

ABSTRACT

Title of dissertation: Spatial and Temporal Characteristics of
Electromagnetic Activity in the Brain Prior to
Reaches to Visual Targets

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The electromagnetic activity in the brain prior to reaching movements has been studied extensively in monkeys using direct cell recordings from neurons and in humans using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). The research presented here extends those lines of investigation into human reaching movements using magnetoencephalography (MEG), an advanced electrophysiological tool that allows analysis of higher frequencies than EEG and better temporal resolution than fMRI. Several new findings of signature events in the electromagnetic activity in the brain associated with visuomotor and cognitive components of a reaching movement are reported in this study. The most fascinating is related to target location: an electromagnetic power increase in the beta band (15-25Hz) occurs in the left intraparietal sulcus 2.5 seconds prior to movement for contralateral targets only – not for ipsilateral targets. It is claimed here that this is electrophysiological evidence of a default bias toward reaches to ipsilateral targets, also known as the “proximity-to-hand effect.”

SPATIAL AND TEMPORAL CHARACTERISTICS OF ELECTROMAGNETIC ACTIVITY IN THE BRAIN PRIOR TO REACHES TO VISUAL TARGETS

by

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Dedication: This represents the culmination of more than ten years of study and work, during which I was inspired, encouraged, and supported by my two wonderful daughters, Olivia and Abigail. Their brilliant minds, kind hearts, and strong character continue to inspire and awe me and make me so incredibly proud. This dissertation represents a meaningful accomplishment for me and it is dedicated to Olivia and Abigail who mean everything to me.

Table of Contents

I. Introduction	pg 1
II. Background: Literature Review	pg 5
III. Dissertation Aim and Hypotheses	pg 42
IV. Experimental Methods and Procedures	pg. 44
V. Data Processing	pg 50
VI. Results	pg 57
VII. Single Trial Analysis	pg 93
VIII. Conclusions	pg 100
IX. Future Studies	pg 115
X. References	pg. 117

List of Figures

- Figure 1: Schematic representation of the time course and components of the Motor Related Cortical Potential prior to voluntary movement. Pg 12
- Figure 2 Schematic representation of Libet's findings. Neural preparation in the brain can begin 1 second before movement onset. The conscious experience of intending the movement begins on average before movement. Pg16
- Figure 3: Contingent negative variation waveforms, beginning four seconds prior to S2 response. Late wave shows larger amplitude for faster response (Brunia and Vingerhoets 1980) Pg 19
- Figure 4: Temporal evolution of B) Beta ERD, C) ERD of mu rhythm, D) rectified EMG channel for one subject during thumb movement. Pg 21
- Figure 5. Nested pathways of reaching network from PMd to Parietal cortex. (Picard and Strick 1996) Pg 30
- Figure 6. Top. Reach region (MIP) in macaque brain. Below. Human analog of MIP, the Parietal Reach Region, (PRR). From Connolly J, Andersen R, Goodale M 2003 Pg 32
- Figure 8. Subject during magnetoencephalography recording. Pg 42
- Figure 9. Subject breaks optical beam on the right with a reach to the right spatial field. Pg 43

I. Introduction: Mindlessness and Margaritas at Happy Hour at Tippy's Taco Shack

Wittgenstein posed the famous query, “What is left over if I subtract the fact that my arm goes up from the fact that I raise my arm?” (Wittgenstein L 1958) It is a philosophical question that arises from one of the paradoxes of neuroscience: movement, the most transparent, directly measurable, evidence of human agency, is itself largely under the control of implicit processes, blocked off and hidden, even from the actors themselves. The covert nature of the human motor system makes the neurological processing that precedes voluntary movement particularly difficult to probe.

Indeed, human movement is not unlike the closed watch Einstein used to describe his efforts at understanding the universe, "we are somewhat like a man trying to understand the mechanism of a closed watch. He sees the face and the moving hands, even hears it ticking, but he has no way of opening the case. If he is ingenious he may form some picture of the mechanism which could be responsible for all the things he observes, but he may never be quite sure his picture is the only one which could explain his observations. He will never be able to compare his picture with the

real mechanism and he cannot even imagine the possibility of the meaning of such a comparison."

In a similar way that few people know much about what is going on inside their watches, people typically know or give little attention to the details of their movements. At a conscious level, the human motor system appears to be organized around higher-order cognitive states such as intention or "wish," as Freud called it. There is generally little awareness of further details: the precise metrics and kinematics, the seamless timing and assembling of dynamic combinations of forces and muscle groups that must be recruited and ordered just-so when we act are mostly unknown to us. For instance, the act of reaching to drink from a glass requires a much different motor program than the act of reaching to throw a glass, but typically people do not concern themselves with those differences. Rather, all that is held in mind is the goal. The unconscious mechanisms that subserve the human motor system take care of the rest.

The research completed here was designed to probe the 'black box' of neurological processing that precedes the initiation of movement. Experiments were modeled to explore action that in real life would occur something like this:

You're at happy hour at Tippy Taco Shack looking out on the coast of Encinatas, Mexico, sipping a strong margarita and snacking on home-made tortilla chips. You reach to pick up a chip from the basket to your right on the bar. Occasionally you reach to pick up the margarita sitting to your left on the bar. That's all you're doing, casually fulfilling your desire for salt and alcohol and pink and purple sunsets--or so you think.

Actually, each time you make these carefree moves, you are in fact resolving physical uncertainty in the space time continuum. More importantly to those who seek to study and understand the human brain, you are using a mix of hard-wired circuitry that evolved on the savannas of Africa over millions of years and an ad hoc cocktail of neurotransmitters and receptor-forming-dendrites that can create new pathways in the brain on a time scale of minutes, to resolve fundamentally human questions. Time for another sip of that margarita.

Ok. Now where were we? Fundamental questions to resolve before you can make your move at the bar toward happy hour happiness, like:

WHICH one do you want this time, a chip or a sip?

WHERE in 3-d space is this target you've selected?

***HOW** does your hand get there since it can't see and has no GPS to call out the step by step navigation?*

And then there's the hard question:

***WHO** is making up your mind anyway? Who is in charge? The drink? The chip? Your hand? A part of your brain? Your whole brain?*

By deductive reasoning, it is clear that you must have answers to all of these questions in order to accomplish your goals at Tippy's Tacos. By experience, we know that we hardly think about things like this at all. Evidence is needed then to settle the contradiction of what's going on at this taco shack in Encinatas. We proceed with an inquiry into the covert cognitive processing that precedes reaching for chips and a margarita by posing two questions reminiscent of those from a 1972 investigation of a different set of covert operations:

WHAT does your brain know and **WHEN** does it know it?

The research presented here utilized magneto-encephalography (MEG), one of the modern tools of neuroscience that have allowed investigation of the black box of covert activity occurring in the brain. Specifically, it was used to examine when and where information is encoded in the brain about two aspects of

reaching movements: the selection of a target of a reach and the spatial localization of the target of a reach. Additionally, imagined reaches were analyzed for characteristic patterns. Finally, pattern recognition techniques were used with single trial data to construct real-time decision prediction models that could someday make it possible to actually “read your mind” about whether you want a chip or a margarita before you have moved a muscle.

II. Literature Review

II.A. Neuropsychological Evidence of the Covert Nature of Events Preceding Voluntary Movement

Feedback and feedforward mechanisms for information processing are common in the brain. The structure of the motor control system, in particular, relies to a great extent on anticipatory programs and forward models. This type of advance preparation provides the ability to respond more quickly to events in the environment, conferring clear advantage from both an evolutionary and everyday perspective.

Forward models in animal studies are established in detail at the neuronal level. It has been shown that aspects of movement are planned and *predicted* in advance. (Hollerman Tremblay Schultz 2000;

Schultz Tremblay Hollerman 2003; Graybiel 1998; Schultz 1997; Aosaki Graybiel Kimura 1994) Advanced programming also appears to be the mechanism that converts repetition of movement sequences into skills or habits. The movements are programmed and stored as seamless 'chunks' to be automatically executed when needed as a whole unit. (Barnes TD, Kubota Y, Hu D, Jin DZ, Graybiel AM 2005; Kennerley SW, Sakai K, Rushworth MF. 2004; Sakai K, Kitaguchi K, Hikosaka O. 2003; Goldstone RL. 1998; Graybiel 1998; Kermadi and Joseph 1995; Aldridge JW, Berridge KC. 1998). Less detail is known about the mechanisms of implicit forward models in human behavior, but evidence is plentiful that such operations exist. The procedural memory system of the human brain has been shown to be the neural substrate for the acquisition of cognitive and motor skills and habits and is characterized by anticipation and feed forward mechanisms. As described in a paper by Pascual-Leone, Grafman and Hallett (1995), "Procedural learning may be used to refer to the process by which repeated exposure to a task, regardless of whether the subject does or does not form a conscious memory of this exposure, eventually results in improved performance on that task." Studies have shown, for example, that reaction times for movements are significantly faster when information about the direction or distance of the target of a

movement is available prior to movement (Deiber MP et al 1996, Bock and Arnold 1992). Reaction times also decrease in motor tasks even when the information about upcoming moves is *implicitly* given, such as in the classic Serial Reaction Time (SRT) paradigm. In this task, subjects execute cued keypress sequences in two conditions: some blocks contain an implicit pattern, while other blocks are completely random. The typical result is that reaction times improve in the blocks with the implicit pattern, but not in the blocks with random cues, implying that the difference is due to the feedforward effects (Honda M et al 1998; Wilkinson L and Jahanshahi M 2007). Similarly, implicit forward models have been documented in studies with eye movements. Efferent copies of eye movement commands have been shown to implicitly update gaze signals that provide a frame of reference for the hand during reaching movements (Pierrot-Deseilligny et al 2003 Lewis RF Gaymard BM Tamargo RJ 1998 Wurtz RH Sommer MA 2006). The efferent copy enables a person to respond to environmental disturbances even before the subjective experience of the disturbance has occurred, as demonstrated in a series of experiments by Castiello and Jeannerod (1991). Motor responses to perturbations of the target in a reaching task were measured and subjects were asked to report their awareness of

the perturbation with the vocalization, “tah”. Corrections in trajectory preceded subjective reports of the target change by 150-300 ms. Studies of forward models in reaching experiments have also shown that the motor system's implicit anticipatory pathways can be powerful enough to override an explicit, volitional “intention” or “will” to move. Pisella et al (2000) asked subjects to point to targets that could unexpectedly change location or color. There were stop signals to create conflict between automatic correction systems and voluntary motor control. Corrections were made by subjects, however, even when instructions were to stop. The correction system for on-line motor control automatically activated even when subjects had another motor intention. Such evidence implies that feed forward models, or stored motor programs, may dominate when they are in competition with volitional, “willed” processes.

Further evidence of the mechanical nature of ‘voluntary’ movement was demonstrated by the subconscious initiation of movement in a study that compared reaction times to perceived and unperceived visual stimuli (Taylor, 1996). Subjects were asked to make a movement as soon as the stimulus appeared, with half of the reaction time tasks containing a masked stimulus that was not

perceived by the subjects. The masked stimulus occurred 50 msec before the larger, perceived stimulus. Reaction times for the perceived and unperceived stimuli were similar, suggesting that unperceived stimuli may trigger “voluntary” movement. This subservience of volitional control to implicit motor commands exhibited by normal subjects in the preceding studies seems similar in some ways to the loss of willed behavior seen in a disorder due to damage of the parietal cortex, known as alien hand syndrome. In this condition, “the ongoing activity exerts a more powerful influence than the intended action,” (Pisella et al 2000) leading patients to mistakenly attribute self-generated actions of their own hand to external forces. For example, Brion and Jedynak (1972) described patient MA this way, “M.A... was putting on his shirt with difficulty, and looking for the sleeves behind his back, when, incidentally, he took hold of one hand with the other; he pulled on it, tried to get away and said, “Let go of my hand. You’re keeping me from getting dressed.” K Goldstein wrote in 1908 of another patient with alien hand syndrome following a stroke, “on one occasion the hand grabbed her own neck and tried to throttle her, and could only be pulled off by force. Similarly, it tore off the bed covers against the patient’s will.....She soon is

complaining about her hand; that it is a law unto itself, an organ without will....”

Evidence from alien hand syndrome as well as other neuropsychological studies of humans with optic ataxia and lesions in posterior parietal cortex (PPC) supports the claim that the posterior parietal region is an important neural substrate for the planning and on-line control of reaching movements (Medendorp, Goltz, Crawford, Vilis 2005 ; Crawford JD, Medendorp WP, Marotta JJ. 2004; Karnath and Perenin 2005).

The neuropsychological evidence just reviewed indicates that aspects of human “voluntary” movement can be implicitly programmed in advance and are not always under volitional control. It also supports the posterior parietal cortex as a region of interest in the study of the related cognitive events that occur prior to reaches. More precise measures of the *time* course in which specific parameters of a movement are planned relative to the time that movement is initiated can be determined with electrophysiological experiments, as examined next.

II. B. Electrophysiological Evidence of Events Preceding Voluntary Movement

The existence of electrical currents in the brain was discovered in 1875 by an English physician, Richard Caton, using exposed brains of rabbits and monkeys. In 1924 Hans Berger, a German neurologist, used ordinary radio equipment to amplify the electrical activity measured on the scalp of a *human* brain. This pioneering work opened up the possibility of evaluating claims about the operations taking place prior to movement without relying solely on parameters of the output such as speed and accuracy. This possibility is being realized today with electrophysiological measurements made by three primary methods: electric fields due to electric currents in the brain are recorded from the surface of the scalp with electroencephalography (EEG) or from a sub-dural grid with electrocorticography (ECOG); and, magnetic fields created by the electric currents in the brain are recorded non-invasively at the scalp using magnetoencephalography (MEG).

Since 1964 when Kornhuber and Deecke first described a negative cortical potential that began 1.5 seconds prior to the onset of a self-paced movement, the motor related cortical potential, the lateralized readiness potential (Coles and Gratton 1986), the contingent

negative variation (Walter et al 1964) and event-related synchronizations/desynchronizations (Pfurtscheller and Lopes da Silva 1999) have become the most-established electrophysiological phenomena associated with human voluntary movement.

II.B.1 Motor Related Cortical Potentials

Motor-related cortical potentials (MRCPs) are stereotyped phenomena that are often detected beginning two seconds prior to voluntary movements. They consist of slow changes in the measured voltage over the sensorimotor cortex as seen in the time series trace in figure 1.

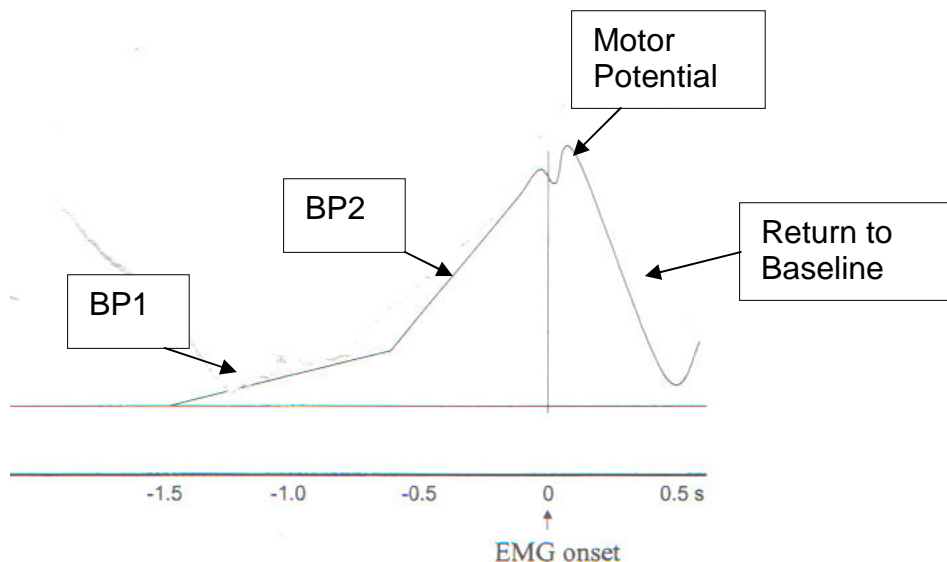


Figure 1: Schematic representation of the time course and components of the Motor Related Cortical Potential prior to voluntary movement.

The MRCP has four distinct stages: an early slowly rising negativity called the *bereitschaftspotential*, labeled BP1; followed by the more steeply rising BP2; a peak just after movement onset labeled Motor Potential (MP); and a return to baseline (Wheaton L et al 2005, Deecke L and Kornhuber HH. 1978, Shibasaki H, et al 1980). MRCPs are detected by averaging multiple events in the time domain and generally require at least 40-50 events to allow detection of the signal within the noise. The *bereitschaftspotential* appears to be a phenomenon restricted to self-initiated or predictable, stimulus-induced movements. It has not been established in conditions of unpredictable, stimulus-induced movements (Jahanshahi M et al 1995 Papa SM 1991). A 2004 EEG study of gestures pushed back the time window of movement-related brain activity even earlier with a demonstration that activation in the posterior parietal area contributes to the MRCP up to 3 seconds before movement onset (Wheaton LA et al 2005).

Simple movement parameters such as force (Kutas and Donchin 1980) and rate (Mackinnon et al 1996), as well as higher order processes such as movement complexity (Simonetta et al 1991) affect the slope, amplitude and latency of the *bereitschaftspotential* (BP) component of the MRCP. These variables of the BP have been shown to be abnormal

in neurological disorders such as Parkinson's Disease (Dick et al 1989; Jahanshahi et al 1995; Cunnington et al 1995; Praamstra et al 1996a), Huntington's Disease (Johnson et al 2001), dystonia (Van der Kemp et al , 1995; Deuschl et al 1995), and cerebellar disease (Shibasaki et al 1978; Verleger et al 1999, Wessel et al 1994) among others. The generators of the MRCP are generally agreed to be sensorimotor cortex and SMA (which includes pre-SMA, SMA proper and the anterior cingulate motor area). The Bereitschaftspotential is typically bilateral at onset and later, during the motor potential, becomes predominantly contralateral to movement.

A host of processes including motor preparation, anticipation, attention, intention, motivation, effort, and timing are proposed to contribute to the MRCP, however, it has proven difficult to disentangle the relative contributions of these processes and relate them specifically to the slope, latency or amplitude of the MRCP.

The exception is the effect of right vs. left hand on the MRCP. The lateralized readiness potential (LRP) is a measure of the asymmetric brain activity associated with left or right hand movements that is consistently observed. It is determined through a double subtraction procedure as follows (Eimer 1998):

- 1) Activity from electrodes on the left side of motor cortex are

subtracted from activity recorded on the right side of motor cortex separately for the left hand movement condition and for the right hand movement condition

2) Then that value that was calculated in step one for the left hand condition is subtracted from the value calculated in step one for the right hand condition.

Since the 1980's many research programs have focused on investigating the relationship between the MRCP and the urge to initiate movement. In a classic experiment often referred to as "Libet's Clock" (Libet B, Gleason CA, Wright EW, Pearl DK. 1983), electroencephalography (EEG) recordings were made while subjects made spontaneous voluntary movements. The subjects were asked to report the time on a clock when they felt the first awareness of the urge to move. This time was called W for "will". The MRCP was analyzed for each subject and compared with time, W. In a striking result, it was found that W occurred 300-500 ms prior to the subject's reported perception of the intention to move, W. See Figure 2.

