Using nonhuman primates to study the micro- and macro-dynamics of neural mechanisms of attention

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Abstract

Cognitive neuroscientists have long desired to directly measure the neural basis of attentional selection with precise temporal and spatial resolution. Here we describe one approach to achieving this goal in which the neural activity underlying selective processing is simultaneously measured at both fine and increasingly global spatial scales in nonhuman primates. This is done by recording the electroencephalogram (EEG) and event-related potentials (ERPs) from monkeys, while more spatially precise measurements are recorded from microelectrodes inside of the brain. This combination of electrophysiological techniques allows us to observe the local (i.e., micro) and global (i.e., macro) neural dynamics of attentional selection as they unfold in real time. In addition, by focusing on EEG and ERP effects found in both human and nonhuman primates, we hope to definitively localize the neural generators of effects that have been used to study attention in human populations for decades.

One of the strengths of electrophysiological techniques is that they provide temporally precise information about the dynamics of cognitive processing that neuroimaging methods tied to blood flow simply cannot. In studies of normal human subjects, we are limited to noninvasive recordings of the raw electroencephalogram (EEG) and the averaged event-related potentials (ERPs). Although these methods do provide excellent temporal resolution of the activity of large ensembles of neurons, they cannot pinpoint the sources of this electrical activity generated inside the brain. When we record electrophysiological data from nonhuman primates, we can span multiple spatial scales by recording different types of activity, all of which have millisecond-to-millisecond temporal precision. Near one end of the continuum of spatial scale, we can measure the action potentials of individual neurons or groups of neurons to understand the role of each cell in the processing of information. We can also relate these action potentials to the postsynaptic potentials simultaneously measured in the vicinity of those neurons by recording the local-field potential (or LFP). An increasing number of studies involve the recording and analysis of both unit activity and LFPs to better understand the neural activity underlying attentional selection inside the brain (e.g., Fries, Reynolds, Rorie, & Desimone, 2001; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). In this chapter, we discuss the unique advantages of recording the EEG and ERPs from surface electrodes on nonhuman primates, in addition to simultaneously recordings of the electrophysiological activity inside the brain during attention-demanding tasks.

Why is it useful to record activity outside of the brain (i.e., EEG and ERPs) concurrently with the neural activity at finer spatial scales inside the brain (i.e., units and LFPs)? There are three objectives of performing these simultaneous recordings. First, by understanding how attention modulates the EEG and ERPs in monkeys we can directly relate these attention effects to those found in humans. This allows us to establish that humans and nonhuman primate models have homologous neural and cognitive mechanisms of attentional selection during information processing. While this is critical for basic scientists, it may have its largest impact in the development and testing of models of diseases in which attention mechanisms are impaired (e.g., schizophrenia, bipolar disorder, and ADHD). Second, once homologous EEG and ERP measures are established, the intracranial recordings allow us to study the neuronal generators underlying these effects. This is because the LFPs generated inside the brain summate via volume conduction and propagate through the skull resulting in the EEG and ERPs we measure on the surface of the head (Schroeder et al., 1995; Schroeder, Tenke, Givre, Arezzo, & Vaughan, 1991 Luck, 2005; Nunez & Srinivasan, 2006). Using the techniques we have applied, we can describe neuronal generators in very specific terms, including: 1) specific cortical and subcortical areas, 2) specific neuronal populations therein, and 3) underlying physiological processes and dynamics. Third, the holy grail of this line of research is to use the activity simultaneously recorded inside and outside the brain to be able us to solve the *inverse problem*. The inverse problem in electrophysiology requires us to localize the source of electrical activity inside the volume of the head based on the observed pattern of voltage measured outside of it (i.e., the EEG and ERPs). This is a very old problem in both physics and neuroscience (e.g., Helmholtz, 1853) and has been extremely difficult to definitively solve without information about the activity inside the brain. Because intracranial recordings are not possible with normal, healthy human subjects, experiments with monkeys provide a unique opportunity to record from multiple brain areas and derive solutions to the inverse problem, which has vexed cognitive neuroscientists interested in attention for almost a century (e.g., Berger, 1929; Luck, 2005).

