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Report

Faster Perceptual Learning through Excitotoxic Neurodegeneration

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Summary

Glutamatergic neural transmission is involved in both neural plasticity [1–3] and neurodegeneration [4–6]. This combination of roles could result in ambivalent effects in which excitotoxic neurodegeneration augments neural plasticity in parallel. Neural plasticity can be induced by exposure-based learning (EBL) that resembles timing properties of long-term potentiation (LTP) protocols (i.e., LTP-like learning) [7, 8]. Even though it has not been demonstrated so far in animal models that perceptual effects of such stimulation protocols are mediated by typical LTP mechanisms, it has been shown that exposure-based learning exerts strong effects on cognitive brain functioning [9] and is modulated by glutamatergic neural transmission [1]. We reveal that exposure-based perceptual learning is more efficient in a human model of excitotoxic neurodegeneration than in healthy participants. Premanifest Huntington's disease gene mutation carriers showed faster increases in perceptual sensitivities than controls. This in turn changed attentional processing in extrastriate visual areas objectified using electroencephalogram data. The emergence of faster learning correlated positively with genetic disease load. Our results confirm an ambivalent action of increased glutamatergic transmission, implying that the process of excitotoxic neurodegeneration is associated with enhanced perceptual learning, which can be used to improve attentional and behavioral control via the alteration of perceptual sensitivities.

Results and Discussion

To test the apparent dual role of glutamatergic neural transmission, we investigated premanifest Huntington's disease (HD) gene mutation carriers. Pathogenic mechanisms in HD largely rely upon excitotoxic processes [4–6]. We reduced the exposure time of long-term potentiation (LTP)-like stimulation, as compared with previous studies [9], to induce behavioral changes. This reduction should diminish learning in controls more than in HD. A competitive change detection task served as a test paradigm, in which pre-HDs and control participants were required to detect a luminance change under four conditions that differed in difficulty [10] (Figure 1) (see also Supplemental Experimental Procedures available online).

In the most challenging condition (competitive trials) (luminance and orientation bilateral [LOB]), luminance changes had to be reported against a simultaneously presented, irrelevant orientation change, (i.e., there were concomitant target and distractor feature changes at different spatial locations). The other three conditions (noncompetitive trials) were characterized by changes in luminance alone (LUM), orientation alone (ORI), or both features simultaneously at the same position (luminance and orientation unilateral [LOU]) (see [9, 10]). Event-related potentials (ERPs) recorded at occipital and parietal electrodes can be used as a marker for attentional processes (see [10–12]). We analyzed event-related lateralizations (ERLs), which provide a neurophysiological correlate of the spatial orientation of attention [11]. This was repeated after the induction of plasticity using an exposure-based learning (EBL) protocol, where changes in the luminance were presented (see Supplemental Experimental Procedures for details). In competitive trials of the above-mentioned task, attention is usually directed to the salient, irrelevant stimulus, which in the ERPs leads to a positive deflection of the N1pc [11]. To process the target stimulus, attentional reallocation processes occur subsequently and have been assumed to be reflected by the N2pc [11]. The conflict of processing the relevant and irrelevant targets in competitive trials is reflected by a frontocentral N2 [12]. Therefore, we recorded ERPs in the present study to demonstrate that EBL affects attentional processing and to examine which of the above-mentioned stages of attentional processing are affected by EBL. Behavioral performance data (rate of correct responses) are summarized in Figure 2.

