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Homologues of human ERP components in nonhuman primates

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Like many electrophysiologists who record the electroencephalogram (EEG) and event-related potentials (ERPs) from humans, I was a heavy user of the techniques before I became aware of the fact that EEG activity was originally observed during recordings from animals, including nonhuman primates (Caton, 1875). It was the 50-year-old studies with animals that motivated Hans Berger's discovery and naming of the EEG recorded from his son, Klaus, and other human subjects (Berger, 1929). Moreover, many users of the ERP technique may be surprised to learn just how rarely the ERP components we use as tools to study human cognition have been studied in other model species, such as nonhuman primates. This chapter chronicles the discovery of ERP components in nonhuman primates. I focus mainly on monkeys but also include evidence from other species when it exists. The discussion generally unfolds chronologically beginning with work from the 19th century and continuing up through current research. During this review I will address differences in the methods and tasks that have been utilized to record ERPs in the different species. Such methodological differences are a necessary complication in electrophysiological studies across species. I conclude by pointing to some of the most glaring gaps in our knowledge and the enormous potential for ERP studies recorded from nonhuman primates to shape what we know about ERP components and cognitive processing in humans.

History of the Electroencephalogram

Continuous EEG was first discovered by Richard Caton (1875), a British physiologist, in his recordings of electrical activity from the surface of the heads of monkeys and other species of animals. Caton (1875, 1877, 1887) recorded from electrodes placed on the skull, dura, and the exposed cortex of monkeys, rabbits, and cats. The activity that Caton observed was just within the range of sensitivity of the galvanometer he used, and initially the voltage fluctuations seemed

like just a noisy baseline before the presentation of a stimulus. Caton called the ubiquitous fluctuations in potential "feeble potentials," which were spontaneous low-frequency variations in voltage that could be modulated by presenting stimuli to the subject.

Quoting from Caton's (1875) brief report: "Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface…" Caton noted that these fluctuations in potential appeared to be related to the function of the underlying brain, with visual stimulation being more effective at modulating the fluctuations of potential than auditory or olfactory stimulation. Caton (1875) also noted that voltage fluctuations were recorded contralateral to the visual field in which a light was shone and were strongest when recording over an area that Ferrier had suggested was related to movements of the eyelids. He also reported that the ongoing fluctuations in potential were modulated by sleep, reduced by anesthesia, and increased immediately prior to death, after which changes in potential were completely absent (Brazier, 1957; Caton, 1887).

It is not clear from his writing why exactly Caton favored the term "feeble potential" for the electrical activity he observed. Potentials generated by peripheral nerves had been shown to be orders of magnitude faster than this activity, potentially making the EEG too slow, in Caton's view, to be involved in the critical operations of the brain. Alternatively, the changes in potential were observed in the baseline periods before any stimulus was presented and therefore when the brain was in a resting state. Finally, this activity was found in all of the species of animals that Caton used, and this may have suggested to him that the activity was not related to the intelligence of the organism. Regardless, coining this term for the electrical fluctuations he observed from the brain was likely a poor choice for his citation rate. Indeed, Caton's discoveries were often overlooked by other 19th century electrophysiologists who repeatedly claimed to

discover EEG and stimulus evoked potentials in many different species (e.g., Beck, 1890; Fleischl von Marxow, 1890). Realizing that his work had gone unnoticed, Caton wrote the editor of the German journal *Centralblatt f. Physiologie* pointing out that the reports published in 1890 had neglected his initial discoveries (Brazier, 1957). However, this attempt appeared to have little effect as his work continued to be overlooked even in England (e.g., Gotch & Horsely, 1891). The discovery of EEG in animals received even less attention in the United States than by Caton's fellow Europeans, where similar reports of EEG did not appear for over fifty years (Bartley & Newman, 1930). Fortunately for 21st century electrophysiologists, one medical doctor in Germany was aware of Caton's contributions to the new field of electrophysiology.

Hans Berger was a physician studying blood flow in the brain before the beginning of World War I (Haas, 2003). Unlike many of his predecessors, Berger was aware of Caton's work with nonhuman primates and other mammals. After returning to medicine at the conclusion of the war, he began similar recordings from humans, largely from his son Klaus. These initial observations formed the data reported in Berger's seminal work demonstrating the existence of alpha and beta wave rhythms in humans (Berger, 1929), the existence of which had been shown previously in dogs (Pravdich-Neminsky, 1913). In his preliminary publications, Berger explicitly acknowledged Caton's research. "Caton had already (1875) published experiments on the brains of dogs and apes in which bare unipolar electrodes were placed either on the surface of both hemispheres or one electrode on the cerebral cortex and the other on the surface of the skull. The currents were measured by a sensitive galvanometer. There were found distinct variations in current, which increased during sleep and with the onset of death strengthened, and after death weakened and disappeared" (Cohen of Birkenhead, 1959, pp. 258). Thus, the use of EEG, and

ultimately ERPs, to study different brain states was inspired by Caton's pioneering research in nonhuman species.

With Berger's reports of EEG recordings from human subjects, the field of human electrophysiology was born. However, Berger's findings were only truly appreciated by readers of English language journals after Edgar Adrian became interested in human EEGs (Walter, 1938). Here again the technique of recording EEG activity from humans would receive a boost from research with animals, if only in serving to recruit a believer in Adrian. Edgar Adrian shared the Nobel Prize with Charles Sherrington in 1932 for his work recording action potentials from individual neurons in the frog and from the sensory organs of a variety of species. Adrian had also noted the low frequency fluctuations in potential during his recordings from fish and insects, such as goldfish and water beetles (Adrian, 1932; Adrian & Buytendijk, 1931). Thus, when Berger reported similar potentials in human subjects Adrian became immediately interested and published replications and extensions of Berger's work (Adrian & Yamagiwa, 1935).

Adrian's longest-lasting contribution to the field of human electrophysiology was probably his work recording from rabbits as Caton had (Adrian & Matthews, 1934). The novelty of the contribution was the utilization of bipolar recordings, which have better spatial resolution than unipolar electrode recording techniques. Adrian and Matthews (1934) noted that the slow waves evident in the EEG are observed only when the active and reference electrodes are placed at a significance distance from each other (i.e., greater than 4 mm). It was with this evidence that Adrian and Matthews (1934) concluded that slow fluctuations in potential that dominate human EEG are due to a summation of activity from networks of neurons that are generally active at the same time but not precisely in phase with each other. It is not surprising that Adrian had

proposed a summation hypothesis to explain EEG as this is similar to the conclusions he had drawn in his Nobel prize winning work with individual neurons. Previously, Adrian had shown that more vigorous limb movements are accompanied by higher rates of action potentials in individual neurons. These observations led Adrian to propose that neurons use modulations of firing rates of action potentials instead of transmitting electrical signals that vary in size to code information. By the early 1940s, electrophysiologists took Adrian and Matthew's summation hypothesis as a given despite Adrian also entertaining the hypothesis that EEG was due to slower activity surrounding the dendrites of neurons (e.g., Adrian & Buytendijk, 1931). The summation hypothesis was the starting point for Kennard (1943) in a series of lesions studies with monkeys that attempted to localize the relative contributions of different structures to the observed spontaneous EEG. The logic of trying to lesion specific parts of the brain to eliminate EEG activity in animals was analogous to that of Lashley in trying to localize the reflex arc (Lashley, 1948) and proved to be just as unsuccessful (see Kennard, 1943; Kennard & Nims, 1942).