It may be obvious to the reader that the combination of electrophysiological techniques we are discussing has the potential to advance our knowledge on a variety of topics in cognitive neuroscience (i.e., sensory processing, memory, decision processes, motor control, etc.). However, we will focus on how attention mechanisms operate, using several examples to illustrate the types of questions that can be addressed with electrophysiological methods that index precise temporal parameters of neuronal activity across multiple spatial scales. Less obvious, perhaps, are the requirements one must satisfy in using a nonhuman animal model to elucidate neuronal generators of ERP components in humans. First of all, an ideal approach requires that the structural and functional approximation of the model to the human be as close as possible. We consider the macaque monkey to be the closest approximation to the human that is feasible for routine study. A second requirement is that the measurements conducted in monkeys and humans be directly comparable. As discussed above, the LFP is an ideal measure for bridging the gap in this area, particularly in combination with simultaneous recordings from the surface of the head. Finally, the experimental paradigms used in monkeys must be very similar, if not identical, to those used in humans. Failing on any of these requirements means that inferences about the neurophysiology of any particular human ERP effect will be *at best* imprecise.

Regarding the requirement to study the same tasks in humans and monkeys, the most heavily used paradigm in ERP studies of attention with human subjects involves presenting stimuli one-at-a-time in a sequential stream (Luck, 2005). In such tasks, subjects are typically instructed to attend to one of two concurrently presented streams and detect one type of stimulus within the attended stream (e.g., Hillyard, Hink, Schwent, & Picton, 1973). This was the type of paradigm utilized by Schroeder and colleagues in a pair of seminal papers (Mehta, Ulbert, &

Schroeder, 2000a, 2000b). These represent some of the first studies to realize the potential of combined electrophysiological measurements of monkey homologues of human ERPs (e.g., Arthur & Starr, 1984; Borda, 1970) to understand the nature of attention. The impact of this work was significantly broader than if activity had only been recorded from inside the brain, because these studies directly related the ERP effects found in the monkeys to known attention effects in humans.

Mehta et al. (2000a; 2000b) presented concurrent streams of interdigitated visual and auditory stimuli to macaque monkeys. These monkeys were required to perform a task in which they detected infrequent targets in one or the other stream. One of the major advantages of this paradigm is that it had been used previously with human subjects to study attention effects while measuring ERPs (Alho, Woods, Algazi, & Naatanen, 1992). This allowed Mehta and colleagues (2000a; 2000b) to record a surface ERP component that appears to be a monkey homologue of the human *selection negativity* (Harter, Aine, & Schroeder, 1982; Harter & Aine, 1984; Hillyard & Münte, 1984; Schoenfeld et al., 2007). While these ERPs were recorded from a surface electrode outside the brain, LFP and multiunit data were recorded from laminar multielectrodes in multiple areas within the brain. These multi-contact electrodes allow activity to be simultaneously recorded from each layer of targeted neocortical and subcortical structures (see Figure 1). The advantage of using these intracranial multielectrodes is that they allow researchers to address questions about the finer-scale dynamics within a brain area that give rise to an ERP attention effect recorded outside the brain. For example, is the attention effect that contributes to the ERP component generated by the LFPs in layer 4 of V4 (i.e., the input layer) and, thus, due to feedforward activity from lower level visual areas? As shown in Figure 1, the findings of Mehta, Ulbert, and Schroeder (2000b) implicate extragranular pyramidal cell ensembles as critical contributors to the selection negativity. That is, Mehta et al. (2000a; 2000b) found that the largest attention effects measured within the brain during the time window of the selection negativity arise in layers 3 and 5 of area V4, apparently due to feedback from areas higher up the anatomical hierarchy.

