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Does TMS on V3 block conscious visual perception?

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ABSTRACT

Primary visual cortex (V1) and extrastriate V2 are necessary for the emergence of visual consciousness, but the effects of involvement of extrastriate V3 on visual consciousness is unclear. The objective of this study was to examine the causal role of V3 in visual consciousness in humans. We combined neuronavigated transcranial magnetic stimulation (TMS) with a computational model of the TMS-induced electric field to test whether or not the intact processing of visual input in V3, like in V1 and V2, is necessary for conscious visual perception. We targeted the stimulation both to V2 and to V3. If TMS of V3 blocks conscious visual perception of stimuli, then activation in V3 is a causally necessary prerequisite for conscious perception of stimuli. According to the alternative hypothesis, TMS of V3 will not block the conscious visual perception of stimuli, because the pathways from V1 to the higher cortical areas that go around V3 provide sufficient visual input for the emergence of conscious visual perception. The results showed that TMS interfered with conscious perception of features, detection of stimulus presence and the ability to discriminate the letter stimuli both when TMS was targeted either to V3 or to V2. For the conscious detection of stimulus presence, the effect was significantly stronger when V2 was stimulated than when V3 was stimulated. The results of the present study suggest that in addition to the primary visual cortex and V2, also V3 causally contributes to the generation of the most basic form of visual consciousness. Importantly, the results also indicate that V3 is necessary for visual perception in general, not only for visual consciousness.

1. Introduction

During the past 25 years, many studies have searched for the neural correlates of the subjective experience of seeing, or visual consciousness, and have advanced our knowledge concerning the time course and activated brain regions that are related to the emergence of consciousness. Nevertheless, it is still unclear which specific cortical and subcortical areas and tracts are necessary for the emergence of visual consciousness. Compared to the large amount of studies focusing on the neural correlates of consciousness (NCC) or to the necessity of different brain regions or tracts for the specific property or feature of visual consciousness (e.g., Koch, 2004, 2012; Koch et al., 2016; Metzinger, 2000; Revonsuo, 2006), the studies concerning the prerequisite brain processes related to the emergence of what is arguably the simplest form of seeing, *the conscious detection of stimulus presence* are still lacking.

The removal of primary visual cortex, V1, causes blindness in humans, and partial lesions of the V1 induce visual field defects (Holmes, 1918; Tong, 2003), demonstrating that V1 is necessary for conscious visual perception. In addition, there is converging evidence suggesting that the adjacent visual area, extrastriate V2, is also necessary for the emergence of visual consciousness as extrastriate lesions are associated with homonymous scotomas (Horton and Hoyt, 1991; McFadzean and Hadley, 1997) and because transcranial magnetic stimulation (TMS) of V2 in neurologically intact humans blocks conscious detection of stimulus presence (Salminen-Vaparanta et al., 2012b). V1 and V2 are linked by dense bidirectional connections in primates (e.g., Burkhalter et al., 1986; Felleman et al., 1997; Felleman and Van Essen, 1991; Maunsell and Van Essen, 1983; Van Essen et al., 1986), and therefore it is logical that both V1 and V2 are required to generate visual consciousness. Slotnick and Moo (2003) determined with fMRI the retinotopic organisation of striate and extrastriate areas in a patient who had an upper right homonymous quadrantanopia and found that the patient's V1 and V2 were intact, but there was a lesion in ventral V3

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and V4. The result suggests that also V3 plays a role in the generation of visual consciousness. The objective of the present study was to examine the causal role of V3 in visual consciousness in humans.

Visual area V3 is an intermediate between anatomically early visual areas (V1 and V2) and higher areas in occipital, temporal and parietal cortex (for review see Arcaro and Kastner, 2015). In humans, it is approximately the same size as V2 (e.g., Sereno et al., 1995; Wandell et al., 2007), but its functional properties are less well understood than for example those of V1, V2 or V5 (Arcaro and Kastner, 2015). Based on studies with non-human primates, the cells in V3 are tuned for motion, orientation, curvature and colour (Felleman and Van Essen, 1987) and to the combination of motion and colour (Gegenfurtner et al., 1997). Several neurons also respond to multiple properties (Felleman and Van Essen, 1987; Gegenfurtner et al., 1997). Studies with monkeys have shown that V3 receives input from V1 layer 4B (Felleman et al., 1997; Van Essen et al., 1986) and superior colliculus (Lyon et al., 2010) and has direct connections to middle temporal area (MT) (Felleman et al., 1997) from where it receives also feedback (Hupé et al., 1998, 2001). It has projections also to V2, V4, V3A, posterior intraparietal area, ventral intraparietal area and dorsal medial superior temporal area (Felleman et al., 1997). FMRI of the resting state correlations between the visual areas in humans shows strong correlation particularly between V3 and V2, but also between V3 and V4 and V5 suggesting the presence of strong anatomical connections between the areas (Genç et al., 2016). Visual area V3A is a visual area neighbouring V3, located higher in visual hierarchy compared to V3, and is distinct from V3 regarding its functional properties and its retinotopy (e.g., Tootell et al., 1997; Van Essen and Zeki, 1978; Zeki, 1978).

TMS over the occipital cortex can enhance or suppress visual perception (e.g., Abrahamyan et al., 2011; Amassian et al., 1989; Corthout et al., 1999; de Graaf et al., 2014; Epstein and Zangaladze, 1996; Jacobs et al., 2014; Kastner et al., 1998; Pascual-Leone and Walsh, 2001; Paulus et al., 1999) and is a useful method in studying the causal roles of specific cortical areas in consciousness. Thielscher et al. (2010) compared different positions of the TMS coil on the scalp with the strength of the induced scotoma and demonstrated high spatial resolution of TMS. This resolution is sufficient to compare the effects of TMS between the visual areas (V1, V2, V3, V3a) (Thielscher et al., 2010; see also Salminen-Vaparanta et al., 2012b; Salminen-Vaparanta et al., 2014; Schaeffner and Welchman, 2017). In addition, Thielscher et al. investigated the effect of TMS to V2, V3 and V3a on visual discrimination of U-shaped hook, and found that stimulation of V3 affected forced-choice visual discrimination, whereas the stimulation of V3a did not have any effect. There are no earlier studies where the role of V3 specifically in consciousness would have been investigated with neurologically healthy humans.