With the exception of some EEG recordings from animals during sleep studies (Desiraju, 1972; Weitzman, 1961), the post-Berger era is where monkey and human research split once again. In this case, it was the electrophysiological methods themselves that split the study of humans and nonhuman primates into distinct literatures (see additional discussion in Chapter 3, this volume). Electrophysiological study of the human brain using EEG and sensory evoked potentials gradually became widespread and then exploded in the mid 1960s with the discovery of ERP components that were sensitive to the task relevance of the stimuli and not just the physical characteristics of the stimulation (Sutton, Braren, Zubin, & John, 1965; Walter, Cooper, Aldridge, McCallum, & Winter, 1964). At the same time, continued refinement of microelectrode recording techniques from individual neurons in the brains of awake monkeys

and other animals yielded richly detailed accounts of how single neurons responded to different stimuli and task contexts (Evarts & Magoun, 1957; Hubel, Henson, Rupert, & Galambos, 1959). This single neuron based unit of analysis contrasts sharply with the discovery of human ERP components that index activity related to specific cognitive operations taking place in large cell assemblies perhaps spanning many different areas. Thus, electrophysiological studies of humans and monkeys operated on very different levels of analysis during much of the 20th century. However, in the mid 1980s research began to unite the literatures again. Perhaps it is not surprising that just as the discovery of the human P3 component launched the human ERP technique into common use (Sutton et al., 1965), the modern era of monkey ERP recordings followed the discovery of a monkey homologue of the human P3 component (Arthur & Starr, 1984).

Monkey homologues of human ERP components

The P3

The P3 or P300 component was one of the first human ERP components discovered that was related to the cognitive processing demands of the eliciting stimulus (see Chapter 7, this volume). Its discovery launched the field of human electrophysiology into view of psychologists and cognitive scientists in a way that research on spontaneous EEG simply had not (Sutton et al., 1965). In the initial experiments it was shown that a larger P3 was elicited by a stimulus of an infrequent category. Subsequently, research showed that the P3 elicited by task-irrelevant infrequent stimuli had a more frontal distribution (i.e., the P3a) than the P3 elicited by task-relevant infrequent stimuli, which had a distribution with a parietal focus (i.e., the P3b, Knight, Scabini, Woods, & Clayworth, 1989). In addition, it was shown that the P3a was reduced in

amplitude by frontal lesions although the P3b was not (Knight, 1991; Knight, Hillyard, Woods, & Neville, 1981). Several decades after finding the broad, positive component we know as the P3b in humans, electrophysiologists working with animal subjects began to search for a similar index of cognitive processing in other species.

Starr and colleagues can be credited with discovering the P3 component first in cats (Wilder, Farley, & Starr, 1981) and then in monkeys (Arthur & Starr, 1984). In fact, previous work had shown a P3-like potential in monkeys but had not required the monkeys to make a discriminative response, so the relevance of the stimuli for the effect could not be established (Donchin, Otto, Gerbrandt, & Pribram, 1971). Arthur and Starr (1984) trained their monkeys to perform a task in which they discriminated the frequency of tones and responded to infrequent target tones. This is precisely the same 'oddball paradigm' in which the human P3 had initially been reported (Sutton et al., 1965) and on which a significant proportion of all human ERP experiments are based (see, e.g., Chapters 4, 5, 6, 11, 14–20, this volume).

Arthur and Starr (1984) reported that monkeys showed a distinct positive potential following infrequent and task relevant tone stimuli embedded in a stream of frequent nontarget tones. The amplitude of the component was modulated systematically by the probability of the target tone (i.e., 10, 30, or 50% targets in a block of trials), just as the human P3b was known to behave. In addition, identical infrequent stimuli that were presented when they were not task relevant did not elicit the large positive component. One of the powerful aspects of the study of Arthur and Starr was that they recorded ERPs from humans in exactly the same task so that the waveforms could be directly compared between species (see Figure 1 in Arthur & Starr, 1984).

There was a crucial difference in the methods used to record monkey ERPs from those used in human ERP recordings despite Arthur and Starr (1984) measuring the monkey P3 using

stimuli and a task that paralleled experiments with humans. The difference was the type of electrodes used to record ERPs in the two primate species. When the EEG is recorded from the scalp of humans, the small potentials produced in the brain need to pass through the brain, dura, bone, and finally skin, with very few large muscle groups interposed between the brain and electrode. In monkeys, however, the skull is surrounded by thick layers of muscle tissue that are mostly connected to the jaw. This varies across species but particularly in macaque monkeys—the preferred nonhuman primate model for a human—the muscle surrounding the skull leads to unacceptable amounts of muscle noise in scalp recordings. This problem is accentuated by the fact that macaques need to be reinforced with food or liquid for their behavior to continue performing a task. This means that the muscles surrounding the skull will be active during the course of each trial as the monkey moves the lips and jaw to consume the reinforcing juice or food slurry and often during stimulus presentation as the animals anticipate the reward delivery. Arthur and Starr (1984) avoided this problem of muscle contamination by recording from screws that were implanted into the skull under general anesthesia.

Recording monkey EEG and the derived ERPs from skull screws has both advantages and disadvantages. An advantage of using screws as monkey EEG electrodes is that they can remain very well anchored to a specific location on the skull across days and even years. The disadvantage of these electrodes is that wires are typically used to provide a connection from the screws to the amplification equipment, and creating a good and stable electrical connection between an orthopedic screw and insulated metal wire on the operating table can be difficult. Even good connections can be compromised by normal activity in an animal's home cage. It might also be viewed as an advantage to record EEG from screws that extend all the way through the skull and often touch the dura when initially implanted. However, if the goal of the

recordings from monkeys is to make direct comparisons to human ERPs and EEG then this is in fact a problem. The electrical signal from the human brain passes through layers of tissue with difference impedance (i.e., dura and bone) before it is recorded on the scalp, causing the signal to spread (for more information, see Chapter 1 in Luck, 2005). This means that by the time electrical activity is recorded from scalp electrodes on humans, the electrical fields have essentially been spatially low-pass filtered (see Nunez & Srinivansan, 2006, for a discussion of the frequency domain effects). The use of skull screws from EEG electrodes will result in signals that have not been influenced by the same factors that influence human EEG. Thus, the voltage distributions of components across the head are not directly comparable when trying to relate signals recorded from skull screws in monkeys to those from scalp electrodes in humans. The advantages of alternative types of monkey EEG/ERP electrodes will be discussed further below.