An interaction "condition × pre-/postmeasurement × group" was significant only for stimuli presented on the right display side [$F(12,207) = 6.13$; $p < 0.001$; $\eta^2 = 0.26$]. In agreement with our hypothesis, EBL increases performance with higher efficacy (i.e., faster) in pre-HDs than in control participants: In the perceptual conflict condition (LOB), an effect was evident [$F(4,69) = 16.13$; $p < 0.001$; $\eta^2 = 0.48$] showing that control participants undergoing 40 min of stimulation and pre-HD participants undergoing 20 min of stimulation demonstrated increased performance at postmeasurement ($t > -6.1$ for all; $p < 0.001$). All other groups (i.e., control participants undergoing 20 min stimulation or no stimulation and pre-HDs receiving no stimulation) did not demonstrate altered performance at postmeasurement ($t < 1.1$ for all; $p > 0.2$). To provide more information about the stimulation time needed to induce EBL, we tested another control group that received 30 min of EBL. The improvement of performance was roughly in between that observed in the groups receiving 20 or 40 min of stimulation, but the resulting performance was still lower than the pre-HD group receiving 20 min EBL (see Supplemental Experiment 1). These data suggest that EBL-induced effects develop in a graded manner. An analysis of the type of errors made in the LOB condition (Supplemental Analysis 1) showed that EBL decreased the rate of missed luminance changes. This suggests that the nature of improvement in the LOB condition is most likely due to an improvement in the ability to detect the feature changes and not an improvement in the localization acuity (for a detailed analysis and

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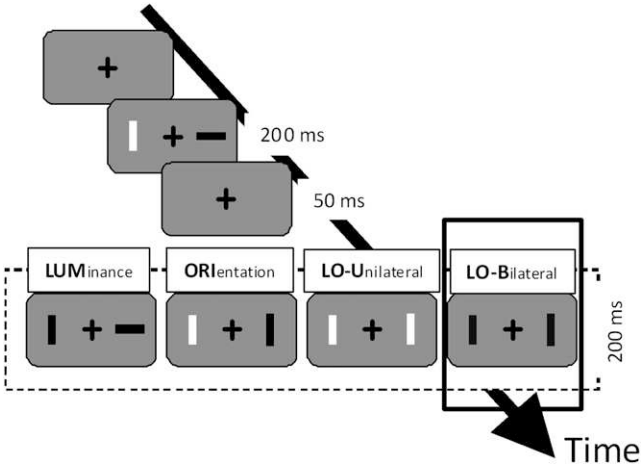

Figure 1. Schematic Overview of the Competitive Attentional Selection Task

The task required participants to detect changes in the luminance of a bar stimulus. Participants were required to press a left response button when a change in luminance occurred on the left and a right response button when changes occurred on the right. When only the orientation of a bar changed, the participants were required to withhold a response.

discussion of error types, see Supplemental Analysis 1 and Supplemental Experiments 2 and 3). No EBL effects were observed in the noncompetitive conditions at the behavioral level ($F < 0.9$ for all; $p > 0.3$). However, when in the noncompetitive conditions the difference in contrast between the stimuli was reduced (Supplemental Experiment 2), which made the task harder and resulted in lower baseline performance, an increase in the detection of the luminance change (i.e., decreased number of missed luminance changes) was observed. To examine the type of spatial selectivity of the EBL-induced changes, we tested whether EBL effects were also specific to a particular position within the stimulated hemifield (Supplemental Experiment 3). We found degradation of learning when the location was displaced within the same hemifield. These data provide several lines of evidence that EBL most likely affects perceptual sensitivity through simple exposure to stimuli, which does not require training [13–16]. Generally, under all conditions tested, after EBL we did not observe changes of reaction time ($F < 0.5$ for all; $p > 0.5$). The ERLs for the LOB condition are provided in Figure 3A, and the ERLs for the noncompetitive conditions are provided in Figure S1. For the noncompetitive conditions, no effect of EBL was evident for the ERLs ($F < 0.8$ for all; $p > 0.4$).

