

Current Biology

Empowering Reentrant Projections from V5 to V1 Boosts Sensitivity to Motion

Highlights

- Paired associative TMS of human V5-V1 affects perception of motion coherence
- TMS plastic strengthening of reentrant V5-V1 connections enhances motion sensitivity
- Perceptual enhancement follows a time course consistent with Hebbian plasticity

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In Brief

Romei et al. show that visual processing of coherent motion, subserved by reentrant connections between extrastriate area V5 and early visual cortex V1, is functionally malleable. Strengthening the synaptic efficacy of the V5-V1 network enhances coherent motion perception following the temporal profile of the Hebbian rule.



Empowering Reentrant Projections from V5 to V1 Boosts Sensitivity to Motion

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SUMMARY

Evidence from macaques [1] and humans [2, 3] has shown that back projections from extrastriate areas to the primary visual area (V1) determine whether visual awareness will arise. For example, reentrant projections from the visual motion area (V5) to V1 are considered to be critical for awareness of motion [2, 3]. If these projections are also instrumental to functional processing of moving stimuli [4–8], then increasing synaptic efficacy in V5–V1 connections should induce functionally relevant short-term plastic changes, resulting in enhanced perception of visual motion. Using transcranial magnetic stimulation (TMS), we applied a novel cortico-cortical paired associative stimulation (ccPAS) protocol to transiently enhance visual motion sensitivity and demonstrate both the functional relevance of V5–V1 reentrant projections to motion perception and their plasticity. Specifically, we found that ccPAS aimed at strengthening reentrant connectivity from V5 to V1 (but not in the opposite direction) enhanced the human ability to perceive coherent visual motion. This perceptual enhancement followed the temporal profile of Hebbian plasticity [9–18] and was observed only when an optimal timing of 20 ms between TMS pulses [2, 3, 5, 6] was used, not when TMS pulses were delivered synchronously. Thus, plastic change is critically dependent on both the direction and timing of connectivity; if either of these requirements was not met, perceptual enhancement did not take place. We therefore provide novel causal evidence that V5–V1 back projections, instrumental to motion perception, are functionally malleable. These findings have implications for theoretical models of visual awareness and for the rehabilitation of visual deficits.

RESULTS

Using a novel cortico-cortical paired associative stimulation (ccPAS) protocol by means of transcranial magnetic stimulation

(TMS) based upon Hebbian principles [9, 10], we tested whether temporarily increasing reentrant connectivity from V5 to V1, considered to be crucial for visual motion [1–8], enhances perceptual sensitivity to motion.

We repeatedly activated the neural pathway between V5 and V1 in 32 healthy volunteers assigned to four ccPAS conditions, in which 90 paired TMS pulses over V5 and V1 were administered at 0.1 Hz frequency [13–19] (see [Supplemental Experimental Procedures](#)). The directionality and timing of the stimulation between V5 and V1 were manipulated across groups, resulting in one experimental and three control groups.

The experimental group received V5-to-V1 ccPAS (Exp_{V5-V1}). During ccPAS, the first TMS pulse was administered to V5 followed by another pulse to V1. The interstimulus interval (ISI) was set at 20 ms, corresponding to the average time for V5 stimulation to exert an effect over V1 processing [2, 3], i.e., the optimal timing for the activation of V5–V1 back projections underlying visual motion perception [2–6]. The specific ISI used was critical to create sequential pre- and post-synaptic activity in the V5–V1 pathway. This is essential for the occurrence of spike timing-dependent plasticity (STDP) [10–12], a form of synaptic plasticity that meets the Hebbian principle that synapses are potentiated if the pre-synaptic neuron fires repeatedly before the post-synaptic neuron [9, 10]. Thus, ccPAS in the Exp_{V5-V1} group was aimed at strengthening reentrant connections from V5 to V1. Control group 1 received V1-to-V5 ccPAS with 20 ms ISI, thus controlling for the directionality of the connectivity (Ctrl_{V1-V5}). Control group 2 received simultaneous V5–V1 ccPAS with 0 ms ISI, thus controlling for timing (Ctrl_{0ms}). Finally, control group 3 received V5-to-V1 ccPAS with 20 ms ISI in sham mode, controlling for nonspecific TMS effects (Ctrl_{sham}).

