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Brain Plasticity: Paradoxical Case of a Neurodegenerative Disease?

A thought-provoking new study has found that symptom-free carriers of the neurodegenerative Huntington's disease present a dramatic two-fold acceleration in perceptual learning.

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The remarkable ease of learning seen in children seems only a distant memory to most of our adult brains. Understanding the factors that might renew such learning in older brains is a main goal of brain plasticity studies. A study published in this issue of *Current Biology* [1] has opened new possibilities by showing dramatically improved learning in pre-symptomatic Huntington's disease carriers.

From Huntington's Disease to Brain Plasticity

Brain systems are shaped by a complex interplay between genes and experience, a process that begins early in development and extends throughout the life span. A major determinant of such brain sculpting is the balance between excitation and inhibition in neural networks [2]. Excitatory-inhibitory co-tuning driven by consistent and reliable patterned sensory stimulation leads to the progressive remodeling of the receptive fields. Such sculpting of connectivity through synaptic activity eventually become associated with a number of structural changes, which in turn ultimately put a brake on further exposure-based modifications [3]. By adulthood, many of these brakes are in place, limiting the potential brain plasticity. This is why children typically recover more gracefully from brain insults than adults.

The recent work of Beste *et al.* [1] aims to link increased excitation and enhanced learning by focusing on a special population of human patients, those who carry the Huntington disease (HD) gene, but are not yet affected by its severe dysregulation (termed pre-HD thereafter). HD is a progressive neurodegenerative disorder caused by mutations of the Huntingtin gene that confer toxic properties to the protein it codes for. This results, among other effects, in massive neural cell death with up to 95% loss of GABAergic medium spiny projection neurons in the striatum, as well as atrophy in the cerebral cortex and white matter. Key symptoms include severe motor, cognitive and psychiatric dysfunctions that lead patients to lose their autonomy at advanced stages of the illness.

Despite intense research, HD remains poorly understood and incurable [4]. HD onset is declared based on severe motor deficits. This does not, however, imply that pre-HD patients are unaffected by the disease. In fact, pre-HD patients show significant deficits in a broad range of cognitive and emotional tasks when carefully tested in a laboratory setting, with deficiencies detectable as early as 15 years before disease onset [5]. These more subtle changes suggest a dysregulation of the balance between excitation and inhibition well before the disease fully sets in.

Learning Capabilities of Pre-symptomatic Huntington's Patients

To test the idea that pre-HD patients may have enhanced learning capabilities, Beste *et al.* [1] exploited a new learning design they have pioneered [6], testing perceptual performance (Figure 1) before and after a plasticity-inducing repetitive visual stimulation 'treatment'. The efficiency of this 'treatment' is measured by changes in perceptual performance from pre- to post-treatment.

To induce plasticity, Beste *et al.* [1] used an exposure-based learning protocol, during which subjects are presented sequences of rapidly (20 Hz) alternating light and dark bars on the computer screen for an extended period of time. The temporal properties of exposure-based learning resemble those used to induce long-term potentiation (LTP) and in this perspective exposure-based learning has been shown to produce plausible behavioral learning effects [6].

The results of the experiments were clear-cut. Before exposure-based learning, pre-HD and control subjects' perceptual performances were identical. After 20 minutes of exposure-based learning, pre-HD patients largely outperformed control subjects, for whom improvement is absent after 20 minutes of exposure-based learning but progressively reaches pre-HD performance level after 40 minutes of exposure-based learning.

The comparison of specific groups systematically yields suspicions of sampling biases and the possibility of confounding factors. Subjects who are genetically tested for HD are more likely