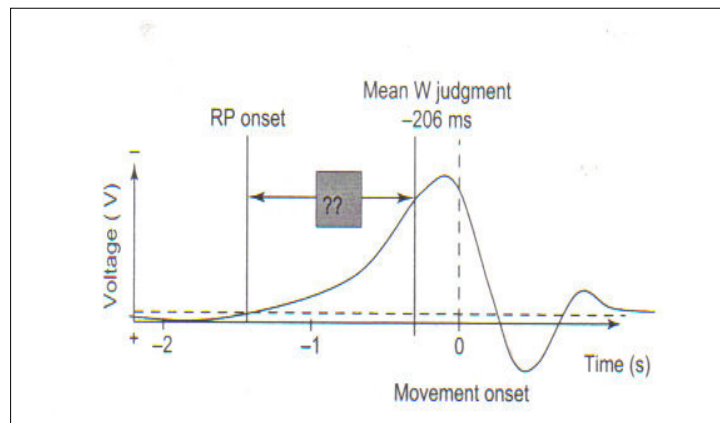


Figure 2 Schematic representation of Libet's findings. Neural preparation in the brain can begin 1 second before movement onset. The conscious experience of intending the movement begins on average before movement.

These findings appeared to demonstrate that the onset of electrical activity associated with movement preparation occurred from a third to a half second prior to the awareness of the intention to move. This evidence seems to suggest that conscious intention, and more generally, the perception of free will, is a mere echo of events planned and initiated covertly by the human brain. The authors concluded, "that cerebral initiation of a spontaneous, freely voluntary act can begin unconsciously, that is, before there is any (at least recallable) subjective awareness that a 'decision' to act has already been initiated cerebrally" (Libet et al 1983). These results were reproduced by Haggard and Eimer (1999) using the lateralized

readiness potential (LRP, the difference in the voltage of right and left central regions). In a task in which subjects moved either their right or left hands, the onset of the LRP always preceded the subjective awareness of the intention to move. These findings demonstrated that, in addition to movement *intention*, movement *effector selection* also might precede awareness.

Evidence for subliminal motor activation processes was also obtained using LRPs in a paradigm that evaluated responses to masked stimuli. When two stimuli are presented quickly and close together the first stimulus is masked; in other words, it is not consciously perceived. Leuthold and Kopp (1988) recorded EEG during a movement experiment in which target location determined response hand. A masked stimulus of a target location preceded a second, perceived, stimulus that also indicated a target location. Both stimuli that were congruent and those that were incongruent with the second stimuli were presented. The LRPs revealed that the masked stimuli triggered an early activation of the LRP. Moreover, on incongruent trials early *incorrect* response activation was observed, whereas early *correct* response activation was present for congruent trials. This evidence supports the idea that sensory stimuli have immediate access to motor response pathways, even though

conscious perceptual analysis of the stimulus does not take place.

*note on detection of MRCP using MEG

In the past it has been difficult to detect the early phases of the MRCP, the bereitschaftspotential (BP), using magneto-encephalography because of cancellation that occurs at the vertex from opposing tangential sources; however, in 1999 it was reported that the BP was detected at -1.9 to -1.7 in the supplementary motor area using MEG (Deecke L, Lang W, Uhl F, Beisteiner R, Lindinger G, Cui RQ.1999).

II.B.2 Contingent Negative Variation

The contingent negative variation, (CNV), is a slow negative wave that begins in the interval between a warning (S1) cue and a "go" (S2) cue (Walter et al 1964). It is considered to have two components (Hamano et al 1997 Connor and Lang 1969). It has been posited that the first component is related to stimulus processing, anticipation or timing; while the second component has been proposed to be related to anticipatory attention, timing or motor preparation (Boxtel and Brunia 1994, Macar and Besson 1985, Loveless 1979). These are hypotheses only. As yet, no general consensus or clear evidence disentangles the putative processes associated with the phenomenon.

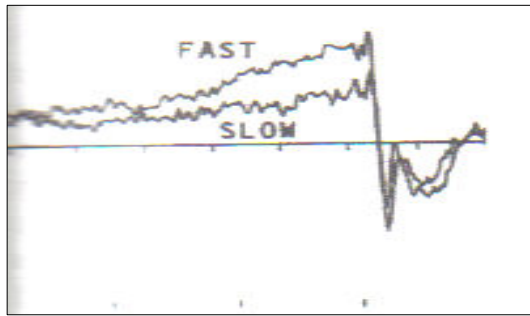


Figure 3: Contingent negative variation waveforms, beginning four seconds prior to S2 response. Late wave shows larger amplitude for faster response (Brunia and Vingerhoets 1980)

II.B.3 Event Related Synchronization and Desynchronization (ERD and ERS)

II.B.3.a Alpha and Beta band ERD and ERS

In 1934 Lord Adrian published a paper on "human brain waves" and identified regular oscillations around 10 - 12 Hz which he termed "alpha rhythm." This is a type of electrophysiological phenomenon which describes electrical activity in the frequency domain; that is, instead of looking at the time course of events, the data have been temporally transformed to measure fluctuations that happen periodically during a particular time window. Decreases in power in the frequency domain are termed Event-Related-Desynchronization (ERD). Increases are termed Event-Related-Synchronizations.

ERD in the alpha band (8-13 Hz), as well as the beta band (13-30 Hz), routinely occurs about two seconds before movement onset over contralateral sensorimotor areas (Toro C, et al 1994, Pfurtscheller 1981, Pfurtscheller G, Lopes da Silva 1999, Jurkiewicz MT et al, 2006 Leocani L et al 1997). Alpha band activity over the sensorimotor cortex is often referred to as the “mu” band. Beta band ERD has been found to be slightly anterior to mu band ERD, suggesting beta ERD may be generated in pre-rolandic motor areas. Beta band has a more discrete somatotopic distribution than alpha band ERD. Alpha ERD appears to be generated in post-rolandic somatosensory cortex with a more diffuse distribution (Pfurtscheller G, Lopes da Silva, 1999; Pfurtscheller G. Stancak Jr., A, Neuper C 1996; Salmelin R, Hamalainen M, Kajola M, Hari R, 1995 ; Crone, NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, Lesser R 1998). Beta ERD is contralateral from the onset and becomes bilateral around execution (Crone, NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, Lesser R ,1998 ; Babiloni C, Carducci Filippo, Cincotti Febo, Rossini Paolo, Neuper C, Pfurtscheller G, Babiloni F,1999 ; Toro C, Deuschl G, Thatcher R, Sato S, Kufta C, Hallett M 1994). Increases in power, known as Event-Related-Synchronization (ERS), occur just after movement onset in the beta band with somatotopic distribution over contralateral sensorimotor cortex (Pfurtscheller G, Lopes da Silva 1999; Leocani L, Toro C, Manganotti P, Zhuang P, Hallett M1997; Toro C, Deuschl G, Thatcher R, Sato S, Kufta C, Hallett M 1994; Pfurtscheller 1981 ; Salmelin et al 1995; Jurkiewicz MT, Gaetz WC, Bostan AC,

Cheyne D 2006). These same patterns of ERD and ERS occur during imagination of movement (Pfurtscheller G, Neuper C, Brunner C, Lopes da Silva FH 2005).

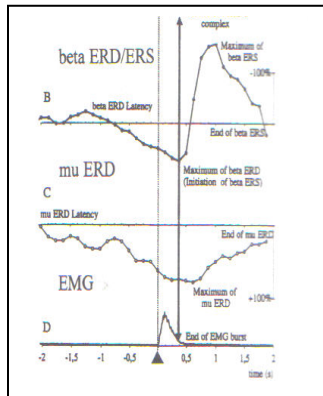


Figure 4: Temporal evolution of B) Beta ERD C) ERD of mu rhythm D) rectified EMG channel for one subject during thumb movement.

II.B.3.b Gamma band ERS

Changes in power in the gamma band have also been reported (Pfurtscheller G, Lopes da Silva 1999), typically close to movement onset, although not as consistently. It is difficult to study them with EEG because of the low amplitudes and because the skull filters out high frequencies in EEG recordings (Nunez PL and Katznelson RD, 1981). With MEG, gamma oscillations have been reported in M1 and S1 during and after movement (Salenius S, Salmelin R, Neuper C, Pfurtscheller G, Hari R 1996;

Ihara A, Hirata M, Yanagihara K, Ninomiya H, Imai K, Ishii R, Osaki Y 2003). In ECOG, gamma ERS has been reported ranging from 30-100 Hz, also both before during and after movement (Crone N, Miglioretti, Gordon, Lesser 1998; Pfurtscheller G, Neuper C, Kalcher J 1993; Szurhaj W 2005). Compared with alpha and beta ERD, the topographical patterns of the gamma ERS are more discrete and somatotopically specific and only occur over *contralateral* sensorimotor cortex while alpha and beta changes can be observed over ipsilateral cortex as well as contralateral cortical areas . (Crone N, Miglioretti, Gordon, Lesser 1998; Pfurtscheller G, Neuper C, Kalcher J 1993) .

Gamma oscillations have been consistently reported in movement experiments with monkeys using local field potentials (LFP's), which correspond to the collective discharge of local neuronal clusters on a similar scale as those sampled by EEG and MEG (10^4 - 10^6 neurons). As reported in a 2005 study, (Scherberger H, Jarvis MR, Andersen RA. 2005) an increase in synchronization (ERS) in local field potentials of frequencies up to 100 Hz was observed in the *planning phase* and at movement onset in a reaching task with monkeys. Donoghue et al (1998) reported high frequency oscillations (20-90Hz) in their monkey studies and suggested they were more likely to be related to movement planning than motor execution

(Donoghue JP, Sanes JN, Hatsopoulos NG, Gaal G, 1998). MacKay and Mendonca (1995) reported gamma ERS at movement onset in a reaching task with monkeys. Mehring et al (2003) and Shenoy et al (2003) were able to decode movement direction in reaching tasks with gamma oscillations in the local field potentials (Mehring C, Rickert J, Vaadia E, Cardoso de Oliveira S, Aertsen A, Rotter S 2003; Shenoy KV, Meeker D, Cao S, Kureshi SA, Pesaran B, Buneo CA, Batista AP, Mitra PP, Burdick JW, Andersen RA. 2003). LFP's in the range of high gamma up to high frequency oscillations (HFOs) were recorded in monkeys' motor cortex during hand movements. Eighty Hz - 200 Hz oscillations were relevant for discriminating four directions of hand movements (Richert et al 2005).

Although it has been posited that oscillations in the gamma band serve to link spatially distant cell assemblies (Singer 1993), it has been shown by Kopell et al (2000) that gamma oscillations are not able to synchronize over the long conduction delays corresponding to signals traveling a significant distance in the brain. These authors suggest that gamma rhythms are used for relatively local computations, whereas the beta band is used for higher level interactions involving distant structures (Kopell N. Ermentrout GB Whittington MA, Traub RD, 2000). In general, changes in power in the electromagnetic fields recorded by EEG, MEG and ECOG are thought to reflect dynamic shifts in

synchronization of firing of neuronal ensembles. These shifts in oscillatory properties have been found to parallel changes in functional states of the brain, suggesting such phenomena may represent the organization of neuron populations into temporary functional groups, depending on the momentary computational demand.

II.C Electrophysiological Research of Brain Activity Preceding Reaching Movements

Reaching is one of the most complex of common human movements. The complexity arises from several factors that include the need for:

- calculation of kinematics in 3 dimensional space,
- dynamic musculoskeletal control over multiple muscle groups with a large number of degrees of freedom
- and, perhaps most interesting from a systems neuroscience perspective, the integration and even hybridization of motor and visual inputs to the brain.

Specifying how those visual and motor inputs are combined or parceled out by the brain is a monumental and intriguing challenge all its own. Even as various measures and associations are made

between physiological phenomena and functional properties, it should always be with the qualifier that the actual primitives of the neural coding are something we may not even be able to imagine. Indeed, identifying the fundamental functional units of a reach encoded by the brain will bring a deeper understanding of the brain than the relatively simple task of distributing them, once discovered, onto the anatomical maps.

Currently the functional architecture of a 'reaching system' model is being constructed mostly with components that are strictly motor or strictly visual, although some studies have discovered neurons with receptive properties that are a hybrid of both (Ferraina S, Johnson PB, Garasto MR, Battaglia-Mayer A, Ercolani L, Bianchi L, Lacquaniti F, Caminiti R 1997; Buneo C, Jarvis M, Batista A, Andersen RA 2002; Crawford JD, Medendorp WP, Marotta JJ, 2004). Purely motor system variables that have been found to modulate neuronal activity during a reach include effector (laterality, dominance), direction, load, velocity, force, muscle length and joint angles. Visual system variables modulated by a reach include target localization in 3-d space, target location (peripheral vs foveal), target size (metric vs relative), persistent vs remembered targets, and target motion (covert displacement, smooth pursuit). In addition to purely visual and purely motor properties, single cell studies with monkeys have

demonstrated that parietal and frontal neurons appear to have combinatorial properties, that is, they are tuned to features of both sensory and motor inputs during a reach (Lacquaniti 1997; Crawford JD, Medendorp WP, Marotta JJ, 2004). For example, certain neurons in the intraparietal sulcus appear to be tuned to such a hybrid dimension. Their activity can be used to read out the spatial correspondence between the image on the retina and the position of the hand, referred to as the motor error vector (Ferraina S, Johnson PB, Garasto MR, Battaglia-Mayer A, Ercolani L, Bianchi L, Lacquaniti F, Caminiti R 1997; Buneo C, Jarvis M, Batista A, Andersen RA 2002).

Such hybrid features are thought to arise from the computational demands specific to organizing 2-d visual information from the retina and proprioceptive information from the joints and muscles of the body into a 3-d map that can be used to direct the muscles in the arm to the target. As an example of the complexity of the computations, consider that to perform a transformation from retinal to body-based coordinates would require not only combining information about the retinal location of an image and the direction of gaze relative to the body, but during head movements the transformation must take into account a *translation* with respect to the retinal reference frame and a *rotation* with respect to the shoulder

reference frame. The most commonly accepted working theory on how this gets done is that the various inputs, in retina-, shoulder-, arm- or hand based coordinates are re-mapped either through a series of transfer functions or a parallel network of transfer functions. Single cell recordings with monkeys have yielded some possible encoding schemes in this process. In area 7a neurons' firing rates depend on both the location of the target in retinal coordinates and the direction of gaze. The signal corresponding to gaze direction is represented as a constant input to all neurons irrespective of their preferred stimulus angle. Shifts in gaze then result in an overall gain modulation of the retinotopic visual field. This gaze-dependent gain field combines two different input signals in a non-linear, multiplicative way (Buneo CA, Andersen RA 2005). In the parietal reach region (PRR), area 5, a different coding scheme appears to be in place. Those neurons were found to represent the vector subtraction of the hand location from the target location, with both locations in retinal coordinates. This vector difference has been called the motor error vector (Buneo C, Jarvis MR, Batista AP, Andersen RA 2002; Ferraina S, Johnson PB, Garasto MR, Battaglia-Mayer A, Ercolani L, Bianchi L, Lacquaniti F, Caminiti R 1997).

Related to the general challenge of identifying the functional primitives of behavior, there is also the difficulty of interpreting claims

about anatomical regions that are purported to be the “neural correlate” of a particular mental state or event. For example, consider the anatomical regions reported in recent papers to subserve target selection of reaching movements. Cisek and Kalaska titled their report published in 2005, “Neural Correlates of Reaching Decisions in *Dorsal Premotor Cortex*”, after demonstrating that neurons in that cortical region of monkeys were modulated by the direction and selection of a reach target (Cisek P and Kalaska JF 2005). Yet, after a similar study of reaching movements, a different set of authors claimed in 2007, “Target Selection signals for arm reaching in the *posterior parietal cortex*” (Scherberger H, Andersen RA, 2007).

Similar ambiguity exists in the literature regarding claims of lateralization of target location processing. Two independent PET (positron emission tomography) studies concluded that the representation of spatial information about a target is localized to the *right* hemisphere, specifically the temporo-parietal region (Butler A et al 2000; Kertzman et al 1997). However, an EEG study of externally triggered pointing and event-related lateralization reported no hemispheric effects. Instead it found that a premotor focus of the ERL was contralateral to the arm used for pointing while a parietal cortex focus was *ipsilateral* to the *target* (Berndt I, Franz VH, Bulthoff HH, Wascher E 2002). An

fMRI study reported that parietal activation was found to be significantly greater to targets *ipsilateral* to the *hand* (Medendorp WP Goltz HC, Crawford JD, Vilis T, 2004).

Most of the details about the anatomical pathways that have been implicated in reaching movements come from studies with monkeys. Single cell or local field potential recordings are often made during 'instructed delay' tasks. This is a paradigm which has the same structure as the S1/S2 paradigm discussed earlier in the section on contingent negative variation responses. In these tasks, an instruction stimulus, usually a visual cue, specifies information about the movement, but the subject has to wait for a second cue which is the instruction to perform the movement. These studies have revealed a highly nested cortical network of connections between posterior parietal cortex and dorsal premotor cortex that underlies the covert processing that precedes reaching movements (Hoshi E and Tanji J 2007; Johnson PB, Ferraina S, Caminiti R 1993; Picard and Strick 1996; Caminiti et al 1996; Battaglia-Mayer et al 2001) Parallel cortico-cortical pathways from the superior parietal lobule to PMd form a gradient with the most rostral regions of PMd connected with the most caudal regions of PPC and moving inward until the most caudal region of PMd connects with the most rostral region of PPC (Johnson PB, Ferraina S, Caminiti R 1993). See figure 5.