To test the effect of ccPAS on visual perception, participants performed a motion coherence discrimination task before (i.e., at baseline [BSL]) and immediately after the ccPAS phase (T0) and after 30, 60, and 90 min (T30, T60, T90; see [Figure 1A](#)). The motion coherence discrimination task consisted of a two-alternative forced choice where participants had to report the direction of coherent motion (leftward or rightward) for ten different magnitudes of motion coherence ranging from 0 (random motion) to 80% coherence ([Figures 1B and 1C](#)). For each experimental condition and time, we determined the motion sensitivity threshold, calculated as the minimum percentage of motion coherence necessary to discriminate the coherent direction of the moving dots with an accuracy of 75% (see [Supplemental Experimental Procedures](#)).

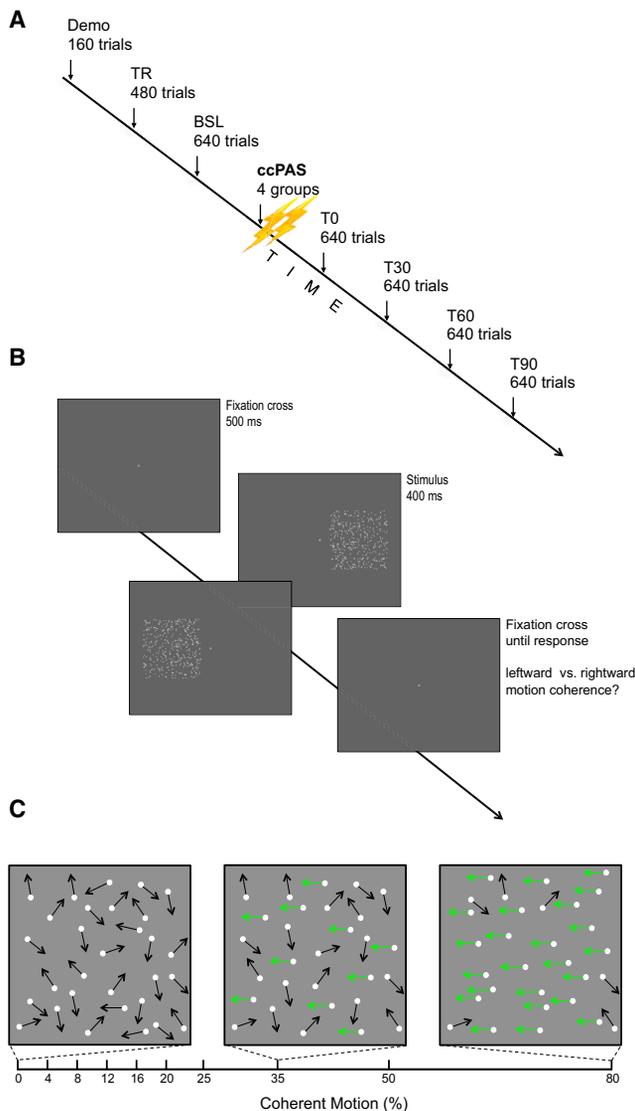


Figure 1. Experimental Design and Procedures

(A) Timeline of the experiment. For each participant, the experiment began with a preparation phase composed by a demo block (Demo) aimed to familiarize the participant with the basic mechanisms of the motion coherence task and a training session (TR) of three blocks, performed to allow the participant to reach a stable performance level before the actual experiment. This preparation phase was followed by a baseline session (BSL). After the BSL measurement, participants were randomly assigned to one of four groups, therefore undergoing either the experimental or one of the three control ccPAS protocols. Participants had to perform the same task immediately (T0), 30 (T30), 60 (T60), and 90 (T90) minutes following ccPAS protocol. One session consisted of four blocks of 160 trials each.

