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Activation of SC during electrical stimulation of LGN: retinal antidromic stimulation or corticocollicular activation?

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Abstract

We have recently used combined electrostimulation, neurophysiology, microinjection and functional magnetic resonance imaging (fMRI) to study the cortical activity patterns elicited during stimulation of cortical afferents in monkeys. We found that stimulation of a site in lateral geniculate nucleus (LGN) increases the fMRI signal in the regions of primary visual cortex receiving input from that site, but suppresses it in the retinotopically matched regions of extrastriate cortex. Intracortical injection experiments showed that such suppression is due to synaptic inhibition. During these experiments, we have consistently observed activation of superior colliculus (SC) following LGN stimulation. Since LGN does not directly project to SC, the current study investigated the origin of SC activation. By examining experimental manipulations inactivating the primary visual cortex, we present here evidence that the robust SC activation, which follows the stimulation of LGN, is due to the activation of corticocollicular pathway.

Keywords: Monkey; Cortical microstimulation; fMRI; Signal propagation; Cortical microcircuits; Inhibition; Recurrence; Superior colliculus; Visual cortex

1. Introduction

Electrical stimulation (ES) of the brain in humans and animals has been used for over a century now, and although some might say it is a crude approach to studying the detailed mechanisms underlying various neural computations, microstimulation undoubtedly has made significant contributions to our knowledge in both basic and clinical research [1]. Indeed, ES often provides a causal link between the activity of various brain regions and perception or action, and it has recently found widespread applications in electrotherapy and neural prostheses as well. The combination of ES with functional magnetic resonance imaging (esfMRI) may substantially increase the impact of this technique in both translational and basic research. For instance, ES may prove to be an excellent tool for the study of projective fields or of effective connectivity and plasticity, e.g., Ref. [2], as well as for spatially resolved mapping of the networks underlying electrostimulation-induced behaviors. We have therefore developed and optimized esfMRI for experiments in anesthetized and behaving monkeys [3,4] and recently used it to study the effects of stimulation of visual thalamus on corticocortical signal propagation [5]. Our findings demonstrated that ES of the lateral geniculate nucleus (LGN) in the thalamus suppresses the neural activity of its projection regions in visual cortex. When ES was applied to LGN, the connected site of primary visual cortex (V1) showed increased blood oxygen level-dependent (BOLD) signals, while decreased signals were observed in extrastriate areas. The strong reductions in BOLD signal could be reversed by injections of γ-aminobutyric acid (GABA) antagonists in V1, suggesting that suppression is due to synaptic inhibition.

Interestingly, in the aforementioned experiments, stimulation of LGN consistently activated superior colliculus (SC) and pulvinar, even though neither structure receives direct LGN input [5]. The SC BOLD responses could be — in principle — mediated either by antidromic stimulation of retinal cells or by activation of corticocollicular pathway. In mammals, some 30% of the retinal ganglion cells bifurcate to innervate both LGN and SC [6,7]. Activation of such cells after LGN stimulation could potentially underlie the SC BOLD responses. But a recent study in which the LGN of monkeys was stimulated during the execution of a sequential

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double-saccade task provided evidence arguing against such a thalamo-retino-tectal signal propagation [8].

Alternatively, the BOLD increases in SC could result from the activation of the Meynert cells of the deep cortical layers (V & VI) of V1, which are known to project to SC [9–12]. Given that these very same layers receive monosynaptic input from LGN [13–15], it is reasonable to assume that the signals generated by the LGN stimulation propagate through the LGN-V1-SC pathway. In the present study, we have examined this hypothesis by analyzing data obtained from experiments in which V1 was deactivated either by intracortical lidocaine injections or by low-frequency ES (see Ref. [5]). Our results support the proposition that the SC activation during LGN stimulation reflects thalamo-cortico-tectal signal propagation.

2. Methods

This study involved six fMRI experiments in four healthy monkeys (*Macaca mulatta*) weighing 7–10 kg. All experiments and surgical procedures were approved by the local authorities (Regierungspräsidium) and were in full compliance with the guidelines of the European Community (European Union directive, 86/609/EEC) for the care and use of laboratory animals.

