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Report

Improvement and Impairment of Visually Guided Behavior through LTP- and LTD-like Exposure-Based Visual Learning

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Summary

Cellular studies have focused on long-term potentiation (LTP) and long-term depression (LTD) to understand requirements for persistent changes in synaptic connections [1–3]. Whereas LTP is induced through high-frequency intermittent stimulation, low-frequency stimulation evokes LTD [4]. Because of the ubiquitous efficacy of these protocols, they are considered fundamental mechanisms underlying learning. Here we adapted LTP/LTD-like protocols to visual stimulation to alter human visually guided behavior. In a change-detection task, participants reported luminance changes against distracting orientation changes. Subsequently, they were exposed to passive visual high- or low-frequency stimulation of either the relevant luminance or irrelevant orientation feature. LTP-like high-frequency protocols using luminance improved ability to detect luminance changes, whereas low-frequency LTD-like stimulation impaired performance. In contrast, LTP-like exposure of the irrelevant orientation feature impaired performance, whereas LTD-like orientation stimulation improved it. LTP-like effects were present for 10 days, whereas LTD-like effects lasted for a shorter period of time. Our data demonstrate that instead of electrically stimulating synapses, selective behavioral changes are evoked in humans by using equivalently timed visual stimulation, suggesting that both LTD- and LTP-like protocols control human behavior but that the direction of changes is determined by the feature incorporated into the stimulation protocol.

Results

Persistent changes in synaptic transmission constitute the foundations of plasticity and learning. However, in humans, it is difficult to study in vivo the outcome of synaptic modifications on behavioral changes induced by stimuli that drive long-term potentiation (LTP)- or long-term depression (LTD)-like processes. Accordingly, debate persists over how persistent changes in human behavior and perception are related to synaptic plasticity processes. Here we show a direct relationship between synaptic plasticity protocols and human learning through the adaptation of LTP-like and LTD-like protocols to low- or high-frequency visual stimulation to induce changes in visually guided behavior in a systematic and frequency-specific way.

Study participants were required to detect a luminance change under four conditions [5] (Figure 1). In the most challenging condition, luminance changes were reported against a simultaneously presented, irrelevant orientation change, i.e., there were concomitant target and distractor feature changes at different spatial locations (competitive trials). In the other three conditions (noncompetitive trials), either only luminance or orientation changed, or both features changed simultaneously at the same position. Under the assumption that higher distractor saliency degrades performance, the difficulty in detecting luminance changes was varied by scaling the length:width ratio of the stimuli, resulting in a low- and a high-saliency condition of the distracting stimulus [5] (Figure 1) (see Experimental Procedures).

To enforce systematic changes in behavior, we applied different stimulation protocols, where either the relevant or the irrelevant feature was used for high- or low-frequency stimulation. High-frequency stimulation involved the presentation of the stimuli with a frequency of 20 Hz for a period of 5 s, followed by a period of 5 s with no presentation of stimulus changes on the screen for a total time period of 40 min. Low-frequency stimulation involved the presentation of the stimulus with a frequency of 1 Hz with no breaks in the presentation of stimulus changes for a duration of 40 min. In the experimental groups, exposure-based visual learning was induced after the first session, which was used to assess baseline performance. Learning outcome was assessed 90 min (post session 1) later. Stability and possible recovery of learning effects were tested 24 hr (post session 2) and 10 days (post session 3) later. Two control groups served to show stable performance in the absence of visual LTP/LTD-like visual stimulation. In control group 1, subjects received no stimulation at all between the test sessions. In control group 2, the fixation cross was also shown. As was done in the other groups receiving stimulation, small positional shifts (serving as catch trials in groups receiving stimulation) were evident (see Experimental Procedures for more details).

In both control groups, for the competitive trials, error rates did not differ among the sessions (all F values < 1; $p > 0.3$; Figure 2). However, in the experimental groups receiving passive exposure, performance in terms of error rates was altered in a stimulation-specific way.