(B) Task sequence. Each trial consisted of a white central fixation cross displayed alone for 500 ms followed by a dot motion coherence stimulus displayed for 400 ms. Here, a single frame of the motion coherence stimulus used in the study is depicted. The motion coherence of the stimulus varied across trials, and it could appear either on the left or on the right side of the cross. To indicate that a response was required, the dot motion stimulus disappeared and the cross remained. A new trial started as soon as the participant pressed the response key on a keyboard indicating whether the coherent motion was perceived moving leftward (left arrow) or rightward (right arrow), regardless of the side of presentation.

(C) Stimuli. Schematic representation of the stimuli used to test the coherence threshold. The coherent motion display contains a set of 400 moving dots, a

The experiment used a $5 \times 2 \times 4$ design with time (BSL, T0, T30, T60, T90) and hemifield (left, right) as within-group conditions and experimental manipulation (Exp_{V5-V1} , Ctrl_{V1-V5} , Ctrl_{Oms} , $\text{Ctrl}_{\text{sham}}$) as a between-groups condition.

A $5 \times 2 \times 4$ mixed-factors ANOVA showed a main effect of time ($F_{4,112} = 2.51$, $p = 0.046$), suggesting that motion sensitivity threshold changed as a function of testing time. Crucially, there was an interaction between time and experimental manipulation ($F_{12,112} = 2.51$, $p = 0.006$), suggesting that any modification of motion sensitivity threshold depended on the specific ccPAS condition. No other main effects or interactions were significant (all $p > 0.1$). As clearly reported in Figure 2, only the experimental group (Exp_{V5-V1}) showed motion sensitivity enhancements, as evidenced by significant threshold shifts toward lower levels of motion coherence between 30 and 60 min following the ccPAS phase, before returning toward baseline values (see also Figures 3 and S1). Bonferroni-corrected t tests indicate that participants assigned to Exp_{V5-V1} are more sensitive to visual motion (lower motion sensitivity threshold) at T30 ($p = 0.003$) and T60 ($p = 0.048$) relative to baseline. Moreover, Bonferroni-corrected t tests comparing Exp_{V5-V1} versus all the other groups confirmed the greater sensitivity of the Exp_{V5-V1} group at T30 (Exp_{V5-V1} versus Ctrl_{V1-V5} : $p = 0.008$; Exp_{V5-V1} versus Ctrl_{Oms} : $p = 0.034$; Exp_{V5-V1} versus $\text{Ctrl}_{\text{sham}}$: $p = 0.003$) and T60 (Exp_{V5-V1} versus Ctrl_{V1-V5} : $p = 0.006$; Exp_{V5-V1} versus Ctrl_{Oms} : $p = 0.046$; Exp_{V5-V1} versus $\text{Ctrl}_{\text{sham}}$: $p = 0.025$). Perceptual enhancement in the Exp_{V5-V1} group was similar across hemifields as suggested by the non-significance of the triple interaction (see Figure S2).

None of the control groups showed a similar increase in performance after ccPAS (Ctrl_{V1-V5} : all $p > 0.19$; Ctrl_{Oms} : all $p > 0.12$; $\text{Ctrl}_{\text{sham}}$: $p > 0.53$), suggesting that perceptual boosting was specifically determined by the ccPAS manipulation when stimulation directionality (from V5 to V1) and timing (20 ms) met the physiological constraints of reentrant connectivity [2, 3]. This pattern of results was substantially replicated when using non-parametric tests (see Supplemental Information).

DISCUSSION

Repetitive paired stimulation, evoking sequential pre- and post-synaptic activity in interconnected neurons, induces Hebbian associative plasticity, prompting those synaptic connections to transiently strengthen [9–12]. Previous TMS studies have shown that similar synaptic strengthening can be induced in the human motor system over two interconnected motor areas through ccPAS administered at an optimal ISI [13–19]. These studies

fixed proportion of which are moving in a coherent direction (except for 0% motion coherence condition), while the remainder move in randomly chosen directions. Coherence of the motion ranged from 0% to 80%, distributed in ten levels (represented on the line below). When the proportion (“coherence level”) is high, task difficulty is low. The coherence threshold is the minimal percentage of dots moving in the same direction needed for the participant to accurately perceive (75% of accuracy) the predominant motion direction. The left panel represents a schematic trial with 0% coherence as all the dots are moving randomly. The central panel represents a trial with 35% coherence in the leftward direction. The right panel represents a trial with 80% coherence in the leftward direction. The arrows illustrate the motion direction of each dot. Green arrows represent the directions of signal dots; black arrows represent the directions of noise dots.