The study of Mehta and colleagues show how the LFP responses enable even more detailed interpretations. Specifically, they calculated the second derivative approximation of the LFPs (i.e., current-source density, or CSD) which provides an index of transmembrane current flow. This serves to measure the first order response to synaptic input at the cellular level (Schroeder, Mehta, & Givre, 1998). Critically, transmembrane currents *cause* both inhibitory and excitatory postsynaptic potentials (IPSPs and EPSPs) that, in turn, determine action potential firing in individual neurons, and *generate* the LFP distribution in the electrically passive extracellular medium surrounding an ensemble of neurons that are synchronously excited or inhibited (Schroeder et al., 1998). These calculations reveal that the effect of attention is actually to suppress the later transmembrane current flow following an attended stimulus relative to the same stimulus when it was unattended. Finally, the concurrent recordings of the local neuronal firing (multi-unit activity) showed that the ERP attention effect is related to disinhibition. Specifically, the effect of attention at the neural level was to suppress the firing of neurons responding to an unattended stimulus relative to an attended stimulus, after the initial visual transient driven by the visual onset (see Figure 1, right panel). In summary, the selection negativity appears to measure an attentional mechanism that suppresses later responses to unattended stimuli relative to those that are potentially task relevant and attended. These findings demonstrate how the combination of methods we are advocating for can reveal the nature of the often complex electrophysiological dynamics between brain areas (i.e., macrodynamics) and within an area (i.e., microdynamics) that underlie the generation of an ERP attention effect measured outside the brain in humans and nonhuman primates. We will return to how these methods can be used to address even more fundamental questions about the nature of brain activity later.

Visual search has been one the principal paradigms used for decades to study attentional limitations in cognitive neuroscience and psychology (Wolfe, 1998a; Wolfe, 2003). Recently, Woodman, Schall, and colleagues (Cohen, Heitz, Schall, & Woodman, 2009; Woodman, Kang, Rossi, & Schall, 2007) began recording ERPs from monkeys performing the same types of visual search tasks performed by humans in ERP studies. This research showed that macaque monkeys exhibit an ERP index of covert attentional selection similar to that previous described in human ERP studies. Specifically, monkeys were shown arrays of objects in which the difference between the targets and distractors was determined by the spatial configuration of line segments. These tasks are particularly demanding when performed by human subjects (Wolfe, 1998b; Woodman & Luck, 1999, 2003) and the monkeys exhibited slower reaction times as the number of distractors in the search arrays increased, similar to the pattern of behavioral effects found with human subjects. Most importantly, the monkeys showed a posterior, lateralized ERP effect that mirrored the effect found in humans. In human ERP studies of visual search, when a target appears in one visual field (e.g., the left hemifield) the waveforms recorded at contralateral, posterior electrode sites (e.g., O1, OR, and T6) becomes more negative than the waveforms at ipsilateral sites when attention is shifted to the target location (Luck, in press; Luck & Hillyard, 1994; Woodman & Luck, 2003). Due to the distribution for this component, and because it is typically observed at about 200 ms poststimulus, this components has been termed the N2pc (for N2-posterior-contralateral). Woodman, Rossi, Kang and Schall (2007) found an apparent homologue of the human N2pc in the macaque monkey. This was established by the attention effect in the nonhuman primates having a similar sensitivity to cognitive manipulations (i.e., the set size and difficulty of the search task), relative timing (i.e., after the initial visual responses), and scalp distribution as the human N2pc (i.e., posterior and contralateral). There was an important difference between the macaque N2pc (or m-N2pc) and that of humans. The m-N2pc was a relative positivity and not a negativity as is typically observed in human subjects. The source of this polarity difference is likely due to differences in the cortical folding between the human and macaque brain. This is likely because the polarity of an ERP effect is dependent upon the orientation of the cortical generator relative to the surface of the head (Schroeder et al., 1995; Luck, 2005; Nunez & Srinivasan, 2006) and the human brain is much more convoluted compared to the relatively smooth macaque brain, leading to the prediction that the human N2pc is generated in cortex that is typically in the fundus of a sulcus whereas the monkey homologue is generated on a gyrus. Thus, both the similarities and the differences allow for testable predictions about the nature of the structures that generate ERP attention effects.