After bilateral intermittent high-frequency stimulation consisting of luminance changes, luminance change detection improved (LTP bilateral luminance group, n = 15). Beneficial effects were stronger under the condition of low distractor saliency [Figure 2A; time point × degree of competition × group; $F(6,144) = 13.22$; $p < 0.001$]. Remarkably, exposure-induced performance improvement was maintained after 24 hr. Retesting after 10 days under conditions of low distractor saliency revealed full maintenance of effect, indicating that exposure-based behavioral improvement can be long lasting ($p < 0.001$). Under high distractor saliency, performance recovered to baseline levels after 10 days ($p > 0.5$) and did not differ from controls ($p > 0.6$). Effects of perceptual learning were evident in all but three subjects. Subjects who learned

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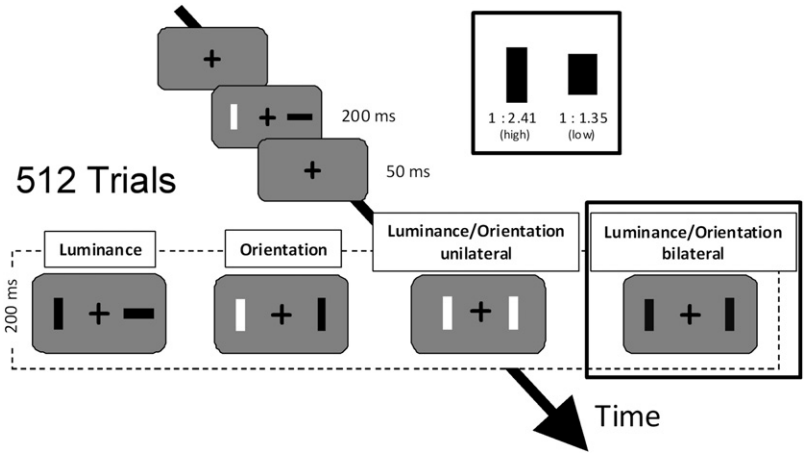

Figure 1. Competitive Change-Detection Task

Schematic overview of the task setup. Subjects had to detect changes of luminance in a change-detection task, where orientation and luminance of an elongated stimulus competed in two successive frames (duration 200 ms each). Between the appearance of these two frames, only the fixation cross was shown for 50 ms. For the second frame, there were four possible conditions, in which (1) luminance of one bar, (2) orientation of one bar, (3) luminance and orientation of one bar, or (4) luminance and orientation of both bars changed. This latter condition (competitive trials) involves perceptual competition between the features presented and therefore is specifically demanding because detectability of a relevant luminance change is distracted by the irrelevant orientation change. After the presentation of the second frame, there was a pause, in which subjects had to respond (intertrial interval between 2000 and 2500 ms). The difficulty of the tasks was further manipulated by varying the saliency of the orientation change by adjusting the length:width ratios of the bars (1:2.41, i.e., high distractor saliency, and 1:1.35, i.e., low distractor saliency).

revealed similar effects across time points. To account for the differences in time course, we assume that on day 10, the effects of the LTP-like protocol were partly decreased, allowing full maintenance of enhanced performance for the easy but not for the more demanding task.

For more information about the location specificity of these effects, a second group of participants underwent a similar exposure; however, only unilateral luminance changes were displayed on the right side (LTP unilateral luminance group, n = 15) [Figure 2B; time point × degree of competition × side × group; $F(6,144) = 4.77$; $p < 0.001$]. Compared to baseline, performance increased for luminance changes presented in the right visual field ($p < 0.001$) but not in the left, nonexposed side ($p > 0.7$), resulting in a differential performance between the two sides ($p < 0.001$). At each assessment (post session, 24 hr, and 10 days), the improvement in right-side performance was similar to that of the corresponding side in the LTP bilateral luminance group ($p > 0.7$). However, no performance differences were observed compared to controls or between sessions on the nonstimulated left side ($p > 0.6$). All but three participants showed learning. In subjects who learned, modulation was similar across time points. These results indicated that brief exposure to LTP-like visual stimulation modulates complex visually guided behavior in humans. Particularly, less-salient stimuli were strengthened in situations in which distracting stimuli made target-directed behavior difficult. The outcome of exposure-based visual learning was less long lasting under conditions of high saliency of the irrelevant distractor. This observation suggests that the magnitude and stability of the effects depend on the physical properties of the stimuli or, more generally, on context and task difficulty.