Following the discovery of a homologue of the human P3 component in monkeys, research focused on understanding the neural activity that gave rise to the component and the conditions under which it could be observed (Arthur & Starr, 1984; Glover, Ghilardi, Bodis-Wollner, & Mylin, 1991; Javitt, Schroeder, Steinshneider, Arezzo, & Vaughan, 1992; Paller, McCarthy, Roessler, Allison, & Wood, 1992). One way researchers have attacked the problem was to understand the role of a specific area and its contribution to the component that was observed on the surface electrodes. In a particularly interesting study, the researchers lesioned the locus coeruleus motivated by the hypothesis that this region is critical for the generation of the P3 component (Pineda, Foote, & Neville, 1989). However, implications of the observation that the amplitude of the primate P3 was significantly reduced by lesioning the locus coeruleus may be limited by the centrality of this structure for excitation in the cortex in general. In

addition, the new world monkeys used in this lesion study are very difficult to train to perform a task. As a result they were passively processing the stimuli in this study which evokes a P3a in humans instead of the more often studied P3b elicited by task-related stimuli. However, these findings parallel those of Kennard (1943) decades before in which the spontaneous EEG was significantly disturbed only when the brainstem was lesioned causing the health of the animal to deteriorate.

Another interesting, although unexpected, result of studying non-human ERP components was the observation of what is often called the missing-stimulus potential (Bullock, 2003). Early ERP studies with humans noted that when a stimulus is omitted from a regular and steady stream of stimuli a component is elicited by the absence of the expected event. This component appears to be similar to the P3 elicited to the presentation of a rare stimulus (Simson, & Ritter, 1976; Simson, Vaughan, & Ritter, 1977). In a surprising series of studies, Bullock and colleagues showed that this missing stimulus potential was found in essentially every organism examined, including invertebrates such as crayfish (e.g., Bullock, 2003; Ramón, Hernández, & Bullock, 2001). We will discuss the implications of this type of large-scale comparative electrophysiology in greater detail in a subsequent section examining unanswered questions resulting from studies of nonhuman ERPs.

Although the discovery of a monkey P3 component made a large splash, it was not the first cognitively modulated ERP component that was discovered first in humans and subsequently found in research with monkeys. The initial report of the Contingent Negative Variation (CNV, Walter et al., 1964) appeared one year before the original report of the P3 component by Sutton and colleagues (1965). Following a similar time course, a monkey ERP component similar to the human CNV appeared in the literature very shortly after the discovery

of the component in humans (Borda, 1970). However, the field's evolving understanding of the CNV in humans resulted in tempered enthusiasm for the ability of monkey studies of the CNV to clarify the cognitive operations indexed by this component. Just as the interpretation of the CNV component was challenged by subsequent research with human subjects (Loveless & Sanford, 1975), the monkey CNV appeared to be less robust to modifications of the experimental paradigm than one would hope (see for example, Donchin et al., 1971).

Sensory and Perceptual Components

The first ERPs studied in humans were those elicited by the sensory processing of stimulus events (e.g., Davis, 1939). The study of nonhuman primate ERPs developed according to a similar path. The first reports of visually evoked potentials in monkeys appeared years before the Arthur and Starr (1984) P3 paper but with much less fanfare (Ripps & Vaughan, 1969; Van der Marel, Dagnelie, & Spekreijse, 1981; Vaughan & Gross, 1969). Van der Marel, Dangnelie, and Spekreijse (1981; Van der Marel, Dagnelie, & Spekreijse, 1984) recorded ERP responses from awake macaque monkeys while they passively viewed stimuli of varying luminance and pattern complexity (e.g., gratings or checkerboards). Van der Marel and colleagues reported that the effects of stimulus onset and offset recorded from monkeys mirrored those from humans during passive viewing of the stimuli (Van der Marel et al., 1984). These findings agree with comparative anatomical studies showing that macaque monkeys and humans have very similar neuroanatomy, particularly with regard to the visual system (Kaas, 2005). Although the general pattern of visual ERPs was similar across the monkeys tested, the size of the visual ERP components varied significantly across individual animals (Van der Marel et al., 1984). This observation mirrors the human ERP literature, in which the amplitude of early

visual ERPs varies significantly across individuals as well. Finally, Van der Marel et al. (1984) note that the visually evoked ERPs from the monkeys were 10-40 ms faster than similar components in humans.

The report of faster sensory ERP components in monkeys than in humans has been corroborated in subsequent studies (Lamme, Van Dijk, & Spekreijse, 1992; Schroeder, Tenke, & Givre, 1992; Schroeder, Tenke, Givre, Arezzo, & Vaughan, 1991; Woodman, Kang, Rossi, & Schall, 2007). Subsequent work also showed that the task relevance of the stimuli does not modulate the latency of these components (Glover et al., 1991). Presumably, the earlier onsets across the sensory and perceptually sensitive components like the N1 and P1 are due to the smaller size of the brains of the nonhuman primates compared to human subjects. Specifically, the larger brains of humans have many more neurons and synapses, meaning that information transmitted through the human brain will have more transmission delays compared to information transmission in the smaller macaque brain. Interestingly, a study of visually evoked potentials in great apes (i.e., gorillas and chimpanzees) suggests that the timing and morphology of the ERP components of our nearest primate relatives are even more similar to our own ERP components than those of old-world monkeys like macaques (Boysen & Berntson, 1985). Size of the brain cannot be a simple scaling factor for temporal relationships among ERP components, however, because the human brain is approximately seven times larger than that of old-world monkeys like macaques (Falk, 1986) while the ERP component latencies are typically only 25% shorter.

Now we return to the observation that even within species the early sensory components differ across individuals. The waveforms from three monkeys performing a visual search task are shown in Figure 1 to provide a concrete and recently published example of the individual

differences in monkey sensory ERPs (Woodman et al., 2007). Figure 1 illustrates the individual differences in amplitude of the early components and their relative speed compared to the human visual ERP components (see Chapter 10, this volume). Examination of the early sensory components evoked by these visual search arrays allows us another way to relate the observed monkey components to those from humans. The early visual components in humans (i.e., the P1 and N1 components) are modulated predictably by raw stimulus strength (Luck, 2005). Thus, as the set size of the search array increases from 2 to 4 to 8 objects the human N1 component would systematically increase in amplitude. As shown in Figure 1, this is precisely the pattern of results we observed in all three monkeys from an electrode approximating the location of electrode Oz in the modified 10/20 system (Jasper, 1958). In other words, as set size increased the amplitude of the first negative ERP component increased as well. The amplitude of this N1 component at the intermediate set size of 4 objects is marked by a dashed line for reference. These waveforms also show an interesting difference between human and monkey ERPs. Whereas the human P1 component shows sensitivity to manipulations of the strength of sensory input just as the N1 does, the monkey P1 does not appear to be modulated in the same manner. This demonstrates the nontrivial nature of finding homologues to the human ERP components. That is, in comparative electrophysiology both similarities and differences between human and monkey ERPs can be found.

