Enhanced Excitability of the Human Visual Cortex Induced by Short-term Light Deprivation

Long-term deprivation of visual input for several days or weeks leads to marked changes in the excitability and function of the occipital cortex. The time course of these changes is poorly understood. In this study, we addressed the question whether a short period of light deprivation (minutes to a few hours) can elicit such changes in humans. Noninvasive transcranial magnetic stimulation (TMS) of the human occipital cortex can evoke the perception of flashes or spots of light (phosphenes). To assess changes in visual cortex excitability following light deprivation, we measured the minimum intensity of stimulation required to elicit phosphenes (phoshene threshold) and the number of phosphenes elicited by different TMS stimulus intensities (stimulus–response curves). A reduced phosphene threshold was detected 45 min after the onset of light deprivation and persisted for the entire deprivation period (180 min). Following re-exposure to light, phosphene thresholds returned to pre-deprivation values over 120 min. Stimulus–response curves were significantly enhanced in association with this intervention. In a second experiment, we studied the effects of light deprivation on functional magnetic resonance imaging (fMRI) signals elicited by photic stimulation. fMRI results showed increased visual cortex activation after 60 min of light deprivation that persisted following 30 min of re-exposure to light. Our results demonstrated a substantial increase in visual cortex excitability. These changes may underlie behavioral gains reported in humans and animals associated with light deprivation.

Introduction
Deafferentation results in cortical reorganization in motor (Kujala et al., 1995) and sensory (Wall et al., 1986; Allard et al., 1991; Merzenich and Jenkins, 1993) systems. In the visual system, retinal lesions lead to rapid increases in the receptive fields of cortical cells near the edge of the deprived occipital cortex (Gilbert and Wiesel, 1992; Pettet and Gilbert, 1992). Behaviorally, visual deprivation leads to better consolidation of spatial memory in animals (Worsham and D’Amato, 1973; Grimm and Samuel, 1976) and results in lower visual recognition thresholds in normal humans (Suiedfeld, 1975). In the absence of vision, blind individuals may experience visual hallucinations (Charles–Bonnet syndrome), interpreted as a release of cortical circuits that follows deprivation of sensory input (Cogan, 1973; Rosenbaum et al., 1987; Fernandez et al., 1997). Moreover, visual deprivation may induce substantial changes in information processing in other modalities. For example, the deprived visual cortex appears to be significantly involved in tactile (Cohen et al., 1997) and auditory (Kujala et al., 1995) discrimination tasks in blind individuals. Therefore, chronic visual deprivation leads to marked changes in excitability and function of the occipital cortex. The time course of these changes is poorly understood.

Here, we hypothesized that light deprivation would result in (i) enhanced excitability of the occipital cortex, and (ii) increased activation of the occipital cortex to incoming visual input. The first hypothesis was evaluated by directly stimulating human occipital cortex using transcranial magnetic stimulation (TMS). When applied to the occipital cortex, TMS can elicit the perception of ‘phosphenes’, flashes/spots of light in the absence of visual stimuli (Marg and Rudyak, 1994). The minimum TMS intensity that evokes phosphenes (phosphenes threshold, PT) and the stimulus–response curves for the phosphenes elicitation (average number or intensity of reported phosphenes at different stimulation intensities) convey information on visual cortex excitability (Afra et al., 1998; Aurora et al., 1998). The second hypothesis was tested using blood oxygenation level dependent (BOLD) functional magnetic imaging resonance (fMRI) as an indirect measure of visual cortex neural activity during photic stimulation (Ogawa et al., 1990). PTs, stimulus–response curves and occipital activation in fMRI were determined in our study as a function of time following light deprivation (180 min in TMS studies and 60 min in fMRI experiments).

