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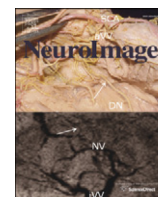

Temporally-structured acquisition of multidimensional optical imaging data facilitates visualization of elusive cortical representations in the behaving monkey

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ABSTRACT

Fundamental understanding of higher cognitive functions can greatly benefit from imaging of cortical activity with high spatiotemporal resolution in the behaving non-human primate. To achieve rapid imaging of high-resolution dynamics of cortical representations of spontaneous and evoked activity, we designed a novel data acquisition protocol for sensory stimulation by rapidly interleaving multiple stimuli in continuous sessions of optical imaging with voltage-sensitive dyes. We also tested a new algorithm for the “temporally structured component analysis” (TSCA) of a multidimensional time series that was developed for our new data acquisition protocol, but was tested only on simulated data (Blumenfeld, 2010). In addition to the raw data, the algorithm incorporates prior knowledge about the temporal structure of the data as well as input from other information. Here we showed that TSCA can successfully separate functional signal components from other signals referred to as noise. Imaging of responses to multiple visual stimuli, utilizing voltage-sensitive dyes, was performed on the visual cortex of awake monkeys. Multiple cortical representations, including orientation and ocular dominance maps as well as the hitherto elusive retinotopic representation of orientation stimuli, were extracted in only 10 s of imaging, approximately two orders of magnitude faster than accomplished by conventional methods. Since the approach is rather general, other imaging techniques may also benefit from the same stimulation protocol. This methodology can thus facilitate rapid optical imaging explorations in monkeys, rodents and other species with a versatility and speed that were not feasible before.

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Introduction

In-vivo functional imaging techniques covering a wide range of spatial and temporal scales have greatly facilitated exploration of the relationships between cognition, behavior, and electrical brain activity. This group of techniques includes electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), capillary intrinsic signals, voltage-sensitive dye imaging (VSDI), electrode array recordings, calcium imaging, functional magnetic resonance imaging (fMRI), NADH and flavoprotein imaging (Adrian and Matthews, 1934; Campbell et al., 1989; Denk et al., 1990; Grinvald et al., 1977, 1984; Hashimoto et al., 2000; Kuhl et al., 1975; Ogawa et al., 1990; Salzberg et al., 1977; Shibuki et al., 2003; for remarkable imaging at the single cell level see a recent review by Scanziani and Häusser, 2009). In mammals, the neocortex plays a preeminent role in generating sensory perception, controlling voluntary movements, carrying out higher cognitive functions, and planning goal-directed behaviors. These remarkable functions of the neocortex cannot be explored in simple model preparations or in anesthetized animals. The neural basis of behavior must be explored in awake, behaving subjects. Because neocortical function is dynamic on the millisecond time scale, the spatiotemporal dynamics of cortical activity must be measured in real time with millisecond temporal resolution. VSDI reveals the membrane-potential dynamics of the neocortical population at millisecond temporal resolution and subcolumnar spatial resolution.

Analysis

Datasets obtained by multichannel techniques from awake animals are often hard to analyze. Two fundamental difficulties can be identified (Mitra and Pesaran, 1999). First, the signal of interest is often contaminated, for various technique-specific reasons, by strong noise which is intensified in the awake animal. Second, there are difficulties associated with the analysis of any high-dimensional dataset. In particular, visualization in more than three dimensions is tricky;

Abbreviations: VSDI, voltage sensitive dye imaging; VSD, voltage sensitive dye; TS, time-structured; TSCA, time structured component analysis; PCA, principle-component analysis; ICA, independent-component analysis; SNR, signal to noise ratio; ECG, electrocardiogram.

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fitting a statistical model to the data is difficult because the number of parameters, grows exponentially with the dimensionality of the problem; and standard tools for analysis that are useful in one dimension become less useful in higher dimensions. With many techniques it is possible to improve the raw data by the use of advanced image processing approaches such as principal components analysis (PCA) and independent-component analysis (ICA) or their variants, or other useful analytic methodologies, some of which require a specific stimulation design (Chen et al., 2012; Engel et al., 1994, 1997; Everson et al., 1997, 1998; Fekete et al., 2009; Gabbay et al., 2000; Kalatsky and Stryker, 2003; Kalatsky et al., 2005; Mitra and Pesaran, 1999; Ribot et al., 2006; Sereno et al., 1995; Sornborger et al., 2005; Yokoo et al., 2001; Siegel et al., 2007). Many of these methods, including PCA and ICA, decompose the data into a set of basis vectors. Ideally, though usually not in practice, some of the basis frames can be identified with the signal, while others can be identified with the noise, allowing the signal to be separated from noise. Within this class of methods, PCA (e.g. Jolliffe, 2002) is the simplest. While this method is highly successful in dimensionality reduction, it often performs poorly in signal separation. The "Fourier-based" optical imaging of slow intrinsic signals, introduced by Kalatsky and Stryker (2003) and Kalatsky et al. (2005), offers a large improvement in signal-to-noise ratio (SNR). Recently, a similar approach was also successfully used for VSDI (e.g. Chen et al., 2012). Additional information on advantages and limitations of previously used methods of analysis is discussed in the Supplementary material (S1).

