Effects of long-term potentiation in the human visual cortex: a functional magnetic resonance imaging study

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Applying functional magnetic resonance imaging techniques, hemodynamic responses elicited by slowly flashing checkerboards (0.25 Hz) were measured both before and after a block of rapidly presented checkerboards (9 Hz – a 'photic tetanus') was delivered. It has been shown previously, using electroencephelography, that this photic tetanus potentiates components of the visual-evoked potential. In the present study, hemodynamic responses in the extrastriate visual cortex were significantly increased to checkerboards presented at a low frequency after the administration of the photic tetanus. These results support the idea that long-term potentiation can be demonstrated non-invasively within the human visual cortex and provide evidence that the plastic changes are localized within the secondary visual cortex. *NeuroReport* 16:1977–1980 © 2005 Lippincott Williams & Wilkins.

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Introduction

Long-term potentiation (LTP) refers to an enduring increase in synaptic efficacy and is the principal candidate synaptic mechanism underlying learning and memory formation [1,2]. LTP has been mainly studied in hippocampal preparations and has also been demonstrated in slices of sensory neocortex [3] and *in vivo*. Repetitive electrical stimulation (a tetanus) of the visual pathway (dorsal lateral geniculate nucleus) in rats has been shown to result in LTP of visual potentials evoked by natural visual stimuli [4]. Furthermore, repetitive visual sensory stimulation itself has been shown to result in LTP in the visual system of the developing tadpole [5]. This is believed to be caused by *N*-methyl-D-aspartate dependent selective potentiation of particular retinotectal synapses. The results of these findings suggest that LTP may underlie the plastic changes that occur within the sensory cortex throughout life.

Recently, Teyler *et al.* [6] reported that rapidly presented visual stimulation (a 'photic tetanus') could non-invasively induce LTP within the intact human cortex. These findings have been extended by showing that LTP can be induced in the anesthetized adult rat by a photic tetanus and that the changes last for at least 2 h after the photic tetanus [7]. Furthermore, the potentiation was localized to the visual cortex and was shown to be *N*-methyl-D-aspartate-dependent [7]. In a related experiment, rapidly presented tone pips (an auditory tetanus) induced LTP within the human auditory cortex (potentiation of the N1 component of the auditory-evoked potential), revealing that sensory-induced LTP is not restricted to vision [8]. These studies demonstrate that LTP of the sensory cortex can be induced non-invasively by the repetitive presentation of sensory stimuli.

Recording with electroencephalography (EEG) in humans, Teyler *et al.* [6], showed that a photic tetanus (a 2 min block of checkerboards presented at 9 Hz) induced LTP (>1 h) of a specific component of the visual-evoked potential (VEP) over the occipital lobe. The potentiated component of the VEP was a late phase of the N1 complex (N1b). As the N1 is a composite of spatially and temporally overlapping subcomponents, little is known about where its subcomponents are generated and how the components relate to visual processing [9]. Attempts to localize the source of activity corresponding to these peaks have been hindered by the 'inverse problem'; that is, given a pattern of surface activation, it is difficult to uniquely identify the source(s) from which this pattern is generated. Low-resolution brain electromagnetic tomography analysis nevertheless implicated bilateral extrastriate areas (as well as the striate cortex) in the generation of the N1b, which is consistent with other findings [10,11].

The present study used virtually identical experimental procedures to test whether LTP in the human visual cortex could be detected with functional magnetic resonance imaging (fMRI). The main questions of interest were what changes, if any, in the blood oxygenation level-dependent (BOLD) signal occur after the presentation of a photic tetanus, and if so, where these changes take place. It has been shown that the BOLD response is linearly related to event-related potential (ERP) amplitudes [12]. As it has been shown that a photic tetanus induces an increase in the N1b component of the ERP [6], we sought to test the prediction that the generators responsible for this ERP component will show a concomitant increase in the BOLD response.

Materials and methods

Study participants

Ten healthy right-handed (preferred painting/writing hand) male volunteers participated in this study. After a full explanation of the nature and risks of the research, participants gave informed consent for the study according to a protocol approved by the local Ethics Committee. All participants had normal, or corrected-to-normal, vision and were free from neurological and psychiatric diseases as indicated by standard examination.