Studies of monkey visually evoked potentials were the first to bring multiple types of electrophysiological recordings to bear on questions of the location of component generation. The primary motivation for the Arthur and Starr (1984) paper was that by establishing the existence of a monkey P3 subsequent research using depth recordings and lesion studies would localize the generator or generators of the component. Using monkeys to investigate the neural

origins of ERP components is an obvious advantage because this nonhuman primate model affords invasive recordings from inside the brain. Schroeder and colleagues published a series of experiments in which they collected ERP data from monkeys simultaneously with recordings of potentials across the different layers of areas such as V1 (Schroeder et al., 1992; Schroeder et al., 1991). These laminar recordings not only show where potentials recorded from the surface of the scalp or skull are being generated in the cortex but whether the candidate activity is an input to an area or activity which arises within the area itself. This technique provides necessary evidence that an area generates electrical fields that contribute to a surface recorded ERP component by demonstrating a polarity inversion as electrode contacts span the dipole generated in a certain brain area. This is, nearby electrodes in different layers of an area simultaneously show positive and negative potentials at the same time. For example, Schroeder and colleagues (1991) showed that the first visual ERP component appears to be generated in the supragranular layers of primary visual cortex while the subsequent components are generated by activity in extrastriate cortical areas. Studies such as this, and those described below, in which the neural generators of specific ERP components are determined using simultaneous depth recordings in the brains of monkeys are all too rare. The paucity of such investigations is likely due to the difficulty of these multilevel recordings and not the richness of the dataset they provide. Nunez and Srinivasan (2006) provide an excellent discussion of how many physicists have spent careers trying to understand principles that span spatial scales and point out that much more of this work is necessary for progress in understanding the signal we are recording from electrodes outside the brain.

Mismatch and Selection Negativity

The 'oddball paradigm' typically used to investigate the P3 component yields a number of other ERP components in human subjects under different types of task demands. In the oddball paradigm, one stimulus (or stimulus class) is more frequent than the other type of stimulus presented in the sequence. In humans, the first difference that is observed between the waveforms elicited by frequent and infrequent stimuli occurs around 200 ms and is known as the mismatch negativity (or MMN; see Chapter 6, this volume). As indicated by its name, the MMN is evidenced by the waveform to the infrequent stimulus being more negative than the waveform elicited by the frequent class of stimuli. The MMN is elicited any time that the eliciting stimulus does not match the predominant stimuli in the sequence, even if those infrequent stimuli are not task relevant, unlike the task-related P3 (or P3b) discussed above (Naatanen, 1990; Naatanen, Gaillard, & Mantysalo, 1978; Woldorff & Hillyard, 1990; but see Woldorff, Hackley, & Hillyard, 1991). Thus, it appears that the MMN is a measure of the brain's recognition—100-200 ms after stimulus onset—that the current stimulus is physically different than the context in which it is presented. Using auditory presentation of stimuli, Javitt and colleagues (1992) have shown that monkeys produce a similar mismatch response to infrequent stimuli when the monkey is not performing a task. As with the visually-evoked ERP waveforms, the MMN in monkeys appears to have an earlier onset (approximately 80 ms poststimulus) than the MMN component in humans (i.e., 200 ms poststimulus). However, the greater than 100 ms discrepancy in the onset of the component between primate species is in need of further study as the between species timing differences is strikingly large compared to other ERP components found in both species.

A slight modification of the paradigm used to elicit the MMN, in which the infrequent stimulus is also a task relevant target stimulus, elicits a different ERP component in humans

called the *selection negativity* (see Chapter 11, this volume). Whereas the MMN appears as a more negative potential for any infrequent stimulus, the selection negativity is a negative going component elicited by infrequent task-relevant target stimuli compared to infrequent nontarget stimuli (Anllo-Vento & Hillyard, 1996; Harter, Aine, & Schroeder, 1982; Hillyard & Münte, 1984; Hillyard, Simpson, Woods, Van Voorhis, & Münte, 1984). To determine whether our primate relatives share this index of attentional selection of task relevant target information, Mehta, Ulbert, and Schroeder (2000a; 2000b) trained monkeys to perform a crossmodal attention task. The researchers then recorded from a skull screw electrode and from multicontact, laminar electrodes in subcortical and visual areas of the cortex (the lateral geniculate nucleus or LGN, V1, V2 and V4). The stimuli were concurrent streams of visual and auditory oddball stimuli, and the monkey alternated between detecting the infrequent stimuli in the visual or auditory stream. The effects of attention were determined by comparing the neural responses from the same stimuli under the condition in which they were to be ignored with the condition in which they were task relevant. That is, the ERPs elicited by a visual stimulus when the stimuli in the interleaved auditory stream were task relevant compared to the ERP response to a visual stimulus when the visual stimuli were the targets. Mehta and colleagues found that the onset of attention effects was earliest in the most downstream area studied (i.e., V4). Effects of attention were later in V2, even later in V1, and nonexistent in the LGN recordings. These findings support the view that the selection negativity originates in anterior cortical areas and this selection signal is fed back to lower-level visual areas.

Schroeder and colleagues have used this same multisensory-attention task to address fundamental questions about the brain dynamics underlying ERPs (Fu et al., 2001; Mehta et al., 2000a, 2000b; Schroeder & Foxe, 2002; Shah et al., 2004). In one of the most fundamentally

important electrophysiological papers in recent years, Shah and colleagues (2004) tested the hypothesis that ERPs are not evoked by the occurrence of a discrete event, like the presentation of a visual stimulus, but instead are caused by the synchronization of ongoing EEG oscillations (e.g., Makeig et al., 2002) (see also Chapters 2 and 3, this volume). Shah et al. (2004) demonstrated that local-field potential fluctuations, recorded in primary visual cortex are generated in response to the presentation of a stimulus and are not simply the phase resetting of ongoing oscillations in the brain. In higher-order perceptual areas, specifically, the inferior temporal cortex (or IT), the amplitude of the stimulus-locked waveforms was due primarily to potentials evoked by the visual stimulus, but IT also showed ongoing oscillatory activity that made a significant contribution to the time-locked ERPs. This paper nicely shows how recordings of local-field potentials in the brain, also known as intracranial EEG (iEEG) in studies of clinical and rodent populations, can provide definitive evidence to distinguish between different models of the cortical dynamics underlying the generation of ERPs.

The N2pc

As described throughout this chapter, electrophysiologists have used three primary types of evidence to support their claims that monkeys exhibit ERP components similar to those found in humans. Studies of monkeys have shown that ERP components have relative timing that is similar to human studies (i.e., are early or late in the sequence of polarity deflections). Studies have also shown primate ERP components are similarly sensitive to stimulus and cognitive manipulations to argue for homology between ERPs of humans and other species. This section provides an example of the use of multiple criteria for establishing homology between a human ERP component and a monkey ERP component. Specifically, we discuss how the criteria of

voltage distribution, timing, and sensitivity to cognitive demands were used to support the conclusion that monkeys have an ERP component related to shifting and focusing visual-spatial attention, similar to that shown in humans.