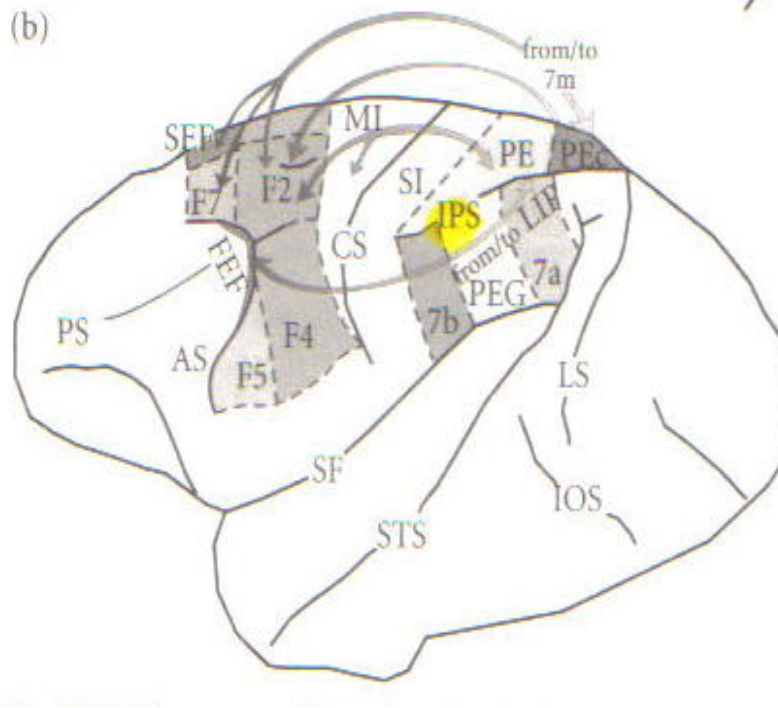


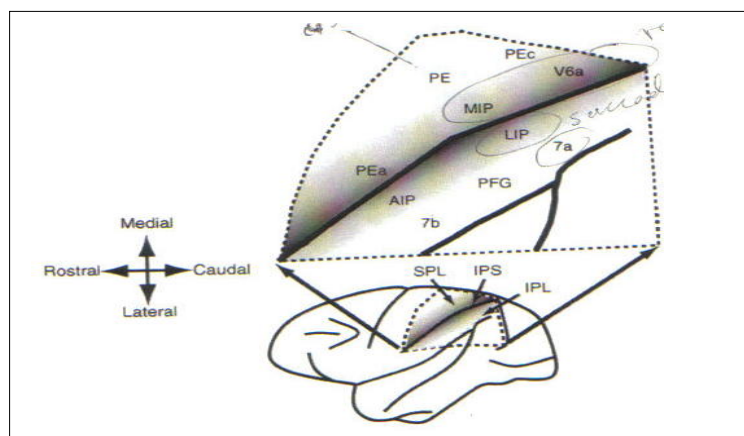
Figure 5. Nested pathways of reaching network from PMd to Parietal cortex. (Picard and Strick 1996)

Human brain imaging studies also support a distributed frontal-parietal network that subserves reaching movements (Medendorp Goltz, Crawford, Vilis, 2005; Kertzman C, Schwarz U, Zeffiro TA, Hallett M1997), as have studies with patients with brain lesions diagnosed with optic ataxia (Karnath HO and Perenin MT 2005)

Saccades and reaches are tightly coupled movements that could reasonably be considered as an action unit. Double dissociation

studies, however, have demonstrated that the intent to saccade and the intent to reach are subserved by different regions of the posterior parietal cortex. The lateral intraparietal region (LIP) neurons have been associated with the intent to saccade and the parietal reach region (PRR) neurons have been associated with the intent to reach. (Snyder LH, Batista AP, Andersen RA, 1997). The parietal reach region (PRR) in monkeys was also shown not only to encode the intention to reach, but to have a response field corresponding to the particular target location of the hand in *eye-centered coordinates* (Andersen R and Buneo C 2002; Buneo C, Jarvis MR, Batista AP, Andersen RA, 2002).

Functional MRI activation showing the human homolog of PRR in its spatial selectivity for the target of a reach was found to be in parietal cortex, situated anterior to the parieto-occipital sulcus, posterior to the sub-parietal sulcus and medial to the intra-parietal sulcus (Connolly J, Andersen R, Goodale M Exp Brain Res. 2003). See figure 6.



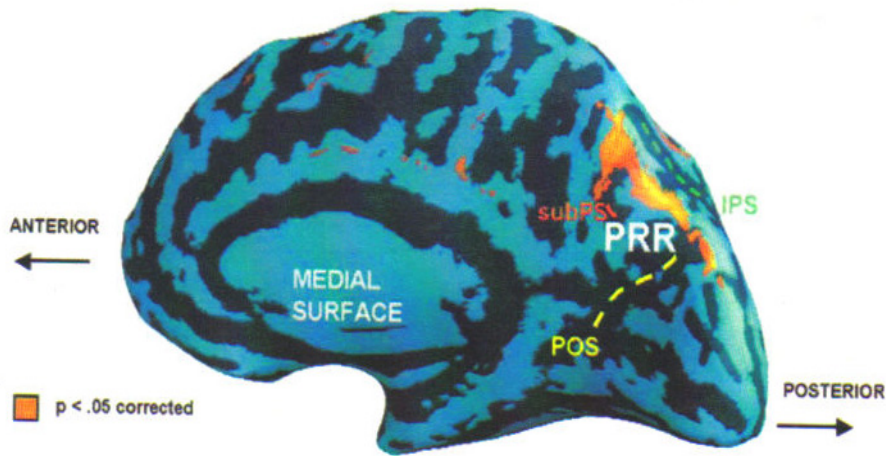


Figure 6. Top. Reach region (MIP) in macaque brain. Below. Human analog of MIP, the Parietal Reach Region, (PRR). From Connolly J, Andersen R, Goodale M 2003

II. D. Free Choice Vs Instructed Conditions in Movement Tasks

Target Selection

Decision making is a crucial aspect of cognitive behavior that has spawned volumes of theories on its neural basis. The results of the diverse types of tasks used to test the theories are as wide-ranging as the tasks and theories themselves. Visuomotor decision making tasks have generally focused on identifying the spatial distribution of

decision processing. For example, movements made by subjects under “free choice” or “instructed” conditions have been associated with different levels of activity in SMA (Deiber MP et al 1991). A PET study of joystick movements reported that the mean SMA activity was higher in a condition of selecting from four possible motions than in a condition of fixed motions (Deiber MP et al 1991). In this same task, the Bereitschaftspotential was found to have higher amplitude in the free choice condition compared with the instructed condition (Praagstra et al 1995, Töge et al 1995). This result was replicated with a finger sequence task by Dirnberger et al (1998). This study also showed a larger lateralization of the BP in the free choice condition. The brain regions associated with free selection of a movement were investigated with repetitive transcranial magnetic stimulation (Hadland et al 2001). The results suggested that the dorsolateral prefrontal cortex and the medial frontal cortex were important during response selection. This agrees with the generally held view regarding targeting decisions that medial premotor areas underlie freely chosen action, whereas lateral premotor areas subserve instructed ones (Passingham 1993, Chen et al 1995, Thaler et al 1995).

A widely discussed theory of the brain mechanism for movement selection is known as the accumulator model. It posits a parallel

distributed network of frontal and parietal regions in which motor programs are stored. Inputs from sensory regions to the fronto-parietal network accumulate until a threshold is reached and movement is generated. Dr. Steven Wise refers to this steady build up in neuronal activity seen at the single cell level in non-human primates as a “ramp to threshold” process (Wise 2003 for a review; Schall 2003 for a review; Gold and Shadlen 2000; Gold and Shadlen 2001; Kim and Shadlen 1999; Schall 1995; Schall and Thompson 1999; Newsome et al 1989; Platt and Glimcher 1999; Shadlen and Newsome 2001). Tests of the accumulator model typically rely on the effects of manipulating sensory inputs on targeting decisions. Indeed, inherent in the accumulator model is the concept that sensation precedes the targeting decision and that the targeting decision precedes action. Tests of the accumulator model with humans are more difficult to design but it has been shown that in a study with free choice of the time to initiate a movement, larger amplitudes in the BP were generated than in instructed conditions (Jahanshahi et al 1995). Other essential features of the accumulator model include that it is a winner-takes-all mechanism and that it is comprised of both “bottom-up” and “top-down” influences. In addition to the obvious “bottom-up” nature of the theory, it includes the biasing of responses by expectations based on past experience with probabilities in the

environment in a “top-down manner”. Such biases are posited to be manifested as altered thresholds for a particular movement. The accumulator model may be thought of as Bayesian in nature in that it relies on hypothesis- testing based on constant updating of a prior state. It has also been noted that it is fractal in nature, in that it bears a close resemblance to the integration of inputs and threshold-driven responses of the neuron itself.

II.E. Magnetoencephalography: Overview

Magneto-encephalography (MEG) was chosen as the neurological investigative tool for these studies for several reasons. First, MEG is a non-invasive technique for measuring electromagnetic activity of the brain: it poses no risk to subjects. Second, unlike other research methods used with human subjects, MEG provides millisecond resolution of brain activity which makes it particularly useful for studying the timing of neurological events. Third, a forward model of magnetic fields due to electric dipoles placed at voxels throughout the brain has proven to be highly accurate in localizing the sources of recorded magnetic fields. Fourth, MEG is less susceptible than EEG to the attenuation of high frequency signals by interactions

with the skull. This independence from the distribution of conductivity within brain structures allows MEG to transmit weak cortical signals and high-frequency cortical signals that are often filtered out of EEG recordings, and provides superior source localization capabilities as compared with EEG. Finally, studies with monkeys demonstrated that shifts in the LFPs recorded from neuronal ensembles were useful in discriminating between functional brain states. Since MEG also samples from close collections of synchronized parallel fibers, shifts in oscillatory properties in the MEG data should also parallel changes in functional brain states. The MEG signals derive from the net effect of ionic currents flowing in the dendrites of neurons during synaptic transmission. In accordance with Maxwell's equations, any electrical current will produce an orthogonally oriented magnetic field. It is this field which is measured with MEG. The net currents can be thought of as current dipoles, which, according to the right-hand rule, give rise to a magnetic field that flows around the axis of its vector component. In order to generate a signal that is detectable, approximately 50,000 active neurons are needed. Since current dipoles must have similar orientations to generate magnetic fields that reinforce each other, it is often the layer of pyramidal cells in the cortex that give rise to measurable magnetic fields. Furthermore, it is

often bundles of these neurons located in the sulci of the cortex with orientations tangential to the surface of the head that project measurable portions of their magnetic fields outside of the head. Magnetic signals are most readily measured using induction coils composed of loops of wire. The spontaneous or evoked magnetic fields emanating from the brain induce a current in these coils, which in turn produce a magnetic field in a special device called a superconducting quantum interference device (SQUID). When a time-varying magnetic flux passes perpendicular to the coil, it induces a time-varying electrical current within the wire. For typical metal wires, this current is quickly dissipated as heat by the electrical resistance of the wire. Clinical biomagnetometers therefore use special induction coils made of superconducting wire. Superconducting coils have essentially no electrical resistance; thus, the amount of current induced within the coil instantaneously tracks even very small changes in the magnitude of the impinging magnetic flux. The SQUID and induction coils of biomagnetometers are generally maintained in a superconducting state by immersion within a liquid helium bath contained in an insulated cryogenic vessel known as a dewar. Because the magnetic signals emitted by the brain are on the order of a few femtoteslas ($1 \text{ fT} = 10^{-15} \text{ T}$), shielding from external

magnetic signals, including the Earth's magnetic field, is necessary so recordings take place in a magnetically shielded room.

III. Dissertation Aim and Hypotheses

The conclusions in the literature just reviewed are contradictory on many points. Some studies concluded that the neurons associated with spatial location of a target of a reach are in parietal regions (Scherberger H, Andersen RA, 2007); others concluded they are in pre-motor regions (Cisek P and Kalaska JF 2005). Some studies concluded that the brain regions that process target location are ipsilateral to the location (Medendorp WP Goltz HC, Crawford JD, Vilis T, 2004) while others concluded the brain regions were contralateral to location (Berndt I, Franz VH, Bulthoff HH, Wascher E 2002). Still other studies concluded that the spatial location of a target was encoded in the right hemisphere, claiming that hemisphere to be specialized for spatial processing (Butler A et al 2000; Kertzman et al 1997). The aim of the research presented here is to investigate several of these contradictory claims regarding the spatial and temporal characteristics of the brain activity preceding reaching movements using more advanced methods. The features of MEG discussed earlier that make it superior to EEG, fMRI or PET will produce results that will add credible support to previous findings it

confirms or evidence that leads to eventually dispel spurious ones the evidence presented here does not favor. More specifically, the research presented here tests hypotheses designed to isolate electromagnetic events that are associated with motor components, with visuomotor components and with cognitive aspects of reaches to a target. These studies are designed not only to add to current knowledge about early processes in human motor control but also to provide the basis for future studies on the human motor system including the perception of volition and attribution.

Analysis of seven aspects of reaching movements was completed to test the following hypotheses:

Hypothesis 1 The characteristics of the temporal and spatial networks of electromagnetic activity prior to reaching movements can be identified in data averaged across subjects.

Hypothesis 2 Reaching movements to targets in the spatial field ipsilateral or contralateral to the effector can be discriminated by the spatial and temporal characteristics of the electromagnetic signals prior to the reach.

Hypothesis 3 The characteristics of the temporal and spatial

networks of electromagnetic activity prior to *imagined* reaching movements can be identified in data averaged across subjects.

Hypothesis 4 Decision-making processes distinguish conditions of movement to a freely-chosen visual target and movement to a visually-instructed target. Differences in the MEG data recorded during these conditions will indicate brain regions and frequencies of activation associated with target selection.

Hypothesis 5 The location of the target of reaching movements to the spatial field either ipsilateral or contralateral to the effector can be predicted prior to movement onset from *single trial* MEG data in *off-line* analysis using pattern recognition techniques to construct classification models.

IV. Experimental Methods and Procedures

IV. A. Subjects

Twenty-two subjects were recruited between the ages of 21 and 32.

All subjects were right-handed and underwent a neurological exam by clinical fellows at NIH to assure that exclusionary criteria, such as neurological damage or disorders, were not present. Due to the

hazards of metal inside the magnetic resonance imaging scanners, subjects were also excluded if they had implanted or otherwise irremovable metal. Subjects were given a copy of the consent form and an opportunity to ask questions regarding the study and its procedures. Witnessed, signed consent was obtained from each subject prior to testing.

IV.B. Experimental Paradigm

An S1/S2, paradigm also referred to as a contingent negative variation or instructed delay paradigm, was used in these studies.

The task was constructed to maximize information acquired for comparisons by nesting multiple conditions within a single task. All conditions required visual fixation in order to eliminate eye movement artifacts and cortical activity not associated with reaching. The task included stimuli that cued six different experimental conditions. All of the conditions are for reaches with the right hand only. They are:

- (1) “all reaches”, comprised of all trials of actual reaching movements including left and right visual targets, free choice and instructed conditions;
- (2) reaches to a spatial target ipsilateral to the effector;
- (3) reaches to a spatial target contralateral to the effector;

- (4) reaches to a visual target in which the location is freely chosen by the subject;
- (5) reaches to a visual location which has been instructed in the task;
- (6) and imagined reaches in which no actual movement occurs.

Subjects were seated at arms' length from a screen displaying the computer-generated visual stimuli. See figure 8. The left and right edges of the screen were the endpoints for the reaching movements. Each trial began with a fixation 'plus' sign and the subject's right wrist resting on a button on a tabletop. The table was positioned in the subjects' lap such that the button was at the midline (left-to-right) of the body. The button was activated when the subject's wrist lifted off, thereby detecting the onset of the reaching movement.

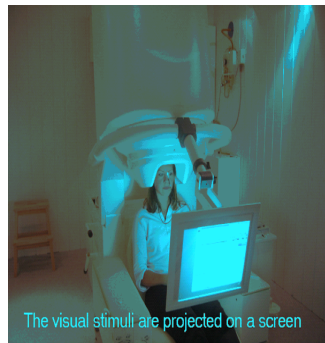


Figure 8. Subject during magnetoencephalography recording.

When a subject reached toward a target, the beam was interrupted and a signal was sent to the data acquisition computer indicating the subject's response was either "Left" or "Right". See Figure 9.



Figure 9. Subject breaks optical beam on the right with a reach to the right spatial field.

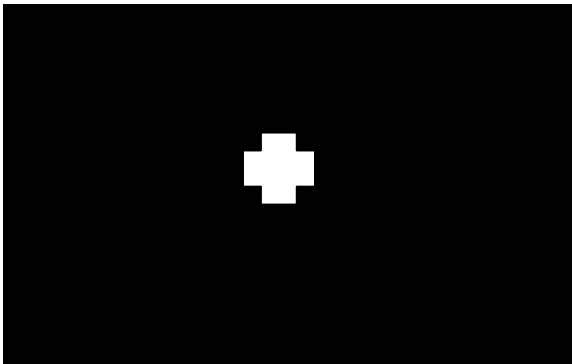
Subjects performed three sessions of 150 reaches each: two sessions with real reaching movements and one with imaginary movements. The task was an S1/S2 response cuing paradigm, also known as a contingent negative variation paradigm (discussed earlier in detail in the introduction section). In the real movement sessions, randomized trials of two interspersed conditions were presented: the

instructed condition with left and right targets cued and the free-choice condition in which a target to the left or to the right was chosen by the subject. See Figure 10.

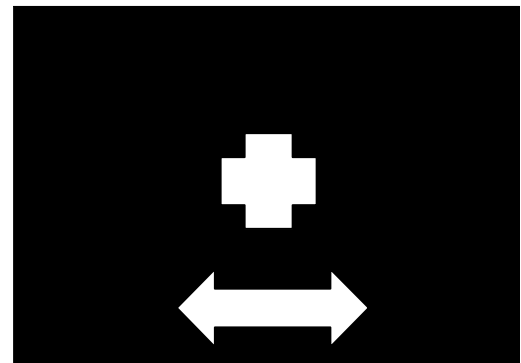
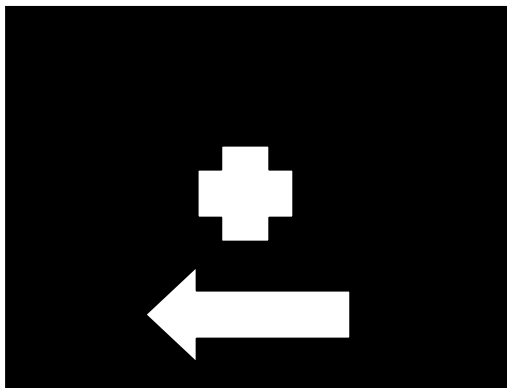
Figure 10. Task instruction script that was read to subjects.

Instructions for Subjects:

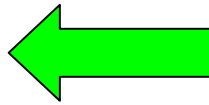
“Begin with your right wrist resting on the cushion. Throughout the experiment keep your eyes focused on the plus sign in the center of the screen.



You will be reaching with your right hand to either the edge of the screen on the left or to the edge of the screen on the right or making no movement at all. You will be presented with two types of screens. The screens with a single-sided arrow such as the one below on the left indicate which direction you should reach. The screens with a double arrow such as the one below on the right indicate that you should choose the direction to reach, either to the left or the right. For any screen, you may choose to rest and not reach at all. This is completely acceptable and will not adversely affect the experimental results at all.



A short time after the screen with the arrows is presented instructing you with a direction to reach or to choose a direction to reach, the arrows will turn green, the signal to begin the movement. Do not begin the reaching movements until you see this go signal.



After each reach, return your wrist immediately to the cushion and wait quietly for the next screen to appear. “

-end instruction script-

Instructed condition: Subjects were first presented with a fixation plus. Two seconds later the S1 cue was presented. In instructed trials this consisted of an arrow in the center as the instruction for which direction to reach. After three seconds \pm 300 ms of jitter the central arrow turned green was the S2 cue signaling the subjects to perform the instructed reaching movement.

Free choice condition: Trials again began with a fixation plus. The S1

cue followed the fixation 'plus' sign. S1 was an arrow pointing in both directions in the center of the screen. This cue indicated that the subjects should choose the direction of the upcoming reach. Three seconds \pm 300 ms of jitter later the double-sided arrow turned green, the signal to perform the reaching movement.