Stimuli

Visual stimuli were based on the parameters described by Teyler *et al.* [6]. Visual stimuli consisted of checkerboards presented to the right or left visual field. The stimuli subtended a 4° visual angle from the vertical and horizontal midline. The stimuli were presented on a projection screen and checkerboard luminance was under experimental control. Presentation of the checkerboards was controlled by Presentation (version 9.3, Neurobehavioral Systems, Albany, California, USA).

Procedure

Participants were required to fixate on a red circular dot in the center of the screen during data collection. During the baseline period, the checkerboards were presented at an average rate of approximately 0.25 Hz (duration 33 ms). Participants underwent two 'pre-tetanus' baseline runs. Each of these consisted of six blocks of checkerboards (three left, three right), in which each block lasted 1 min and contained stimuli (15 presentations) in only one visual field (45 presentations each of left and right checkerboards overall in each baseline block). The blocks of left or right checkerboards were equally presented in a randomized order, with a fixation block (30 s in duration) in between each block. In the photic tetanus condition, participants were again required to maintain fixation while the same checkerboard stimulus was presented at a frequency of 9 Hz to either the left or right visual field for 120 s (1000 presentations). To control for possible hemisphere differences, we randomly assigned the participants to two groups. One group received the photic tetanus in the left visual field and the other group in the right visual field. Subsequently, participants were given a 2-min period with their eyes closed to allow any visual after-effects to dissipate. Following this block of tetanic stimulation, an additional two runs ('post-tetanus'), with identical parameters as the pre-tetanus runs, were collected.

Functional magnetic resonance imaging scanning and task

fMRI was performed on a Philips Intera 3-T whole-body magnetic resonance unit equipped with a transmit–receive body coil and a commercial eight-element head coil array (MRI Devices Corporation, Waukesha, Wisconsin, USA). Functional data were obtained from 31 axial slices covering the whole brain using a single-shot echo planar imaging technique with sensitivity encoding [13] $r=2.0$ (TR=2100 ms, TE=40 ms, flip angle=75°, FOV=220×220, matrix size=128×128, voxel size=$1.7 \times 1.7 \times 4\,mm^3$).

Initiation of stimulus presentation was triggered by the magnetic resonance scanner upon the acquisition of the fourth volume, and during the experiment the stimulus presentation was synchronized with the magnetic resonance acquisition. At the end of each session, a high-resolution T1-weighted volume (TR=20 ms, TE=2.3 ms, flip angle=20°, 180 slices, matrix=224×224, voxel size=$0.98 \times 0.98 \times 0.75\,mm^3$) was acquired for anatomical co-registration.

Functional magnetic resonance imaging data analysis

Artifact elimination and image analyses were performed using MATLAB 6.5 (Mathworks Inc., Natick, Massachusetts, USA), and the SPM2 software package (Institute of Neurology, London, UK). All images were realigned to the first image of the first run, spatially normalized into standard stereotaxic MNI (Montreal Neurological Institute) space, interpolated to a voxel size of $3 \times 3 \times 3\,mm^3$ and spatially smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel. Condition and subject effects were estimated using the general linear model [14]. The effect of global differences in scan intensity was removed by scaling each scan to the global mean of all scans. Low-frequency drifts were removed using a temporal high-pass filter (cut-off of 128 s). We used a box-car function convolved with the canonical hemodynamic response function as reference waveform.

As the effect of the photic tetanus was the main question of interest, the fMRI data sets of 'right tetanized' participants were horizontally 'flipped', resulting in an image data set with reversed transverse orientation (radiological orientation). Therefore, the data of all participants were comparable in the context of voxelwise statistical parametric mapping analysis. These images were used to generate group statistical parametric maps. After estimation of model parameters for each participant, analyses of variance were calculated for the whole group, using the individual contrast images for the main effects, separately for the baseline stimulation on the tetanized visual hemifield and non-tetanized side. As only the effects in the occipital cortices were of interest in this study, the statistical analysis was restricted to this part of the brain. Therefore, a small volume correction was performed as implemented in SPM2 by using mask images containing the occipital lobes of each hemisphere. To test hypotheses about regionally specific condition effects, linear contrasts were employed in the context of a random effects procedure [15]. The results of these statistics were thresholded by using a spatial extent criterion of $k=31$ voxels ($P \leq 0.05$ corrected for multiple comparisons) and a voxel criterion of $t=2.82$ ($P \leq 0.01$ uncorrected for multiple comparisons). Localization of main peak activation was additionally verified using current probability maps of the visual cortex (http://www.bic.mni.mcgill.ca/cytoarchitectonic/#refVisual).