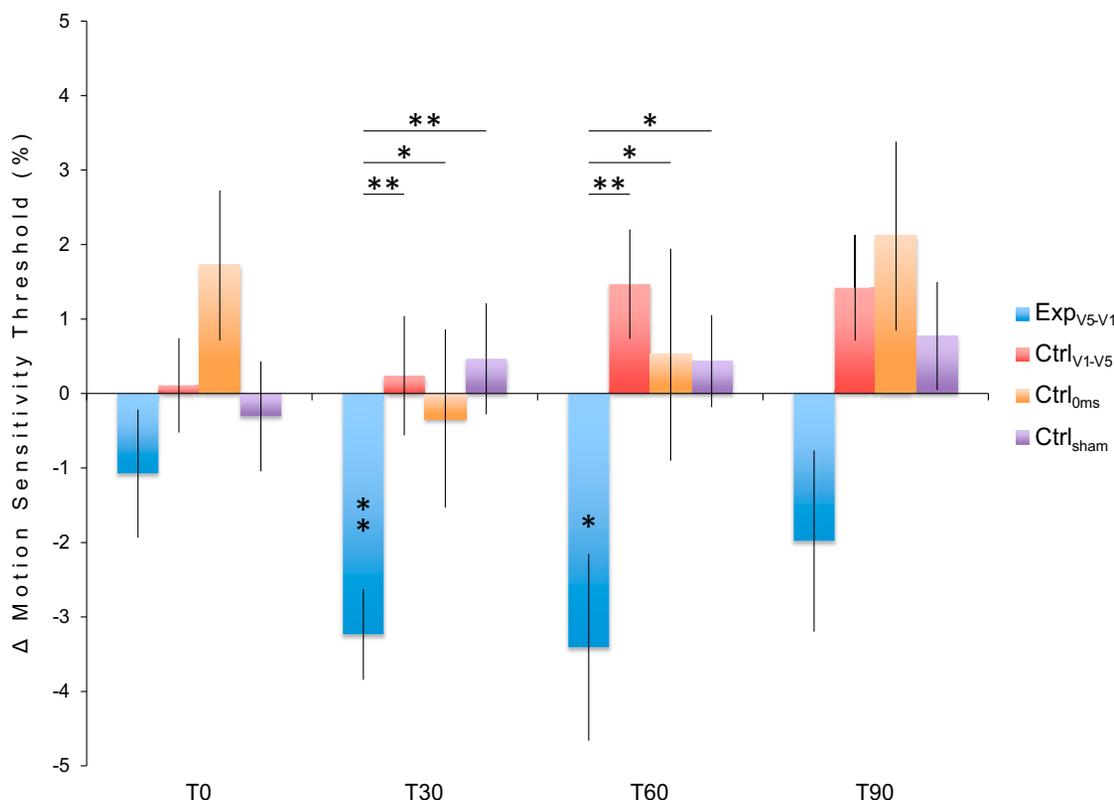


Figure 2. Changes in Visual Motion Sensitivity Induced by Cortico-cortical Paired Associative Stimulation

Only participants assigned to the experimental group (Exp_{V5-V1}; ccPAS: direction V5-V1, ISI 20 ms) showed a reduction of motion sensitivity threshold (baseline corrected) at 30 and 60 min after ccPAS, indicating enhanced visual motion sensitivity. Participants in control group 1 (Ctrl_{V1-V5}; ccPAS: direction V1-to-V5, ISI 20 ms), control group 2 (Ctrl_{0ms}; ccPAS: simultaneous V5-V1 stimulation, ISI 0 ms), and control group 3 (Ctrl_{sham}; V5-to-V1 sham stimulation, ISI 20 ms) showed no significant changes in motion sensitivity threshold over time. Error bars denote ± 1 SEM. Asterisks indicate significant differences ($p < 0.05$, $**p < 0.01$). See also Figure S2 and Table S1.