The two conditions of free-choice and instructed were randomly interspersed to control the timing of the subjects' decision. Since subjects did not know which condition would be presented on any given trial, they were constrained to make a decision within the S1/S2 window.

IV. C. MEG DATA ACQUISITION

All experiments were conducted in the MEG Core Facility at the National Institutes of Health in Bethesda, Maryland. Neuromagnetic data were recorded at 1200 Hz using a CTF 275 MEG system (CTF Systems, Inc., Canada) composed of a whole-head array of 275 radial 1st order gradiometer/SQUID channels housed in a magnetically shielded room. Synthetic 3rd gradient balancing was used to remove background noise on-line. Gradient balancing is an active noise cancellation technique that uses a set of reference channels to subtract background interference.

Three fiducial localization coils were placed at the nasion and auricular points for each subject. These function as landmarks to establish a coordinate system for the subject's head position. They are then used to monitor and warn of excessive head motion during data acquisition. In data analysis the information from the fiducials is used to throw out trials that exceed a movement tolerance threshold. The fiducials are also used in analysis to co-register the head position localized during the MEG recording with the position of the head during the MRI scan. The same fiducial marks are used for the MRI scan immediately following the MEG recording, thereby minimizing the margin of error in the source localization process which depends on accurately aligning the brain-space coordinates of the MEG data with the brain-space coordinates of the MRI data. Sampling frequency was 120 Hz.

Electro-oculogram (EOG) was also recorded during data acquisition.

V. Data Processing

The data was analyzed across subjects for task-related power changes in the magnetic field during the interval between S1 and S2 which characterize six conditions:

- “all reaches”, comprised of all trials of actual reaching movements including left and right visual targets, free choice and instructed conditions;
- reaches to a spatial target ipsilateral to the effector;
- reaches to a spatial target contralateral to the effector;
- reaches to a visual target in which the location is freely chosen by the subject;
- reaches to a visual location which has been instructed in the task;
- and imagined reaches in which no actual movement occurs.

In addition to looking at the characteristics of the electromagnetic activity in the brain associated with each of these six conditions considered alone, comparisons were also made between conditions, including: reaches to the ipsilateral versus contralateral spatial field; free choice versus instructed reaches; and, actual versus imagined reaches.

V.A. Pre-Processing

Each trial of every dataset was visually inspected for artifacts and trials were rejected if artifacts were found. The electro-oculogram channel was inspected for eye movement activity so that trials containing any could be rejected. Continuous head localization

channels which carry the information recorded from the fiducial coils were inspected. All trials in which the threshold for head movement was exceeded were rejected. For each trial, markers were assigned at the 'go' cue and at movement onset indicating the condition presented: left or right target, free choice or instructed condition. The continuous data were epoched into individual trials that extended five seconds prior to the go cue and two seconds after the go cue.

V.B. Data Validation

In order to validate that the data were generally reliable and of good quality, the time series data for several individual subjects were averaged to confirm that the well-established motor readiness field that precedes movement onset was present. Similarly, several data sets were processed with a Fourier Transform into the frequency domain to confirm the presence of the well-established beta band ERD preceding movement onset beginning at -1.5s. Both of these validation measures confirmed that the data were reliable and of good quality.

V.C. Source Localization

For each subject the MRI and MEG head position were co-registered

using the fiducial marks that had been recorded during data acquisition. This aligned the spatial coordinates of the MEG data with the spatial coordinates of the anatomical data from the MRI.

The sources of peak activation, regions oscillating with the largest signal to noise ratio, were identified in the MRI image using SAM (synthetic aperture magnetometry) spatial filters. SAM is a beamformer algorithm that is commonly used with MEG data to identify areas in the brain associated with stimulus or movement-related events. It uses the patterns in the data (determined through a covariance matrix), which are in sensor space, along with a forward model to estimate locations of sources in brain space (Cheyne D, Bakhtazzad L, Gaetz W 2006). The brain is divided into many target locations (voxels with dimensions of 1x1x1mm). For each voxel an optimal spatial filter is then computed, linking the signal at the target location to the signals recorded at the MEG sensor locations. Each spatial filter is designed so that signals from the location of interest are unperturbed, while signals from other locations are attenuated. This focusing, or "beam forming" of the spatial filter is achieved by selectively weighting the contribution that each sensor makes to the overall output of the spatial filter. The output of the spatial filter is a measure of the neuronal activity at that target location. A spatial filter

is sequentially constructed for a set of voxels in the brain, creating a map of activity in the brain, which typically shows peaks in brain regions involved in the task that the subject performed in the MEG scanner. After these maps were created, each of the individual brains were warped into Talairach space using AFNI software (Cox RW, 1996). Finally a grand average was computed and statistically tested.

V.D. Source-Space Time Frequency Analysis

After source localization, the coordinates of the peak activations were identified and used to construct ‘virtual’ channels, which are weighted combinations of sensors that represent the source in brain space. The MEG data were then projected onto these ‘virtual’ channels to allow further analysis to be carried out in *source* space rather than sensor space. Due to the nature of magnetic fields, which are emitted at right angles to electrical current dipoles, this transformation of the data from sensor space to source space was essential in order to interpret the data accurately with respect to the anatomy of the brain.

Time frequency analysis was done with respect to a specified marker. For the conditions of “all reaches” and “imagined reaches”, analysis

was time-locked to the S2, 'go' cue, so that in addition to showing any motor related effects, there would be a more precise representation of any effects directly related to stimulus presentation or to a timing function during the delay period between S1 and S2. For the other four conditions (reaches to ipsilateral spatial field, reaches to contralateral spatial field, reaches to locations freely chosen, reaches to instructed location) analysis was time-locked to movement onset in order to focus on the behavioral components of the task.

After the data was projected onto the virtual channels it was transformed from a time series into the frequency domain. The temporal filter selected was the multi-taper method (MTM). After comparison with Fourier transforms and wavelet methods, MTM was found to have the best time resolution in the upper frequency bands. This was an important factor since one of the areas of particular interest in this study was activity in the high gamma (40-100Hz) range and high frequency oscillation (HFO) range. A 300 Hz low pass filter was applied (using the CTF software, "DataEditor"). A high pass filter of 4Hz was also applied to reduce low frequency movement artifacts. A baseline correction was done by subtracting the mean based on all data in the epoch (five seconds); thereby normalizing to relative changes in power with respect to the average power over the entire

epoch. The scale of the power change, represented by color intensity in the plots, was scaled between 1 and -1 in order to make valid comparisons between different regions. For each data set, a validation procedure was performed at this stage of processing. The data sets were divided into two equal parts and time frequency analysis was performed on each half and compared to insure that there were not spectral effects present that were driven by large artifacts in the data. This was confirmed by visual inspection of the results of each half to ascertain that they were consistent with each other.

V.E. Statistical Analysis of Time-Frequency Power Changes

While the time frequency plots give a useful “big picture” of spectral perturbations over time, statistical testing was performed on each time frequency analysis to determine which spectral perturbation effects were statistically significant. AFNI (Analysis of Functional Neuroimages), the same software used for co-registering the MRI and MEG data and displaying the results of the source localization, was used to run the statistical tests. A basic t-test with a False Discovery Rate (FDR) correction for multiple comparisons was used. Activations with a q value of less than .05 were considered

significant. If there were none at $q=.05$ then a threshold of $q=.1$ was used and activations at this level were also considered significant. Both thresholds for FDR are commonly accepted as significant in the literature for studies with MEG.

VI. Results

VI. A. “All Reaches”, Signature of Right-Handed Reaching Movements

VI.A.1. Location of Peak Activity

Source analysis of “all reaches” as a group yielded a spatially-distributed network as well as a temporal network of various frequency bands. The brain regions found to be activated in this condition were closely related to those that comprise the dorsal stream, “the where pathway”, of visual processing. The following locations of peak activations were found to be significant during the time window of 4.5 s prior to .5s after the presentation of S2, the “go” cue for the condition of “all reaches” ($q=.05$ See figure 13 for color scale for all AFNI images. Note that BA refers to Brodmann Areas. Also note that the cross-hairs visible in the brain images are an artifact of processing and do not convey information about the resulting image).

Further detail on the timing and functional nature of each of these components will be analyzed and discussed later in this paper (pg 68) using time-frequency graphs:

- left medial frontal gyrus (ERS) and left superior parietal gyrus/ BA7 (ERD) in the 5-300 Hz frequency range (figure 14) ;
- right medial frontal gyrus (ERS) and left superior parietal gyrus /BA7 (ERD) in the 5-50 Hz frequency range (figure 15);
- left precentral gyrus/BA4 (ERD) in the 15-25 Hz and 35-45 Hz ranges (figure 16);
- right middle occipital/BA19 and right middle temporal gyrus/BA39 (ERS) in the 40-50Hz range (figure 17);
- left middle occipital gyrus/left BA 18 (ERS) in the 50-150Hz range (figure 18);
- right superior parietal (ERS) in the 150-300 Hz range (figure 19);
- and right medial frontal gyrus (ERS) in the 140-160 Hz range (figure 20)

VI.A.2 Source-Space Time Frequency Plots

Time-frequency plots of the averaged data generated for those regions identified as sources of peak activation for all reaches as a group are displayed in figures 21-28.

VI.A.3. Statistical Significance

VI.A.3.a Sensory Response

The time frequency plots in figures 21 – 28 display changes in power in different frequencies in the different brain regions over time. The power values are baseline-corrected. The baseline was calculated as the average power throughout the entire epoch (-4.5 s to 0.5s with respect to the “go” cue). This average was then subtracted from power at each time point so the average across any horizontal line in the graph is zero. Moreover, the graphs display the results with the power values scaled between 1 and -1 in order to be able to make comparisons across images. In such a comparison, for example, between figure 21 and figure 22, it is clear that the beta ERD at approximately -2.5 seconds is darker blue, indicating a larger desynchronization, on the left hemisphere than the right hemisphere. Visual inspection and comparison of all time-frequency plots (figures 21-28) indicates that responses to the S1 instruction cue were strongest in the middle occipital gyrus, with activation on the left hemisphere of the brain greater than that on the right. More specifically, the response to the SI cue appears to consist of two events beginning at -2.8s with respect to the go cue: a 75-300Hz

ERS burst in the left middle occipital cortex and the onset of a 400ms Beta (15-25Hz) band ERD in left middle occipital cortex. The ERS HFO burst was not evident in the *right* middle occipital cortex. The beta ERD was bilateral but noticeably stronger on the left. These observations were confirmed by statistical testing of the time-frequency results using a standard t-test with a multiple comparisons correction using the false discovery rate method (Figures 29 and 30).

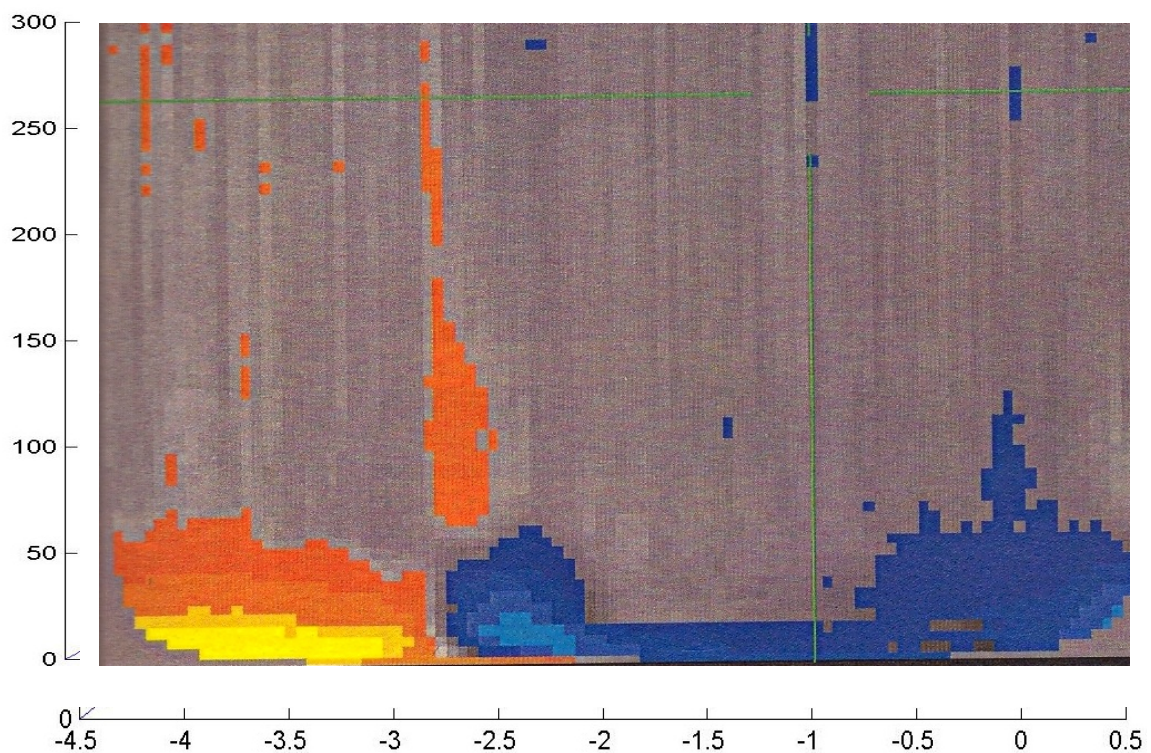


Figure 29. Left Middle Occipital Cortex. Statistical Testing Results of Time Frequency Analysis. HFO burst of ERS and Beta Band ERD coinciding at -2.8s ($q=.05$) note: cross hairs are to be disregarded.

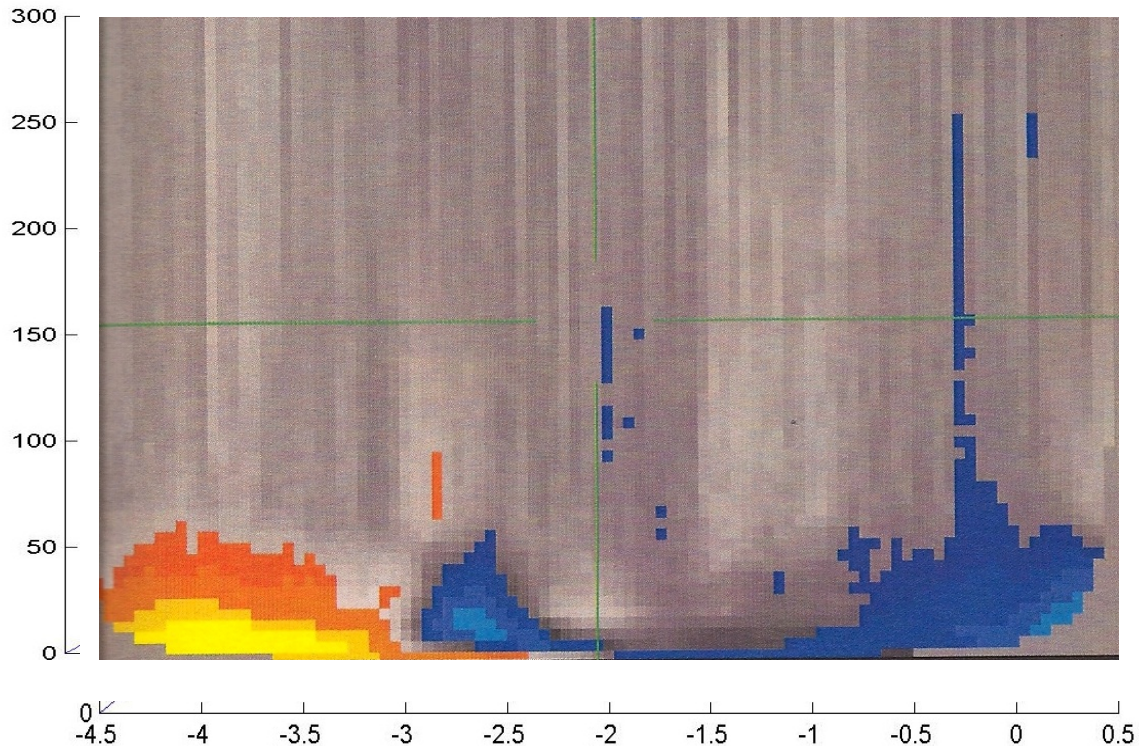


Figure 30. Right Middle Occipital Cortex. Statistical Testing Results of Time Frequency Analysis of Grand Average of All Reaches. Absence of HFO burst of ERS and weaker Beta Band ERD at -2.8s compared with Left Middle Occipital Cortex in figure 29 ($q=.05$) note: cross hairs are to be disregarded.

VI.A.3.b. Motor Preparation

Visual inspection of the time frequency plots showed activity just prior to S2, the 'go' cue, was centered in contralateral parietal cortex and in central motor areas. The well established pattern of beta band ERD can be seen beginning two seconds prior to movement onset in motor cortex, with stronger levels in the left hemisphere, as expected given the well-established contralateral structure of cortical activation associated with motor processing (figures 25 and 26). In addition, beta band ERS is present at -2.2 seconds with respect to the go cue

in left motor cortex only. It is not present in the right motor cortex.

Statistical testing of the time-frequency transformed data confirms these patterns (figures 31, 32).

Superior parietal cortex also has a strong beta band ERD occurring earlier than that in the motor cortex, although with less intensity (figures 33 and 34). Similar to the primary cortex activity, the parietal activation appears to be lateralized to the left hemisphere.

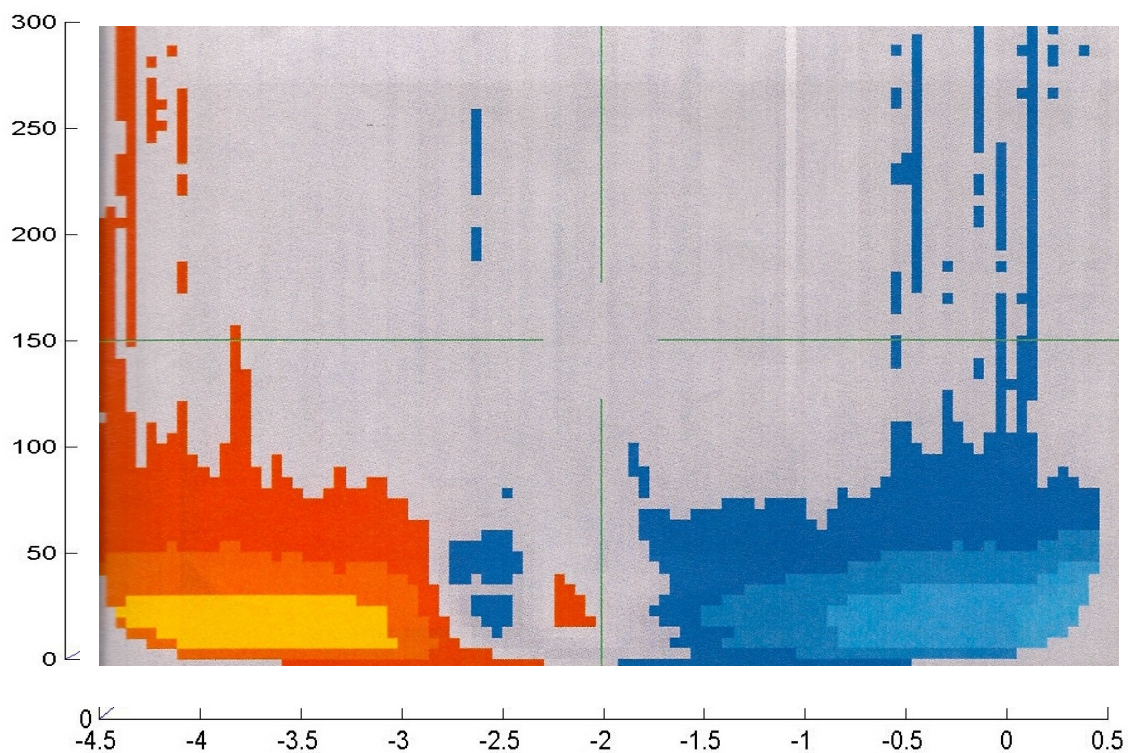


Figure 31 Left Central Motor Cortex. Statistical Testing Results of Time Frequency Analysis of Grand Average of all reaches. Beta Band ERD seen 1.8s prior to movement onset. Beta Band ERS occurs at -2.2 s with respect to the go cue in left motor cortex only, not in right motor cortex. ($q=.05$) Disregard cross-hairs.