Regarding the asymmetry in the N1 range, EBL effects were only evident for right-sided luminance changes [$F(4,69) = 31.25$; $p < 0.001$; $\eta^2 = 0.64$] in controls receiving 40 min stimulation [baseline: 2.1 ± 0.3; poststimulation: -2.2 ± 0.4; $t(14) = 9.26$; $p < 0.001$] and pre-HDs receiving 20 min stimulation [baseline: 2.1 ± 0.3; poststimulation: -2.1 ± 0.5; $t(14) = 9.21$; $p < 0.001$] (see Figure 3A). The polarity change of the N1pc observed is compatible with the interpretation that attention is no longer directed to the distractor (positive N1pc deflection) but is instead directed to the target stimulus in the poststimulation session (negative N1pc deflection). This change is most likely mediated by modulation of extrastriate visual areas (BA18) (Figure 3B), as suggested by standardized low-resolution brain electromagnetic tomography (sLORETA) analyses [17]. The other experimental groups did not reveal any difference between the measurements ($t < 1.2$ for all; $p > 0.15$). BA18 and BA19, which have repeatedly been shown to generate the N1 [18], are core structures for the selection of visual stimuli [19] and have been proposed to be involved in mediating visual perceptual learning [20]. Attentional allocation has been suggested to emerge as a function of perceptual evaluation based on stimulus attributes [21] and depends on stimulus saliency [22]. Because the most salient stimulus governs the initial allocation of attention [22], we suggest that changes in attentional control, as reflected in the electroencephalogram parameters examined, may occur as the consequence of EBL mechanisms increasing sensory (perceptual) sensitivity. Attention is not a necessary prerequisite for perceptual learning [23, 24], but the current results suggest that attentional processes are affected by EBL. Due to improved perceptual sensitivities subsequently changing

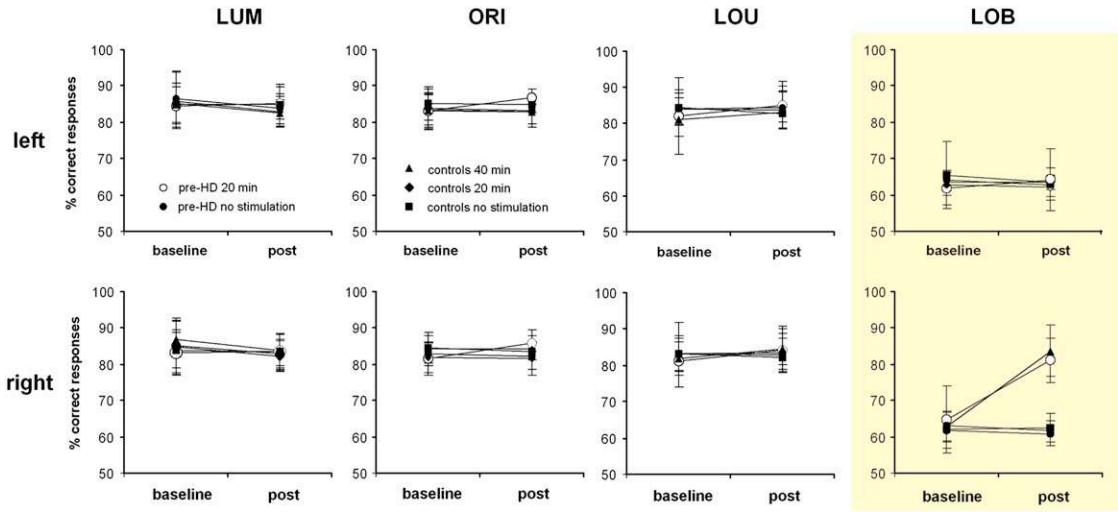

Figure 2. Performance in the Different Trial Types

The upper row denotes performance on left-sided luminance changes; the bottom row denotes performance on right-sided luminance changes. Note that chance level is 33% for each condition. Error bars represent SEM. See also Supplemental Analysis 1 and Figures S3 and S4.