Design and Methods
Subjects
Sixteen healthy normal volunteers with no history of migraine, visual deficits or neurological abnormalities were investigated (11 men, 5 women, age 26.8 ± 5.4 years) in TMS experiments. Five different normal volunteers (2 men, 3 women, mean age 32 ± 2.6 years) were studied using fMRI. All subjects gave their written informed consent, and the protocol was approved by the Institutional Review Board. Subjects were naive to the experimental purposes.

Transcranial Magnetic Stimulation
All experiments were conducted in a dark room with just enough light for the investigator to perform the study (residual luminance in the room was near zero). Additionally, completely non-transparent goggles were placed to accomplish total darkness. Subjects wore a cotton swimmer’s cap. A grid of 3 × 3 points, with each point 2 cm apart, was drawn on the cap with the center of the grid overlying Oz (International 10/20 system). In addition to these occipital positions, TMS was delivered to parietal locations P3 and P4 and to the air (near the ear). Additionally, sham stimulation was delivered to occipital positions (involving tilted placement of the coil so that the sound, sensation and muscle twitch elicited by the coil at the back of the head was similar to occipital stimulation). The different positions and air were randomly stimulated. Subjects were instructed to report any potential subjective sensations (visual, tactile or/and auditory) evoked by TMS. A Cadwell high-speed magnetic stimulator (Cadwell Laboratories Inc., Kennewick, WA), equipped with a 7.5 cm figure-of-eight shaped coil (coil orientation parallel to the midline and current flowing in the cranio-caudal direction) was used to deliver magnetic stimuli.

If a phosphen was reported, subjects were asked to describe its shape, color, brightness (on an arbitrary scale of 1–5, 5 the brightest phosphen) and location in the visual field as being displayed on the face of an imaginary clock in front of them. The entire course of the study consisted of four main sessions and three control experiments.
Session 1
This had an exploratory purpose to identify subjects with reproducible TMS-induced phosphenes. Subjects were initially blindfolded in a dark room. Approximately 45 min following the onset of light deprivation, TMS was delivered to all grid points (five stimulations for each condition), starting at 40% maximum stimulator output and increasing in 10% steps until phosphenes were reported or maximum stimulator output was reached. If single-pulse TMS failed to elicit phosphenes (in 11/16 subjects), the same procedure was repeated using pairs of TMS stimuli of equal stimulus intensity separated by a 50 ms interstimulus interval (Ray et al., 1998). Stimuli (single or pairs) were given every 10 s. Only phosphenes reported in the visual field contralateral to the site of the stimulation were considered accurate. Additionally, consistency in the report of phosphenic characteristics upon stimulation of the same position was evaluated. All subjects who reported accurate and consistent phosphenes in session 1 participated in session 2. Pairs of TMS stimuli were used in the following sessions.

Session 2
This session was designed to test the reliability and intersession reproducibility of the reported phosphenes. Stimulation parameters and sites were the same as those used successfully in session 1. Subjects could continue with the study only if their accuracy level was >80%, and if control and sham stimulations failed to produce phosphenes. Subjects meeting these criteria participated in sessions 3 and 4.

Session 3
Five subjects met these criteria and participated in this session. PT was defined as the minimum intensity of stimulation able to elicit phosphenes in three out of five trials at any given scalp location. Stimulation intensities started at 30% maximum stimulator output and were increased in 2% steps. Stimulus–response curves were also obtained to determine the number and intensity of the reported phosphenes. PTs were determined at the onset of the light deprivation period and 45, 90, 135 and 180 min later. Stimulus–response curves were determined at the onset of the experiment and after 180 min of light deprivation.

Extraocular muscle EMG activity and eye movements were monitored using a Counterpoint electromyograph (Dantec Medical, Skovlunde, Denmark) and Ag/AgCl electrodes attached to the right orbicularis oculi muscle and to the lower lid. At the end of each session, subjects were asked to report sensations elicited by voluntary blinking.

Session 4
In this session, subjects underwent 90 min of light deprivation. Following this time period, they were re-exposed to room light (390 lux) and PTs were tested repetitively for at least 120 min.