When it was first discovered, researchers hypothesized that the human N2pc was generated in ventral extrastriate visual cortex due to feedback from higher-level structures that control the deployment of attention (Luck & Hillyard, 1994). In a recent study, Cohen and colleagues (Cohen et al., 2009) tested this hypothesis by measuring the m-N2pc while simultaneously recording activity in the frontal-eye field (or FEF). The FEF is a prefrontal brain structure that has been shown to be involved in the deployment of covert attention during visual search (Schall & Hanes, 1993; Thompson, Bichot, & Schall, 1997; Thompson, Biscoe, & Sato, 2005; Thompson, Hanes, Bichot, & Schall, 1996), making it a possible source of the feedback hypothesized to generate the m-N2pc. Figure 2 illustrates the basic finding that the attention effects measured in the FEF neurons (i.e., blue traces) and FEF LFPs (the green traces) occurred prior to the onset of the m-N2pc measured at lateral posterior ERP electrode sites (the red traces). In addition to the timing of the FEF attention effects occurring prior to onset of the m-N2pc, Cohen and colleagues (2009) found that there was a significant correlation between the amplitude of the LFPs recorded within the FEF and the trial-by-trial variations in the amplitude of the m-N2pc. Thus, these simultaneous recordings of monkey ERPs and the neural activity inside a specific attentional-control structure demonstrate how the methods we are advocating can test specific hypotheses that are typical intractable in studies using healthy human subjects.

As we mentioned above, simultaneously recording activity from surface electrodes (i.e., the ERPs and EEG) and within the brain not only tell us about the neural origins of attention effects but also address fundamental questions about dynamics underlying all noninvasive electrophysiological measurements. When we record ERPs to study attention, or any other cognitive process, we typically assume that averaging together many trials reveals the fluctuations of potential evoked by the event of interest, while averaging out the EEG noise (Woodman, in press). However, some electrophysiologists have proposed that instead of ERPs revealing the potentials generated by an event, they may actually be due to a phase resetting of the ongoing rhythms inherent in the EEG, even when the brain is apparently in a resting state (Caton, 1887; Makeig et al., 2002; Sayers, Beagley, & Henshall, 1974). Shah and colleagues (Shah et al., 2004) recently showed how the simultaneous electrophysiological recordings inside and outside the brain can settle such debates. They showed that stimulus-locked ERPs are predominately generated by activity evoked during sensory and cognitive processing by recording the surface EEG and ERPs simultaneously with the LFPs and multiunit activity within striate and extrastriate areas of the brain. These findings indicate that perceptual processing of a visual stimulus is an evoked process with minimal contributions from a resetting of ongoing rhythms in the brain. However, this does not mean that some cognitive mechanisms might not take advantage of the ongoing oscillations in the brain to perform their particular operation. In fact, there are indications that as cortical processing proceeds away from the sensory receptor surface (i.e., up the hierarchy to higher order areas), there may be a progressive increase in the contribution of phase resetting of the LFP, and ultimately to scalp ERP generation (Shah et al., 2004). Attention appears to be just this kind of opportunist, taking advantage of inherent system dynamics to boost neural signals from task-relevant stimuli.

Following the line of work on how brain oscillations are related to ERPs and attention effects, Lakatos, Karmos, Mehta, Ulbert, and Schroeder (2008) examined how activity across different frequency bands are related to attentional selection of stimuli in different modalities. This study showed that when macaque monkeys attended to a stream of sequentially presented visual or auditory stimuli with the goal of detecting infrequent targets, as in the cross-modal task described above, the low frequency LFP activity became entrained to the stimulus presentation rate (i.e., 1.5 Hz, in the delta-frequency band). More specifically, the phase of these low frequency oscillations took a specific form. The negative peak of the 1.5 Hz delta-band oscillations brought on a period of high excitability, in which bursts of multiunit action potentials and high frequency LFP activity were observed. When the delta oscillation was at its most positive, the opposite was found. This low-frequency positivity resulted in a phase of low excitability in which action potentials and high frequency LFPs did not occur. Lakatos and colleagues (2008) went on to show that these high excitability phases at the negative peaks of the delta oscillations resulted in faster reactions times. These findings are consistent with the proposal that such oscillations could underlie slow-wave ERPs found in both monkeys and humans when preparing for the presentation of a task-relevant stimulus (i.e., the contingent-negative variation, or CNV, Borda, 1970; Walter, Cooper, Aldridge, McCallum, & Winter, 1964).

