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Functional signature of recovering cortex: Dissociation of local field potentials and spiking activity in somatosensory cortices of spinal cord injured monkeys

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ABSTRACT

After disruption of dorsal column afferents at high cervical spinal levels in adult monkeys, somatosensory cortical neurons recover responsiveness to tactile stimulation of the hand; this reactivation correlates with a recovery of hand use. However, it is not known if all neuronal response properties recover, and whether different cortical areas recover in a similar manner. To address this, we recorded neuronal activity in cortical area 3b and S2 in adult squirrel monkeys weeks after unilateral lesion of the dorsal columns. We found that in response to vibrotactile stimulation, local field potentials remained robust at all frequency ranges. However, neuronal spiking activity failed to follow at high frequencies (≥15 Hz). We suggest that the failure to generate spiking activity at high stimulus frequency reflects a changed balance of inhibition and excitation in both area 3b and S2, and that this mismatch in spiking and local field potential is a signature of an early phase of recovering cortex (<two months).

Introduction

After spinal cord injury, considerable recovery of sensory function often occurs over a period of days to months. These recoveries include simple hand use (Ballermann et al., 2001), tasks involving fine cutaneous touch, and temporal or spatial information processing (for reviews see Kaas and Collins (2003), Kaas and Florence (2001b) and Nathan et al. (1986)). In humans, light touch and pressure sensation often recover quickly and completely; while vibration and proprioception recover slowly and never become completely normal (Bors, 1979), suggesting differential recovery of frequency specific channels in the somatosensory pathways. A primate model with a unilateral destruction of the dorsal column pathway, although not a typical model of spinal cord injury, offers a unique experimental platform for examining the roles of cortical reactivation and reorganization in functional and behavioral recoveries after deafferentation. In this model of spinal cord injury, input-deprived brain regions in primary somatosensory cortex (S1) regain their responsiveness to stimuli (reactivation), but the somatotopy remains abnormal (reorganization) (Darian-Smith and Brown, 2000; Florence et al., 1998; Graziano and Jones, 2009; Jones, 2000; Kaas et al., 1983, 2008; Manger et al., 1996). Such cortical reactivation and reorganization in S1 are believed to be crucial for the recovery of simple hand use and regaining of some forms of touch sensation (Darian-Smith and Ciferri, 2005).

The abnormal phantom sensations that develop in humans after deafferentation implicate higher cortical areas beyond S1 such as second somatosensory cortex (S2) (Flor et al., 1995; Knecht et al., 1998; Tandon et al., 2009). However, to date, little is known about the neuronal basis of brain recovery following spinal cord lesion and even less about the role of higher areas such as S2, knowledge that is vital for developing new therapies aimed at functional recovery (Pons et al., 1988; Vierck, 1998; Vierck and Cooper, 1998). Little is known about the interareal differences during the reactivation process in earlier somatosensory cortices of area 3b and S2 in primates. By quantifying and comparing the neuronal responsiveness of simultaneously recorded area 3b and S2 neurons from reactivated cortex weeks after dorsal column section, this study examined whether area 3b and S2 cortex exhibit similar functional reactivation profiles. As the third study in the series (Chen et al., 2012; Qi et al., 2011) here we report the stimulus-frequency dependent dissociation in response efficiency between spiking and local field potentials recorded simultaneously from the input-deprived but reactivated area 3b and S2 cortex. A better understanding of the reactivation process may lead to new therapies to aide functional recovery following spinal cord injury.

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There is a growing recognition in recent years that LFPs and spiking activity reflect different aspects of neuronal processing at different spatial and temporal scales. LFP integrates predominantly synaptic input signals from a population of neurons in a relatively larger cortical region whereas spiking activity carries the output signal. To date, the precise relationship between LFP and spiking activity remains elusive (Berens et al., 2008a, 2008b; Boynton, 2011; Conner et al., 2011; Logothetis, 2003; Logothetis et al., 2001). There is evidence for a functional or task specific relationship between these two different types of signals (Bartolo et al., 2011; Ekstrom, 2010; Rauch et al., 2008). Furthermore, most of what we know about the reactivation properties of somatosensory cortex following spinal cord injury comes from microelectrode recordings in which only spiking activity was evaluated. To our knowledge, no study has systematically examined the cortical responsiveness of reactivated cortex after spinal cord injury by recording both spiking and LFP responses. Immunohistological evidence of altered excitatory and inhibitory neurotransmission systems, as well as our functional imaging findings, led us to hypothesize that subthreshold electrical activity plays a key role in promoting cortical reactivation, and ultimately behavioral recovery (Chen et al., 2012; Garraghty et al., 2006; Mowery and Garraghty, 2009). As a test of this hypothesis, the present study aims to 1) characterize the response properties of spiking activity and LFPs, 2) determine the relationship between changes in spiking and LFP, and 3) examine whether spiking activity and LFP response differ in input-deprived and reactivated versus normal cortical area 3b and S2. We find that the local field potential (LFP) response to skin indentations remains robust at all frequencies in both area 3b and S2; however, neuron spiking activity fails to follow at high stimulus frequencies.