have shown that the ISI at which one targeted region (e.g., the premotor cortex) exerts a physiological effect on an anatomically connected second region (i.e., the motor cortex) is also the ISI at which ccPAS can induce Hebbian-like cortico-cortical connection changes (e.g., 6–8 ms for premotor-motor circuits; compare [15, 16] with [20, 21]). Such ccPAS studies have supported the notion of STDP by showing a causal and directional change of influence of the first over the second targeted region [16, 19]. However, little is known about the impact on behavior of such an experimental increase in synaptic efficiency, and no study to date has tested ccPAS protocols over the visual system.

Seminal studies in animals have provided *in vitro* and *in vivo* evidence of Hebbian plasticity in the visual system [10, 22, 23]. Our study goes beyond previous animal evidence by providing the first demonstration that directly fostering Hebbian plasticity in a cortical visual circuit has an impact on behavior. We demonstrated for the first time that ccPAS over two interconnected visual regions with an ISI consistent with evoking pre- and post-synaptic activity necessary for STDP [2–6] affects visual perception. In particular, we showed that stimulation aimed at increasing synaptic efficacy in back projections from V5 to V1 transiently boosted visual motion sensitivity. Such perceptual enhancement was evident for at least 60 min, and its time course resembled that of Hebbian-like physiological effects observed in

animal studies as well as in studies using ccPAS over the human motor system [10–19].

Our findings provide causal evidence that short-term synaptic strengthening of reentrant V5-V1 connections can enhance motion perception. This supports the view that reentrant connectivity from higher-order to early visual areas subserves integrative visual functions [1–8, 24]. Animal studies have shown that suppression of V5 in the visual system weakens V1 responses to moving bar stimuli, in particular when stimuli have low salience [25], which suggests a top-down amplification mechanism in the processing of visual motion. This mechanism is also thought to promote visual awareness of motion [1, 26, 27], and TMS studies in humans have provided causal evidence of the role of V5-V1 backward connectivity on motion visual awareness as probed by TMS-induced visual phosphenes [2, 3]. However, evidence indicates that backward connectivity is important also for efficient processing of actual moving stimuli [4–7], even when motion stimuli are not consciously perceived [5]. This suggests that the top-down gain control function of backward connections [6, 25] is not limited to subserving awareness [2, 3] and reflects a general principle of visual cortical information processing [6, 8, 24]. Remarkably, our study is the first to directly show that synchronous stimulation of V5 and V1 aimed at strengthening backward connections improves the perceptual processing of