Here, we combined functional magnetic resonance imaging (fMRI) - guided TMS with computational modelling of the TMS-induced electric field (EF) to test whether or not the intact processing of visual input in V3, like in V2 (Salminen-Vaparanta et al., 2012a), is required for conscious visual perception. If TMS of V3 blocks conscious visual perception of stimuli, then activation in V3 is a causally necessary prerequisite for producing conscious visual perception of stimuli. According to the alternative hypothesis, TMS of V3 will not block the conscious visual perception of stimuli, because activation in V1 and V2 and in the structures that receive the ascending input from V1 and V2 offer sufficient visual input for the emergence of conscious visual perception. A further question was that if V3 is necessary, is there a difference in the necessary time intervals between V2 and V3? We used a similar method as was used in Salminen-Vaparanta et al. (2012a) but the TMS was targeted to V3 whereas V2 served as a control site in the present study. As in previous studies, the target of stimulation was controlled with the spherical modelling and individual retinotopic maps of V2 and V3.

2. Materials and methods

2.1. Participants

Eight neurologically healthy students or personnel of the University of Turku (age 20–32 years, three males) whose V2 and V3 could be stimulated in a manner that during V3 stimulation, the EF strength in V2 was sufficiently lower than the EF strength in V3 and vice versa took part in the TMS experiment. This group was preselected on the basis of the individual locations of their V2 and V3 areas from the larger group of participants whose visual cortex retinotopy was determined with fMRI (see 2.2.). All of them had normal or corrected-to-normal vision. Each participant gave a written informed consent and the Ethical Committee of The Hospital District of Southwest Finland approved the protocol of the experiment. The experiment was accomplished according to the declaration of Helsinki. Participants were either paid for their participation or given course credits for introductory psychology courses at the University of Turku.

2.2. MRI and fMRI

The visual stimuli and stimulation protocol for MRI and fMRI were adopted from a previous study (Henriksson et al., 2012). Stimuli used for multifocal mapping in the fMRI experiment were contrast-reversing 24 checkerboard patterns (3 rings extending at 1–3.2°, 3.2–6.7°, and 6.7–12° eccentricities, and 8 wedges) forming a circle (Vanni et al., 2005). These were presented in a temporally orthogonal sequence of frames. The circle had a central gaze fixation dot. Visual stimulus presentation was controlled by the Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA). The stimuli were presented via MRI-compatible goggles (VisualSystem by NordicNeuroLab, Bergen, Norway) that had an 800 × 600 pixel matrix for stimulus presentation. The optics of the goggles gives a total field of view of 30 × 22.5° in horizontal and vertical dimension, respectively. Therefore, 0.75° of the uppermost and lowest parts of the stimulation area were not seen by participants. However, those regions were out of interest for the purposes of the present TMS study.

MRI data were acquired with the Philips Ingenuity TF PET/MRI system equipped with a 3 T magnet and a headcoil Sense Head 32.[1] The MRI experiment included 4 identical fMRI blocks, acquisition of high-resolution T1-weighted (256 × 256 matrix, 1 × 1 × 1 mm voxel size) and T2-weighted (96 × 96 matrix, 2.67 × 2.67 × 3 mm voxel size) images. fMRI was performed using echo-planar imaging (EPI) to obtain blood oxygenation level-dependent signal. A single-short T2*-sensitive pulse sequence was used to acquire 132 volumes with 29 oblique slices in an interleaved ascending order with 1.8 s TR, 30 ms TE, 60° flip angle, 80 × 80 matrix, and 3 × 3 × 3 mm voxel size. Four dummy scans preceded each EPI session.

The collected fMRI data were processed with the SPM8 version of the Statistical Parametric Mapping (Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab 8.2.0 (Mathworks Inc., Sherborn, MA). Because only a band of brain tissue was scanned for activations, the whole-brain T2 image (with the same slice orientation) was used as a common spatial reference to achieve better coregistration result between the functional and structural images of each participant. The functional images were corrected for time differences in slice acquisition (using the middle slice in space as a reference) and for head motion with rigid-body transformation-based realignment. The statistical analysis was performed in individual space of each participant.

The general linear model was fitted using 24 regressors per session representing stimulation periods of each of 24 visual field areas and

[1] For one of the participants, the fMRI and MRI data that was used in the present study was collected earlier for the experiment Koivisto et al. (2011a) (see for methods).

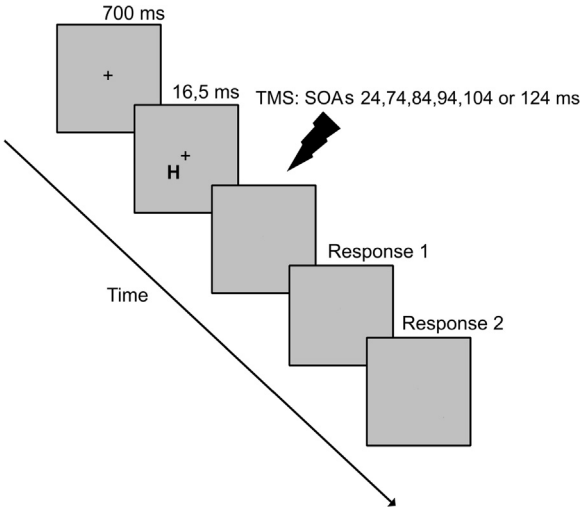

Fig. 1. The temporal sequence of a single TMS trial. The TMS pulse was applied in a random order at one of the six visual stimulus-TMS SOAs or no TMS was delivered. The first response was forced-choice letter-discrimination and the second response subjective rating where the participants evaluated their visual experience of the stimulus.

convolved with the default hemodynamic response function. Each session also included six realignment parameters as nuisance regressors to additionally account for head motion. After model estimation, a map of t-statistics was obtained for activation specific to stimulation of each of the 24 visual field regions. We visualized SPM T-maps on the anatomical 3D-image and identified the borders between the subareas of V1, V2, V3 and V3a at the vertical and horizontal meridian. The approximate center of each subarea was determined via visual inspection.

2.3. Stimuli and procedure in TMS and no TMS experiments

The visual stimuli and behavioural tasks were adopted from a previous study (Salminen-Vaparanta et al., 2012b). Visual stimuli were three dark grey letters (H, T, O, diameter 0.23°, 3 cd/m^2) presented on a light grey background (28 cd/m^2) on the monitor positioned 90 cm away from participants' eyes. In a single trial (see Fig. 1), a fixation cross was presented on the center of the screen for 700 ms, followed by one of the letter stimuli (2.8° away from fixation). The monitor was set to 60 Hz refresh rate, and thus, the duration of the visual stimulus was one frame, that is, 16.7 ms. The fixation cross and the letter stimulus disappeared at the same time. The next trial began after the participant had given the responses.