Experimental procedures

Animal preparation and surgery

Four adult squirrel monkeys (*Saimiri bolivians*) and six hemispheres were included in this study. Unilateral dorsal column section between spinal cord cervical segments C4–C6 was carried out under aseptic conditions under deep anesthesia (1–3% isoflurane) (Jain et al., 1997, 2008; Qi et al., 2011). The monkeys with spinal cord injuries were subject to fMRI imaging before and up to four times after spinal cord lesions, as described elsewhere (Chen et al., 2012). After 8 weeks of post-lesion recovery, hand representation in areas 3b and 1 (details described in Qi et al., 2011) and S2 of contralateral somatosensory cortex was mapped with microelectrodes. For electrophysiological recording experiments, animals were initially sedated with ketamine hydrochloride (10 mg/kg, mixed with atropine 0.05 mg/kg) and then maintained with isoflurane (0.8–1.1%), which was delivered in a 70:30 O_2/N_2O mixture. Animals were intubated and artificially ventilated, and blood oxygen saturation and heart rate (Nonin, Plymouth, MN), electrocardiogram, end-tidal CO_2 (Surgivet, Waukesha, WI), and respiration (SA Instruments, Stony Brook, NY) were externally monitored. Body temperature was monitored (SA Instruments) and maintained between 37.5 and 38.5 °C. All experimental procedures were in compliance with and approved by the Vanderbilt University Animal Care and Use Committees and followed the guidelines of the National Institute of Health Guide for the Care and Use of Laboratory Animals.

MRI methods

All MRI scans were performed on a 9.4T Varian Inova magnet (Varian Medical Systems, Palo Alto, CA) using a 3 cm surface transmit-receive coil centered over the SI cortex contralateral to the stimulated hand. Four 2 mm thick oblique image slices were centered over the hand region in primary somatosensory cortex around central sulcus. To evoke cortical response, 8 Hz vibrotactile stimuli were presented for 30 s duration blocks. The probe was lightly touching the skin during the off blocks (30 s). Functional MRI data were acquired from the same 4 slices using a gradient echo planar imaging (GE-EPI) sequence (TE = 16 ms; TR = 1.5 s; 0.575 × 0.575 × 2 mm^3 resolution). fMRI activation maps to individual digit stimulation is overlaid on the T2* weighted gradient echo structural image (TR, 200 ms; TE, 14 ms; 78 × 78 × 2000 μm^3 resolution) for display (Fig. 1). For details about the fMRI data acquisition and analysis, see Chen et al. (2012b).

Stimulus protocol for electrophysiology

The fingers were secured by gluing small pegs to the fingernails and fixing these pegs firmly in plasticine (a brand name of modeling clay), leaving the glabrous surfaces available for vibrotactile stimulation by a rounded plastic probe (1 mm in diameter) connected to a piezoelectric device (Noliac, Kvistgaard, Denmark). Piezos were driven by Grass S48 square wave stimulators (Grass-Telefactor, West Warwick, RI) at a rate of 2, 8, 15, 30 and 50 Hz. Indentation depth of the probe was 0.34 mm when it was measured at low frequency. The probe was in light contact with the skin before the vibrotactile stimuli were delivered. At each stimulus frequency, each stimulation trial was consisted of a prestimulus period (500 ms), a stimulus presentation period of 3 s when vibration (with a fixed pulse duration of 10 ms for all frequencies) was applied, and then a poststimulus period (500 ms). At each recording site (either different penetration sites or different recording depths (>300 μm in distance) along one penetration), a total of 60–100 trials were recorded. To drive both area 3b and S2 neurons simultaneously and effectively, stimuli were presented at the shared receptive field of both area 3b and S2 neurons. We only recorded the electrical responses when receptive fields were on the fingers (mostly distal finger pads).

Extracellular recording and data analysis

Cortical electrical signals in response to different vibrotactile stimuli were recorded using a Multichannel Acquisition Processor system (Plexon Inc., Dallas, TX) in which signals were passed through a unit-gain head-stage and a preamplifier through which each input channel was separated into two output channels that underwent different analog filtering, with one channel recording the higher frequencies of neuronal spikes and the other channel recording the lower frequencies of local field potentials. In all cases voltages were measured against an epidural electrode that was placed at the frontal midline that was made accessible by one bur hole in the skull. The recorded broadband neural signals were filtered between 300 Hz and 8 kHz, amplified and digitized at 40 kHz to obtain spike data. Single units were isolated online with Rasputin software (Plexon Inc.) and characterized in terms of their basic response profile. Spike sorting was repeated offline using the Plexon Offline Sorter to ensure that all action potentials were well isolated throughout the recording session. Spiking response to different frequencies of vibrotactile stimulation was computed in peri-stimulus time histograms (PSTHs) with 10 ms bin width. The mean spontaneous discharge per second was subtracted from the discharge per second recorded with different stimuli to determine stimulus-related discharge rates. We have focused our analysis on four measures: spontaneous firing rate, mean firing rate, response efficacy (RE), and the power of steady-state evoked LFPs. The firing rate during spontaneous period was defined by (number of action potentials) / (time period before stimulus onset). Baseline time period before each stimulus onset was 3.4 s. We conducted *t*-tests to examine the statistical significance of the spontaneous firing rates in normal and input-deprived cortex. The response efficacy (RE) was designed to compare fairly the neuronal spiking ability across different stimulus frequencies and was computed as a metric (Melzer et al., 2006):

$$RE = \frac{number\ of\ spikes\ within\ an\ epoch / duration\ of\ the\ epoch}{number\ of\ stimulus\ pulses}.$$

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