In human observers, the N2pc component is a negative-going ERP waveform, typically elicited 170-200 ms after the onset of a visual search array with a posterior distribution that is contralateral with respect to where attention is deployed in the visual field (see Chapter 12, this volume). The N2pc is maximal at posterior and lateral electrode locations approximately 200-ms poststimulus as attention shifts to a target or potential target item in the left or right visual field (Luck, Girelli, McDermott, & Ford, 1997). ERP studies of the N2pc in humans performing visual search have been successful in revealing aspects of covert attention that cannot be observed using behavioral methods alone (Luck, 1994; Woodman & Luck, 1999, 2003a, 2003b). Of particular relevance are recent studies demonstrating that shifts of attention during visual search can be measured using this lateralized component of human ERPs. Studies by Woodman and Luck (1999; 2003b) demonstrated that the N2pc component shifts between hemispheres as attention shifts between potential target items in visual search arrays. The N2pc has also been shown to be an index of a perceptual selection mechanism (Luck & Hillyard, 1994b; Woodman & Luck, 2003a) that serves to suppress information from distractor objects surrounding the attended item (Luck et al., 1997). Source estimation procedures suggest that this ERP component may be generated in the human equivalent of macaque area V4 or TEO in the inferior temporal cortex (Luck & Hillyard, 1994b). Generally consistent with this, a magnetoencephalographic study found that the N2pc is accompanied by a temporal lobe magnetic field that spans much of the duration of the electrical N2pc component (Hopf et al., 2000).

To determine whether monkeys exhibit a homologue of the human N2pc component, Woodman, Kang, Rossi & Schall (2007) examined the waveforms recorded from lateral-posterior electrode sites in three monkeys performing visual search. The visual search task required monkeys to view an array without shifting gaze until they could make one saccade directly to the target object. This task required monkeys to rely on covert attention to select and process the target prior to the overt eye movement because reward would rarely be obtained if monkeys moved their eyes prior to covertly analyzing the search array. The set size of the search array varied randomly from trial to trial between 2, 4, and 8 objects. Across days the monkeys searched for a different target object such that all stimuli served as both targets and distractors, ruling out the possibility that the lateralized effects could be entirely due to a physical stimulus confound (Naatanen & Michie, 1979). The onsets of saccades were detected offline, and ERP waveforms from 20 ms preceding an eye movement were truncated. Thus, the average at each poststimulus time point was the mean of the remaining presaccadic waveforms.

The three monkeys in this study were implanted with arrays of electrodes that included posterior-lateral electrode locations, as well as parietal, central, and frontal locations. This array allowed the researchers to test for potential homologues of the human N2pc with the same contralateral and posterior distribution. Although these implanted arrays were composed of fewer electrodes than used with humans, the arrays provided greater coverage and density than is typical of nonhuman ERP recordings in which the modal number of EEG electrodes is one. The electrode array implants were constructed from Teflon-coated braided stainless steel wire and amphenol pins. During aseptic surgery, 1 X 1 mm holes were drilled into the surface of the skull allowing the terminal end of the electrode to be tightly inserted. The use of these small electrode contacts implanted in the skull has several advantages. First, compared to the typical procedure

of recording from skull screws that span the entire thickness of the bones of the skull, the electrode implants of Woodman et al. (2007) maximize the similarity of the resistive characteristics and tissue through which signals must pass in humans and these nonhuman primate recordings. It should be noted that the skull itself is multilayered and that the different layers of bone have different conductive properties (Nunez & Srinivasan, 2006). By inserting the electrode into the most exterior 1 mm of the 3-5 mm thick skull, much of the electrical pathway was preserved across species while avoiding the tremendous noise present when recording from the scalps of the far more muscle-headed macaque monkeys. Second, as the tissue reacts to the implantation of skull screws, it is common for the bone to grow over the exposed tip of the screw penetrating the brain case. Thus, the impendence of skull screw electrodes is initially very low and can measurably change over time as additional bone layers form between the metal of the screw and the dura surrounding the brain. In contrast, the impedance of the electrodes of Woodman et al. (2007) were 2-5 kΩ at 30 Hz, which is comparable to the values of EEG electrodes used in human studies. The impedance of these electrodes remains stable for upwards of five years in healthy monkeys. Third, the electrode leads can be covered by skin that is sutured back over the skull. This allows for the EEG electrodes to be minimally invasive once implanted.

Before discussing the ERP findings it is first necessary to discuss the behavioral results from the search task. As with human subjects, the monkeys' saccadic reaction times (RTs) were fastest at set size 2 and slowest at set size 8. This is shown in Figure 2, with the saccadic RT next to the waveform for each set size. Unlike the early sensory components, the amplitude and latency of the N2pc component are known to be related to how rapidly human observers can shift attention to a target in a search array. Specifically, more efficient visual

search is associated with larger amplitude N2pc components due to less temporal variability in when attention can be focused on the target (Luck et al., 1997; Luck & Hillyard, 1994b).

The waveforms shown in Figure 2 are representative of the pattern found across the three monkeys from which ERP data was recorded during search. First, note that right visual field targets elicited a waveform that was more positive at the left hemisphere electrode site than at the right hemisphere site beginning approximately 150 ms poststimulus. The onset of this contralateral positivity is marked by the dashed line to indicate the point at which the ipsi- and contralateral waveforms were significantly different from each other. Conversely, the waveforms elicited by left visual field targets were more positive at the right hemisphere electrode than the left hemisphere site. As discussed below, this component appears to be a contralateral positivity whereas the human component is a contralateral negativity. Second, this contralateral positivity was sensitive to the set size of the eliciting array. As set size increased, the amplitude of the contralateral positivity decreased, the onset appeared to shift later in time, and the duration of this difference was more variable. Third, as shown in Figure 2, we confirmed that on catch trials in which no target was present the waveforms elicited by the nontarget arrays were essentially identical to those ipsilateral to the target in a search array. This parallels findings from humans shown nontarget search arrays (Luck & Hillyard, 1994a) and provides another example of using manipulations of a task in both species to determine the functional similarity of the waveforms in the two species. Moreover, these data allow us to assess whether the hemispheric difference observed in the monkeys is an ipsilateral negativity or a contralateral positivity. As shown in the green traces in Figure 2, the waveforms recorded on nontarget trials are essentially the same as those elicited by ipsilateral target arrays. These findings support the conclusion that shifting attention to the target location in the search array elicits a contralateral positivity. To clearly

show the similarity between the macaque and human components, we ran human subjects in exactly the same visual search task as that used with the monkeys. Figure 3 shows the data from monkey P and the data from human J.A. for purposes of directly comparing this attention-related component across species of primates. As you can see the set size manipulation elicits nearly identical effects by shifting the onset and the peak amplitude of the contralateral component back in time in both the human and monkey. Thus, this apparent macaque N2pc (or mN2pc) behaves identically to the characteristics of the human component in terms of contralateral distribution and sensitivity to attentional demands of a visual search task.

The mN2pc exhibits the same anterior-posterior distribution as the human N2pc. Specifically, Figure 4 shows the waveforms recorded from the three pairs of posterior to anterior electrodes implanted in monkey P. The mN2pc is observed over the most posterior pair of electrodes but is noticeably and significantly reduced at the next more anterior electrodes and absent at the most anterior pair of electrodes. This distribution mirrors the posterior-to-anterior distribution of the N2pc recorded from humans performing visual search (Luck & Hillyard, 1994a). In summary, the mN2pc recorded from all three monkeys exhibits the timing, distribution and sensitivity to attentional demands that functionally define a monkey homologue of the human N2pc.