The above results showed that application of an LTP-like protocol improved visually guided behavior when the relevant stimulus was used. We hypothesized that this effect might result from neural facilitation of the luminance feature. This hypothesis predicts that performance should be degraded when the competing, irrelevant orientation feature is used for the LTP-like protocol, because under these conditions orientation is strengthened, which would degrade detection of the luminance change. To test this hypothesis, we applied an LTP-like protocol to enhance the irrelevant orientation stimuli in a different group. Participants (n = 16) underwent exposure to unilateral orientation changes on the right side (LTP unilateral orientation group).

As predicted, the performance for luminance detection decreased. Conceivably, facilitation of the orientation feature impaired the detection of luminance changes presented simultaneously at the opposite location, because of the increased relative saliency of this irrelevant feature [Figure 2C; time point × degree of competition × side × group; $F(6,144) = 3.85$; $p < 0.003$]. All but one subject showed similar effects of LTP-like stimulation across time points. This effect of enhanced distraction on visually guided behavior lasted longer (persistent at day 10) in situations with high distractor saliency ($p < 0.003$). On the other hand, under conditions of low distractor saliency, we observed recovery to baseline when testing 10 days after exposure to LTP-like visual stimulation. No alterations in sensitivity for luminance changes between sessions or relative to controls were observed ($p > 0.8$) on the side exposed to orientation changes (Figure 2C). These results suggested that on a behavioral level, the effects of an LTP-like protocol depended on the feature that is incorporated in exposure-based learning protocols. This dependence shows that although the temporal structure of the protocol and the invoked neural mechanism are the same in both cases, the effects on a behavioral level can be opposite.

In contrast to cellular LTP, which facilitates synaptic transmission, suppression of synaptic efficacy is induced by low-frequency stimulation resulting in LTD [4, 6]. To test whether a low-frequency visual stimulation protocol is similarly able to alter human behavior, we conducted two experiments using LTD-like protocols. Furthermore, we hypothesized that similar to the opposing net effects evoked by the LTP-like protocols incorporating different features, the LTD-like protocols might be used to both impair and improve performance in visually guided behavior, dependent on task requirements.

In a first experiment, we tested the hypothesis that a protocol of low-frequency luminance changes suppresses luminance change detection (LTD unilateral luminance group, n = 14). After 40 min of an LTD-like protocol using luminance, we observed significantly reduced detectability of luminance changes on the stimulated side compared to baseline ($p < 0.001$) [Figure 2D; time point × side × group;