Attentional selection of a stimulus or stream of stimuli has long been associated with increases in the firing rates of neurons that represent the attended location or features of that stimulus (e.g., Goldberg & Wurtz, 1972; Moran & Desimone, 1985; Mountcastle, Anderson, & Motter, 1981, see also Thompson & Schall, 2011, in this volume). However, the study of Lakatos and colleagues (Lakatos et al., 2008) and other recent evidence demonstrating the coupling of low and high frequency activity with increases in firing rates (Canolty et al., 2006; Fries et al., 2001), suggest that attentional selection of a stimulus or modality of input is made possible by long-range connections in the brain. These long-range connections can then be used to coordinate the sensitivity of the neurons in the brain areas necessary to perform a given task. It has long been a mystery as to how our brains coordinate the large number of regions needed to process the task-relevant stimuli and initiate the appropriate behavioral responses. This new wave of studies reporting how different types of neural activity are related, appear to show how the particularly difficult questions about attention and cognitive control can be answered without appealing to the concept of an omnipotent cognitive homunculus (Attneave, 1960). Thus, the simultaneous recordings of multiple types of electrophysiological signals we described here are starting to provide answers to some of the most difficult theoretical puzzles about the neural implementation of attentional selection.

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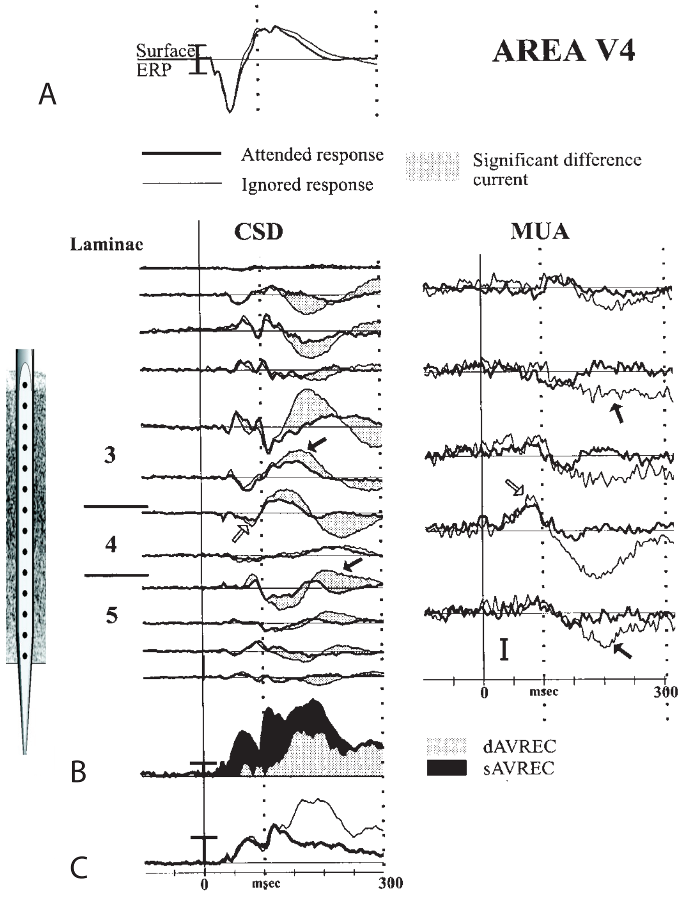
Figure Captions

Figure 1. Findings from Mehta et al. (2000b). The laminar activity profile recorded in V4 and a surface ERP electrode. A) Laminar current-source density (CSD) and multi-unit activity (MUA) profiles elicited by attended stimuli (thick lines) and the same stimuli when ignored (thin lines) at each recording contact. The MUA profile shows the initial feedforward excitation centered in lamina 4 (open arrow), followed by a suppression of activity below baseline (filled arrows). Both the late CSD amplitude and the suppressed MUA are reduced for the attend condition relative to the ignore condition. CSD scale bar = 0.5 mV/mm^2; MUA scale bar = 2 µV. B) Overlay of the simple AVerage RECtified current flow waveforms (sAVREC) and difference AVerage RECtified waveforms (dAVREC). Full-wave rectifying of each waveform and then averaging across the profile, difference derived from subtracting ignore waveforms from attend waveforms prior to rectification. The sAVREC reflects the total transmembrane current flow across conditions and the difference the net difference in transmembrane current flow between attend and ignore conditions. Reprinted with permission from Cerebral Cortex, Oxford University Press.