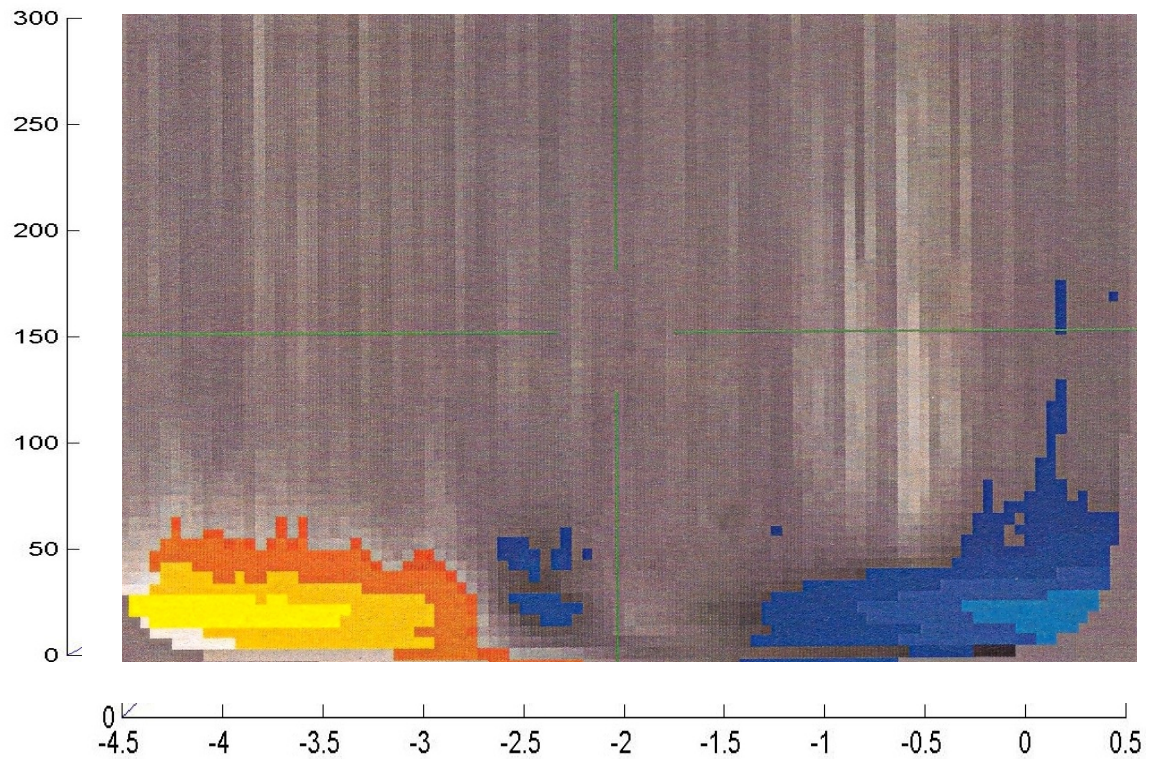


Figure 32. Right Central Motor Cortex. Statistical Testing Results of Time Frequency Analysis of Grand Average of all reaches. Beta Band ERD seen 1.8s prior to movement onset. Beta Band ERS at -2.2 s with respect to go cue in left motor cortex only, not in right motor cortex. ($q=.05$) Disregard cross-hairs.

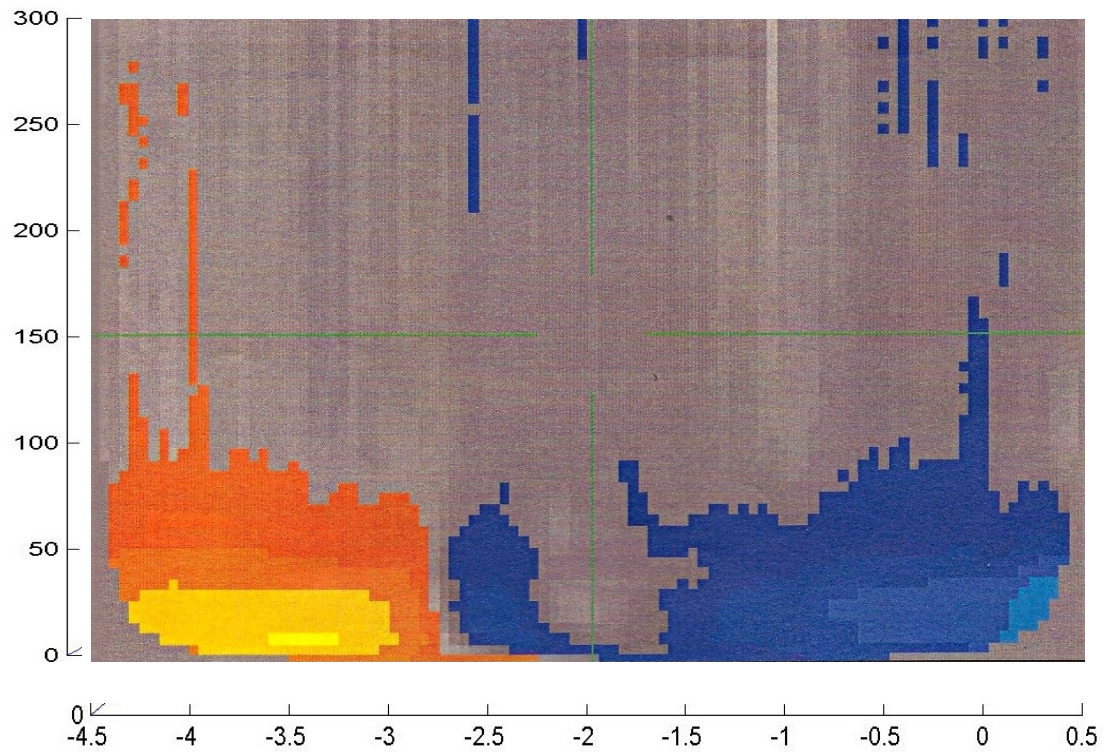


Figure 33. Left Superior Parietal Cortex. Statistical Testing Results of Time Frequency Analysis of Grand Average of All Reaches. Bilateral ERD 1.8 s prior to movement onset. ($q=.05$) Disregard cross-hairs.

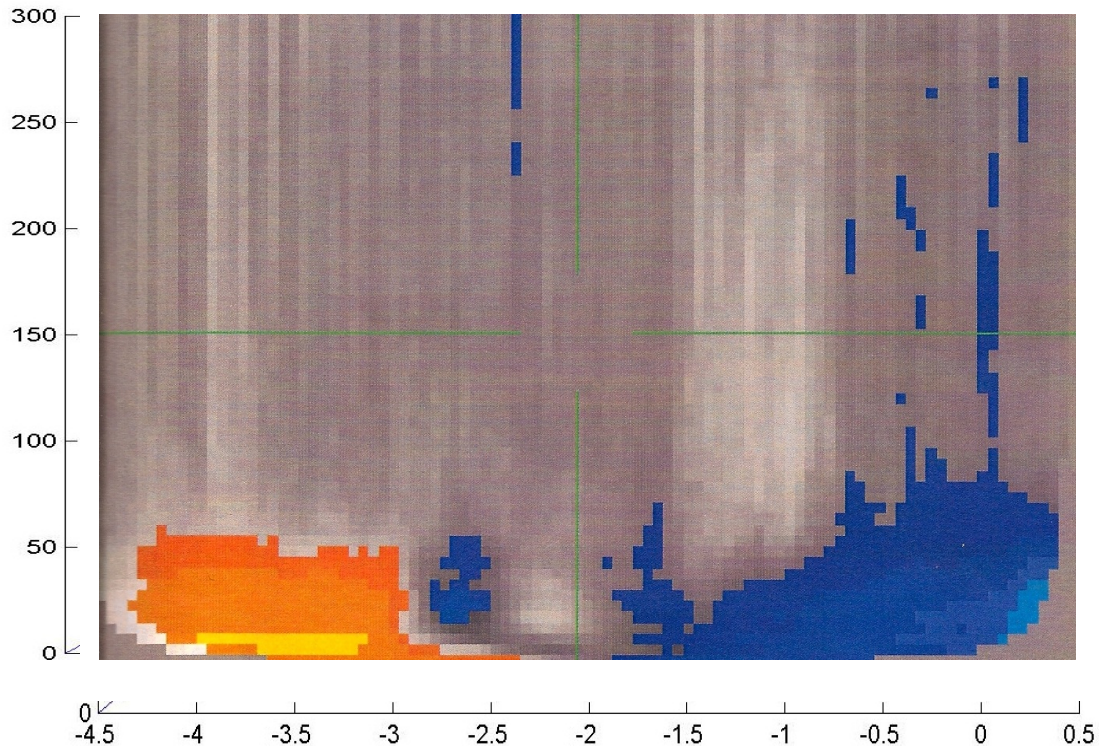


Figure 34. Right Superior Parietal Cortex. Statistical Testing Results of Time Frequency Analysis of Grand Average of All Reaches. Bilateral ERD 1.8 s prior to movement onset. ($q=.05$) Disregard cross-hairs.

VI.A.3.c. Cognitive Components

The frontal sources identified by SAM are likely associated with cognitive aspects of the task. There are clear patterns in the time frequency plots of both left and right frontal cortex (figures 27 and 28). The HFO bursts of ERS at -4s and -1s in left frontal cortex occur precisely one second prior to S1 and S2, respectively. These seem likely to be a brain correlate of an aspect of timing. The more precise

nature of the burst at -4s and the less narrow nature of the burst around -1s would support this view since there was a jitter of ± 300 ms in between S1 and S2 but no jitter before S1 presentation. There is approximately a smearing of 300 ms of the event that precedes S2, which would be the case if that event is based on the timing between S1 and S2. Statistical testing of the time frequency results does not show these timing- associated HFO bursts at a q value of .05 (figure 36) but does show them as significant at $q=.10$, a threshold that is less rigorous than .05 but also commonly reported.

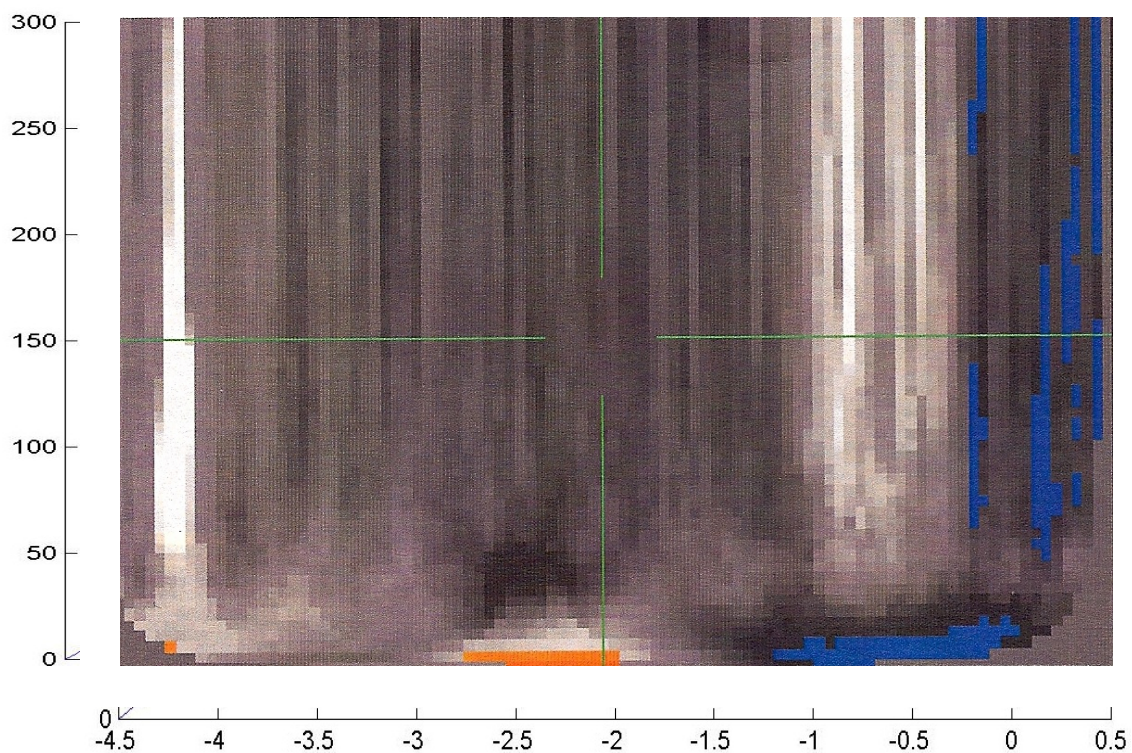


Figure 35. Left Frontal Cortex. Statistical testing results of grand average of 'all reaches' condition. $q=.05$ Note: disregard cross-hairs.

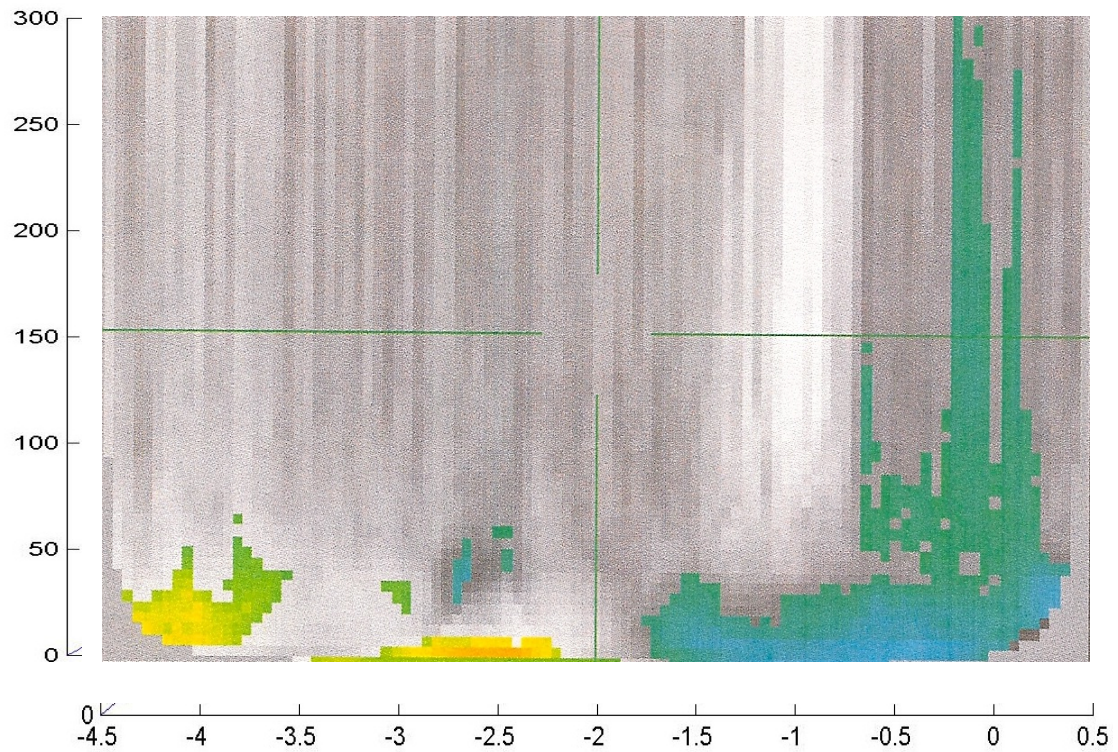


Figure 36. Right Frontal Cortex. Statistical Testing Results. Grand Average of “all reaches’ condition. ($q=.05$) Note: disregard cross-hairs.

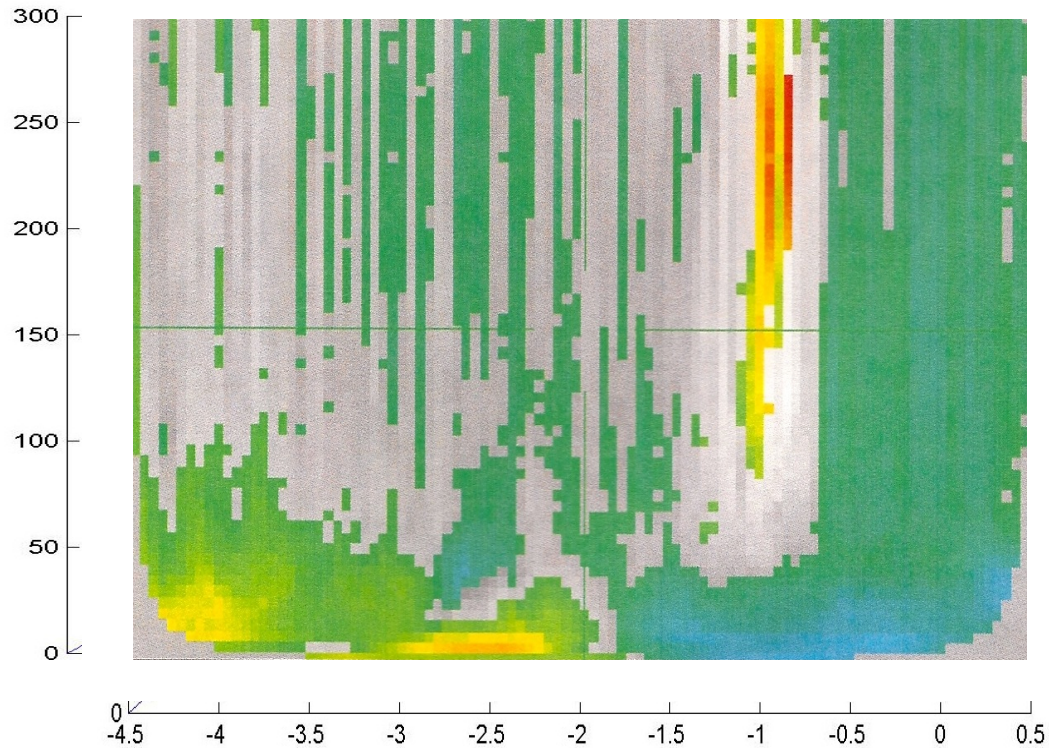


Figure 37. Right Frontal Cortex. Statistical Testing Results of Grand Averages, All Reaches condition. ($q=.10$) Disregard cross-hairs.