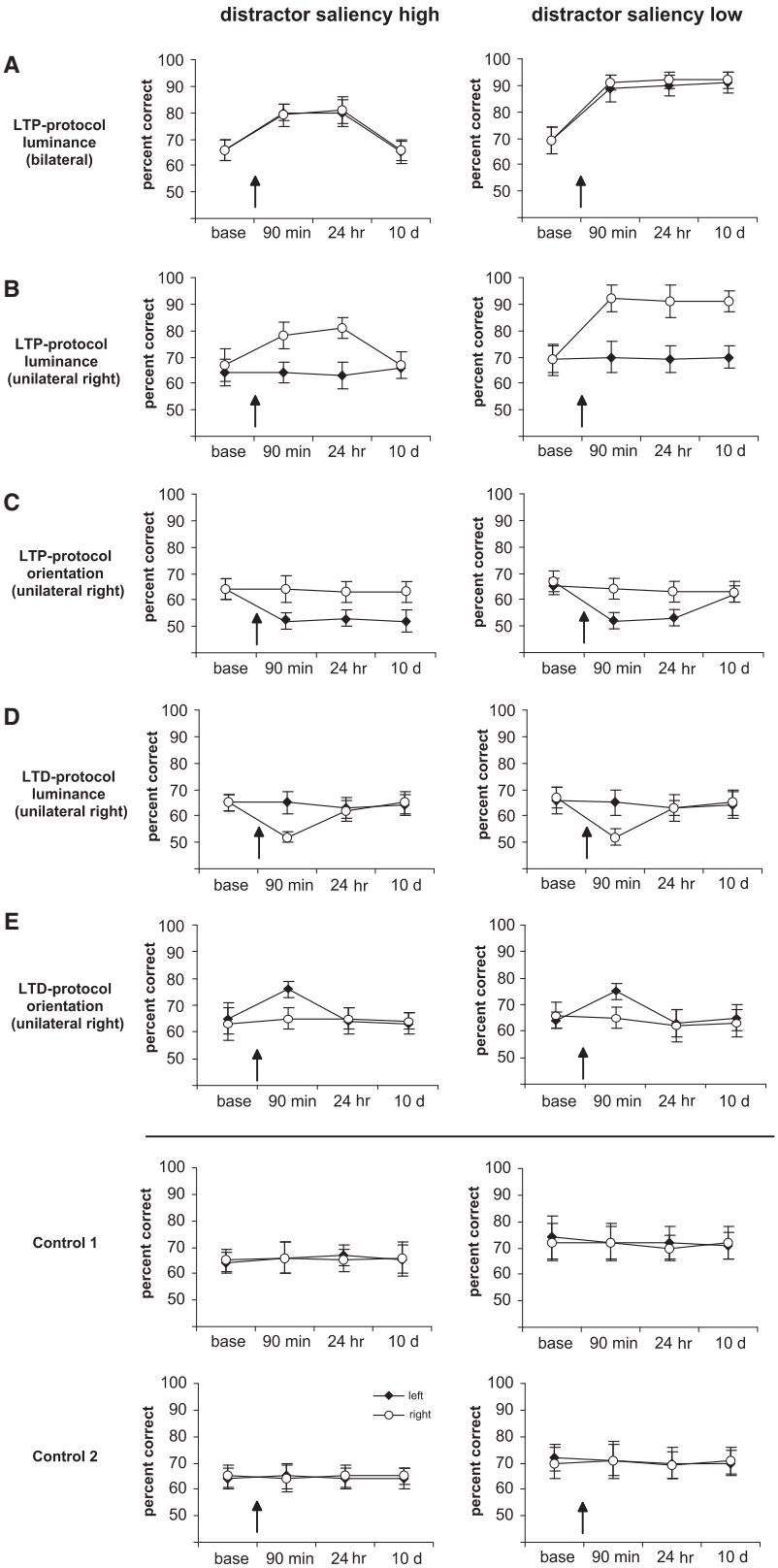

Figure 2. Performance in Competitive Selection Trials

Performance in the "LTP bilateral luminance" group (A), the "LTP unilateral right luminance" group (B), the "LTP unilateral right orientation" group (C), the "LTD unilateral right luminance" group (D), and the "LTD unilateral right orientation" group (E). Mean error rates (± standard error of the mean) for the groups are given for each time point: baseline (base), 90 min later (90 min), 24 hr later (24 hr), and 10 days later (10 d). Error rates are given for conditions of high and low distractor saliency. Black diamonds represent luminance detection performance on the left side of the fixation cross; white circles represent luminance detection performance on the right side of the fixation cross; black arrows represent conduction of the different exposure-based visual learning protocols for the experimental groups and the sole catch-trials procedure in control group 2.

$F(6,141) = 17.78$; $p < 0.001$]. Changes in performance were restricted to the stimulated right side, with no differences on the left side ($p > 0.6$). In contrast to LTP-like protocols using luminance changes, exposure to low-frequency luminance changes did not result in differences between the conditions of low and high distractor saliency ($p > 0.5$). The effects of LTD-like protocols were more transient than those observed following LTP-like exposure; performance had recovered to baseline 24 hr after stimulation ($p > 0.7$) and remained at this level when tested after 10 days. Two subjects did not show effects of LTD-like stimulation. All other subjects revealed similar modulation of performance across time points.

In another experiment, we applied an LTD-like protocol containing orientation to decrease the irrelevant orientation feature in a different group. Participants ($n = 12$) underwent exposure to low-frequency unilateral orientation changes on the right side (LTD unilateral orientation group). We found enhanced detection of the relevant luminance changes presented simultaneously at the opposite location [Figure 2E; time point × degree of competition × side × group; $F(6,139) = 8.11$; $p = 0.001$]. We suggest that the LTD-like orientation protocol suppressed the orientation feature, which led to a decrease in the relative saliency of the irrelevant feature. Two subjects did not show effects following this LTD-like protocol. All remaining subjects revealed similar changes across all time points. In both LTD-like experiments, the effects were short lived, and the magnitude of effects was comparable for high and low distractor saliency ($p > 0.6$). On the side exposed to orientation changes, no alterations in the performance between sessions or relative to controls were observed ($p > 0.5$). In contrast to error rates, reaction times were not affected by any of the above exposure protocols (all F values < 0.9; $p > 0.4$).