The visual stimuli were presented in a randomized order in the lower or upper visual field. The lower visual field was contralateral in relation to the hemispheric position of the TMS coil, whereas the upper visual field was ipsilateral in relation to TMS. In each trial, the participants' task was first to identify the letter stimulus (3-alternative forced-choice task) and then to evaluate their visual experience of the stimulus according to the scale (Salminen-Vaparanta et al., 2012a): (1) I saw the stimulus clearly, that is, I saw at least a feature of the letter from which I could recognize it, (2) I did not see the stimulus clearly, but I saw a trace on the screen, or (3) I did not see anything at all, only the fixation point. The participants gave responses for the forced-choice letter-discrimination task with left and right index fingers and middle finger of the right hand, and for the subjective rating with the thumb of the right hand.

The contrast level of the visual stimuli was set individually before the actual experiment by systematically increasing or decreasing the luminance of the stimuli between the stimulus blocks (30 trials/block). Ten steps were used to either increase or decrease the contrast of the letter. The aim of the contrast level setting was 80% correct without TMS. Acceptable level was 75–85% correct. Contrast level hunting was continued as long as required to find the acceptable level.

There were 20 trials for each visual field position (contralateral lower vs. ipsilateral upper field) at each visual stimulus-TMS pulse onset-asynchrony (SOA). The TMS pulse was applied in a random order at one of the six SOAs: 24, 74, 84, 94, 104 and 124 ms. The experiment was divided into 8 TMS blocks (four blocks per stimulated area), and the stimulated area was changed after each block. One block included five trials per SOA per visual field and four trials without visual stimulus where the TMS pulses were delivered at the SOAs of 24 ms. Thus, there were 64 trials in each block. Participants received 480 pulses in total in the main experiment. The participant did two no-TMS blocks (36 trials/ block) before the TMS experiment and twice again at the end of the session.

We analyzed the subjective ratings with the same approach as before used by Salminen-Vaparanta et al. (2012a). Given that the aim of the study was to investigate the most elementary form of visual consciousness, the conscious detection of stimulus presence, we combined the trials where participant gave response (1) I saw the stimulus clearly, that is, I saw at least a feature of the letter from which I could recognize it and (2) I did not see the stimulus clearly, but I saw a trace on the screen in subjective ratings. In the rest of the trials, participants reported that they saw nothing on the screen. In addition, we analyzed the reports when participants gave the response (1) I saw the stimulus clearly, that is, I saw at least a feature of the letter from which I could recognize it. This variable enables to observe the effects of TMS on conscious perception of stimulus features, or, conscious identification of letter stimuli.

2.4. TMS

The eXimia™ TMS magnetic stimulator (Nexstim Ltd.) with figure-of-8 Nexstim bipulse coil (outer winding diameter = 70 mm) was used to generate TMS pulses. Participant's head was stabilized by a chin rest and the coil was in a holder to keep it tight against the participant's head. MRI-guided Navigated Brain Stimulation (NBS) system (eXimia 2.2.1; Nexstim Ltd.) was applied to observe the relation between TMS coil and the brain. It provided also the modelling of the intracranial EF of TMS pulses. The NBS system estimates the intracranial EF distribution with the spherical model which has shown to be of sufficient accuracy to compare the effects from different visual areas (Thielscher et al., 2010). When all sources of errors are taken into account the approximate spatial resolution of the NBS system is 5.7 mm (Ruohonen and Karhu, 2010). The orientation of the TMS-induced EF was horizontal.

To target TMS, we selected the representation of the region located between 1° and 3.2° to the lower left from the fixation point (Fig. 2). The hemisphere to be stimulated was selected individually with the aim to find a subarea where dorsal V2 and V3 could be stimulated in a manner that during V3 stimulation, the EF strength was lower in V2 than in V3 and vice versa. For three participants, the right hemisphere was stimulated, and for four participants, the left hemisphere was stimulated.

TMS intensity was determined for the main experiment as follows: TMS was delivered to V2 at the SOAs of 24 and 84 ms (20 trials/ SOA). The decrease in the accuracy of the responses at the SOA of 84 ms compared to the no-TMS baseline and to the 24 ms SOA had to be at least 15%. The hunting procedure was started with the 40% from the stimulator output intensity and increased or decreased by 5% depending on the participant's results. To stimulate V3, we used the EF strength in the target area that was aimed to keep the same as in V2 during the V2 stimulation. In the main experiment, the stimulator output intensity was on average 55% for V2 and 59% for V3 from the maximal output. This rendered EF strength of 136 V/m on average for V2 and 138 V/m for V3. To induce visual suppression due to TMS on the target area, the estimated EF strength in the non-target adjacent

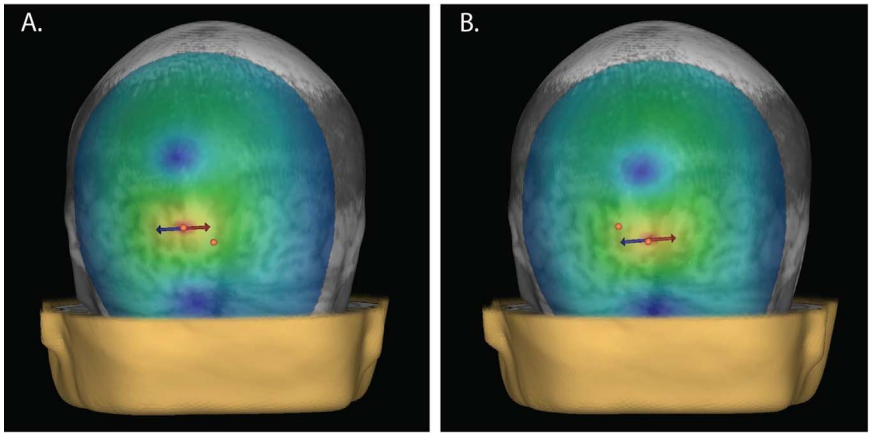

Fig. 2. The 3D image of one representative participant illustrates the EF distribution on the cortex when TMS was targeted to V3 (A) or to V2 (B). The orange spot between the two arrows indicates the location of the modelled maximum EF strength at the selected stimulation depth and the colours blue–green–yellow–red illustrates the EF strength in an increasing order. The direction of the EF of the second peak of the biphasic pulse is illustrated by the red arrow and the EF direction of the first peak by the blue arrow. In A., another orange spot marks the approximate center of the retinotopically equivalent V2, whereas in B., it shows the approximate center of the retinotopically equivalent V3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

areas should be kept under the level required to induce suppression.[2] During the V2 stimulation, the EF strength was on average 76,9% in retinotopically equivalent V3 from that of the EF strength in V2, and during V3 stimulation the EF strength was on average 79% in retinotopically equivalent V2 from that of the strength in V3. For all the participants, the difference between the areas was at least 13%. We modelled the EF strengths also in the retinotopically equivalent adjacent visual areas in V1 and V3a (See Supplementary Materials for all the modelled EF strength values). The TMS data was collected in two sessions and the TMS stimulation level hunting was carried out during the first session.