The other interesting pattern to appear in the frontal cortex during the “all reaches” condition is a theta rhythm ERS just after S1 from -2.9s to -2.2s and a theta rhythm ERD 1.5s to .5s prior to S2 in both left and right frontal cortex. The functional significance of frontal theta rhythms is much speculated on in the literature. There is a wide range of cognitive functions attributed to this phenomenon including reward, feedback, attention and most recently evidence pointing to a decision-making function (Cohen MX, Elger CE, Fell J 2008). The variables

that might modulate the theta rhythm in this task include decision-making since many of the trials were free-choice; a timing function since there is a strong timing aspect in all trials; or finally, the recently much-discussed theta oscillation coupling with high frequency oscillations as a mechanism for integration of spatially distributed networks such as the one that is activated in this task.

VI. B. Reaching Movements to Ipsilateral and Contralateral Targets

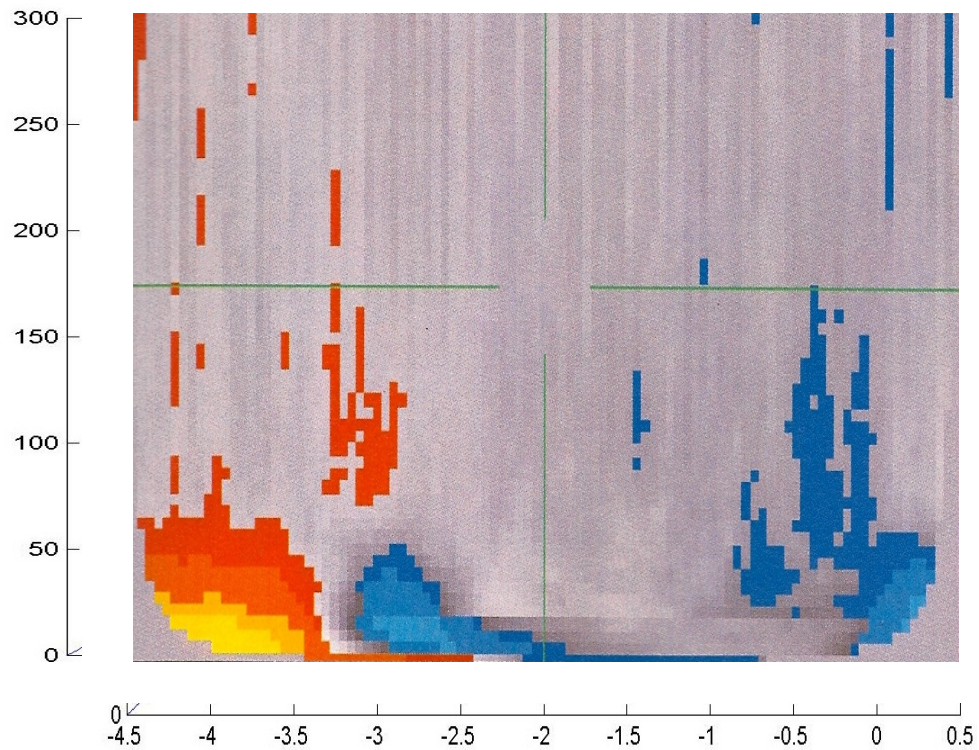
VI.B.1. Location of Peak Activity

Results of the source analysis for the conditions of reaches to a contralateral target and reaches to an ipsilateral target revealed sources were generally the same as those for the condition of all reaches. (NOTE: It is important to remember that the analysis of location of target discussed here was time locked to movement onset and not the 'go' cue in order to focus on motor –related components; whereas the all reaches condition discussed earlier was time-locked to the 'go' cue to emphasize stimulus-related events. Times for the same events in the different conditions will therefore be approximately 500ms different due to the reaction time for the movement.)

VI.B.1. Statistical Tests of Time Frequency Analysis of Reaches to Ipsilateral or Contralateral Targets

As before, virtual channels were created from the sources of peak activation that were identified through SAM analysis. Those channels were then used for time frequency analysis of the data in source space. Statistical testing was performed on the resulting frequency plots. As in the analysis of the condition of all reaches, the response to S1 is centered in the left middle occipital/temporal region with an HFO burst of ERS and a beta band ERD for reaches to both the ipsilateral and contralateral targets (figures 38 and 39).

(A)



(B)

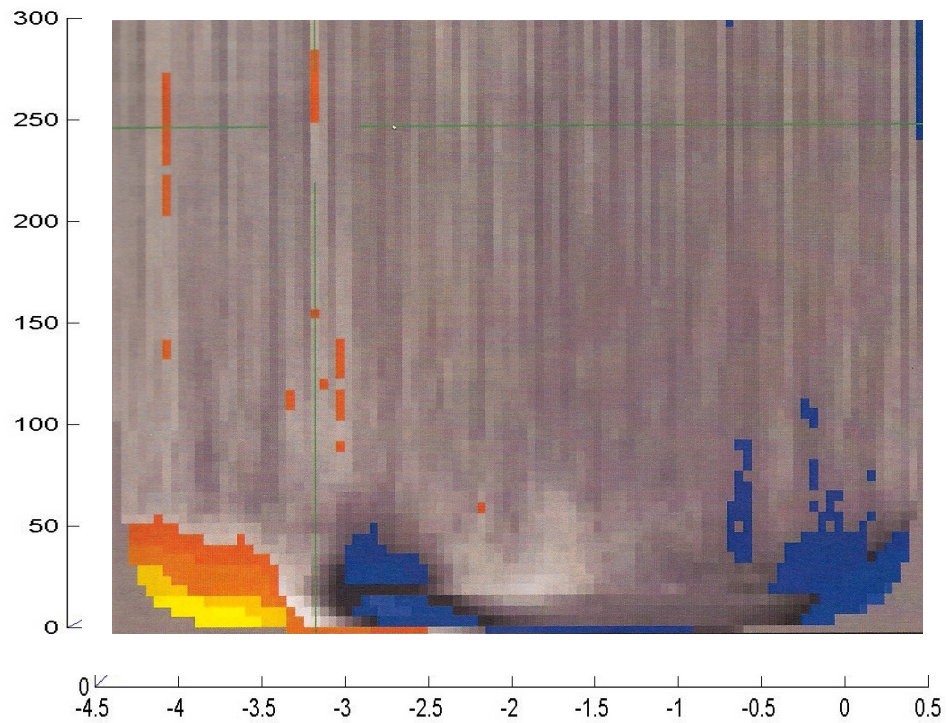
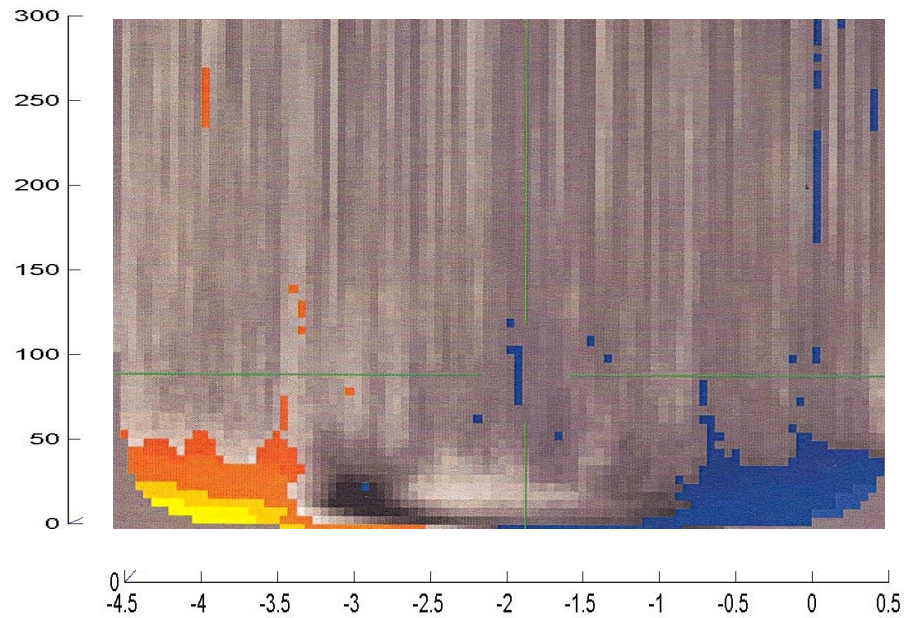


Figure 38. (A) Left Middle Occipital/Temporal Cortex. Statistically significant areas of activation for reaches to the contralateral target (B) Statistically significant areas of activation for reaches to the ipsilateral target.

No significant response to S1 was discovered in right middle occipital cortex (figure 39).

(A)



(B)

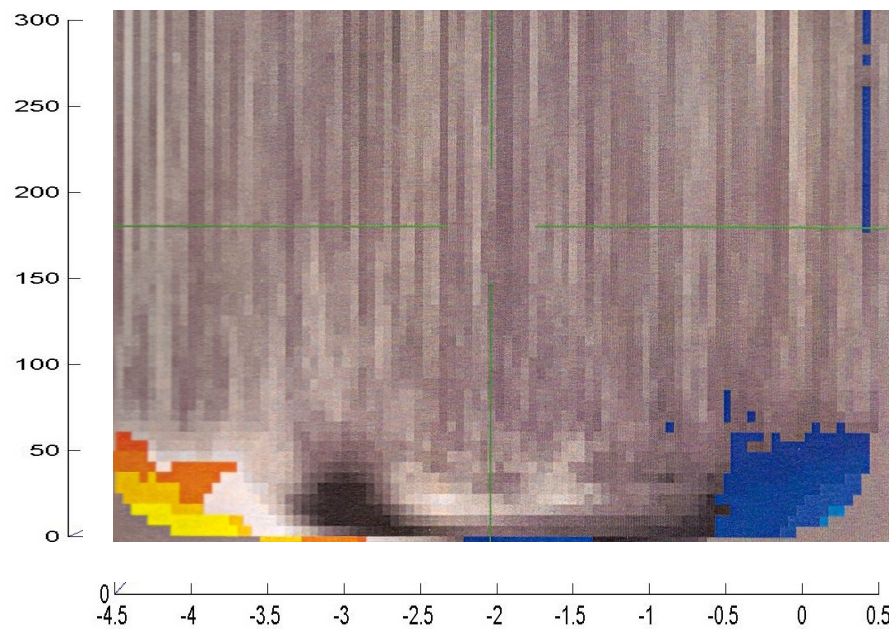
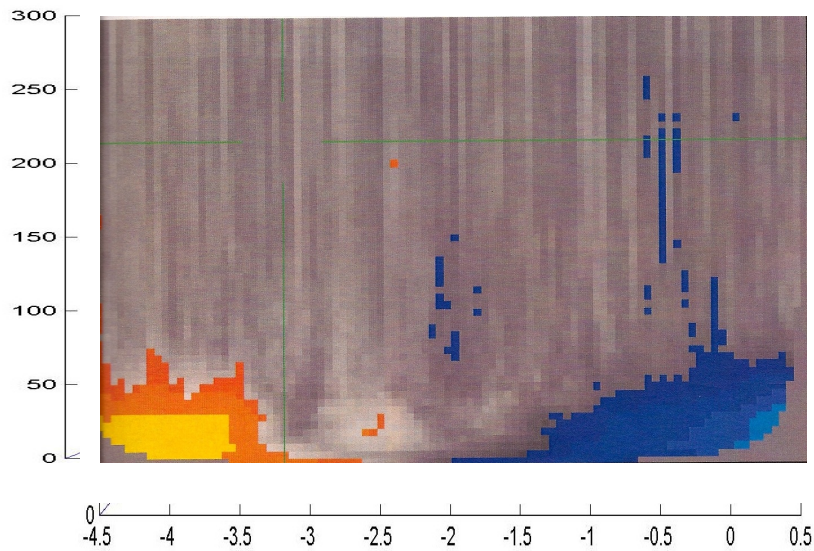


Figure 39. . (A) Right Middle Occipital Cortex. Statistically significant areas of activation for reaches to the contralateral target (B) Statistically significant areas of activation for reaches to the ipsilateral target. ($q=.05$) Disregard cross-hairs.

The right intraparietal sulcus had more intense activation from -1.5s to movement onset for reaches to the right (ipsilateral) target than to the left (contralateral) target (figure 40).

(A)



(B)

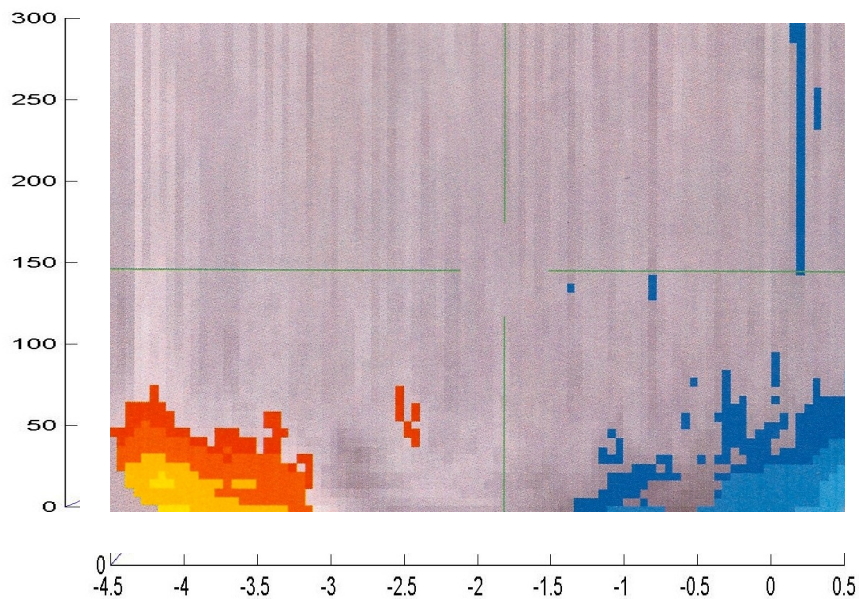
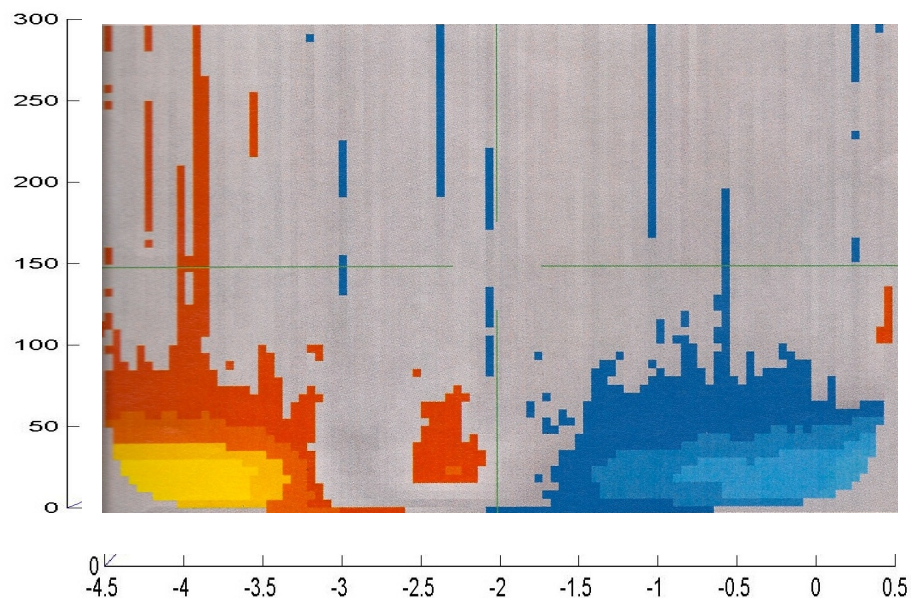


Figure 40. (A) Right Intraparietal Sulcus. Statistically significant areas of activation for reaches to the contralateral target (B) Statistically significant areas of activation for reaches to the ipsilateral target. ($q=.05$) Disregard cross-hairs.

The most interesting finding in the analysis of reaches to ipsilateral and contralateral targets occurred in the left intraparietal sulcus (figure 41). In this region, reaches to the contralateral (left) target activated a strong Beta band ERS from -2.7s to -2.3s (with respect to movement onset); whereas there was no significant activation for reaches to the ipsilateral (right) target in that same time period ($q=.05$). Additionally, the beta band ERD 1.5s prior to movement was stronger for reaches to the contralateral (left) target than for reaches to the ipsilateral (right) target in the left intraparietal sulcus (figure 41).

(A)



(B)

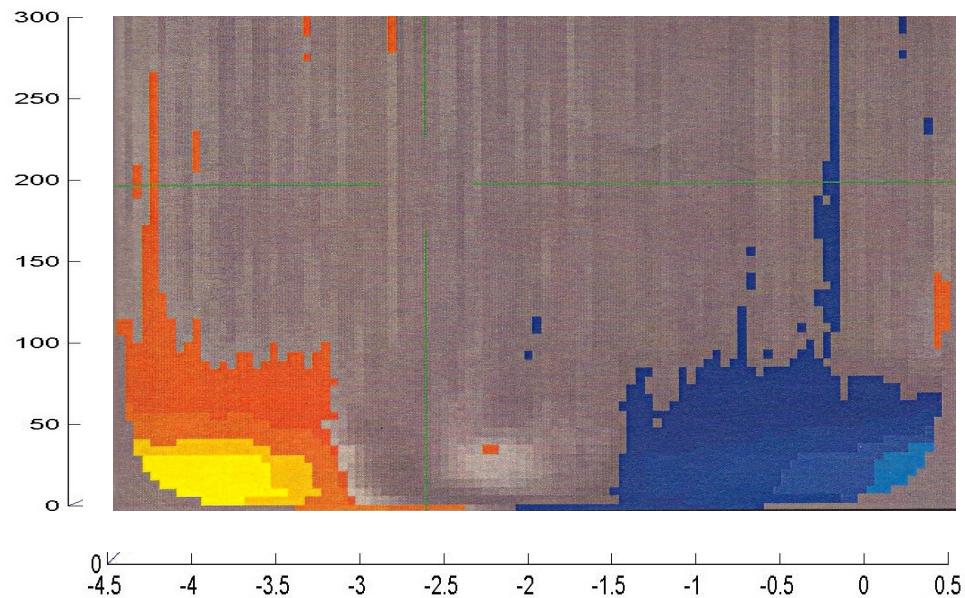


Figure 41 (A) Statistical map showing significant areas of activation in left intraparietal sulcus for reaches to the contralateral target (B) Statistical map showing significant areas of activation in left intraparietal sulcus for reaches to the ipsilateral target. ($\alpha=.05$) Disregard cross-hairs.

The source of this activation in left intraparietal sulcus is shown in figures 42 and 43. It is within 1mm of the left inferior parietal lobule, within 1mm of the left superior parietal lobule and BA 7 and 2mm from BA 39.