False-alarm frequencies (indications of luminance changes in the absence of change) were generally not different between groups in each condition and in each session (all F values < 0.5; $p > 0.5$). Reaction times and error rates were higher in each group for trials with

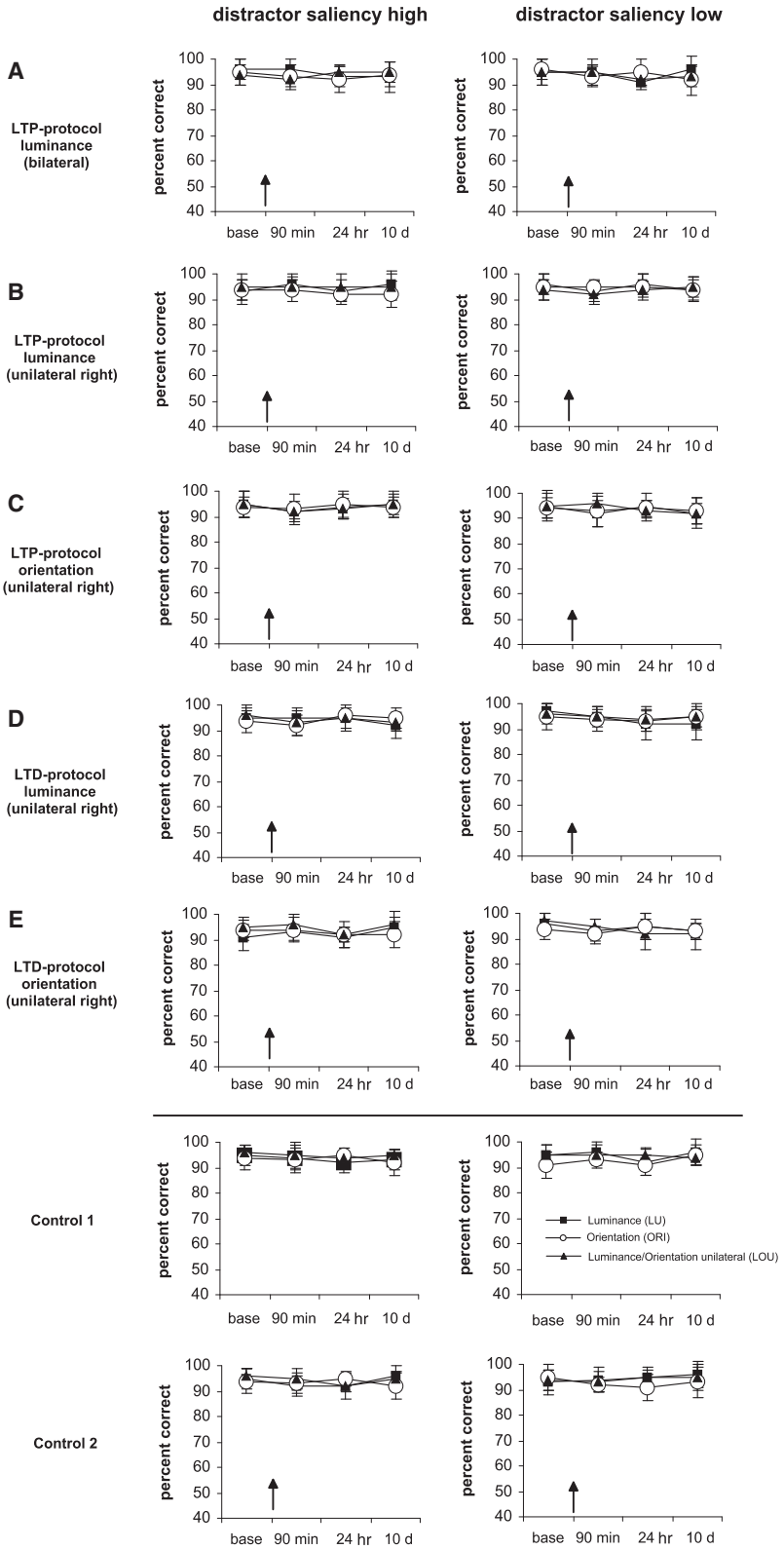

Figure 3. Performance in Noncompetitive Trials

Performance in the "LTP bilateral luminance" group (A), the "LTP unilateral right luminance" group (B), the "LTP unilateral right orientation" group (C), the "LTD unilateral right luminance" group (D), and the "LTD unilateral right orientation" group (E). Mean error rates (± standard error of the mean) for the groups are given for each time point: baseline (base), 90 min later (90 min), 24 hr later (24 hr), and 10 days later (10 d). Error rates are given for conditions of high and low distractor saliency. Black diamonds represent luminance detection performance on the left side of the fixation cross; white circles represent luminance detection performance on the right side of the fixation cross; black arrows represent conduction of the different exposure-based visual learning protocols for the experimental groups and the sole catch-trials procedure in control group 2.

concomitant target and distractor feature changes at different spatial locations. The same was true for the condition of high saliency (all F values > 8; $p < 0.001$). These results are comparable to other recent data [5]. In all noncompetitive trials, error rates did not differ among groups and sessions (all F values < 1.1; $p > 0.3$; Figure 3), which is most likely due to a ceiling effect, because participants typically reached 90% to 95% correct responses.

Discussion

We examined the potential of exposure-based learning to modulate complex visually guided behavior in humans. Our data demonstrate that exposure to either high- or low-frequency stimulation protocols, adapted from synaptic plasticity studies, modulates visual behavior, displaying a profound location and feature selectivity. These protocols were very effective, because brief exposure (~40 min) strongly altered performance of participants, with effects persisting for at least 10 days.