Results

Table 1 lists the comparisons of hemodynamic responses for the 'pre-tetanus' and 'post-tetanus' baseline runs separately for baseline stimulation in the tetanized and non-tetanized visual hemifield. As noted above, the terms 'left hemisphere' and 'right hemisphere' are not applicable here as we have 'flipped' data for the participants who received a right hemifield photic tetanus and combined their data with those who received a left hemifield photic tetanus. As shown in Fig. 1 and listed in Table 1, the comparison of 'post-tetanus' vs. 'pre-tetanus' revealed increased activation in the visual cortex, specifically in bilateral extrastriate regions, corresponding to Brodmann's area 18 and 19 when the stimulus was presented to the tetanized hemifield. No significant increases were observed when stimuli were presented to the non-tetanized hemifield. The reverse comparison, of 'pre-tetanus' vs. 'post-tetanus' revealed no significant results for stimulation on the tetanized hemifield. For stimulation on the non-tetanized hemifield, the comparison revealed activational increases in the ipsilateral visual cortex.

Discussion

Our results indicate that there is a significant increase in the BOLD response bilaterally in the extrastriate visual cortex after a photic tetanus. As expected, the increase was seen only when comparing the post-tetanus stimulation with the baseline stimulation in the tetanized field. No differences in the visual cortex were found when contrasting the post-tetanus BOLD response with the baseline BOLD in the non-tetanized field. Contrasting the pre-tetanus BOLD response with the post-tetanus BOLD response in the tetanized field also showed no significant results in the visual cortex. These results indicated that the photic tetanus was responsible for the increase in the extrastriate BOLD response and was specific to the tetanized field.

This pattern of increased BOLD supports previous EEG findings [6] of significant potentiation of the N1b component of the VEP (128%). The generators of this component have been suggested to be within either Brodmann's area 18, 19, or both [9] and to lie outside the primary visual cortex. The bilateral distribution of this component to a unilateral presentation of visual information suggests a transcallosal connection (see Fig. 1). Previous fMRI findings [10] also support this claim. Further work will need to be done to specifically localize where the changes seen here occur (i.e. retinotopically map the visual areas).

The increase in BOLD, as well as the increase in VEP amplitude, after the photic tetanus, suggests an increase in neuronal output. It has been found that the BOLD signal and ERP amplitudes are linearly correlated [12,16], and it has thus been suggested that an increase in BOLD signifies are synchronized synaptic activity [12]. Multiple theories on what the BOLD signal represents exist, but there seems to be a general agreement that an increase in the BOLD signal amplitude reflects a decrease in deoxygenated hemoglobin concentration, either due to increased inflow of arterial blood or due to a decrease in metabolic demand. Blood flow is positively related to neural activity, for example, via the influence of several neurotransmitters [17]. It is possible that in our study, tetanus increased neuronal output through

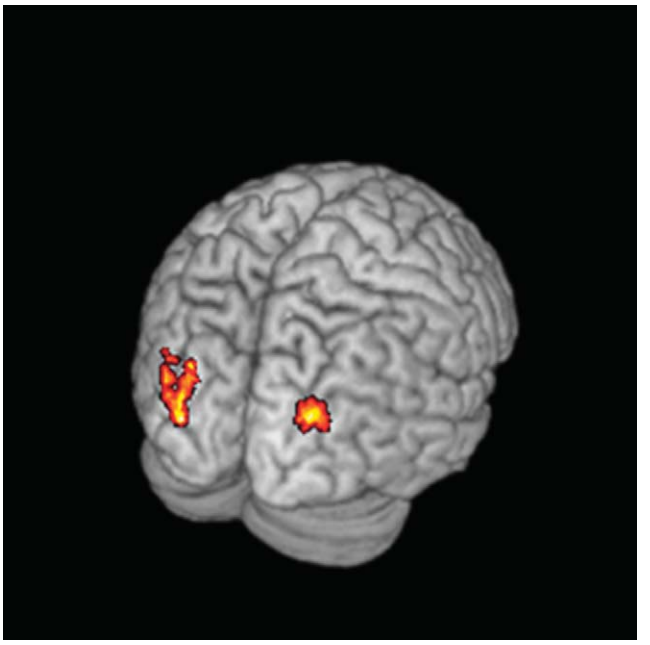

Fig. 1 Activation pattern of the comparison 'post-tetanus' vs. 'pre-tetanus' in the tetanized hemifield. SPM(*t*) maps are overlaid on a structural magnetic resonance imaging brain. The results show increased blood oxygenation level-dependent activation bilaterally in the extrastraiate visual cortex after the presentation of a photic tetanus.