2.1. Preparative surgery and anesthesia

All surgical procedures for implantation have been described in detail elsewhere [5,16,17]. Briefly, MRI-compatible skull-form-specific head holders and chambers were made out of PEEK (polyetheretherketone; TecaPEEK, Ensinger, Inc., Nufringen, Germany) and implanted stereotaxically on the cranium of each animal using aseptic technique. The implants were secured with custom-made ceramic screws (zirconium oxide Y_2O_3-TPZ 5x1, Pfannenstiel, Germany). As a prophylactic measure, antibiotics (enrofloxacin; Baytril) and analgesics (flunixin; Finadyne vet.) were administered for 3 to 5 days. All surgical procedures were carried out under general anesthesia (balanced anesthesia consisting of isoflurane 1.3% and fentanyl 3 μg/kg iv as needed), the induction and maintenance of which were performed by trained personnel.

2.2. Anesthesia for fMRI experiments

During the fMRI experiments, anesthesia was maintained with remifentanil (0.5–2 μg/kg/min iv) in combination with a fast-acting paralytic mivacurium chloride (3–6 mg/kg/h iv). The physiological state of the animal was monitored continuously and maintained tightly within normal limits: body temperature at 38.5°C–39.5°C; end-tidal CO_2 of 33 mmHg; oxygen saturation of over 95%. Acidosis was prevented by the administration of lactated Ringer's solution with 2.5% glucose, infused at 10 ml/kg/h, and intravascular volume was maintained by the additional administration of colloids (hydroxyethyl starch, 20–30 ml over 1–2 min or 20 ml/kg/h).To ensure that the absence of a "typical" anesthetic, e.g., isoflurane, desflurane or propofol, did not cause stress to the animal, we measured catecholamines and optimized dosages to ensure unaffected physiological responses at normal catecholamine concentrations.

2.3. Positioning of the microelectrode in LGN

The chambers for LGN microstimulation were placed at the coordinates AP=8, ML=12 on average. The stimulation electrodes (100-μm Ir wire, coated with glass and beveled to 300–600 kΩ at 1 kHz) were lowered through a custom-made grid fitted into the recording chamber. Once the electrodes were at the desired location in LGN, we aligned the visual projector and plotted the receptive field of the multiple units. Stimulation sites were further adjusted so as to ensure reliable electrically evoked BOLD activation on the operculum of the brain. After site selection, they were permanently fixated, and the grid was sealed with biocompatible silicon (WPI, Sarasota, FL, USA; Kwik-Cast).

2.4. Visual stimulation and ES

Drops of 1% cyclopentolate hydrochloride were instilled into each eye to achieve mydriasis, and hard contact lenses (Wöhlke, Kiel, Germany) with the appropriate dioptric power were used to bring the eyes to focus on the stimulus plane. Visual stimuli were presented binocularly initially with SVGA fiberoptic projectors (Silent Vision; AVOTEC, Stuart, FL, USA) and later with our own custom-made MR-compatible visual stimulator. Subject's fiberscopes were aligned to the fovea of each eye using a modified fundus camera (RC250; Zeiss). The visual field of the scope was 30×23 degrees in visual angle. Visual stimuli were generated on-the-fly by an OpenGL-based custom program. Receptive fields were plotted with small rotating polar-checkerboard patterns (5×5 degrees). The BOLD responses were tested with the same patterns with 100% contrast and in full-field configuration. The effects of electric stimulation were optimized with a number of different pulse-types, different current strengths and durations. Here we present data obtained with biphasic charge-balanced pulses with 200-μs duration and a frequency of 3 to 200 Hz (pulse train 200 ms on and 200 or 400 ms off, typically 250 or 500 μA current strength).Stimulus events were synchronized to the MR image acquisition and controlled by PCs running custom-made programs under the QNX real-time operating system [18].

2.5. fMRI and lidocaine injection

We made measurements in a vertical 4.7-T scanner with a 40-cm-diameter bore (BioSpec 47/40v; Bruker Medical, Ettlingen, Germany) as described previously in detail [5,17]. Customized, small radiofrequency coils (30–80 mm diameter) were used to increase the sensitivity for the MR signal underneath a recording chamber. For controlled positioning