In studies exploring the conditions for changing synaptic connection strength in the long term, two fundamental forms of stimulation protocols have been identified: high-frequency stimulation, used to evoke cellular LTP effects [1–3], and low-frequency stimulation, which leads to synaptic depression [4, 7]. Instead of electrically stimulating single synapses or groups of synapses, we showed that selective changes of behavior can be evoked by using equivalently timed visual stimulation in humans. This effect occurred despite the fact that the participants were not actively attending to the stimuli used for induction of learning processes (cf. [8, 9]). Instead, participants were required to focus on the fixation cross and report any small spatial shifts (catch trials). Our results conclusively demonstrate that using pure unattended exposure-based learning protocols, human behavior can be changed in a systematic way. The fact that task performance can be rendered more or less efficient by pure exposure to visual stimulation can be taken as an argument that the effects of exposure-based learning have far-reaching consequences for the control of human behavior.

The experiments reported here extend previous studies about the effectiveness of repetitive stimulation, which demonstrated changes of perceptual or sensorimotor performance [10–18]. Typically, behavioral modifications are obtained through training and practice [19–23]. However, in recent years, a novel form of perceptual learning has been established that is also based on exposure to stimuli: the so-called task-irrelevant learning occurs in the absence of conscious awareness of stimuli that were used for learning under conditions when the irrelevant stimuli were consistently presented during a task performance [8, 24]. As a means of explaining such effects, it has been suggested that internal reinforcement signals triggered by task processing or rewards reinforce the learning of the irrelevant features [24]. Recent work has shown that perception of single-formant transitions can be improved through unattended exposure, but this involved pairing with a parallel discrimination task [25]. On the other hand, learning is possible without any exposure to stimulation. For example, persistent alteration in visual perception has been demonstrated following mental imagery, suggesting that neural processes underlying perceptual learning can be based on mentally generated signals [26].