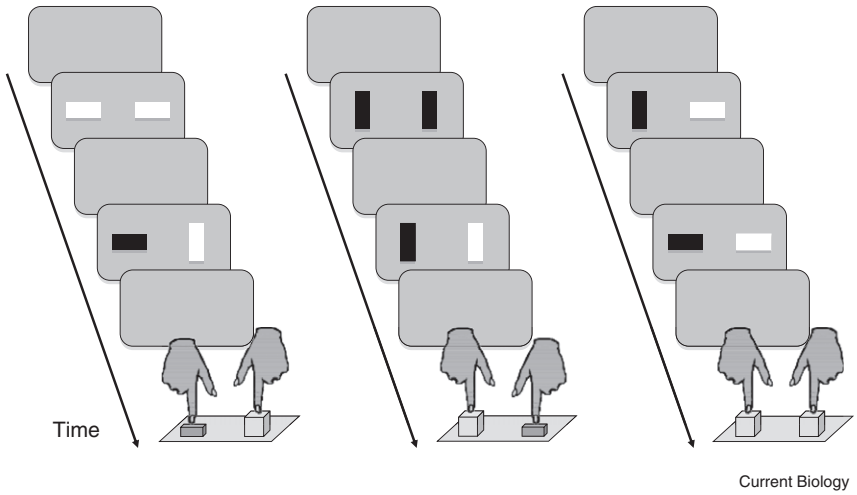

Figure 1. Examples of the luminance detection task used to assess learning.

In a first 200 ms frame, subjects were shown two bars shortly followed by another 200 ms display of two bars. Each bar had a set orientation (vertical or horizontal) and luminance (lighter or darker than the background color). Across frames, the bars could differ either by luminance, by orientation or by both. Participants were to report the location of luminance changes when they occurred, ignoring the orientation change. Correct responses are shown for each example trial. Increase in probability of detecting the luminance change provides a measure of learning.

to take antidepressants [7], some of which might boost learning [8]. Pre-HD subjects might be more motivated to perform well and higher levels of attention improve exposure-based learning [9]. The presence of these confounds, however, is unlikely. For each pre-HD patient Beste *et al.* [1] collected the 'disease burden score' — an index of the Huntingtin mutation strength — and found that it correlated with learning-induced performance improvement; pre-HD patients with the highest disease burden scores showed greater learning.

These results are spectacular in the face of the massive literature showing subtle cognitive impairments in pre-HD patients [5]. Their strength is such that it may be worth considering the inclusion of this experimental setup — a fast, efficient and cheap diagnostic tool — in the battery of tests used to predict HD onset.

Molecular and Cellular Mechanisms at Play

It has been repeatedly shown that glutamate receptors, and in particular NMDA receptors are involved in both LTP and learning [10–13] as well as in Huntington's disease [14–16]. Mice in which NR2B (a subtype of NMDA receptor subunit) was overexpressed in the forebrain show a stronger LTP and perform better in some learning tasks [13]. Interestingly, these same NR2B-containing receptors seem to be responsible for altered NMDA receptor function in various mouse models of HD and overexpressing the NR2B subunit in an HD model mouse exacerbates selective striatal neuron degeneration [14]. Overactivation of NMDA receptors in HD could also be increased by defective glutamate uptake by astrocytes [17]. Finally, memantine (a NMDA receptor blocker) was shown in HD model mice to reverse motor learning deficits, confirming a role for NMDA receptor [16]. Crucially, the exposure-based learning treatment used here also relies on NMDA receptors as illustrated by the fact that memantine impedes such learning in healthy humans [18].

The evidence thus suggests that an increased activation of NMDA receptors in early HD might enhance the degenerative process, increase LTP and speed learning. This does not, however, imply that in early HD excitotoxicity is the *cause* of faster learning, as hinted by the title of the Beste *et al.* [1] paper. It is more likely that increased NMDA receptor activation is the common cause of excitotoxicity and faster learning. That NMDA receptors play an 'ambivalent' role with 'good' and 'bad' effects is well documented. Early attempts to block excitotoxicity in stroke with NMDA receptor antagonists quickly revealed its risks for learning and memory [19]. This ambivalence was also found when studying the 'pro-death' and 'pro-survival' signals mediated by NMDA receptors in what has been termed the "NMDA receptor paradox" [20]. Similarly, when HD develops, overexpression or overactivation of various forms of NMDA receptors may lead to faster learning and to neurodegeneration. But the fact that these two effects are likely to occur in parallel, rather than in sequence, leaves some hope that the bad effects may be selectively blocked. Adapting the exposure-based learning procedure pioneered in the present study to animal models in future research could be a productive way to characterize the respective mechanisms subtending enhanced learning and excitotoxicity in Huntington's disease.

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