Because the spatial accuracy of TMS stimulation was particularly important for the purposes of the study, we removed the trials where TMS-targeting failed more than 4 mm from the target. In total, 243 trials were removed from three participants. The participation of one participant was cancelled due to the insufficient number of trials (less than ten trials per SOA in V2 stimulation). Other two participants had on average 17 and 18 trials per SOA in V2 stimulation and 16 and 20 trials per SOA in V3 stimulation. Thus, here we report the data from seven participants.

2.5. The low EF V2 stimulation

In addition to the main experiment, participants participated in an experiment where TMS was targeted to V2 with a TMS intensity that kept the EF strength in V2 same as it was in the V2 target area during the V3 stimulation in the main experiment. We call this “low EF V2 stimulation”. The experimental procedure was same as in the main experiment. We counterbalanced the order of stimulation conditions, so that with the four participants the low EF V2 stimulation was done first and with three participants the main experiment was done first. The low EF V2 stimulation and main experiment were done in separate sessions.

3. Results

3.1. No-TMS trials

For the stimuli presented to the lower visual field, participants responded correctly in 75% (SE 0.04) of the trials. They reported that they saw at least a feature of the letter from which they could recognize it in 53% (SE 0.07) of the trials, and in total in 98% (SE 0.004) of the trials they reported that they saw *at least* a trace on the screen (i.e., responses 1 and 2 summed together). Thus, only in 2% of the trials they reported that they saw no stimuli on the screen.

For the stimuli presented to the upper visual field, participants responded accurately to the correct letter in 86% (SE 0.02) of the trials. They reported that they saw at least a feature of the letter from which they could recognize it in 72% (SE 0.08) of the trials, and in 99% (SE 0.005) of the trials they reported that they saw at least a trace on the screen (i.e., responses 1 and 2 summed together). Thus, only in 1% of the trials they reported that they saw no stimulus on the screen. These results demonstrate that when TMS was not applied, participants almost always reported that they saw at least a trace on the screen. For the accuracy of the responses, the difference between upper and lower field stimuli in the no TMS baseline condition was not significant, but regarding the conscious perception of stimulus features, $F(1,6) = 8.46$, $p < 0.05$, $\eta_p^2 = 0.585$, and stimulus presence, $F(1,6) = 15.00$, $p < 0.01$, $\eta_p^2 = 0.714$, the difference was significant.

The “No-TMS” -trials were applied before and after the TMS trials. The accuracy for the upper visual field stimuli was 85% before TMS and 87% after it, and for the lower visual field the values were 75% and 75% respectively. The stimulus features were rated to have been consciously perceived in the upper visual field in 71% of no-TMS trials before TMS trials, and 73% after TMS trials; for the lower visual field, the corresponding values were 54% and 53% respectively. The presence of the stimulus was consciously detected in 100% of trials in the upper field before TMS, and in 99% after TMS; the corresponding values in the lower visual field were 98% and 98%, respectively. We analyzed with repeated measures analyses of variance (ANOVA) with Moment (2: before/after] and Visual field (2: upper/lower) whether or not accuracy and awareness ratings in no-TMS baseline differed depending on whether the no-TMS trials were performed before or after the TMS-trials. The analyses did not reveal any significant differences between accomplishing no-TMS trials before or after the TMS trials (accuracy: $F(1,6) = 1.0$, $p = 0.77$; feature ratings: $F(1,6) = 0.001$, $p = 0.97$, presence ratings: $F(1,6) = 0.18$, $p = 0.69$), suggesting that the no-TMS baseline did not change during the testing sessions.

3.2. TMS trials

To analyse how visual Area (2: V2, V3), Field (2: upper, lower) and TMS (7: 24, 74, 64, 84, 104, 124 ms, no-TMS) affected response accuracy and ratings of subjective conscious visual perception, we carried out ANOVA. When the assumption of sphericity was violated, Huynh-Feldt correction was applied to p-values. Post hoc analyses comprised Pairwise comparisons to compare results at each SOA between TMS and no-TMS baseline conditions.

Visual inspection of Fig. 3 suggests that stimulation of both V2 and V3 had an effect on the response accuracy and on the conscious perception of features and stimulus presence, and that the effect would be

[2] Visual suppression diminishes fast by decreasing the TMS stimulator output intensity, which was shown by Thielscher et al. (2010) who reported that by decreasing the stimulator output intensity by approximately 15% from the suppressive level, the orientation discrimination accuracy in the forced-choice task increased from the chance level to 100% correct.