The approach of repetitive stimulation relies exclusively on stimulation protocols used in synaptic plasticity studies [11, 18]. For example, brief episodes of repetitive stimulation result in an improvement of perceptual performance. Controversy persists about the effectiveness of passive stimulation in driving changes in perception. For example, prolonged and "passive" stimulation has been reported to be insufficient to drive plastic changes [27, 28]. These apparent discrepancies can be settled when assuming that sensory stimulation, to be effective, must incorporate principles such as temporal (high-frequency) or burst-like stimulation as essential in stimulation protocols used to explore synaptic plasticity processes [15]. Under conditions of identical exposure duration, LTP and LTD procedures differ in the number of stimuli applied, which is an inevitable consequence of using different frequencies. In cellular experiments, high-frequency stimulation is needed to cause the postsynaptic cell to depolarize in order to relieve the magnesium blockade of the NMDA receptors. On the other hand, LTD is believed to develop from persistent weak synaptic stimulation such as low-frequency stimulation, which results in slow rises in postsynaptic calcium. From that, we conclude that the factor that determines the learning outcome in our experiments is frequency rather than the number of stimulus exposures. On the other hand, insight into possible influences of variables such as interburst interval or the tradeoff between number of stimuli and duration of application requires further experiments.

In addition to demonstrating the possibility of improving or impairing complex human behavior by LTP- and LTD-like stimulation protocols, our experiments go one step further by demonstrating that the modulatory effects of LTP- and LTD-like protocols on a behavioral level depend only on the feature used during exposure: even though the structure of a protocol and the invoked neural mechanism are identical, the behavioral effects can be the reverse of each other. Conversely, contrasting learning mechanisms can induce an equivalent behavioral outcome. This observation suggests that processes evoked by LTP- or LTD-like stimulation modulate human behavior. What determines the direction of modulation is the feature that is incorporated in exposure-based learning protocols. However, it must be acknowledged that the commutability of effects evoked by LTP- or LTD-like stimulation on visually guided behavior was limited with respect to the temporal stability of effects, which was lower in the alterations evoked by LTD-like stimulation. Such protocol-specific effects have already been described for cellular LTP and LTD protocols [7, 18]. These results also show that changes in visually guided behavior induced by exposure-based learning are different from priming, because in the case of priming, the low-frequency stimulation (LTD-like) would increase, not decrease, sensitivity.

Change-detection tasks as employed in our study have been used to address the role of stimulus saliency for attentional processes. The biased-competition model of attention assumes that various aspects or features (e.g., A and B) of incoming information compete with each other to gain control over behavior [29–32]. Whether feature A (e.g., luminance changes) wins the competition and controls behavior depends on (1) the relative saliency of feature B (e.g., orientation changes) and (2) intentional biases favoring feature A that are simultaneously adverse for processing feature B [30]. It is well established that stimulus saliency and intention modulate biased-competition attention processes [30, 33]. Our data are the first demonstrating that, in addition, exposure-based learning protocols efficiently and specifically modulate the sensitivity to that feature incorporated into the exposure-based learning protocol; this incorporation shifts the existing competition bias either toward (LTP-like) or away from (LTD-like) the exposed feature. In this way, exposure-based learning, which exerts long-lasting effects, provides a powerful tool to modulate and control mechanisms governing visual attention and behavior.

In summary, our results show that exposure-based learning strongly modulates visually guided behavior, displaying a profound selectivity and temporal stability. However, to be efficient, stimulation must conform to requirements described for protocols specifically altering synaptic transmission and synaptic efficacy. Thus, our data show that the application of canonical protocols fundamental in regulating and controlling synaptic plasticity can be used to interfere directly with human behavior. From this observation, we conclude that the use of canonical stimulation protocols might be an ultimate way to modulate behavior directly in humans.

Experimental Procedures

Participants

In total, 126 naive participants were enrolled in the study. These participants were separated into seven groups of 18 participants each (male and female equally). Individuals were excluded from analysis if baseline performance in each trial type was not above a level expected by chance alone. Furthermore, participants were excluded from analysis if more than 5% of catch trials were missed and no false alarms occurred during catch trials. This study was approved by the ethics committee of Ruhr-Universität Bochum. All participants gave written informed consent.

Change-Detection Task

The paradigm used to examine the effect of exposure-based learning was a change-detection task in which orientation and luminance of an elongated stimulus compete to govern behavior, similar to that used in [5]. The stimulus material was presented on a 100 Hz monitor and consisted of two vertically or horizontally oriented bars, presented 1.1° left and right of a fixation cross (Figure 1). The bars were either darker or brighter than the background (30 cd/m^2), with a Fechner contrast of 0.2 (20 cd/m^2 when darker; 45 cd/m^2 when lighter). Luminance and orientation were randomly intermixed in all possible combinations for the first frame.