Table 1 Peak activations observed for the comparison of 'pre-tetanus' and 'post-tetanus' baseline runs separately for baseline stimulation on the tetanized and non-tetanized visual hemifield

'Post-tetanus' vs. 'Pre-tetanus'					'Pre-tetanus' vs. 'Post-tetanus'				
Contralateral/ ipsilateral	BA	*k*	*t*-value	*x*, *y*, *z*	Contralateral/ ipsilateral	BA	*k*	*t*-value	*x*, *y*, *z*
Stimulation in the *tetanized* hemifield									
Ipsilateral	18	56	5.54	−30, −84, 9	No suprathreshold voxel				
	18*		5.54	−27, −90, 6					
Contralateral	18/19	33	5.27	30, −87, 24					
Stimulation on the *non-tetanized* hemifield									
No suprathreshold voxel					Ipsilateral	18*	76	5.40	12, −96, 3

The coordinates are given according to the MNI (Montreal Neurological Institute) space together with its t-scores and corresponding Brodmann areas (BA). Asterisks indicate the probability (10–20%) that the peak voxel lay within V2 according to probability maps of the visual cortex. Note: As the data from the study participants who received a photic tetanus in their right visual field was 'flipped' and combined in the analysis with those who received a left visual field photic tetanus, 'left' and 'right' sides are no longer applicable; rather, tetanized and non-tetanized hemifields are used.

LTP, which in turn, through its associated signal cascades, induced a long-lasting increase in metabolism. Thus, the increase in BOLD may be due to increased vascularization to the area, through increased release of either Ca^{2+} or other neurotransmitters, which have been shown to soften arterial walls. NO and glutamate could be involved as they are known to play a major role in LTP [18]. Nonetheless, this increase in BOLD signal is found specifically within the extrastriate visual cortex, which could to be due to recurrent activity or possibly reverberation within or across the hemispheres of the neocortex [19], as mentioned in Teyler *et al.* [6]. Additionally, it has been suggested that increases in BOLD may be related to Hebbian mechanisms of plasticity [20].

LTP has been proposed as the basis for many plastic changes within the sensory cortices [3,4,21]. It has been demonstrated in the visual cortex of developing [3] and adult [4] animals. Considerable evidence exists to show that *N*-methyl-D-aspartate-dependent LTP-like mechanisms contribute to the development of the visual system [3]. Additionally, visual system LTP has been inferred as the basis for increases in perceptual learning such as in genres like contrast sensitivity, or visual after-effects in adult humans [22].

The current findings give further support to the claim that sensory-induced LTP in humans is a useful new paradigm for studying alterations in cortical function non-invasively [6,8]. Whether this neurophysiological process is also evident in other domains for which short and long plasticity has been shown (e.g. auditory, motor or sensory) remains to be proven in future experiments [23–25]. This approach may have utility as a diagnostic tool in neurodegenerative disorders as a biomarker of altered cortical physiology. A recent study, involving participants with partial cortical blindness, found that repetitive training with visual stimulation increased BOLD responses within the visual cortex, along with concomitant changes in visual function. BOLD responses were increased within the visual cortex after training [26].

Conclusion

A photic tetanus has been shown to induce LTP-like change in the human visual system, as measured non-invasively by EEG. We now show that this change is also detected in the BOLD signal from fMRI, and localized to the extrastriatal visual cortex, a location that supports the putative suggestions made on the basis of low-resolution brain electromagnetic tomography source estimations performed on VEPs in our previous EEG study [6].