It is interesting to note that the human index of covert attentional deployment is a negative potential whereas this component in the monkey is a positive potential. This was not completely unexpected due to differences in cortical folding between species. Because ERPs are generated by tissue that when active generates open electrical fields, the cortex is believed to be the principle generator of such electrical potentials (Luck, 2005; Nunez & Srinivasan, 2006). The folding of the cortical surface that contains the generating tissue will therefore, determine the

polarity of the observed ERP component homologue. An inversion of the cortical surface relative to the skull results in a polarity inversion of an ERP component. For example, the human C1 component is of opposite polarity when it is evoked by an upper versus a lower visual field stimulus due to activation of neurons on opposite banks of the calcarine sulcus (Clark, Fan, & Hillyard, 1995). Source estimation procedures suggest that the human N2pc may be generated predominately in ventral visual areas such as V4 and IT. Whereas monkey V4 is located on a superficial gyrus, the proposed human homologue based on functional imaging data is in an area that has both sulci and gyri (Orban, Van Essen, & Vanduffel, 2004). It is possible that in humans the N2pc is generated in the subregion of the anatomical homologue of V4 that is folded in a sulcus. Individual differences in the folding of human cortex could invert the N2pc and occasionally instances have been observed in my research with humans in which contralateral positivities were found in humans as well. However, structural MRIs of those subjects were not available to test the hypothesis that these individuals had an anomalous pattern of folding in ventral visual cortex. Thus, the likely explanation for the polarity difference observed between human and monkey attention-related lateralizations is that the mN2pc component is generated by cortical tissue that is inverted in the macaque relative to the orientation of the functionally homologous tissue in humans.

In summary, the study by Woodman and colleagues (2007) provides an example of how comparative electrophysiological studies can use multiple types of evidence to show that an ERP component found across species is indexing the same operations during information processing. Establishing homology between ERP components found in two different species is the first step toward using an animal model to better understand the neural circuitry underlying the generation of the ERP component. Monkey models of human information processing offer the possibility

of recording from structures in the brain and performing lesions studies to determine which areas in the brain are involved in the generation of a given component. Research is currently underway to localize the neural generators of the mN2pc component using these converging operations.

So much to do, so much resolution

Despite the sizable body of fundamental work examining ERP recorded from nonhuman primates, it has not yet been established whether monkeys exhibit homologues of many of the electrophysiological indices that we use to study cognitive processes in humans. The other volumes in this book document the progress that has been made defining the cognitive functions indexed by a large number of distinct ERP components in human subjects. However, researchers have yet to look for many of these ERP components in monkeys. This means that there is a need for many basic comparative electrophysiological studies. Obviously, the category of ERP components related to language processing and use cannot be studied in nonverbal species. However, it is possible that we can study more general semantic processing in nonhuman primate models using components that were discovered in ERP studies of language. For example, the N400 component is elicited by semantic incongruities (see Chapter 15, this volume) regardless of whether meaning is communicated through words (Kutas & Hillyard, 1980) or pictures (Nigam, Hoffman, & Simons, 1992). This may be a way of studying semantic processing across species without the use of linguistic stimuli. Another limitation to consider is that the variety of ERP components that can be studied is constrained by the type of task a monkey can be trained to perform. Finally, all monkeys are overtrained on tasks relative to the modest amount of practice human subjects receive before an experiment and we must consider

whether the training of nonhuman primates renders monkey ERPs qualitatively different than human components found in the same tasks.

The neural origins of ERP components have not been definitively localized in the human brain because only rarely can potential generators of ERP components be studied intracranially in patient populations (Halgren et al., 1980; Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005). In addition, the temporal resolution of most imaging techniques makes them too slow to functionally localize the generators of an ERP component, which is often a brief neural event (e.g., 100 ms in duration). Interestingly, Caton's (1875) initial report of EEG in animals was presented as evidence for localization of function. Specifically, the observation that lateralized visual stimuli would elicit larger contralateral responses was taken as support for specialization of function by cortical regions (Brazier, 1957). Indeed, this was the implication of citing Ferrier's work in the initial reports of feeble potentials and stimulus evoked fluctuations (Caton, 1875; 1887). As it remains today, the issue of localized versus distributed processing in the brain was hotly debated with the pioneers of the fledgling field of electrophysiology viewing many of their findings as most relevant to this debate (Adrian & Matthews, 1934; Berger, 1929; Caton, 1887; Walter, 1939). Viewing EEG and ERPs as evidence for localization of function seems ironic given the limited spatial resolution of these techniques. The spatial resolution of imaging techniques with current technology is far beyond the ability of the ERP technique to localize function to regions of cortex. It seems that an area in which monkey ERPs can have the greatest impact is in our ability to have the temporal resolution of the ERP technique with the spatial resolution of depth recordings in specific brain areas.

Viewing EEG and ERP recordings from humans and nonhuman species through the lens of history brings several fundamental questions into focus. Perhaps the most basic among these

lingering concerns is that we do not really understand the EEG signal in which ERPs are embedded. What is the function of the spontaneous synchrony evidenced by EEG? Why does the presentation of a stimulus cause the ongoing alpha-dominated EEG to be reduced in amplitude? This stimulus induced alpha desychronization was one of the first observations made by Caton (1887) and yet its cause is still unknown. At the dawn of the era of ERPs in the field of electrophysiology, Donald Lindsley pointed out that despite the great enthusiasm for ERPs to answer questions about cognition, the fundamental questions about the basic EEG signal remained unanswered (Donchin & Lindsley, 1969). Basic comparative ERP studies also still have much to discover. Bullock (2003) observed missing-stimulus potentials in every species he examined and was led to wonder what electrophysiological measures of cognitive processing are unique to humans. What is it that underlies our cognitive abilities that are so far beyond even our closest primate relatives? Whereas this chapter focused on the components that appear to be the same across primates, understanding what makes humans special will require us to also focus on the differences between human ERPs and those of other species of animals.

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Figure Captions

Figure 1. ERP waveforms recorded from a posterior midline electrode in monkey Q (A), in Monkey P (B), and in Monkey S (C) across set size 2, 4, and 8. The relevant active electrode on each monkey was equivalent to Oz and the common frontal reference electrode is analogous to Fz. Waveforms recorded from all three monkeys show a complex of early negative-going components sensitive to the amount of sensory stimulation as a function of set size (marked by the arrows on the waveforms from monkey Q). The dashed horizontal lines mark the amplitude of the set size 4 peak of the first negativity. Adapted from Woodman et al. (2007).

Figure 2. ERP waveforms recorded from the left posterior (left column) and right posterior electrodes (right column) from monkey P for right (blue traces) and left visual field targets (red traces), and target-absent trials (green traces) across set sizes 2, 4, and 8. Following a visually-evoked negativity, a contralateral positivity was observed beginning ~125 ms poststimulus for lateralized targets, but not when targets appeared on the horizontal midline (data not shown) as in human observers. The amplitude of the monkey homologue of the N2pc (mN2pc) was modulated by the set size of the visual search array presented. Dashed vertical lines mark the onset of the mN2pc. The number above the waveform indicates the mean saccadic response latency for contralateral targets.

Figure 3. Comparison of average ERP waveforms recorded from the posterior pair of electrodes on monkey P (left) with waveforms from electrodes OL/OR on human J.A. (right) performing the same oculomotor search task across set sizes.