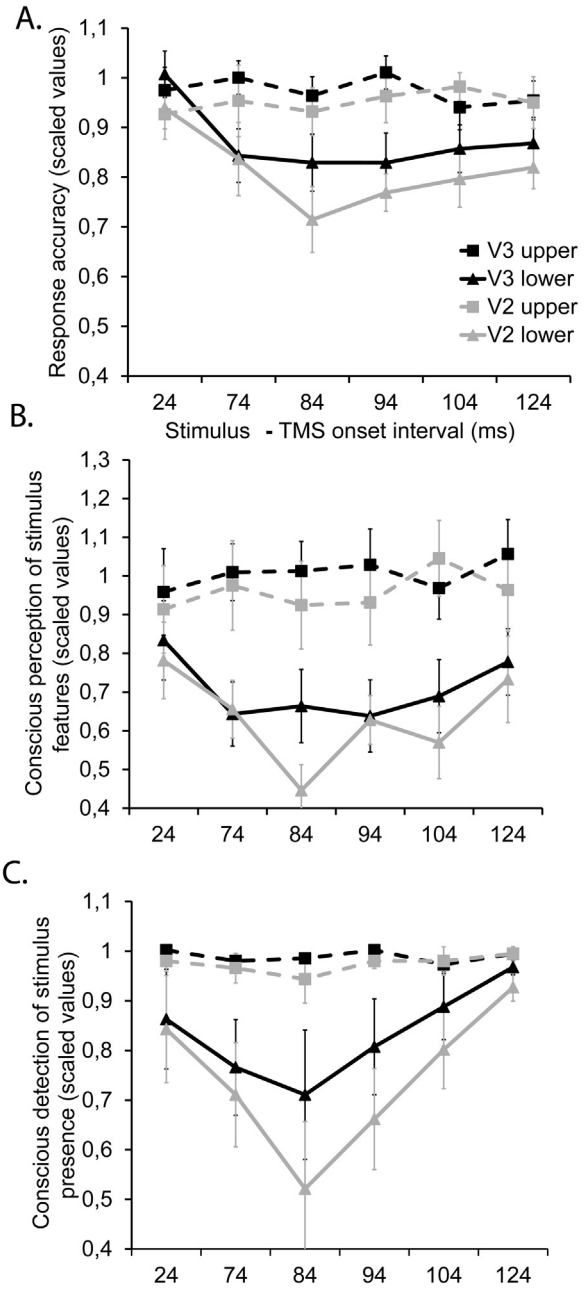

Fig. 3. A. The proportion of correct responses, B. conscious visual perception of stimulus features, and C. conscious visual detection of stimulus presence when TMS pulses were targeted to the lower visual field representation in V2 or V3 24–124 ms after the visual stimulus onset. The results are scaled so that 1 represents the baseline performance when no TMS was applied. The statistical analyses were done with the raw data.

stronger in V2 than in V3 stimulation for the lower visual field stimuli. We explored if statistics support this impression. For the response accuracy, Field, $F(1,6) = 16.58$, $p < 0.01$, $\eta_p^2 = 0.734$, and TMS, $F(6,36) = 4.37$, $p < 0.005$, $\eta_p^2 = 0.421$, showed main effects. More errors were done for the lower visual field stimuli than for the upper visual field stimuli. TMS influenced accuracy when pulses were delivered at the SOAs of 84, 94, 104 and 124 ms (ps < 0.05) compared to the no-TMS baseline. Importantly, there was no main effect of the Area showing that in both areas, the accuracy was affected by the stimulation.

We determined that participant had a conscious perception of stimulus features when they gave the response 1 in the subjective rating, that is, "I saw the stimulus clearly, that is, I saw at least a feature of the letter from which I could recognize it". For the conscious perception of stimulus features, Field, $F(1,6) = 23.63$, $p < 0.005$, $\eta_p^2 = 0.797$, and TMS, $F(6,36) = 2.38$, $p < 0.05$, $\eta_p^2 = 0284$, had main effects. On average, the stimuli presented to the lower visual field were seen less clearly than the stimuli presented to the upper visual field. TMS and Field, $F(6,36) = 4.19$, $p < 0.005$, $\eta_p^2 = 0.411$, interacted. For the upper visual field stimuli, the effect of TMS was not significant whereas for the lower visual field stimuli, the effect of TMS was significant, $F(6,36) = 4.00$, $p < 0.005$, $\eta_p^2 = 0.4$. The stimulation suppressed conscious visual perception of stimulus features at the SOAs from 84 ms to 104 ms (ps < 0.05) and at the SOA of 74 ms the effect approached significance ($p = 0.054$) when compared with no-TMS baseline. Note that the stimulation area did not have any effects, suggesting that stimulation of both areas suppressed conscious perception of stimuli in the lower visual field.

To investigate the effect of TMS on the most basic form of visual consciousness, the conscious visual detection of stimulus presence, we calculated the relative frequency of the sum of the trials where participants gave subjective rating (1) I saw the stimulus clearly, that is, I saw at least a feature of the letter from which I could recognize it and rating (2) I did not see the stimulus clearly, but I saw a trace on the screen. Thus, in the rest of the trials participant reported that (s)he saw nothing on the screen. Area, $F(1,6) = 22.23$, $p < 0.005$, $\eta_p^2 = 0.787$, Field, $F(1,6) = 7.77$, $p < 0.05$, $\eta_p^2 = 0.564$, and TMS, $F(6,36) = 4.96$, $p < 0.05$, $\eta_p^2 = 0.453$, showed main effects. On average, stimulation of V3 suppressed less conscious detection of stimulus presence than stimulation of V2, and stimuli presented to the lower visual field were seen less frequently than the stimuli presented to the upper visual field. TMS and Field interacted, $F(6,36) = 4.97$, $p < 0.05$, $\eta_p^2 = 0.453$. Further exploration of the interaction revealed that TMS had a significant effect only for the stimuli presented to the lower visual field, $F(6,36) = 5.06$, $p < 0.05$, $\eta_p^2 = 0.458$ at the TMS SOAs of 74–94 ms and the SOA of 124 ms (*ps* < 0.05). Thus, at these SOAs participants often reported that they did not see any stimulus appearing on the screen. Area and TMS, $F(6,36) = 4.27$, $p < 0.05$, $\eta_p^2 = 0.415$, also interacted and Area x Field approached significance, $F(1,6) = 4.83$, $p = 0.07$, $\eta_p^2 = 0.446$, indicating some differences between the areas as a function of SOA.

Given that the focus of this study was in the differences between V2 and V3 in conscious perception, and that also statistics indicated differences between the areas, we studied the areas separately. In V2 stimulation, there was a main effect of Field, $F(1,6) = 10.44$, $p < 0.05$, $\eta_p^2 = 0.635$, and TMS, $F(6,36) = 5.9$, $p < 0.005$, $\eta_p^2 = 0.496$, and an interaction between TMS and Field, $F(6,36) = 5.35$, $p < 0.005$, $\eta_p^2 = 0.471$. For the upper visual field stimuli, the effect of TMS was not statistically significant, whereas for the lower visual field stimuli, the effect of TMS was significant, $F(6,36) = 5.96$, $p < 0.005$, $\eta_p^2 = 0.498$. Conscious detection of the presence of stimulus was suppressed when TMS was delivered at the SOAs 74–124 ms (ps < 0.05). In V3 stimulation, the main effects of Field, $F(1,6) = 4.91$, $p = 0.069$, $\eta_p^2 = 0.450$, and TMS, $F(6,36) = 3.36$, $p = 0.06$, $\eta_p^2 = 0.359$, and the Field x TMS interaction, $F(6,36) = 3.44$, $p = 0.051$, $\eta_p^2 = 0.364$, approached statistical significance. Further analyses showed that the effect of TMS was significant for the lower visual field stimuli, $F(6,36) = 3.41$, $p < 0.01$ $\eta_p^2 = 0.362$. None of the SOAs diverged statistically significantly from the no-TMS baseline, although the SOAs of 74 ms and 84 ms approached significance (*ps* 0.056 and 0.074 respectively). Also for the upper visual field, the effect of TMS became significant $F(6,36) = 2.5$, $p < 0.05$, $\eta_p^2 = 0.294$, with the SOA of 104 ms approaching significance ($p = 0.68$).