The difference in activation in the left intraparietal sulcus between reaches to targets in the ipsilateral or contralateral spatial field was confirmed by a two group t-test comparison with $q=.10$.

The results of the analysis of (ipsilateral target – contralateral target) are shown in figure 45. The circled blue region represents a stronger ERS for reaches to the contralateral target just after S1 and the circled yellow/orange regions represent earlier and stronger ERD for reaches to the contralateral target just prior to movement onset.

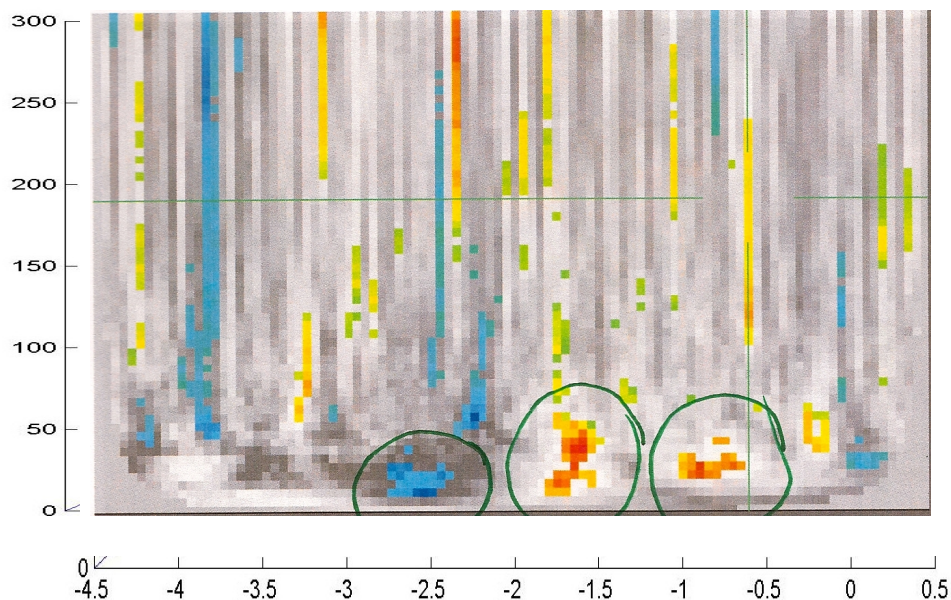
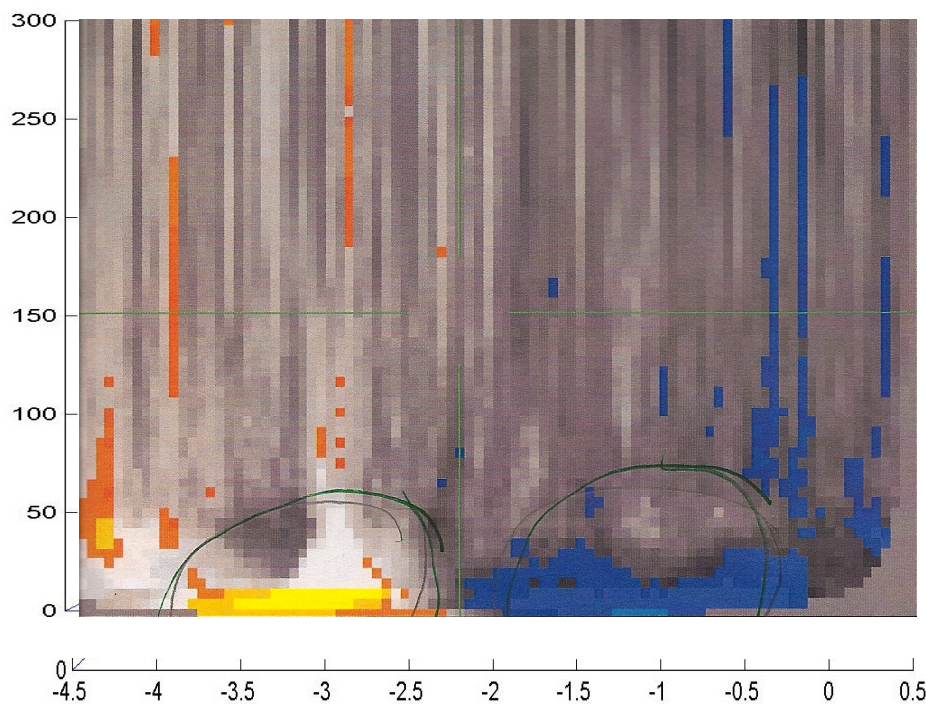


Figure 45. Left Intraparietal Sulcus. Statistically significant activation for right target minus left target. Circled blue region is a negative value after subtraction which represents stronger ERS to left target than to right target. Circled orange/yellow regions represent earlier and stronger ERD for targets to the left (contralateral) See figure 41 for beta ERD for contralateral reaches only resulting in this statistical result.

The only other region with a statistically significant difference in activation between these two conditions was the right frontal cortex. The frontal theta rhythm is stronger in reaches to the left (contralateral) target (figure 46). The subtraction of activity during reaches to left target from activity during reaches to right target was statistically significant at $q=.1$ as can be seen in figure 47. The circled blue region (-3s to -2.5s) represents a negative value and thus a stronger ERS for left targets than for right. The circled orange region (-1.7s to -1.3s) represents a positive difference for right- left, and thus a stronger ERD for left targets than for right in this time period.

A)



(B)

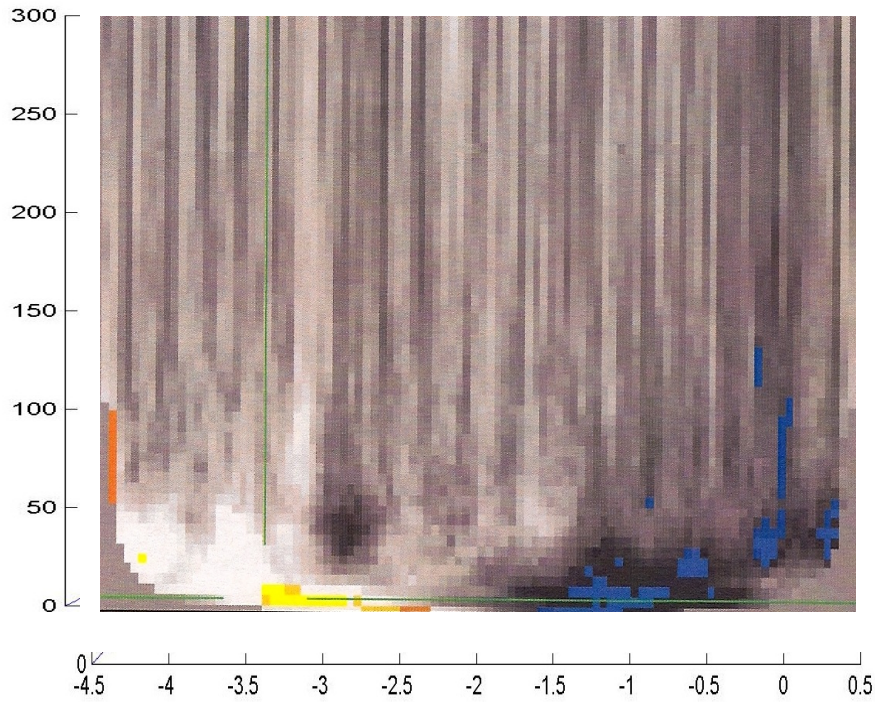


Figure 46. (A) Right Frontal Cortex. Statistically significant activation for reaches to contralateral (left) targets. (B) Statistically significant activation for reaches to ipsilateral (right) targets. $q=.05$

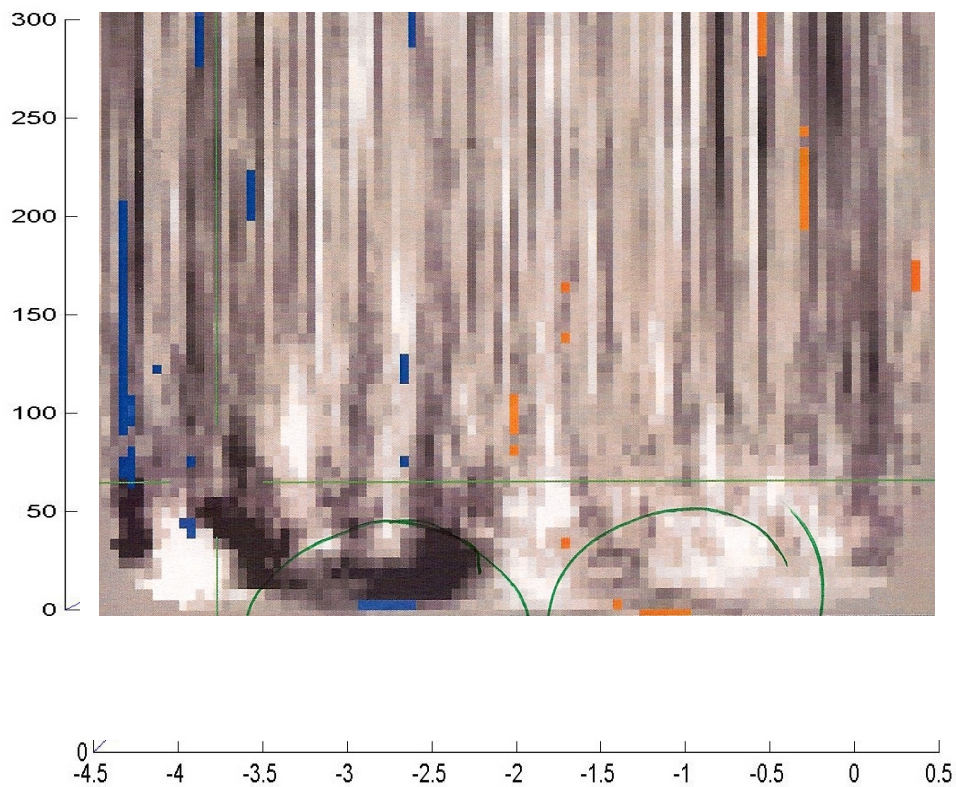


Figure 47. Right Frontal Cortex. Statistically significant activation in a two-group comparison of reaches to right target minus reaches to left target. $q=.1$

No differences were found between conditions of left and right target location in other brain regions tested: right and left middle occipital cortex, left and right motor cortex, or left frontal cortex.

VI. C. Reaching Movements under Free-Choice Condition

VI.C.1. Location of Peak Activity

In the free-choice condition subjects were given an S1 cue that allowed them to choose the target on the left or the target on the right. For the group analysis, all free-choice reaches were analyzed across the target location variable. The free-choice group included reaches to both left and right targets so the factor of target location cancels out in the average and any new effects observed in this analysis should be strictly due to the cognitive component of decision-making.

SAM analysis identified four sources of peak activation during the free-choice reaching condition:

- left superior parietal lobule and left precuneus, ERD for the frequency bin of 5-300 Hz
- left middle occipital gyrus, ERD for the frequency range of 5-50Hz
- right superior frontal gyrus, ERS for the frequency bins of 5- 300Hz, 5-50Hz and 150-300Hz
- right middle occipital gyrus, ERS for 50-150 Hz

VI.C.2 Source-Space Time-Frequency Plots

Using the coordinates of the sources generated by SAM, virtual channels were created. Time-frequency analysis in source space was possible using these virtual channels. Plots of this analysis are in the figures that follow.

Visual inspection of the time-frequency plots for the left and right middle occipital cortex (figure 48) show patterns similar to all reaches: beta band ERD, with stronger intensity on the left cortex, following S1 and just after S2. In addition there appears to be a bilateral gamma to high gamma rhythm ERS following the S1 beta band ERD.

(A)

(B)

The source-space time-frequency plot of choice-condition reaches for the right frontal cortex (figure 50) has the effect seen previously of ERS in the theta rhythm just after S1 and ERD in the theta rhythm just before S2. These effects were statistically significant with $q=.05$. In addition there was a statistically significant beta band ERD from -2 to -1.5s from movement onset that had not been observed in analysis of other reaching conditions in this study.

VI.C.2.a. Trends

The phenomenon of theta-modulated HFO bursts is evident in the time-frequency plots of Left Middle Occipital Cortex, Right Middle Occipital Cortex (figure 48) and Left Superior Parietal Cortex (figure 49) in the condition of “free-choice” reaches. It is a noteworthy and interesting trend throughout the entire analysis time window; however, this trend did not meet the threshold for statistical significance at $q=.10$.

VI. D. Reaching Movements under Instructed Condition

VI.D.1. Location of Peak Activity

The instructed condition was analyzed across target location so that it includes all instructed reaches to either the left or right spatial field.

SAM analysis yielded peak activation for this condition in the following locations:

- right superior frontal gyrus, ERS in the frequency range of 5-300 Hz
- right inferior parietal lobule, ERS in the frequency range of 5-50Hz
- left precuneus, ERD in the range of 5-50Hz
- right middle occipital, ERS in the range of 50-150 Hz

VI.D.2 Source-Space Time-Frequency Plots

The time frequency analysis for the right middle occipital source showed statistical significant for beta ERD after S1 and the beta ERS that follows it (figure 51). The beta ERD following S1 effect is also statistically significant in the left middle occipital cortex; however there is no beta band ERS effect as there was on the right middle occipital cortex (figure 52).

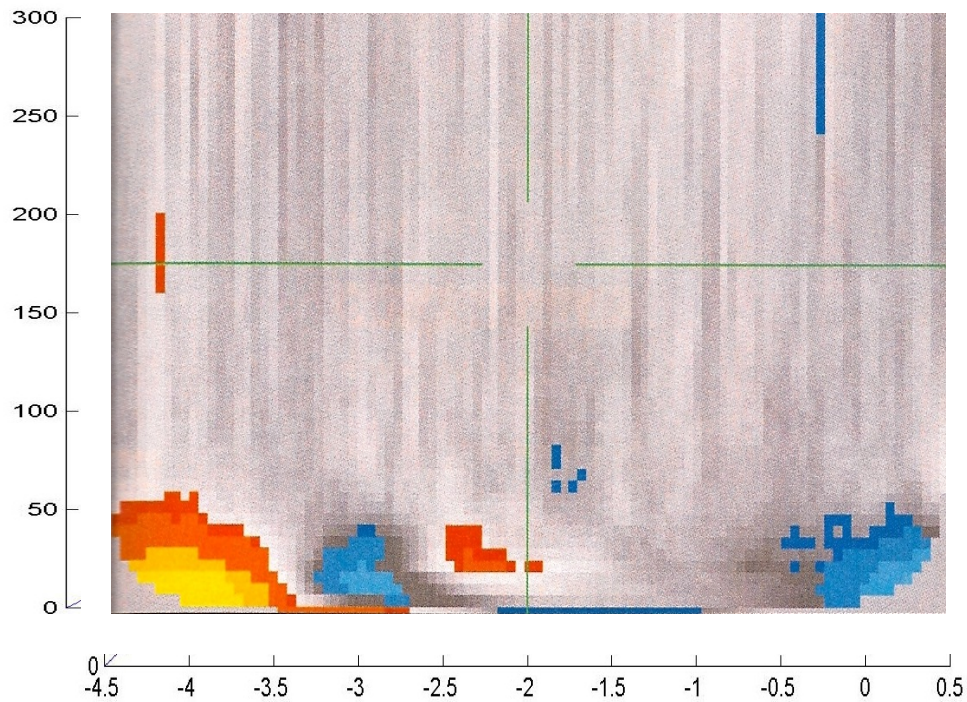


Figure 51. Right Middle Occipital Cortex. Statistically significant activation in source-space time-frequency plot of instructed condition reaches. ($q=.05$) Disregard cross-hairs.

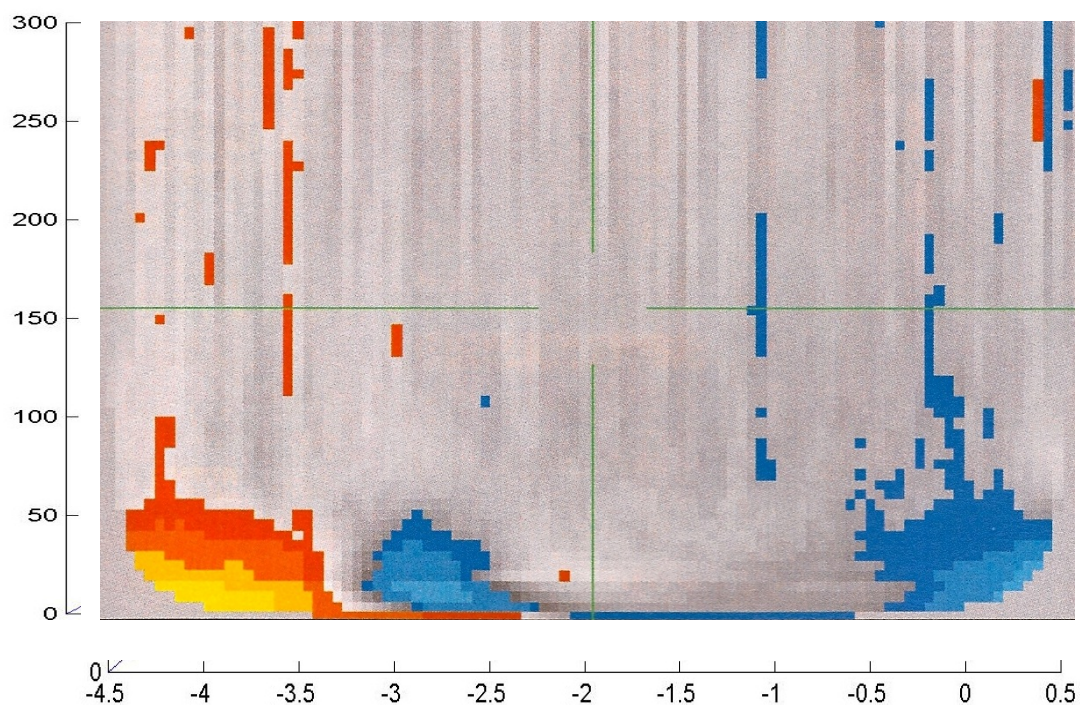


Figure 52. Left Middle Occipital Cortex. Statistically significant activation in source-space time-frequency plot of instructed condition reaches. ($q=.05$) Disregard cross-hairs.

In the instructed condition, the beta ERS that occurs around -2.5s in the right but not left middle occipital cortex is also a statistically significant effect in the right inferior parietal cortex (figure 53, $q=.05$). The beta ERD just after S1 that was found to be stronger on the left side of posterior cortex in the all reaches condition is not evident in the right inferior parietal cortex for the instructed condition, supporting this phenomenon as lateralized to the left posterior cortical structures.

