner for helpful discussion of the Huntington's disease literature, J. Carroll for preparation of graphics, G. Howard and S. Ordway for editorial review, and D. McPherson and L. Manuntag for administrative assistance. This work was supported by grants (to L.M.) from the National Institutes of Health.

Author Information Reprints and permissions information is available at npg.nature.com/reprintsandpermissions. The authors declare competing financial interests: details accompany the paper at www.nature.com/nature. Correspondence should be addressed to L.M. (lmucke@gladstone.ucsf.edu).