In each trial, two frames of these stimuli were presented for 200 ms in rapid succession. Between the appearance of the two frames, a short break of 50 ms was set in which only the fixation cross was visible. Either the

luminance or the orientation of one bar, the luminance and orientation of one bar, or the luminance and orientation distributed across the two bars changed between the two frames. This latter condition (competitive trials) is specifically demanding because detectability of a relevant luminance change is distracted by the irrelevant orientation change. The difficulty of the tasks was further manipulated by varying the saliency of the orientation change, by adjusting the length:width ratios of the bars (1:2.41, i.e., high distractor saliency, and 1:1.35, i.e., low distractor saliency) while holding the area covered by the bars constant at 0.76 cm^2 [5]. With an observation distance of 56.5 cm, the bars with a length:width ratio of 1:2.41 had a size of 2.41° by 1° visual angle. The participants were required to detect changes in luminance and to ignore orientation changes, pressing a button with the index finger of the left or the right hand at the side where the change appeared. If no change occurred, participants were required to press a third, centrally placed button. Overall, 512 trials were presented in a random order, 128 for each condition (four change conditions at two levels of saliency). The intertrial interval varied between 2000 and 2500 ms.

Stimulation Protocols

In total, seven groups were investigated, two control groups and five experimental groups, in which different stimulation protocols were applied to alter change-detection performance. In all groups, change-detection performance was assessed at four time points: prior to stimulation (baseline), 90 min after stimulation, 24 hr after the second assessment, and 10 days after the third assessment.

In the "LTP bilateral luminance" group, a high-frequency stimulation protocol was applied using changes in the luminance of the elongated bar stimuli, which were presented bilaterally to the fixation cross. Changes in luminance occurred with a frequency of 20 Hz for a period of 5 s, followed by a period of 5 s with no presentation of luminance changes on the screen. This sequence was repeated 256 times, resulting in approximately 40 min of stimulation.

The "LTP unilateral right luminance" group was the same as the "LTP bilateral luminance" group, except that only the right side of the fixation cross was stimulated. A vertical or horizontal bar was presented at the left of the fixation cross, either darker or brighter than the background. No changes in orientation or luminance of this left-sided stimulus occurred during stimulation.

In the "LTD unilateral right luminance" group, luminance changes were presented with a low frequency (1 Hz). The bar orientation was vertical for half of the trials and horizontal for the other half. Bar orientations were counterbalanced across participants.

In the "LTD unilateral right orientation" and "LTP unilateral right orientation" groups, orientation changes instead of luminance changes were presented in a way otherwise analogous to the "LTD unilateral right luminance" and "LTP unilateral right luminance" groups. In these cases, bar luminance was dark for half of the trials and bright for the other half. Bar luminance was counterbalanced across participants.

To ensure that the participants looked at the fixation cross, 10% of the trials during the stimulation procedure were catch trials. Catch trials occurred with equal frequency in the periods containing or lacking luminance changes. The fixation cross was shifted by a 0.2° visual angle out of the original position during the catch trials. Participants were asked to press a button whenever a catch trial occurred. In all cases, the contrast of the stimuli against the background and the positioning of the stimuli on the monitor were similar to the competition paradigm. A large length:width ratio of the stimuli was used (1:2.41).

In control group 1, there was no visual stimulation between the first and second test sessions but a pause for the same duration as used for the stimulation procedure. Participants in control group 2 were presented only with the background screen including the fixation cross, and an identical catch-trial procedure (shifts of the fixation cross) was applied.

Statistical Analysis

Performance scores (error rates and reaction times) were analyzed using repeated-measures analyses of variance (ANOVAs). The repeated-measures ANOVAs included distractor saliency (high/low), side (left/right from the fixation cross), and test session (baseline, 90 min, 24 hr, 10 days) as within-subject factors and group as the between-subject factor. Greenhouse-Geisser correction was applied when appropriate. Post hoc tests were Bonferroni corrected when necessary. Kolmogorov-Smirnov tests revealed that all relevant variables were normally distributed (all $z < 0.7$; $p > 0.3$; one-tailed). As a measure of variability, the standard error of the mean together with the mean is given. Statistics were computed with SPSS 15.

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