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References

1. Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 1973; **232**:331–356.
2. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 1993; **361**:31–39.
3. Komatsu Y, Fujii K, Maeda J, Sakaguchi H, Toyama K. Long-term potentiation of synaptic transmission in kitten visual cortex. *J Neurophysiol* 1988; **59**:124–141.
4. Heynen AJ, Bear MF. Long-term potentiation of thalamocortical transmission in the adult visual cortex *in vivo*. *J Neurosci* 2001; **21**: 9801–9813.
5. Zhang LI, Tao HW, Poo M. Visual input induces long-term potentiation of developing retinotectal synapses. *Nat Neurosci* 2000; **3**:708–715.
6. Teyler TJ, Hamm JP, Clapp WC, Johnson BW, Corballis MC, Kirk IJ. Long-term potentiation of human visual evoked responses. *Eur J Neurosci* 2005; **21**:2045–2050.
7. Clapp WC, Eckert MJ, Teyler TJ, Abraham WC. Induction of long-term potentiation in rat visual cortex by rapid sensory stimulation. Program No. 42.8. *2005 Abstract viewer/itinerary planner*. Washington, District of Columbia: Society for Neuroscience; 2005 [Online].
8. Clapp WC, Kirk IJ, Hamm JP, Shepherd D, Teyler TJ. Induction of LTP in the human auditory cortex by sensory stimulation. *Eur J Neurosci* 2005; **22**:1135–1140.
9. Di Russo F, Martinez A, Sereno MI, Pitzalis S, Hillyard SA. Cortical sources of the early components of the visual evoked potential. *Hum Brain Mapp* 2002; **15**:95–111.
10. Nelles G, Widman G, de Greiff A, Meistrowitz A, Dimitrova A, Weber J, *et al*. Brain representation of hemifield stimulation in poststroke visual field defects. *Stroke* 2002; **33**:1286–1293.
11. Jeffreys DA, Axford JG. Source locations of pattern-specific components of human visual evoked potentials. II. Component of extrastriate cortical origin. *Exp Brain Res* 1972; **16**:22–40.
12. Arthurs OJ, Williams EJ, Carpenter TA, Pickard JD, Boniface SJ. Linear coupling between functional magnetic resonance imaging and evoked potential amplitude in human somatosensory cortex. *Neuroscience* 2000; **101**:803–806.
13. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. *Magn Reson Med* 1999; **42**:952–962.
14. Friston KJ, Holmes AP, Worsley KP, Poline JB, Frith CD, Frackowiak RS. Statistical parameter maps in functional imaging: a general linear approach. *Hum Brain Mapp* 1995; **2**:189–210.
15. Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ. Multisubject fMRI studies and conjunction analyses. *Neuroimage* 1999; **10**:385–396.
16. Horovitz SG, Skudlarski P, Gore JC. Correlations and dissociations between BOLD signal and P300 amplitude in an auditory oddball task: a parametric approach to combining fMRI and ERP. *Magn Reson Imag* 2002; **20**:319–325.
17. Marcar VL, Loenneker T. The BOLD response: a new look at an old riddle. *Neuroreport* 2004; **15**:1997–2000.
18. Magistretti PJ, Pellerin L. Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Philos Trans R Soc Lond B Biol Sci* 1999; **354**:1155–1163.
19. Hebb DO, *The organization of behaviour. A neuropsychological theory*. New York: Wiley; 1949.
20. Pleger B, Foerster AF, Ragert P, Dinse HR, Schwenkreis P, Malin JP, *et al*. Functional imaging of perceptual learning in human primary and secondary somatosensory cortex. *Neuron* 2003; **40**:643–653.
21. Kudoh M, Shibuki K. Importance of polysynaptic inputs and horizontal connectivity in the generation of tetanus-induced long-term potentiation in the rat auditory cortex. *J Neurosci* 1997; **17**:9458–9465.
22. Skrandies W, Lang G, Jedynak A. Sensory thresholds and neurophysiological correlates of human perceptual learning. *Spat Vis* 1996; **9**:475–489.
23. Hirose H, Kubota M, Kimura I, Yumoto M, Sakakihara Y. N100m in adults possessing absolute pitch. *Neuroreport* 2004; **15**:1383–1386.
24. Koeneke S, Lutz K, Wustenberg T, Jancke L. Long-term training affects cerebellar processing in skilled keyboard players. *Neuroreport* 2004; **15**: 1279–1282.
25. Schaefer M, Rothemund Y, Heinze HJ, Rotte M. Short-term plasticity of the primary somatosensory cortex during tool use. *Neuroreport* 2004; **15**: 1293–1297.
26. Pleger B, Foerster AF, Widdig W, Henschel M, Nicolas V, Jansen A, *et al*. Functional magnetic resonance imaging mirrors recovery of visual perception after repetitive tachistoscopic stimulation in patients with partial cortical blindness. *Neurosci Lett* 2003; **335**:192–196.