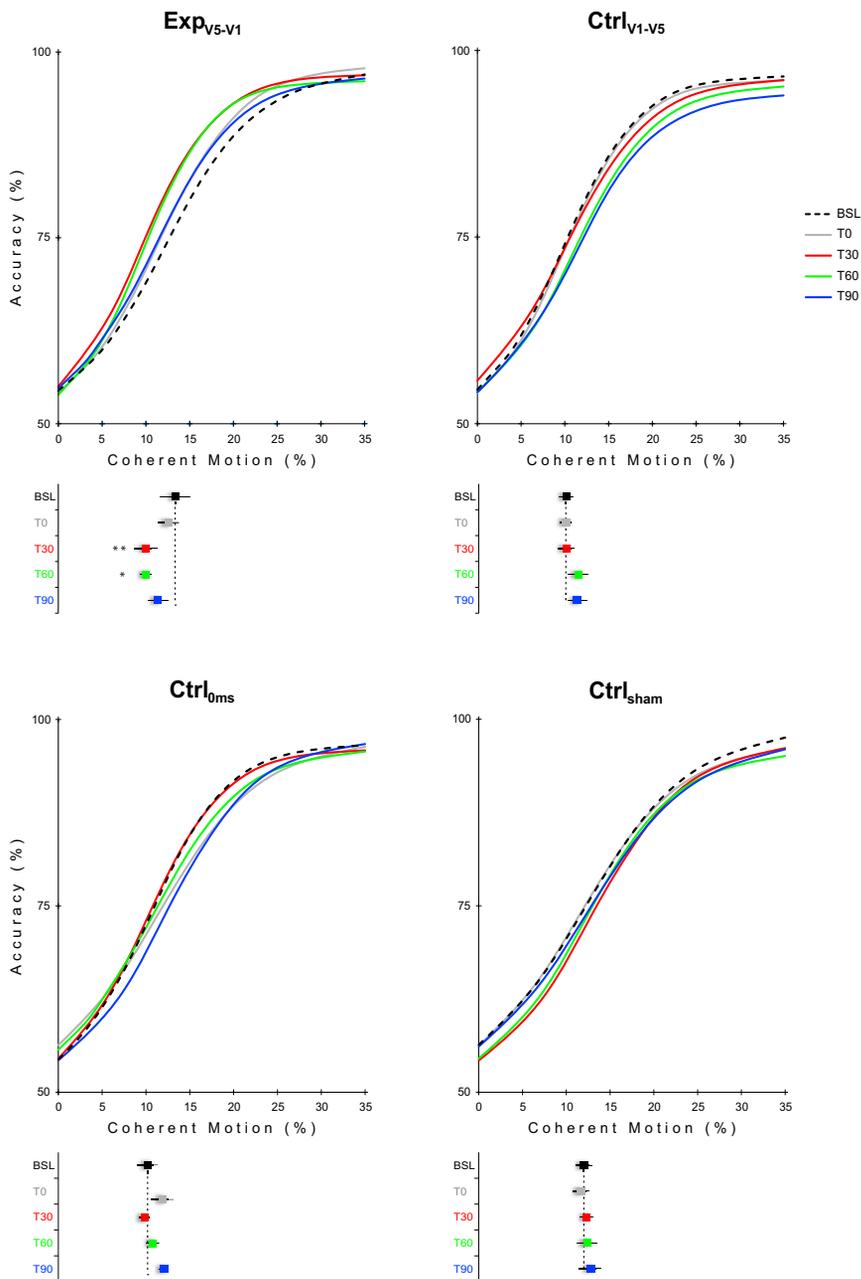


Figure 3. Curve Fitting and Groups' Performance

Sigmoid curve fits (top panels) and participants' average performance (bottom panels) are plotted for each group as a function of time before and after the ccPAS protocol has been applied. The black dotted line represents the baseline session (BSL); gray, red, green, and blue lines represent task performance at 0 (T0), 30 (T30), 60 (T60), and 90 (T90) minutes after the end of the ccPAS protocol, respectively. The motion sensitivity threshold was determined by taking the percentage of coherent motion where the logistic function had a value of 75% of correct responses. The motion sensitivity threshold represents the percentage of coherent motion necessary to discriminate the coherent direction of the moving dots with an accuracy of 75%. Below each graph, the averaged motion sensitivity threshold (and SE) across participants, in each of the four groups, are plotted for each session. Only in the Exp_{V5-V1} group is there a significant TMS-induced decrease in the motion sensitivity threshold, at T30 and T60 relative to BSL, as indicated by the asterisks ($*p < 0.05$, $**p < 0.01$). This reduction shows an enhancement in sensitivity to the global motion task. See also [Figure S1](#) for a representation of averaged data points for each group and each time.

reversing the order of the stimulation (i.e., first TMS pulse over V1, second over V5) would strengthen feedforward rather than backward connectivity in the network. Our findings suggest that backward more than feedforward connections are amenable to plastic boosting of visual perception, which is in keeping with their top-down modulatory role [1–8, 24, 25]. However, it should be noted that the ISI of the ccPAS was selected based on the timing of causal interactions that V5 exerts over V1 [2, 3], and, thus, other ISIs may be effective for modulating perceptual function via changes in feedforward connectivity. Visual tasks strongly relying on bottom-up processes

coherent motion. Notably, we specifically tested for a novel account of the functionality of reentrant projections, namely the plasticity of the V5-V1 circuit, by manipulating its pre- and post-synaptic nodes according to the Hebbian rule as implemented through this novel ccPAS protocol. The most immediate consequence of this novel intervention approach is that participants in the experimental group (Exp_{V5-V1}) experienced an enhanced perception of motion coherence. In contrast, none of the participants in the control groups (including Ctrl_{V1-V5} controlling for directionality of the stimulation) improved their perception at any testing time following the TMS application, when compared to their pre-TMS BSL measure.