Figure 4. ERP waveforms recorded from monkey P for right visual field targets (blue traces) and left visual field targets (red traces) across all pairs of lateralized electrodes for search arrays with two items. The amplitude of the mN2pc was maximal and significant at the most posterior pair of electrodes (ps < .01) and decreased progressively at more anterior electrodes.

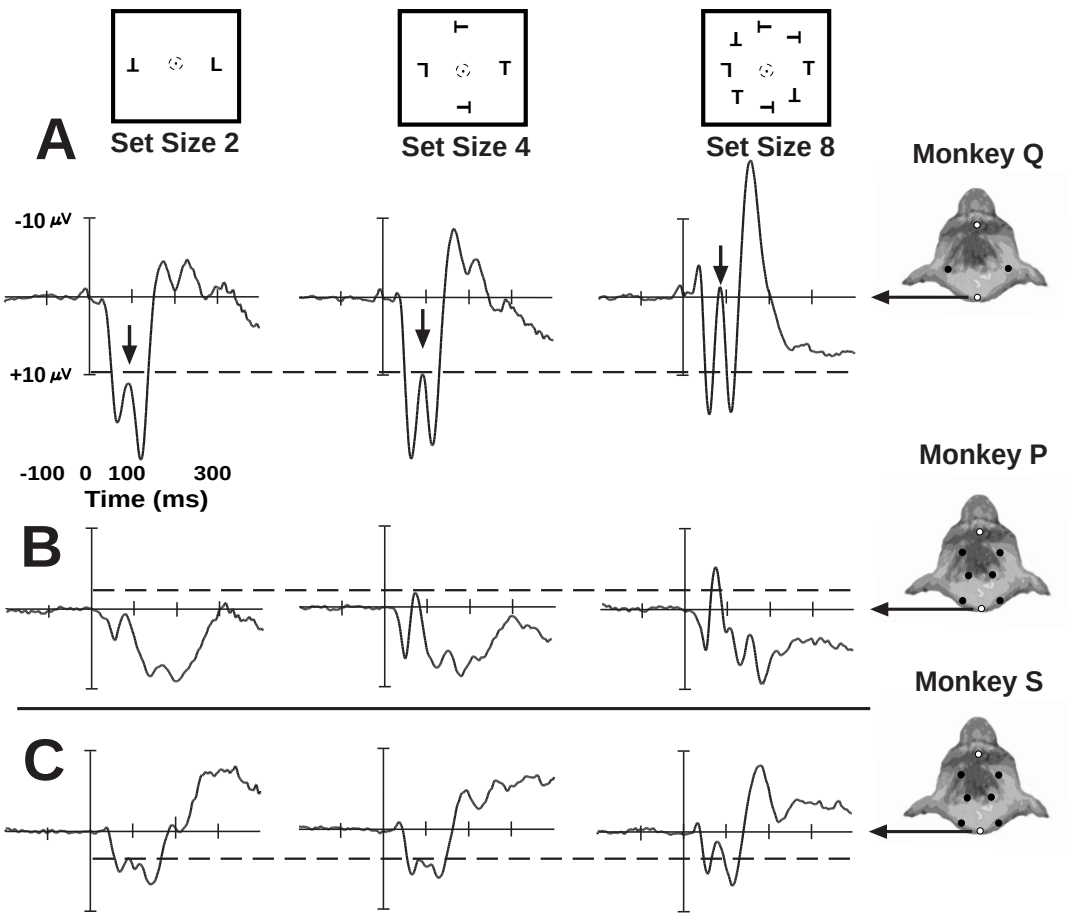
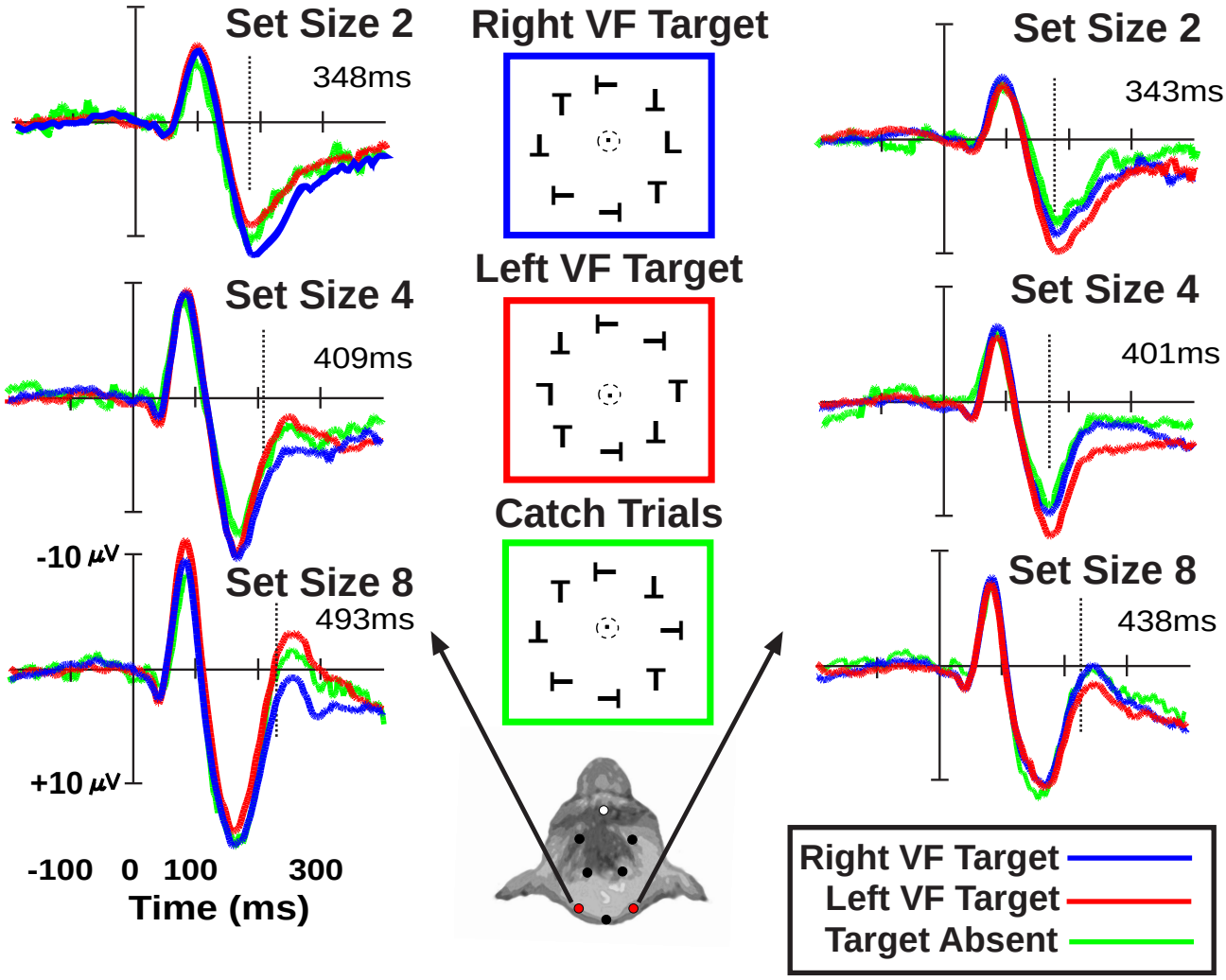


Figure 1. ERP waveforms recorded from posterior midline electrode on monkey Q (A), P(B) and S (C) across set size 2, 4, and 8. The relevant active electrode on each monkey was approximately equivalent to Oz and the common frontal reference electrode is analogous to Fz. Waveforms recorded from all three monkeys show a complex of early negative-going components sensitive to the amount of sensory stimulation as a function of set size (marked by the arrows on the waveforms from monkey Q). The dashed horizontal lines mark the amplitude of the set size 4 peak of the first negativity. Adapted from Woodman et al. (2007).