Voltage-sensitive dye imaging

Optical imaging based on voltage-sensitive dyes (VSD; Grinvald et al., 1984) is an established method for studying spatiotemporal patterns of cortical representations. It allows the simultaneous recording of large neuronal ensembles over relatively long periods of time, with submillisecond time resolution (for a review see Grinvald and Hildesheim, 2004). Thus, VSDI offers high temporal as well as high spatial resolution (e.g., ~0.1 ms and ~50 μm), and has been successfully used to study many sensory and motor modalities, mostly in the visual system (Arieli et al., 1995; Benucci et al., 2007; Chavane et al., 2011; Chen and Seidemann, 2012; Chen et al., 2006, 2008; Grinvald et al., 1994; Jancke et al., 2004; Kenet et al., 2003; Orbach et al., 1985; Petersen and Sakmann, 2001; Sharon and Grinvald, 2002; Tsodyks et al., 1999) and the somatosensory cortex, (Crochet and Petersen, 2006; Derdikman et al., 2003; Ferezou et al., 2006, 2007; Kleinfeld and Delaney, 1996; Orbach et al., 1985; Petersen et al., 2003).

Over the years VSDI has been significantly improved, in particular with regard to rendering the phototoxicity and pharmacological side effects of the dyes insignificant under the conditions used. Difficulties remain, however, in VSDI of dynamic cortical representations in behaving animals. First, the fractional change of the signal is often very small, with only 10^{-4} to 10^{-3} of the total fluorescence intensity reaching the detectors (note however, that the most relevant parameter is the final SNR rather than signal size in terms of fractional change). Nevertheless, signal averaging and image processing are often required in order to achieve a high SNR. Second, the VSD-dependent neuronal signal is typically masked by strong non-neuronal signals originating from heartbeat pulsations and respiratory signals superimposed on it. These two physiological signals are considered as noise or artifacts in the sense that they do not reflect neuronal activity. Other types of noise sources include 0.1 Hz vasomotion artifacts and shot noise. The large amount of data required for averaging out the noise necessitates long recording sessions, which impose additional "load" on animal performance in experiments with trained animals. This undertaking, albeit non-trivial, has proved at least partially successful in awake behaving monkeys (Ayzenshtat et al., 2010; Chen and Seidemann, 2012; Chen et al., 2006, 2008, 2011, 2012; Grinvald et al., 1991; Meirovithz et al., 2009, 2012; Palmer et al., 2012; Reynaud et al., 2011; Seidemann et al., 2002; Shtoyerman et al., 2000; Sit et al., 2009; Slovin et al., 2002), as well as in rat and mouse somatosensory cortices (Ferezou et al., 2006, 2007; Petersen et al., 2003). Nevertheless, as with any elaborate technology, additional improvements of the SNR are desirable. Here we describe how a large improvement in the quality of the functional maps was accomplished in 10 s data acquisition.

Methods

Animals

All experiments were carried out under a protocol approved by the Institutional Animal Care and Use Committee (IACUC), whose guidelines are consistent with the NIH guidelines. Two adult male *Macaca fascicularis* monkeys, SM and MM, were used in this study. The surgical procedure has been reported in detail previously (Shtoyerman et al., 2000; Slovin et al., 2002) and is outlined briefly in the following text.

Head holder and chambers for optical recording

Implantations were performed under sterile conditions. The monkeys were anesthetized, ventilated, and provided with an intravenous catheter. A head-holder and two cranial windows (25 mm internal diameter) were placed over the primary visual cortex and cemented to the cranium with dental acrylic cement. Appropriate analgesics and antibiotics were given postoperatively.

Craniotomy, durotomy, and artificial dura

Several months after the above procedure, the monkeys underwent craniotomy and the dura mater inside the chamber was resected to expose the visual cortex. The anterior border of the exposed cortex was always 3–6 mm anterior to the lunate sulcus. Typically, the center of the chamber was 0° 4° below the representation of the vertical meridian in V1 and 2°–4° lateral to the horizontal meridian. A thin, transparent silicone artificial dura was implanted over the exposed cortex (Arieli et al., 2002). During the entire imaging period, we opened and cleaned the chambers two to five times a week, depending on the condition of the cortex and the dura. The monkeys were awake during this painless procedure. Local and systemic antibiotics were applied according to microbiological examinations of the fluids in the chamber. While using local antibiotics above the artificial dura over the long period (several months) of VSDI, we did not observe any effects of the antibiotics on our results. The cortical tissue was never in direct contact with the antibiotics and the cortical surface was always carefully washed only with sterile artificial cerebrospinal fluid (ACSF).

Staining the cortex with VSD

At the beginning of each VSDI session, the monkeys were taken to a sterile operating room and seated in a primate chair. The chamber was carefully opened and the artificial dura was removed for staining. The cortical surface was washed with sterile ACSF. We used a new oxonol VSD, RH-1916 (a close analog of RH-1691 (Shoham et al., 1999) in which the paramethoxyphenyl substituent on the rhodanine moiety was substituted by paramethyl phenyl N-rhodanine). To ensure that the dye solution (0.2 0.3 mg/ml) was sterile, it was filtered through a 0.2-μm filter. After 2 h of staining, the chamber was reopened and the cortical surface was washed with ACSF until the solution was as clear as the ACSF. At the end of the staining the artificial dura was placed back over the cortex. Hard agar solution was gently poured onto the real dura in the periphery of the cranial window, and a more dilute and transparent agar solution was used to fill the chamber, above the artificial dura. Overall, the staining procedure of the cortex lasted for ~3 h (from the time that the monkey was brought to the sterile room until it was transferred to the imaging setup). Preparing the monkey in the imaging setup took another ~30 min. During the entire painless staining procedure and preparation time for imaging, the monkeys

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