Control Experiments (Sessions 5, 6 and 7)
These experiments were performed with subjects who had participated in sessions 3 and 4. In session 5, reproducibility of the deprivation-induced changes in PT was investigated in three subjects. PT was determined at 45 min intervals during 135 min of light deprivation. Session 6 was designed to assess the effects of repetitively testing PTs without light deprivation. PTs were measured twice within 45 min without light deprivation (n = 5). In session 7, subjects (n = 5) underwent repetitive determination of PTs (also in the absence of light deprivation) after one night of sleep deprivation to mimic the mild drowsiness reported in the light deprivation experiments.

Functional Magnetic Resonance Imaging
fMRI was performed on a 1.5 T GE Signa scanner equipped with whole body echo-planar gradients and a standard birdcage head coil. Using gradient-echo echo-planar imaging (EPI), two sets of 160 functional images were acquired in each subject before light deprivation, after 60 min of light deprivation, and after 30 min of re-exposure to room light (390 lux). Visual stimuli were presented binocularly via well-fitted lightproof goggles by flashing a matrix of 5 × 6 red LED (arranged in rectangular shape 1.2 × 1.5 cm) at 2 Hz. Head movement was minimized using an adjustable headband and cushions. Functional images consisted of T1*-weighted images (64 × 64 matrix, 24 × 24 cm FOV, ±6.5 kHz bandwidth, TR/TE = 2500/50 ms) at each of 17 slice locations (5 mm apart, no gap) covering the occipital lobes. The total scanning time for each set was 6 min and 40 s consisting of 30 × 1000 ms of rest in between photic stimulation. Anatomical scans consisted of multiple high-resolution, T1*-weighted whole-brain axial three-dimensional spoiled grass (3D SPGR) data set (256 × 256 × 124, 24 cm in-plane FOV, 1.0–1.2 mm slice thickness, flip angle of 30°, TR/TE = 35/8 ms, 1 NEX).

Imaging time series were realigned, normalized to standard Talairach stereotaxic space and smoothed with a Gaussian kernel of 5 mm full-width half-maximum using Statistical Parametric Mapping software (SPM96, http://www.fil.ion.ucl.ac.uk/spm). After removing global changes in activity using proportional scaling, statistical parametric maps (SPMs) of voxels with significant MR signal increase during visual stimulation compared to rest (z score > 3.09, P < 0.05 corrected for multiple comparisons) were constructed.

Statistical Analysis
PTs and stimulus–response curves were compared at different time intervals following the onset of deafferentation using a repeated-measures ANOVA model. Individual intervals were compared using a two-tailed paired t test. The number of significantly activated voxels in the fMRI experiments and the mean percentage change in signal intensity before and after light deprivation and after re-exposure to light were compared using paired Wilcoxon signed-rank tests. The significance level was set to P < 0.05.

Results
Perceptions Elicited by Transcranial Magnetic Stimulation
Of the 16 participants in the study, nine (56%) reported visual sensations induced by TMS, similar to the findings of other investigators (Meyer et al., 1991). Of these nine subjects, five reported accurate and consistent phosphenes (see Design and Methods). Colored phosphenes were reported by three subjects at high stimulation intensities (70% stimulator output and above). Examples of these reports included: ‘a bright red flash at 9 o’clock’, ‘a yellow star at 1 o’clock’ and ‘a greenish sphere at 5 o’clock’. None of the subjects reported phosphenes following control or sham stimulations. No moving (kinetic) phosphenes were reported. Optimal grid points for elicitation of phosphenes were always located in the upper third of the grid.