One may wonder why no change in performance was detected following ccPAS in the Ctrl_{V1-V5} group. In principle,

may be particularly sensitive to manipulations of feedforward connectivity [28].

It might be worth noting that during Exp_{V5-V1} ccPAS, the stimulation of V5 may induce not only orthodromic activation of backward V5-to-V1 connections, but also antidromic activation of feedforward V1-to-V5 connections. Thus, one may consider the possibility that during Exp_{V5-V1} ccPAS, stimulation of V1 could reactivate the same feedforward connections, and this repeated pairing may also contribute to the observed plastic effect. Indeed, studies have shown that repeated TMS pairing over the same region can induce STDP [29]. However, such induction is selective for very short ISIs (~ 1.5 ms) [30], making it unlikely that it played a major role in the plastic effects we detected. While our study supports the hypothesis of Hebbian

strengthening of V5-V1 backward connections, future studies are needed to elucidate the possible contribution of additional mechanisms underlying ccPAS aftereffects.

In sum, our study suggests that ccPAS can enhance visual perception of motion in participants where the V5-V1 circuit is critically manipulated by repeatedly pairing pre- and post-synaptic nodes in the direction and timing that are optimal for strengthening these reentrant connections. This provides a novel mechanistic insight into the circuit and computational basis of visual perception by providing causal evidence of its malleability and demonstrating that this strictly depends on the timing and directionality of the repeated ccPAS manipulation.

This new demonstration of the malleability of the network governing visual processing paves the ground for future exploration of brain mechanisms responsible for integrative visual functions. While our offline ccPAS procedure addressed the basic features of associative plasticity in the cortical network for motion perception, future investigations might use a state-dependent approach [31–33] and pair ccPAS with specific motion directions in order to boost direction-specific perceptual tuning. Our study may also have implications for understanding more general mechanisms of perceptual learning [34] and fine-tuning interventional approaches aimed at enhancing perception, for example by combining training and neuromodulation strategies. However, physiological evidence indicates that ccPAS aimed at strengthening a given pathway may also induce weakening of non-stimulated pathways [19]. Thus, future studies are needed to understand the impact of such neural changes on behavior, as, in principle, the ccPAS protocol may be useful but also detrimental depending on the stimulated pathway and the task at hand.

We have probed the effects of associative plasticity on the motion perception reentrant network. There has been no attempt in the previous literature to explore this aspect of motion perception. Currently, it is not obvious whether and how our ability to make sense of motion signals depends on the capacity of the circuit to adapt to the environment. Here, we specifically shed light on the mechanisms by which reentrant connections become functionally adaptive. This has important implications for the way we perceive, conceptualize, interpret, and learn motion patterns, from simple to more complex spatio-temporal structures. Our study may have implications for the recovery of abilities that have been lost as a result of disorders such as stroke, as it suggests possible therapeutic interventions aimed at enhancing motion perception, and sensory processing in general.

Conclusions

We have enhanced motion coherence perception for an extended period through the application of the ccPAS protocol. This enhancement was critically dependent on mimicking the temporal features of Hebbian plasticity, by exactly pairing the nodes of the network subserving motion perception in the right direction and at the right time. The effects we observed are the result of a plastic modification of the circuit and not a mere interference with the circuit. As such, they provide novel mechanistic insights into the way the circuit functions. These findings have implications for theoretical models of visual perception as well as for the rehabilitation of visual deficits through non-invasive brain stimulation. Moreover, this novel protocol provides a novel perspective on current

models of perceptual learning and its potential underlying neurophysiology.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, two figures, and one table and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2016.06.009>.

AUTHOR CONTRIBUTIONS

V.R. and A.A. conceived the experiment. V.R., P.B.H., and A.A. designed the experiment. E.C. performed the experiment. All authors analyzed the data and wrote the manuscript.

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