We included also trials where no visual stimulus was presented but only the TMS was delivered 24 ms after the visual stimulus onset. When no visual stimulus was presented, participants reported in 96% of no-TMS trials and 92% of the TMS trials that they saw nothing on the screen which suggests that their subjective reports concerning their conscious perception were valid. We used signal detection analysis (Stanislaw and Todorov, 1999) to test how well the participants subjectively distinguished whether a stimulus was presented or not. Hits

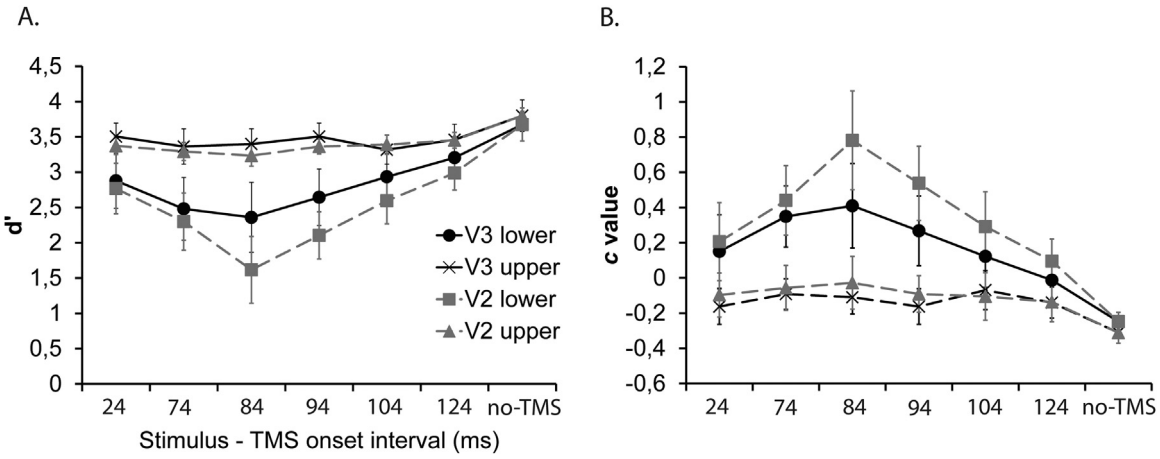

Fig. 4. D-prime (A) and C values (B) calculated from subjective ratings when TMS pulses were targeted to the lower visual field representation in V2 or V3 24–124 ms after the visual stimulus onset or no TMS was delivered.

were the responses where the stimulus was present and the participants gave the response (1) I saw the stimulus clearly, that is, I saw at least a feature of the letter from which I could recognize it or (2) I did not see the stimulus clearly, but I saw a trace on the screen in subjective ratings whereas the false alarms were the responses where no visual stimulus was presented but participant gave a response 1 or 2 in subjective ratings. For the measure of sensitivity that is not affected by response bias, we calculated a d′ value. A value of zero signifies an incapability to discriminate signals from noise, whereas larger values suggest a better ability to discriminate signals from noise (Stanislaw and Todorov, 1999). The average d′ value was 2.93 (see Fig. 4). Field, $F(1,6) = 10.17$, $p < 0.05$, $\eta_p^2 = 0.629$ and TMS, $F(6,36) = 9.73$, $p < 0.005$, $\eta_p^2 = 0.619$, had significant effects on d′. In addition, TMS and Field interacted, $F(6,36) = 5.59$, $p < 0.01$, $\eta_p^2 = 0.482$. Both, for the lower visual field stimuli, $F(6,36) = 8.55$, $p < 0.005$, $\eta_p^2 = 0.588$, and for the upper visual field stimuli, $F(6,36) = 7.78$, $p < 0.05$, $\eta_p^2 = 0.565$, all the SOAs diverged significantly from the no-TMS baseline (ps < 0.05). Thus, TMS increased inability to discriminate the signals from noise. The effect of TMS for lower visual field stimuli was significant in V2, $F(6,36) = 9.53$, $p < 0.001$, $\eta_p^2 = 0.614$, and in V3, $F(6,36) = 5.90$, $p < 0.05$, $\eta_p^2 = 0.496$, stimulation.

We calculated *c* value to measure the response bias. It is measured in units of standard deviation from a zero point and a *c* value of zero is neutral whereas a negative value signifies a bias toward responding that signal (i.e., the stimulus) was present[3] (Stanislaw and Todorov, 1999). The average c value (response bias) was 0.01 – indicating, on average, no bias towards responding that signal was present. Area, $F(1,6) = 23.55$, $p < 0.005$, $\eta_p^2 = 0.797$, Field, $F(1,6) = 10.17$, $p < 0.05$ $\eta_p^2 = 0.629$, and TMS, $F(6,36) = 5.48$, $p < 0.005$, $\eta_p^2 = 0.477$, had significant effects on *c* value. In addition, TMS and Field, $F(6,36) = 5.59$, $p < 0.001$, $\eta_p^2 = 0.482$, and Area and TMS, $F(6,36) = 5.66$, $p < 0.001$, $\eta_p^2 = 0.486$, interacted. For the lower visual field stimuli, $F(6,36) = 6.03$, $p < 0.001$, $\eta_p^2 = 0.501$, the SOAs of 74–94 ms diverged significantly from the no-TMS baseline (ps < 0.05), suggesting that TMS biased the participants to respond that the stimulus was not presented rather than that it was presented. For the upper visual field stimuli, the effect of TMS was not significant, $F(6,36) = 1.83$, $p = 0.194$. The effect of TMS became significant for lower visual field stimuli for both V2, $F(6,36) = 7.15$, $p < 0.001$, $\eta_p^2 = 0.544$, and V3, $F(6,36) = 3.79$, $p < 0.05$, $\eta_p^2 = 0.387$.