Phosphen Thresholds
All subjects showed a decreased PT over the course of the 3 h period of light deprivation. During this time period, mean PT dropped from 63.0 ± 8.3 to 48.0 ± 7.6% (P = 0.0001) (Fig. 1A,B). Although a large reduction in the PT occurred during the first 45 min, a significant decrease of PT could still be detected between 45 and 90 min after onset of the deprivation (from 54.0 ± 5.5 to 51.0 ± 8.2%, P = 0.02). This decrease in the PT was reproduced in control session 5 (decrease of PT from 70.0 ± 10.0 to 50.0 ± 8.7% after 135 min; P = 0.02).

PTs returned to normal values ~120 min following reexposure to light (session 4) (Fig. 2). In the absence of light deprivation, PTs tested 45 min apart showed no significant changes (control session 6; PT 53.0 ± 9.7 and 52.0 ± 8.4, P = 0.37). Similarly, testing during sleep deprivation-induced drowsiness did not result in PT changes in the absence of light deprivation (control session 7; PT 53.0 ± 9.7 and 54.0 ± 12.0, P = 0.91).

In three subjects, phosphenes could be elicited below the TMS intensity, which led to blink responses or eye movements. Voluntary blinking did not produce phosphenes in any subject.
Phosphene Stimulus–Response Curves

Stimulus–response curves for the number of elicited phosphenes 180 min after light deprivation onset was steeper than that obtained before light deprivation. These differences became significant at 50 and 60% maximum stimulator output ($P = 0.02$). At higher stimulus intensities, a plateau level was reached (Fig. 3). Although the average reported intensity of phosphenes had a higher value after 180 min compared to the onset of the experiment at intensities <70%, this difference was not significant (Fig. 4).

fMRI

Before light deprivation, the visual cortex was significantly activated in response to photic stimulation in all subjects. The Talairach coordinates of peak activity were (x, y, z ± SD) –1 ± –7.0, –82.6 ± –16.4, 12.8 ± 14.0 corresponding to Brodmann’s areas 17, 18 and 19. In all subjects, the number of activated voxels and mean change in MR intensity increased significantly following 60 min of light deprivation ($P = 0.043$ for both parameters). This increase was maintained in all subjects 30 min after reexposure to light (Fig. 5A,B). There was no significant activation in the lateral geniculate bodies.

Discussion

Our results demonstrated that the excitability of the visual cortex to TMS and its hemodynamic responses to incoming visual input are increased following light deprivation.

Brain Regions Responsible for TMS-induced Phosphenes

Phosphenes can be elicited by direct occipital electrical stimulation (Bak et al., 1990) and also by TMS delivered to occipital sites (Meyer et al., 1991). A similar occipital site at a depth of 1.5–2 cm from the scalp surface has been identified as that mediating the phenomenon of TMS-induced visual suppression (Epstein et al., 1996), possibly in medially located bends in geniculo-calcarine or corticofugal fibers (Amassian et al., 1994). Given the relatively low TMS stimulus intensities used in our study and the use of a focal coil, a superficial stimulation
site (which could include the visual cortex and adjacent subcortical fibers) seems to be the most probable site of phosphene induction. For different reasons, it is unlikely that TMS directly stimulated the retina under our experimental conditions. First, optimal scalp positions for eliciting phosphenes were occipital (>8 cm away from the retina) and the magnitude of the electric field induced by TMS drops rapidly as a function of the distance between the coil and target neural structures (Maccabee et al., 1991a,b; Roth et al., 1991). Second, more anterior stimulating positions closer to the retina failed to elicit phosphenes. Third, there is a clear topographic specificity of phosphenes elicited by TMS (contralateral to the stimulated position). Fourth, while light deprivation can increase retinal excitability during a period of adaptation of ∼30–40 min (Peachey et al., 1992a,b), PTs in our study continued to decline beyond this time period. Therefore, the decreased threshold of TMS-induced phosphenes identified after light deprivation is likely to reflect genuine changes in occipital cortex excitability.

