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Transcranial magnetic stimulation-induced 'visual echoes' are generated in early visual cortex

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ABSTRACT

Transcranial magnetic stimulation (TMS) of the early visual areas can trigger perception of a flash of light, a so-called phosphene. Here we show that a very brief presentation of a stimulus can modulate features of a subsequent TMS-induced phosphene, to a level that participants mistake phosphenes for real stimuli, inducing 'visual echoes' of a previously seen stimulus. These 'echoes' are modulated by visual context at the moment of magnetic stimulation, showing that they are generated in early visual areas, and that the brain processes these 'echoes' as if they are factually presented stimuli. This shows that TMS can re-activate weak visual representations in early visual areas. Based on the pattern of contextual modulation of visual echoes, we theorize that perception of these echoes is not a passive reactivation of residual activity in early visual cortex, but an active interpretation of the combined activity of TMS-induced neural noise and cortical state.

Transcranial magnetic stimulation (TMS) of the occipital areas is a widely used tool in the study of visual processing, ever since Amassian et al. [1] demonstrated that occipital TMS can disrupt visual perception [7]. However, apart from disrupting visual processing, occipital TMS can also induce perception of a phosphene, a local increase of brightness. Phosphenes can be used to study excitability of early visual cortex: when cortical excitability is increased, the threshold at which participants report to see phosphenes, is lowered. Using this methodology, effects of for example visual imagery, top-down processing, ongoing rhythmic brain activity and migraine on visual cortex excitability have been demonstrated [2,12,14,16].

Although phosphenes are usually reported to be featureless, the appearance of phosphenes seems to be determined by cortical state at the moment of magnetic stimulation. When a participant has adapted to a red stimulus, for example, TMS of early visual cortex results in perception of a red phosphene instead of a colorless phosphene [15]. Even briefly presented stimuli can alter phosphene appearance: applying TMS over the visual cortex at a relatively long latency after presenting a visual stimulus has been reported to result in a 'replay' or 'echo' of that stimulus [21]. Apparently, TMS does not simply add random activity to the visual system, but interacts with ongoing neural activity in early visual areas, potentially 'boosting' sub-threshold activity over a threshold at which this activity gets registered by the visual system as a real stimulus.

However, phosphene perception seems to depend on processing in a fairly large cortical network [18]. Therefore it remains unclear whether the integration of cortical state and TMS-induced activity occurs higher in the visual processing hierarchy, or state dependent effects of TMS are indeed the result of an interaction between the TMS-induced activity and endogenous activity in early visual areas.

Here we provide further evidence for the latter hypothesis, by showing that TMS of the early visual areas can re-activate representations of stimuli that have been presented right before magnetic stimulation, resulting in a visual 'echo' that cannot be discriminated from a real visual stimulus, confirming earlier reports of TMS-induced 'replay' or 'echoes' [21]. Moreover, we show that the features these visual echoes are modulated by visual context at the moment of magnetic stimulation, by using tilt illusion stimuli: visual echoes suffer from the tilt illusion, just as real stimuli do. Given that the tilt illusion is the effect of contextual modulation in the primary visual cortex, this demonstrates that the visual echoes most likely originate in V1 [4,20]. Together, our results show that TMS of the early visual cortex interacts with sub-threshold activity in early visual areas, 'boosting' it over a threshold and triggering the visual system to reprocess and interpret this combined representation as if it was a real visual stimulus.

Seven healthy volunteers have given their written informed consent to participate in this experiment (18–20 years old, three females). All participants reported no history of medical problems,

Abbreviations: TMS, transcranial magnetic stimulation; V1, primary visual cortex; EEG, electroencephalography; ERP, event related potential.

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and had normal or corrected-to-normal vision. They received a payment of 10 euros per hour for their participation. This study was approved by the ethics committee of the Department of Psychology of the University of Amsterdam, and conducted according to the declaration of Helsinki.

A Magstim 200 (The Magstim Company, Whitland, UK) magnetic stimulator was used for magnetic stimulation. Magnetic pulses were delivered using a 140 mm circular coil, with the lower rim placed 1.5–2.0 cm above the inion, with the coil oriented vertically (relative to the floor). Stimulation at this location is known to suppress perception around 100 ms after stimulus onset, and targets the early visual areas (V1, V2, V3) [1,7]. The coil was positioned in such a way that no uncomfortable contractions of neck and facial muscles were reported, but that the subject still did see phosphenes. Phosphenes were described as a horizontal bar or distortion throughout the entire visual field, in the middle of fixation. Stimulator output was set to 90% of maximum. Stimulation was monophasic, with current direction being counterclockwise. Please note that in pilot experiments in another laboratory the effect was replicated in five other subjects with biphasic stimulation. Subjects were seated in a chair, with their heads in a chin rest to minimize head movements.

Stimuli were generated on a PC using in-house written presentation sofware, and presented on a 14 in. BenQ TFT monitor (BenQ Inc., Shuzhou, China). A TFT monitor was used to avoid visual artifacts induced by the TMS pulse, as on CRT monitors. Actual stimulus presentation times were checked using an oscilloscope connected to a photosensor. We presented white (145.4 cd/m^2) gratings (7.5 cycles per degree) on a grey (136.2 cd/m^2) background. Background gratings were $4^\circ \times 4^\circ$ of visual angle, and were tilted either 10° to the left or 10° to the right. In the middle there was an aperture of $1^\circ \times 1^\circ$, in which a smaller grating (7.5 cpd) was flashed. This small grating (the target grating) could be either tilted 15° to left or to the right, or upright. During psychophysical pilot trials, these settings yielded the largest tilt effect. Each trial was preceded by an initial fixation period of 2000 ms, during which the background grating was already presented. Trial onset ($t = 0$) started after the fixation period. Tilt of the background grating was chosen at random. At the start of the trial, a target patch was flashed for 16.7 ms. The target patch was tilted to the left in 25% of all trials, tilted to the right in 25% of all trials, and upright in 50% of all trials. In half of all trials, the tilt of the background grating changed from left to right or vice versa, 150 ms after onset of the target grating.