3.3. Low EF V2 stimulation

In addition, participants performed the same experiment as above while the EF strength in V2 was kept similar to that in V2 during V3 stimulation (low EF V2 stimulation). The purpose was to control that the observed effects in V3 stimulation were not caused by the distributed EF in V2 when TMS was targeted to V3. As in the main experiment, we carried out ANOVA with Huynh-Feldt correction applied to p-values when the assumption of sphericity was violated. In accuracy, Field, $F(1,6) = 11.09$, $p < 0.05$, $\eta_p^2 = 0.649$, showed main effect. There were more errors for lower visual field stimuli than for upper visual field stimuli (the mean 0.72 and 0.85 correspondingly; Fig. 5). For the lower visual field stimuli in TMS condition, the mean was 0.72 and in no TMS condition 0.73 whereas for the upper visual field the values were 0.85 and 0.85 correspondingly. Thus, the participants responded less accurately to the stimuli in the lower visual field than to the stimuli in the upper visual field in the no-TMS and TMS conditions, but because TMS and Field did not interact, $F(6,36) = 0.69$, $p = 0.67$, the difference between the fields was not related to TMS. For the conscious perception of stimulus features and stimulus presence there were no statistical significant effects. Thus, low EF V2 stimulation did not have an effect on accuracy or conscious visual perception.

In addition, for the further confirmation, we compared performance for lower visual field stimuli between the V3 stimulation and low EF V2 stimulation. For the accuracy of the responses, it showed only a main effect of the visual field, $F(1,6) = 16.99$, $p < 0.01$, $\eta_p^2 = 0.739$, and TMS, $F(6,36) = 2.96$, $p < 0.05$, $\eta_p^2 = 0.331$. When the conscious visual perception of the features for the lower visual field stimuli in low EF V2 stimulation were compared with the V3 stimulation condition, it showed main effect of the Area, $F(1,6) = 5.98$, $p = 0.05$, $\eta_p^2 = 0.499$, and Field, $F(1,6) = 14.47$, $p < 0.01$, $\eta_p^2 = 0.707$, and the interaction of Area x Field, $F(1,6) = 10.99$, $p < 0.05$, $\eta_p^2 = 0.647$, indicating that perception of the lower field stimuli was influenced more by TMS of V3 than low EF V2 stimulation. For the conscious visual detection of the stimulus presence, there was main effect for the Field, $F(1,6) = 6.06$, $p < 0.05$, $\eta_p^2 = 0.503$, and the interactions of Area and TMS, $F(6,36) = 3.76$, $p < 0.05$, $\eta_p^2 = 0.385$, and Area x Field x TMS, $F(6,36) = 3.87$, $p < 0.05$, $\eta_p^2 = 0.392$. Thus, these further analyses gave additional evidence that low EF V2 and V3 stimulation, indeed, differed from each other in respect to the conscious perception. Thus, the suppression of consciousness in V3 stimulation was not due to the distribution of EF in V2.

[3] D value and c value get an unlimited value if hit rate is 1.0 or false alarm is zero and thus cannot be analyzed. Thus, when either the false alarm rate (i.e., no visual stimulus was presented but participants responded that they saw a stimulus) was zero or the hit rate (i.e., the visual stimulus was presented and participants responded that it was present) was 1.0, d′ and c′ were calculated as suggested by Macmillan and Creelman (2004): Zeros were converted to 1/(2 N) and ones were converted to 1–1/(2 N) where N is the number of trials.

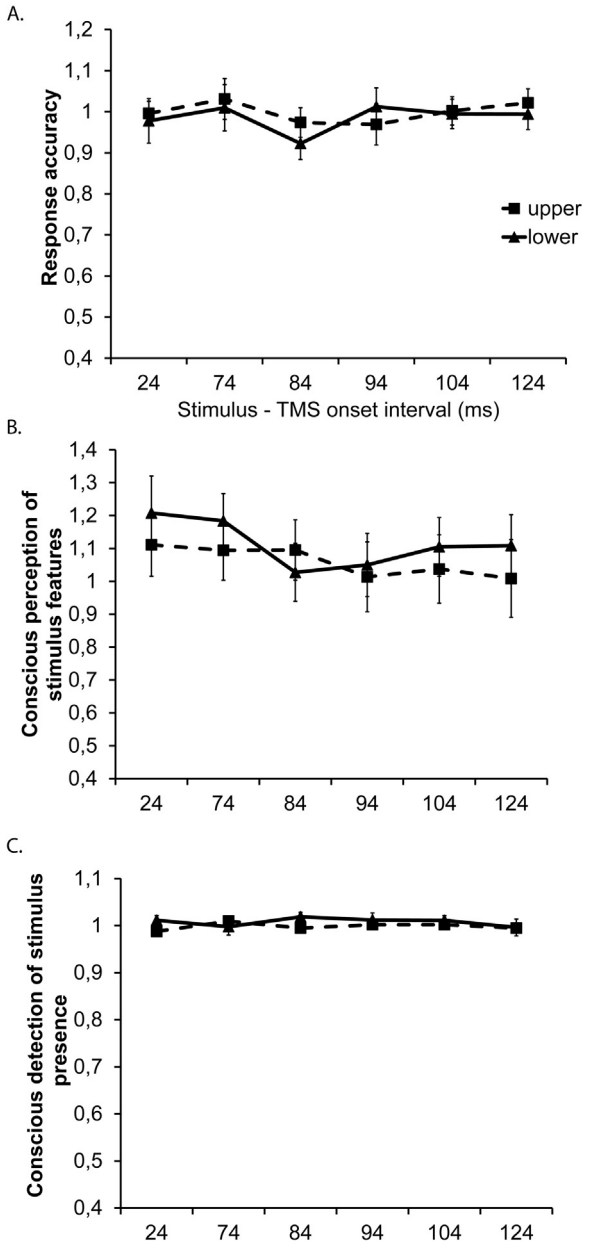

Fig. 5. The behavioural performance in the experiment where low TMS intensity was used and stimulation was targeted to V2. A. shows the proportion of correct responses in letter discrimination accuracy, B. conscious visual perception of stimulus features, and C. conscious visual detection of stimulus presence when TMS pulses were targeted to the lower visual field representation 24–124 ms after the visual stimulus onset. The results are scaled so that 1 represents the baseline performance when no TMS was applied. The analyses were done with the raw data.