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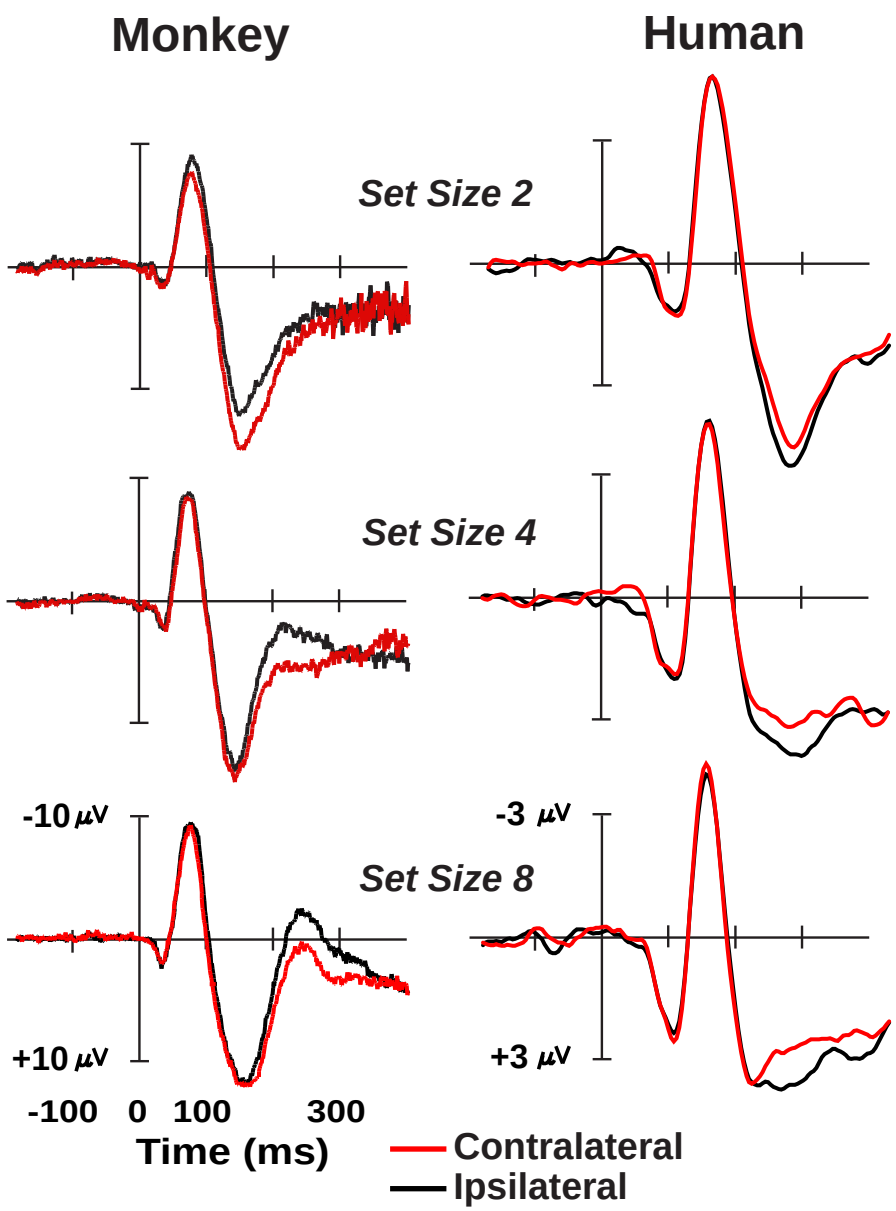

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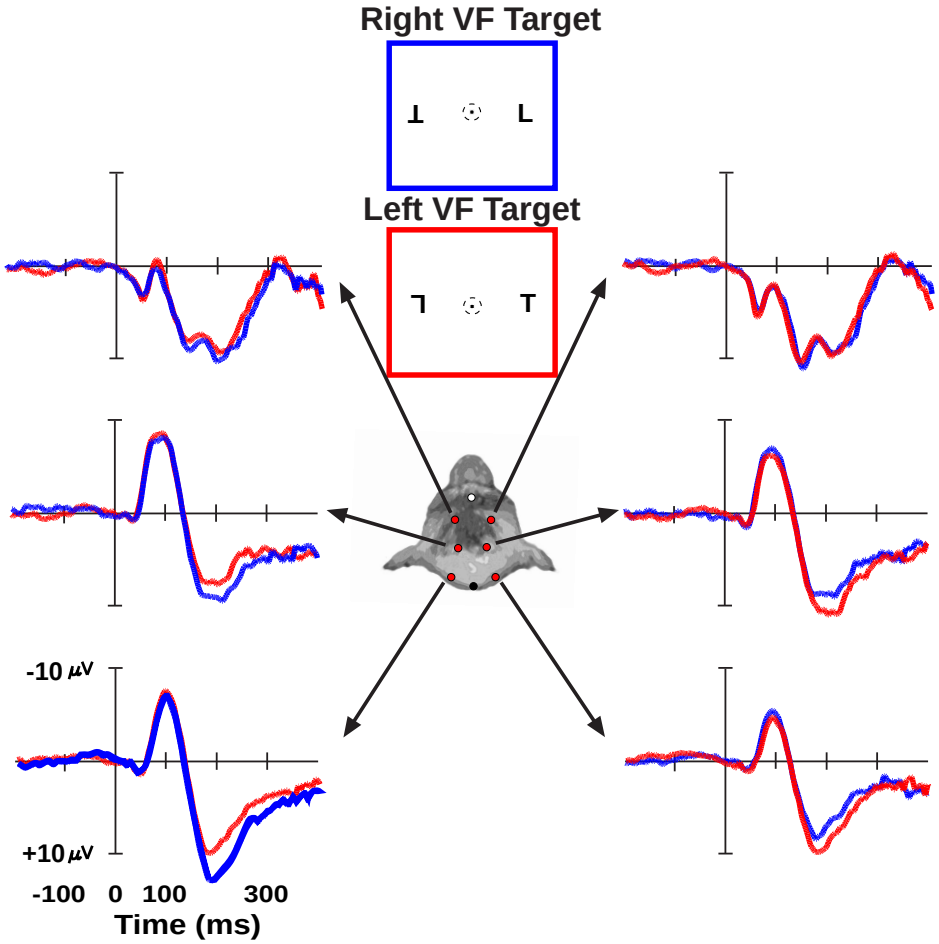

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