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Dependence of BOLD signal change on tactile stimulus intensity in SI of primates☆

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Abstract

Recently, we have demonstrated that the fine-digit topography (millimeter sized) previously identified in the primary somatosensory cortex (SI), using electrophysiology and intrinsic signal optical imaging, can also be mapped with submillimeter resolution using blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging at high field. In the present study, we have examined the dependence of BOLD signal response on stimulus intensity in two subregions of SI, Areas 3b and 1. In a region(s)-of-interest (ROI) analysis of Area 3b, BOLD signal amplitude increased linearly with increasing amplitude of an 8-Hz vibrotactile stimulus, and BOLD signal was sustained throughout the stimulation period. In contrast, in Area 1, a significant BOLD signal response was only observed with more intense stimuli, and ROI analysis of the dependence of BOLD response showed no significant dependence on stimulus intensity. In addition, activation was not sustained throughout the period of stimulation. Differing responses of Areas 3b and 1 suggest potentially divergent roles for subregions of SI cortices in vibrotactile intensity encoding. Moreover, this study underscores the importance of imaging at small spatial scales. In this case, such high-resolution imaging allows differentiation between area-specific roles in intensity encoding and identifies anatomic targets for detailed electrophysiological studies of somatosensory neuronal populations with different coding properties. These experiments illustrate the value of nonhuman primates for characterizing the dependence of the BOLD signal response on stimulus parameters and on underlying neural response properties.

Keywords: fMRI; Somatosensory cortex; Digits; Stimulus intensity; Gamma-variate; Linearity

1. Introduction

Blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) is an increasingly widely used noninvasive tool for functional brain mapping in humans and animals [1–11]. The BOLD signal change associated with changing regional brain activity results from a complicated interaction of changes in cerebral blood flow, cerebral blood volume and cerebral metabolic rate for oxygen following neuronal activation [12–16]. The continued development of BOLD fMRI as a quantitative probe of neuronal activity in humans requires a detailed understanding of the quantitative dependence of the BOLD signal on neural activity and particularly how accurately changes in underlying neural activity can be inferred from changes in the BOLD signal. The nonhuman primate, by virtue of allowing correlated measurements of BOLD signal change

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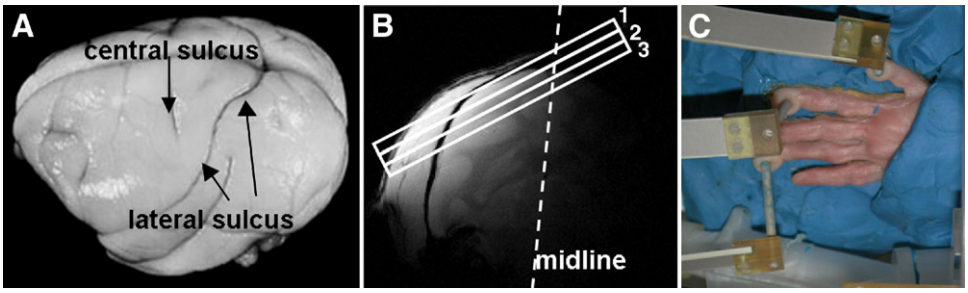

Fig. 1. Oblique slices and piezo stimulation. Landmarks including central and lateral sulci are visible on squirrel monkey brain and are used to identify SI (A). A high-resolution coronal image is collected to locate somatosensory cortices and to guide the placement of three oblique slices parallel to the SI cortex (B). Multiple fingers of the monkey's hand are secured by gluing small pegs to the fingernails and fixing these pegs firmly in plasticine. Rounded plastic probes (2 mm in diameter) are placed on glabrous surfaces and connected to a piezoelectric device (Noliac) providing vibrotactile stimulation (C). Piezos were driven by Grass stimulators (Grass-Telefactor) at a rate of 8 Hz with a 30-ms pulse duration. The displacement of the piezo is proportional to the driving voltage.

and neurophysiological responses to the same stimulus, offers a unique opportunity to study the nature of these dependences in a species whose cerebral anatomy, cortical organization and cytoarchitecture closely resemble those of humans.

By combining BOLD fMRI, optical imaging and electrophysiology studies in the same animals, we have demonstrated a close correspondence of the fine somatotopy delineated by the three different mapping methods and have demonstrated that high-field BOLD fMRI is capable of resolving the somatotopic organization of individual digits in single-condition activation maps in Area 3b of the primary somatosensory cortex (SI) with submillimeter spatial resolution [17]. In earlier studies, Chen et al. [18,19] used a combination of optical imaging and electrophysiology to study the response properties of optical intrinsic signal (OIS) and their relationship to and dependence on the response properties of neurons in activated regions across a range of sensory stimuli. These studies demonstrated a complex dependence of the amplitude and spatial extent of OIS response on the detailed nature of a tactile stimulus that reflected the recruitment of different and often overlapping populations of slow and rapidly adapting neurons, depending on the specific properties of the sensory stimulus. Nonetheless, they observed that, for a specific vibrotactile stimulus, increasing stimulus intensity (by increasing the amplitude of the mechanical indentation of glabrous fingerpads) evoked an increasingly strong and more spatially extensive OIS response in Area 3b and more variable responses in Area 1. The increased amplitude of the optical signal correlated with an increased single-unit activity (unpublished data). Thus, we hypothesized that stimulus intensity is encoded in SI (Areas 3b and 1) by both increased neuronal firing rate and recruitment of more neurons.

The goal of this study was to extend our previous fMRI and optical imaging studies of SI to begin to examine the influence of stimulus intensity on the spatial extent and amplitude of the BOLD signal in Areas 3b and 1 in anesthetized squirrel monkeys.

2. Materials and methods

2.1. Animal preparation

As previously described [17], squirrel monkeys (four monkeys) were anesthetized with ketamine hydrochloride (10 mg/kg)/atropine (0.05 mg/kg) im, intubated and maintained under isoflurane anesthesia (0.8–1.1%) delivered in a 70:30 O_2:NO_2 mixture with mechanical ventilation. The anesthetized intubated animals were placed in a custom-designed MR cradle with the head secured using ear and eye bars. Lactated Ringer's solution was infused intravenously (2–3 ml/h/kg) to prevent dehydration during the course of the study. SpO_2 and heart rate (Nonin, Plymouth, MN), electrocardiogram, ET-CO_2 (22–26 mmHg; Surgivet, Waukesha, WI) and respiration rate (SA Instruments, Stony Brook, NY) were externally monitored and maintained. Temperature (37.5–38.5°C) was monitored (SA Instruments) and maintained via a combination of a circulating water blanket (Gaymar Industries, Orchard Park, NY) and a flow of warm air (SA Instruments). Real-time monitoring was maintained from the time of induction of anesthesia until full recovery. All procedures were in compliance with and were approved by the Institutional Animal Care and Use Committee of Vanderbilt University.

2.2. Stimulus protocol

Vibrotactile stimuli were delivered to individual digits as follows. The anesthetized animals' fingers were secured by gluing small pegs to the fingernails and fixing these pegs firmly in plasticine, leaving glabrous surfaces available for vibrotactile stimulation by a rounded plastic probe (2 mm in diameter) connected to a piezoelectric device (Noliac, Kvistgaard, Denmark). Piezos were driven by Grass stimulators (Grass-Telefactor, West Warwick, RI) at a rate of 8 Hz with a 30-ms pulse duration (Fig. 1). Stimulus intensity was varied by varying the maximum displacement amplitude of the plastic probe tip at this fixed vibratory frequency. Probe displacement is proportional to piezo driving voltage. For most studies, three stimulus intensities