Half of all trials were experimental trials: in these trials, a TMS pulse was given 300 ms after presentation of the target grating, whilst leaving the aperture grey. The other 50% of the trials were control trials. In these trials a second grating was flashed (16.7 ms) 300 ms after the target grating, immediately followed by a TMS pulse. 50% of these control gratings were upright, 25% were tilted to the left, and 25% were tilted to the right. At the end of the trial, participants were prompted to indicate the tilt of the gratings they had seen using the left and right buttons. Participants could either report zero, one or two gratings, and were instructed to be conservative in their report and only report tilt when they were absolutely sure they had seen a real stimulus. Tilt of the gratings had to be reproduced in the order in which participants had perceived them. Participants were kept naïve towards the purpose of the experiment and were not informed about the background changes. All participants did 20 blocks of 64 trials. See Fig. 1(a).

Magnitude of the tilt effect was measured in terms of 'left'-responses to the center gratings as a function of background tilt. In order to assess the effect of background tilt on perceived tilt of visual echoes, we compared reported tilt of visual echoes in trials in which the background remained constant with reported tilt in trials in which the background changed. If the appearance of a visual echo is not influenced by background tilt, no difference is to be expected, whereas we would expect a difference if background tilt does affect perceived tilt of visual echoes. Statistical analyses (repeated measures ANOVAs) were conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL).

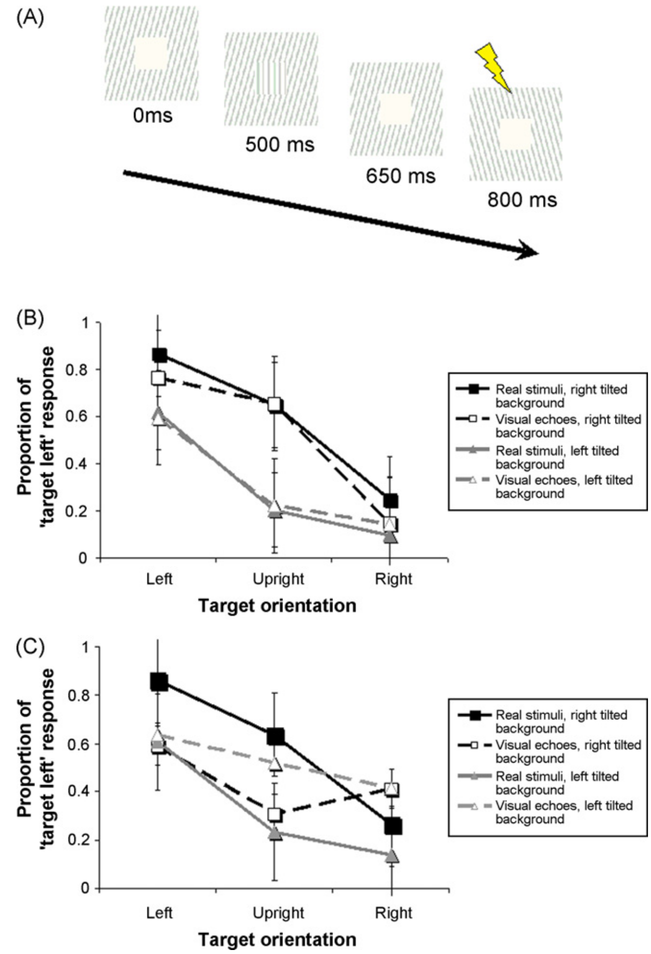

Fig. 1. (a) Typical trial run. Trials started with a 500 ms fixation period during which the background grating was present. A target grating, either tilted left or right, or vertical (shown here) was flashed for 16.7 ms; 150 ms after target grating onset the background tilt changed on 50% of the trials (change shown here). 300 ms after target onset, a TMS pulse was given to the early visual cortex. (b) Tilt modulation of real stimuli (solid lines) and visual echoes (dotted lines) by background tilt, without a background change. Echoes are perceived as almost identical to the real stimuli. (c) As in (b), but now with background change. Changing the background between presentation of the target and magnetic stimulation inducing the visual echo has a significant effect on tilt modulation of the visual echo.

Participants reported visual echoes in 33% of trials in which no real second stimulus was presented. We observed a strong tilt illusion for real stimuli: the proportion of 'tilted left' responses was significantly larger for all target grating orientations when the background was tilted to the right then when the background was tilted to the left, whether the stimulus was accompanied by a TMS pulse or not (see Table 1 and Fig. 1(b)). For visual echoes in trials without

Table 1
Magnitude of tilt effect for real stimuli, measured in increase in proportion of 'left-tilted' responses for patches presented on a right-tilted background as compared to patches presented on a left-tilted background. SD in brackets; $^*p < .05$, $^{**}p < .01$.

	Patch tilt		
	Left	Upright	Right
No subsequent background change	$.25^*$ (.25)	$.45^{**}$ (.32)	$.15^{**}$ (.11)
With subsequent background change	$.25^{**}$ (.08)	$.40^*$ (.35)	$.12^*$ (.12)