4. Discussion

This study explored the role of the anatomically early extrastriate area V3 in the letter stimulus discrimination, conscious visual perception of stimulus presence and stimulus features. The results showed that TMS in V3 blocked conscious perception of stimulus presence and features and decreased the ability to discriminate the letter stimuli. Given that TMS impaired both the performance in the forced-choice task and the conscious perception the results indicate that V3 is necessary for visual perception in general, not only for visual consciousness. In line with this interpretation is the result from a study by Peters and Lau (2015) which showed that if objective discrimination is above chance level, it is likely that also conscious perception of the stimulus emerges. We controlled the possibility that low EF in retinotopically equivalent, adjacent, V2 induced by TMS targeted to V3 would induce the suppression. There were no remarkable differences between stimulation of V2 and V3 regarding time intervals when TMS was efficient in suppressing visual perception, but overall, TMS in V2 was more efficient in blocking the conscious detection of stimulus presence than TMS in V3.

The present data indicated that the functional contribution of V3 is necessary for visual consciousness of stimuli. This is interesting, as so far the literature indicates only few cortical regions which seem to be necessary for conscious detection of stimulus presence: V1 (Holmes, 1918; Tong, 2003), V2 (Horton and Hoyt, 1991; McFadzean and Hadley, 1997; Salminen-Vaparanta et al., 2012a) and regions in the right parietal cortex (Heilman et al., 2012; Kerkhoff, 2001; Vallar, 1998). In addition, there are a few reports that damage to specific regions in the prefrontal and frontal areas induce visuospatial neglect (Damasio et al., 1980; Heilman and Valenstein, 1972; Maeshima et al., 1994). There are only few reports of patients who have a damaged V3 including detailed examination of their conscious visual perception or visual perception more generally. However, Slotnick and Moo (2003) determined with fMRI the retinotopic organisation of striate and extrastriate areas in a patient who had an upper right homonymous quadrantanopia and found that the patient's V1 and V2 were intact, but there was a lesion in ventral V3 and V4. The finding lends support for the present results that a functionally intact V3 is necessary for visual perception and consciousness. In addition, Horton and Hoyt (1991) reported homonymous quadrantanopias in two patients with extrastriate lesions but in their study the early visual areas were not determined with functional imaging (See also McFadzean and Hadley, 1997).

As to the question why the functional contribution of V3 is necessary for the emergence visual consciousness, there are at least three different possibilities. One explanation is that V3 is necessary as a preconscious stage of processing transmitter of visual input between the lower visual areas V1 and V2 and the higher cortical areas where the stimulus will emerge to consciousness. Another possibility is that the internal functional activity of V3 as such is directly responsible for the stimulus emerging into visual consciousness. Based on studies with non-human primates, the cells in V3 are tuned for basic properties of stimuli, such as, motion, orientation, and colour (Felleman and Van Essen, 1987; Gegenfurtner et al., 1997). Third, it is possible that feedback from V3 to V1 or V2 contributed to the suppression. In humans, a recent fMRI study has shown strong resting-state correlation between V2 and V3 suggesting also strong anatomical connections between the areas whereas V1 shows strong internal correlations between dorsal and ventral areas (Genç et al., 2016). Therefore, it is possible that V1, V2 and V3 operate in intense interaction when generating visual consciousness. Support for a view that the early visual areas play a central role in the emergence of visual subjective experience is lent by studies showing that compared to the higher visual areas (V4, V5, LO), TMS-induced visual sensations, called phosphenes, are induced more likely by the stimulation of V1, V2, V3 and V3a (Schaeffner and Welchman, 2017; see also Murphey et al., 2009) and that the underlying mechanisms of phosphenes involve the temporally coordinated activation of interconnected visual areas (Pascual-Leone and Walsh, 2001; Salminen-Vaparanta et al., 2014; Silvanto, 2008; Silvanto et al., 2005, 2007). The results of a recent TMS study showed that stimulation of V3 and V3a were even more likely to induce phosphenes than stimulation of V1 and V2 (Schaeffner and Welchman, 2017).

Conscious perception and its proper neural correlate is preceded and followed by some neural processes which are not a part of the minimally sufficient mechanisms of the conscious experience of the target (Aru et al., 2012; Revonsuo, 2006) and with the methods used in this study these processes could not be dissociated. On basis of electrophysiological studies on visual consciousness, it seems clear that the effects of V2 or V3 TMS on visual perception around 70–120 ms after

the stimulus-onset cannot reflect the processes that follow conscious experience, because such processes occur later, around 300 ms (Koivisto and Revonsuo, 2010; Koivisto et al., 2016). Thus, although the areas (V1-V3) are clearly involved in the emergence of visual consciousness, it is not clear if these areas are directly involved in the generation of the contents of consciousness, or if they are parts of preconscious processing stages that contribute earlier than when the content emerges to consciousness by activation of some other brain area or activation network in later time windows.

The study by Salminen-Vaparanta et al. (2012a) showed that letter discrimination performance and conscious perception of stimulus features were affected by TMS of V2 in the same time window (44–104 ms), but conscious detection of stimulus presence was affected in a shorter time window (up to 84 ms). Similarly in de Graaf et al. (2012) and in Koivisto et al. (2011b), TMS to early visual cortex was necessary for a longer time window for discriminating more complex stimuli (e.g., an arrow shape or face) than for discriminating the orientation of a visual stimulus. The statistics of the present study did not support the view that the contribution of V2 and V3 would be necessary for shorter time window for simpler perception and for longer time window for more complex perception - although by visual inspection there was a difference between the conditions with longer suppression for conscious perception of stimulus features than for stimulus presence. The results of this study, however, are not directly comparable with the study of Salminen-Vaparanta et al. (2012a) due to the differences in the experimental procedure regarding the determination of TMS stimulation intensity, the TMS-visual stimulus onset asynchronies etc.

In summary, earlier studies have shown that intact primary visual cortex and V2 are necessary for conscious detection of stimulus presence, and the results of the present study indicate that also V3 has a causal role in generation of conscious experience. However, although V3 seems to be necessary for conscious visual perception, its role in stimulus-independent visual experiences is unclear. Thus, it is possible that V3 is not necessary for internally arisen visual experiences, for example for hallucinations or dreams which seem to correlate with the activation of occipito-parietal area (Siclari et al., 2017). Further studies should investigate the roles of other extra striate areas, particularly V4, parietal and frontal cortex in generation of conscious detection of stimulus presence.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.11.013.

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