Figure 2. Findings of simultaneous recordings of the macaque N2pc (m-N2pc) and the LEFs and single unit responses in the FEF of a monkey. (A) Shows an example of the stimuli presented to monkeys. This is an example of a search array with a set size of 8 objects. (B) An example session from one monkey. (C) The cumulative distribution functions of the timing of attentional selection of the visual search targets from the different electrophysiological signals (i.e., m-N2pc ERP component in red, FEF LFPs in green, FEF neurons in blue) and RTs (dashed line) across recording sessions from two monkeys.



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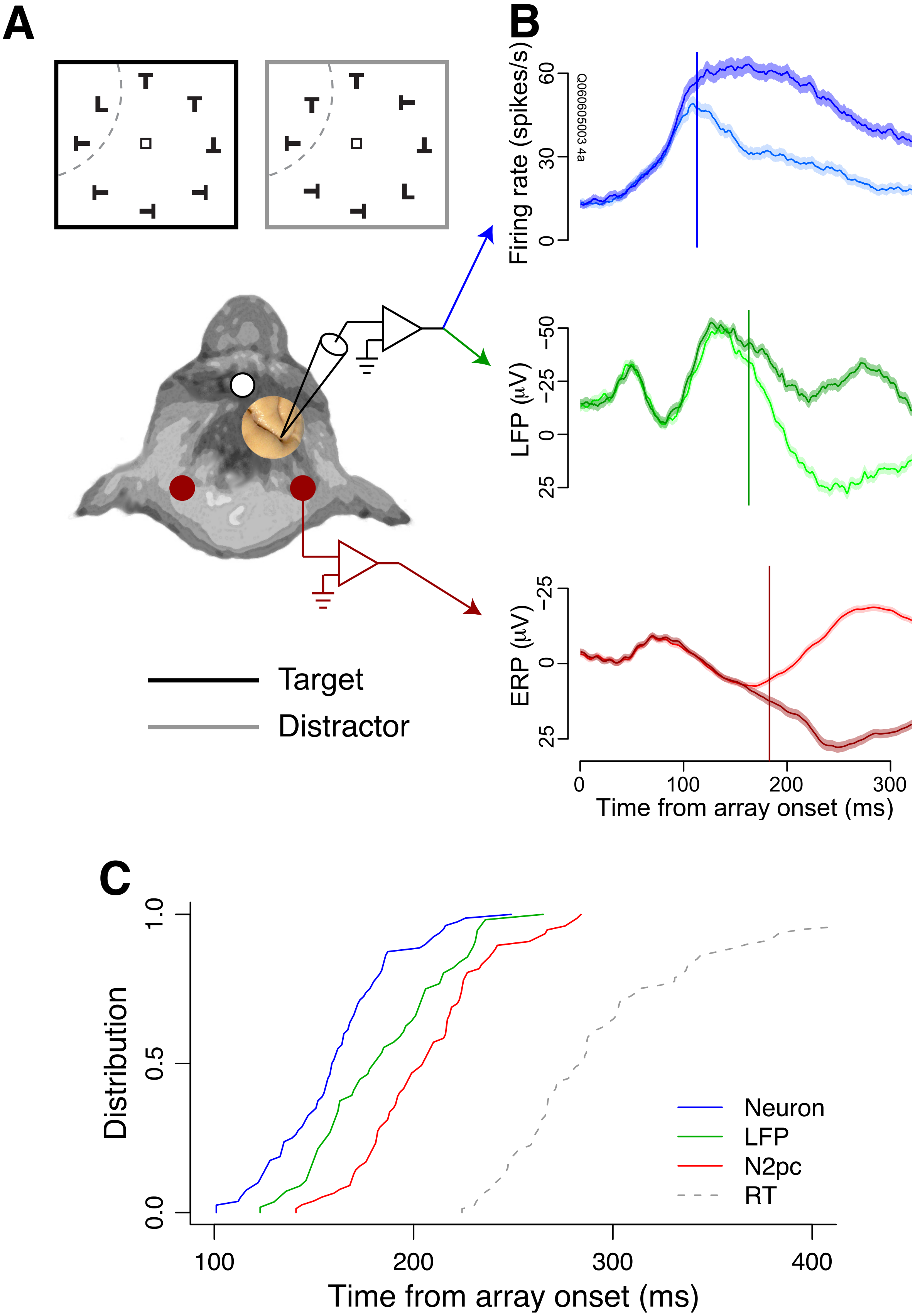
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