In additional control experiments, we found that phosphenes usually occurred independently of eye movements or blinking. Similarly, TMS intensities required to elicit phosphenes were below those needed to induce eye movements or blinking. Furthermore, voluntary blinking failed to elicit phosphenes. For these reasons, we conclude that TMS-induced phosphenes as studied here do not represent perceptual correlates of intra- or extraocular movements. Another control experiment was designed to test the effects of drowsiness (experienced by most subjects during the light deprivation period) on cortical excitability. We found that drowsiness induced by sleep deprivation failed to elicit changes in PT and therefore cannot explain the excitability changes associated with light deprivation. Another control experiment tested the effects of repeatedly stimulating the occipital cortex with TMS on PTs. Repetitive determination of PTs in the absence of light deprivation also failed to induce excitability changes in the occipital cortex, demonstrating that application of TMS alone cannot elicit the excitability changes described.

Figure 5. (a) Number of activated voxels (log) and (b) mean MR signal intensity change of activated voxels in the occipital cortex to photic stimulation before, 60 min after the onset of visual deprivation and 30 min following re-exposure to light. A significant increase after 60 min of light deprivation could be seen in both parameters, which was maintained following 30 min of re-exposure to light. (c) An example of visual cortex activation in one subject at three different levels. Error bars indicate standard errors.
Changes in occipital cortex responses to visual stimuli following light deprivation

fMRI provides an objective measure of cortical activity that, unlike TMS-evoked phosphenes, did not rely on the subjects' perceptions. The results from this fMRI study showed increased neural activity in the occipital cortex to incoming visual inputs following light deprivation that persisted for at least 30 min after reexposure to light. This result could be explained if the excitability of the visual cortex increased following light deprivation. Indeed, increased fMRI signal is detected in situations with increased cortical excitability such as in the Charles–Bonnet syndrome or in patients with unilateral occipital lobe epilepsy (Jueptner and Weiller, 1995; Frytche et al., 1998, Masuoka et al., 1999). While it is conceivable that changes in excitability in the occipital cortex result in enhanced activation to incoming visual input, a cause–effect relationship between both cannot be assessed in this experimental design. An alternative explanation is that the increased visual cortex activity is secondary to light deprivation-induced changes in the visual pathway distal to the visual cortex (most likely the retina). Such a change would result in a net increase in the input reaching the cortex. Against this interpretation is the stability of changes in visual cortex activity beyond 30 min (in which retinal adaptation is completed) after re-exposure to light (Fig. 5A) (Marmor, 1989; Peachey et al., 1992b). If the enhancement in occipital signal was secondary to retinal excitability changes, it should have substantially decreased within 30 min.

Possible Mechanisms of the Short-term Increase in Visual Cortex Excitability

The fast development of the changes in the PT is compatible with ‘unmasking’ of previously existing connections at a cortical level. Several mechanisms could mediate this effect. A decrease in GABA receptors and the GABA-synthesizing enzyme (glutamic acid decarboxylase, GAD) has been found in different animal models of deafferentation in the visual cortex (Hendry et al., 1990; Jones, 1993; Rosier et al., 1995). GABA levels are known to change in humans within minutes of deafferentation (Leyv et al., 1999) or after administration of a single oral dose of the antiepileptic vigabatrin (Petroff and Rothman, 1998). Therefore, changes in GABA levels could be operational in this setting. In addition to GABA, regulation of activity of muscarinic acetylcholine receptors may play an important role in visual cortex plasticity. For example, intracortical infusion of anticholinergic drugs inhibits plasticity in kitten visual cortex (Gu and Singer, 1993). N-Methyl-D-aspartate (NMDA) receptors may play a potential role in this phenomenon too. Blockade of NMDA receptors reduces ocular dominance plasticity in animals (Bear et al., 1990; Rauschecker et al., 1990; Daw, 1994). The relative contribution of these mechanisms to our results is presently under investigation.

In conclusion, our results demonstrated an enhanced excitability of the visual cortex associated with short-term visual deprivation. This phenomenon may underlie behavioral gains reported following light deprivation in humans and in animals.

Notes

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