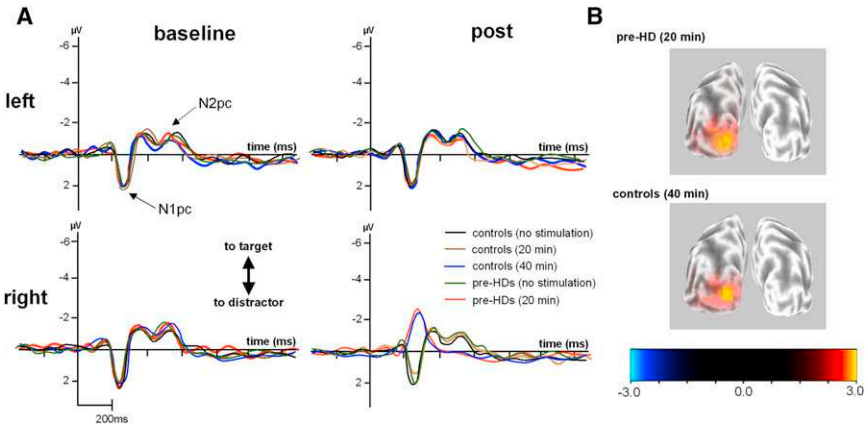

Figure 3. Event-Related Lateralizations

(A) Posterior (PO7/PO8) ERLs of the electroencephalogram in the competitive condition (LOB) are shown, separated for the different experimental groups and luminance changes presented on the left (upper row) and right (bottom row) of the fixation cross. Negative deflections denote the orientation of attention toward the target; positive deflections denote the orientation of attention toward the distractor. The different colors of the ERL traces represent the different experimental groups.

(B) sLORETA results comparing the N1pc in pre-HDs receiving 20 min stimulation and control participants receiving 40 min stimulation before and after conduction of LTP-like exposure-based learning. The color scale denotes the strength of differences between the contrasted conditions mapped onto the brain.

See also Supplemental Analyses 2 and 3 and Figures S1–S4.

attentional allocation processes, no attentional reallocation processes are necessary after EBL to process the target stimulus. This is supported by the N2pc data [10] (see Figure 3A), which was attenuated poststimulation, compared with baseline in pre-HDs undergoing 20 min stimulation [baseline: -1.5 ± 0.13; poststimulation: 0.22 ± 0.16; $t(14) = 6.51$; $p < 0.001$] and control participants undergoing 40 min stimulation [baseline: -1.48 ± 0.12; poststimulation: 0.12 ± 0.7; $t(14) = 7.73$; $p < 0.001$]. Further indirect support comes from the frontocentral N2 data (Supplemental Analysis 2) showing that the degree of conflict induced by the stimuli (frontocentral N2 effects) [16] was reduced after EBL. Brain areas modulated encompassed BA19 for the N2pc and BA24 and BA6 for the frontocentral N2 (see Supplemental Analysis 3).

As can be seen in Figure S3, effects induced by EBL were evident at the single-subject level in pre-HDs in all but one pre-HD subject. Yet, the degree of change induced by EBL varies considerably across pre-HD subjects. This variation is related to the individual genetic disease load and hence a major causative factor for the pathophysiological mechanisms in HD: EBL effects were higher in pre-HDs with a higher disease burden score [25] (all $r > 0.67$; $p < 0.003$), a correspondingly earlier estimated age of onset (all $r > -0.7$; $p < 0.002$) [26], or fewer years until the estimated age of onset [26] (all $r > -0.49$; $p < 0.01$) (see Figure S4). These findings suggest that the modulating influence of perceptual learning becomes stronger when pathogenic mechanisms are more intense. The at least partly genetically determined increased tone of glutamatergic neural transmission in pre-HDs [4] may make it easier for N-methyl-D-aspartic acid (NMDA) receptor-dependent processes to modify synaptic efficacy in course of EBL. The results suggest that there are "functional islands" in neurodegeneration, in which enhanced NMDA neural transmission boost cognitive processes as long as these cognitive processes depend solely on the enhanced NMDA receptor turnover. This is supported by other data, showing that manifest diseased HD patients reveal a paradoxical increase in auditory sensory memory and attentional processes, most likely also through NMDA-related excitotoxic mechanisms (see [5]). This increase occurred in parallel to deficits in classical memory functions and other cognitive processes (see [5]) and stresses the special role of NMDA neural transmission in HD and for circumscribed cognitive functions. Results accounting for cognitive declines in HD when examining other learning functions can be reconciled with these data patterns, because for these processes a multitude of other factors besides the NMDA system play an important role [27]. Nevertheless, the current results challenge the common view of neurodegeneration and its effect on (cognitive) brain function. Future studies should examine other forms of learning to broaden the relationship between learning and excitotoxicity.

Supplemental Information

Supplemental Information includes Supplemental Analyses, four figures, one table, Supplemental Experimental Procedures, and Supplemental Experiments and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2012.08.012.

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