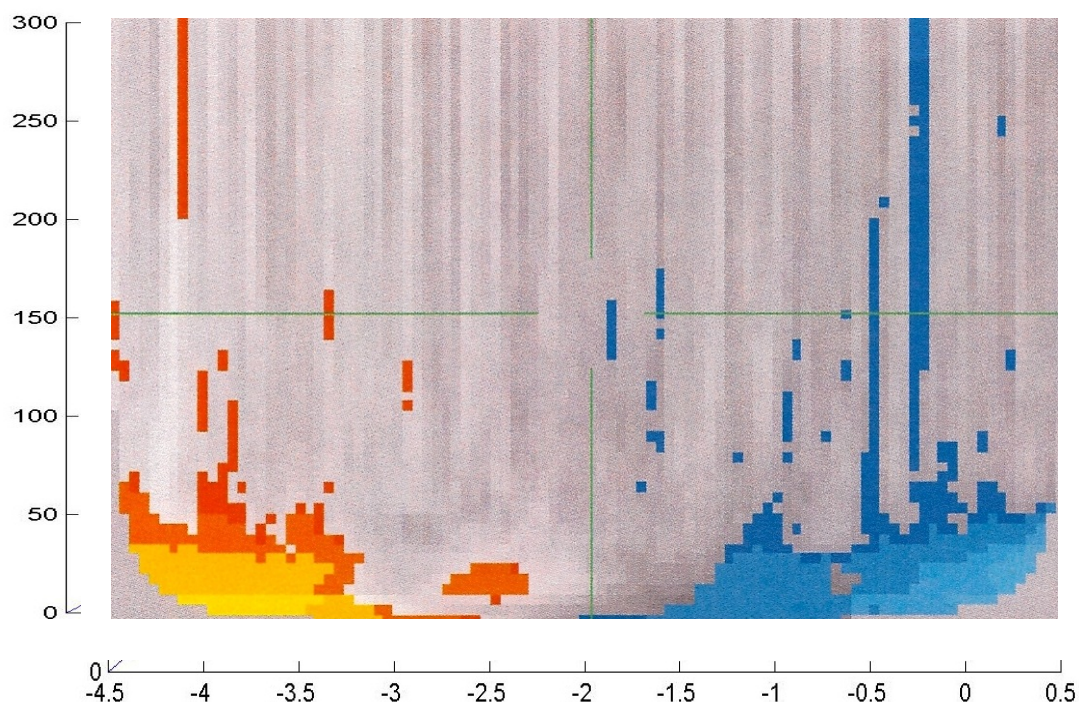


Figure 53 . Right Inferior Parietal Cortex. Statistically significant activation in source-space time-frequency plot of instructed condition reaches. ($q=.05$) Disregard cross-hairs.

In right frontal cortex, the time frequency analysis shows one statistically significant effect associated with the instructed reaches: a beta band ERD 1.5 seconds prior to movement onset (figure 54). This effect was observed 2 seconds prior to movement in the free-choice condition.

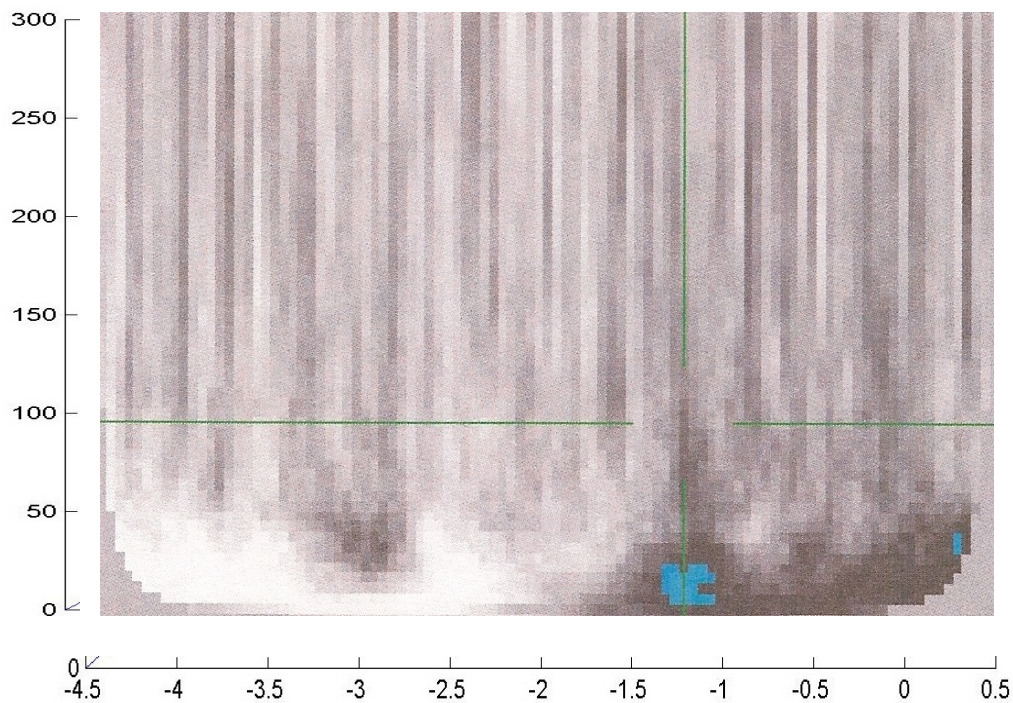


Figure 54. Right Frontal Cortex. Statistically significant activation in source-space time-frequency plot of instructed condition reaches. ($q=.05$)

VI.E. Free Choice Minus Instructed, Two Group Comparison

In a two group t-test with multiple comparisons corrections, the

statistically significant effects that distinguished the instructed and free choice conditions occurred in right frontal cortex (figure 55). The frontal theta rhythm ERS that follows S1 and the frontal theta rhythm ERD that precedes S2 were larger in the choice condition than in the instructed condition. Also, the choice condition had a beta band ERD around -2 seconds that was not present in the instructed condition.

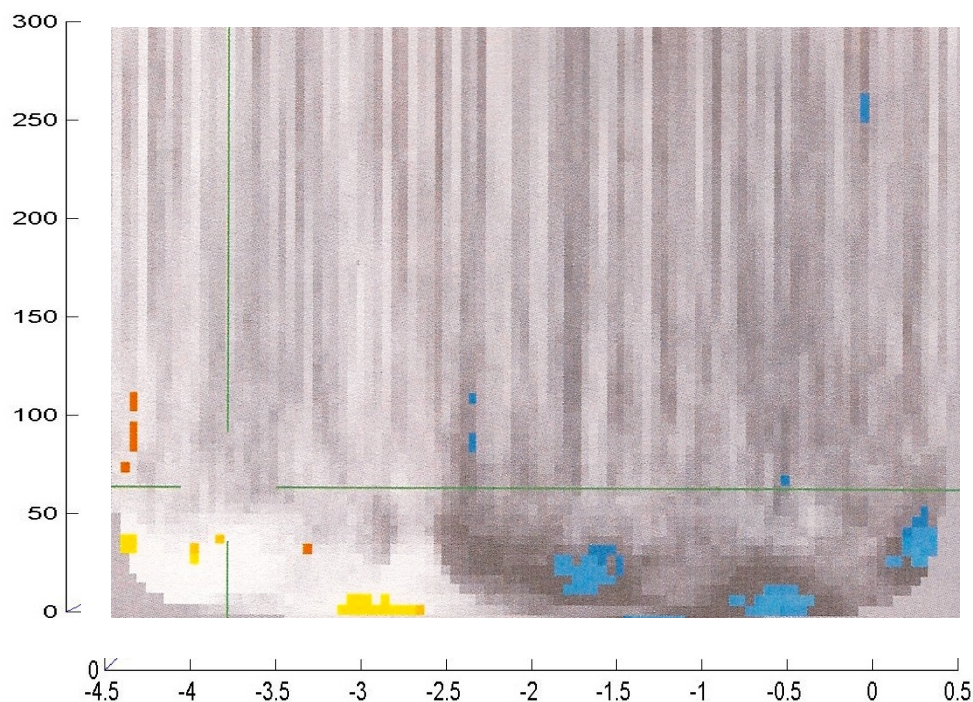


Figure 55. Right Frontal Cortex. Statistically significant activation in source-space time-frequency plot of two group t-test, choice condition minus instructed condition. ($q=.10$) Disregard cross-hairs.

VI. F. Imagined Reaches

VI.F.1. Location of Peak Activity

There were less data for analysis for the imagined reaches condition than for the other condition because subjects got sleepy during the recording sessions so the sessions had to be shorter. Also note that because there is no movement onset in this condition, analysis is time-locked to the go cue as it was for the condition of “all reaches”. SAM analysis of the imagined reaching condition yielded the following peak sources of activation:

- left inferior parietal lobule, BA40, ERD in 15-25Hz
- left precuneus and BA7, ERS in 40-50 Hz
- left BA18, ERS in 50-60Hz
- left middle occipital gyrus, ERS in 60-70 Hz
- right middle temporal gyrus, ERS in 130-140 Hz
- right superior frontal gyrus, ERS in 35-45 Hz

VI.F.2 Source-Space Time-Frequency Plots

Virtual channels were created at the sources identified by SAM. Time frequency analysis in source space using these virtual channels produced interesting effects in three regions. In the right middle temporal region (figure 56), the familiar burst of HFO ERS and the beta band ERD occurs just after S1. In addition, an effect is evident that was not seen in previous analysis in this study: a beta band ERS

1.5 seconds prior to the go cue. In previous conditions, the movement-related beta band ERD would be beginning at about this time. Because no actual movement is produced, this event could be associated with the function of blocking a motor program that has been prepared. Similarly, in the left inferior parietal region there is no movement-related beta band ERD (figure 57) as there had been in all other reaching conditions analyzed in this study.

The time frequency plot of the source in right frontal cortex produced the same interesting ‘timing’ marks that were also present in the “all reaches” condition (figure 58). The effect likely emerges from the fact that these are the only two conditions that were analyzed time-locked to the S2 ‘go’ cue, thereby increasing the precision of the responses to the presented stimuli. One difference notable in this effect in the time frequency plots for ‘all reaches’ and imagined reaches is that the

timing-related events in the 'all reaches' condition occur 1 second prior to S1 and S2 whereas in the imagined reaches trials, the timing-related events occurred .5 s prior to S1 and S2. The imagined reaches trials took place in a separate session following the real reaches session. Training effects or actual differences in the timing of covert brain processes associated with imagined movement could account for the different timing of the "timing-related" events in real and imagined reaches.

VII. Single Trial Analysis, Pattern Recognition

Analysis of single trial data is extremely challenging because of the low signal to noise ratio. Data mining and pattern recognition techniques are being applied to a wide spectrum of fields today: the identification of terrorist networks, automatic recognition of handwritten zip codes on postal mail, irregular/fraudulent credit card use, speech recognition technology, and computer-aided diagnosis for physicians, to name a few. In the case of the research presented here, patterns were extracted from the electromagnetic activity in the

brain to classify the target of a reaching movement: either to the ipsilateral field or to the contralateral spatial field. The basic steps of pattern recognition are very similar despite the application: reduction of noise, extraction of statistically relevant features, and construction of a model based on those features and classification of new inputs by the model.

Essentially, the goal is to find features of the data that form an invariant pattern associated with one class and not with the other. Usually not all data points acquired are relevant to classification. Moreover, using irrelevant data can actually degrade the model's performance on new inputs by over-fitting to the extraneous information. Feature selection is the process used to address these issues before a model is constructed. The feature selection process not only contributes to the success of the final model, it also contributes more generally to the understanding of the phenomenon being examined because the most important features for classification are likely related to signature aspects of the coding/structure of that phenomenon.

VII.A. Pre-Processing

VII.A.1. Mark and Epoch

Marker files were created for each trial for movement onset and left or right response. Each trial was epoched into a five-second interval starting one second prior to S1 and ending one second after S2. These intervals were further binned into 500ms time windows.

VII.B. Temporal Transform

Matlab software was used to perform temporal transformation of the data. The Welch method of power spectral density (PSD) estimation was used to transform the data into the frequency domain. The length of the FFT and thus the width of the frequency bins used in analysis was varied to optimize classification accuracy.

VII.C. Feature Pre-selection and Selection

Partial Least Squares Regression was used to select features and to determine weights for the classification model.

VII.D. Classification and Cross-Validation

Leave-one-out cross-validation (LOOCV) was used to compute classification accuracy. In LOOCV, a single observation from the original sample was used as the validation data and the remaining

observations are used as the training data.

A Receiver Operating Characteristics (ROC) Curve was generated for various levels of features and PLSR components.

VII.E. Single Trial Classification Results

The spatial field of the target was able to be classified in nine of the sixteen subjects using single trial data. Classification accuracies between 78%-98% were achieved in the time window from -2 seconds to -1.5 seconds from movement onset. In a power analysis completed prior to data collection, it had been concluded that 300 trials would be required per subject in order to have sufficient power to find an effect between the two classes using single trial data. Indeed the datasets in which it was not possible to classify the location of the target had fewer than 250 trials due to artifacts, technical difficulties in the recording or excessive head motion.

A scatter plot showing the distribution of left and right trials after features were selected and weighted is shown in figure 59 for one subject. In the scatter plot of figure 59, the model score plotted on the y-axis of is the sum of a weighted combination of features obtained from multivariate regression. The x-axis of figure 59 is a question index in which each dot represents one trial. The horizontal line drawn through the scatter plot represents a chosen threshold value. Trials with model scores above this threshold are classified as reaches to the right while trials with model scores below the threshold are classified as reaches to the left. The corresponding ROC curve is in figure 60.

In an ROC curve the straight, diagonal line as seen in figure 60 represents classification of 50%, or chance for a two class condition. The blue line represents the results of the classification as a trade-off between true positive rate (classify left when left) and false positive rate (classify left when right). If the classifier identified every trial as left, it would have both a high true positive and false positive rate. Depending on the context of the experiment and its applications, the

investigator determines if it is worth increasing the FP rate in order to increase the TP rate. The results shown in figure 60 are very good since in order to get a true positive rate of 95%, the false positive rate only needs to be 20%.

The features used for classification were pairs consisting of a frequency bin of width 18 Hz ranging from 1- 300 Hz and an MEG sensor. The single trial classification analysis was done in sensor space rather than source space, however future studies are planned for single trial classification using the virtual sensors representing source space found using SAM analysis. Issues regarding transferring data and analysis outputs between the different analysis software and operating systems currently used for single trial versus averaged data must first be resolved. The features used for classification of the data for the subject whose data is shown in figures 59 and 60 are listed below and displayed in sensor space in figure 61:

MLT15 99-108 Hz

MLT16 99-108 Hz

MLT27 18-27Hz

MRC61 153-162 Hz

MRF52 91-99Hz

MLC13 135-144Hz

MRP23 18-27Hz

MRP55 91-99Hz

MZO 01 171-180Hz

MLO14 18-27Hz

MLO31 18-27Hz

MLP11 99-108Hz

MLP57 180-189Hz

VIII. Conclusions

Results of this study indicate there is evidence for several characteristic electrophysiological phenomena in the averaged and single trial data preceding reaching movements. The results from the testing of each hypothesis will be reviewed and interpreted in greater detail later in this section, however the highlights are summarized by these claims:

- (1) The electrophysiological correlate of the proximity-to-hand effect (Tipper SP, Lortie C, Baylis GC 1992 Bryden PJ, Roy EA 2006 Meegan DV, Tipper SP 1998 . Welsh TN, Zbinden M. 2009) demonstrated in behavioral studies is a beta band ERS in the intraparietal sulcus which represents an over-ride of a default bias for reaches to ipsilateral space. This electrophysiological event in averaged data can be used to identify whether a person is reaching for a target in the left or right spatial field two seconds before movement onset.
- (2) Human sensitivity and anticipation of periodic events is neurologically encoded in part by a high frequency electrophysiological signal in *left* frontal cortex associated with a feed-forward timing mechanism.
- (3) The widely observed phenomenon of frontal theta rhythms,

largely believed to be cognitive in nature (Cohen MX, Elger CE, Fell J 2009, Tsujimoto T, Shimazu H, Isomura Y, Sasaki K. 2003), was observed in this study in conditions of increased complexity, either physically (crossing mid-line) or cognitively (decision-making). The evidence reported here supports either a function of decision-making or of binding spatially distant ensembles of neurons into a temporary network for this phenomenon.

- (4) Choosing between target locations elicits activation that is not present when the target location is instructed in *right* frontal cortex in averaged data two seconds prior to movement. A right hemispheric specialization in frontal cortex for spatial selection (but not spatial localization) of targets accounts for this finding.
- (5) Using single-trial electrophysiological data recorded from the scalp, it is possible to predict the spatial location of the target of a reach two seconds prior to movement.

The results of each hypothesis tested in this study will now be reviewed and interpreted in further detail.

Hypothesis 1 The characteristics of the temporal and spatial networks of electromagnetic activity prior to reaching movements can be identified in data averaged across subjects.

The first effect observed in the interval of interest, between the S1 cue and movement onset, occurred immediately after the S1 instruction cue at -3 seconds with respect to the S2, 'go' cue: a burst of increased power in an HFO rhythm in the middle occipital gyrus, followed by the onset of a 400ms beta band power decrease in the same region. These events were bilateral but significantly stronger in the left hemisphere of the brain. The effects, which immediately follow the presentation of a visual stimulus and occur in secondary visual cortex, are most certainly related to processing of the S1 cue; however, the lateralization of the effect to the left hemisphere, contralateral to the effector of an upcoming movement, may represent a modulation by early components of reaching preparation.

Just after the beta band ERD in left posterior regions, and two seconds prior to the S2 'go' cue, power increases in the beta band simultaneously in occipital and motor regions. The focus of this effect in regions associated with visual and motor processing suggests that it processes components related to both the sensory and movement

aspects of the reach such as target-related information. The timing of the effect which links the sensory processing of the cue instructing the location of the target and the motor-related ERD effects also supports a role for this effect in coding target-related information for the upcoming movement.

A strong beta band power decrease, long-established as associated with motor preparation, begins in the primary motor cortex approximately two seconds prior to movement onset. An earlier motor preparation component begins at approximately 2.5 seconds prior to movement onset in superior parietal cortex. Both of these motor-related components are stronger on the left hemisphere, contralateral to the movement effector (the right hand).

Interesting spectral effects were found in left and right frontal cortex (figures 27 and 28) during the task. The HFO bursts of ERS at -4s and -1s in left frontal cortex occur precisely one second prior to S1 and S2, respectively. The temporal precision with which these events predict the onset of S1 and S2 points to timing as a possible functional correlate of the bursts. While statistical testing of the time frequency results did not show these timing- associated HFO bursts as significant at a q value of .05 (figure 36), they were significant with $q=.10$.

Another interesting pattern seen in frontal cortex during the “all reaches” condition were power changes in the theta rhythm activity. Theta ERS followed by theta ERD were localized to both left and right frontal cortex. The functional significance of frontal theta rhythms has been attributed to a wide range of cognitive functions including reward, feedback, attention and decision-making (Cohen MX, Elger CE, Fell J 2009, Tsujimoto T, Shimazu H, Isomura Y, Sasaki K. 2003). The variables that might modulate the theta rhythm in this task include decision-making since many of the trials were free-choice; a timing function since there is a strong timing aspect in all trials; or, the recent findings of theta oscillation coupling with high frequency oscillations as a mechanism for integration of spatially distributed regions (Doesburg SM, Green JJ, McDonald JJ, Ward LM 2009 Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT 2006 , Tort AB, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ 2008 Jensen O, Colgin L 2007 Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsaki G. 2008) such as the many activated in this task.

Hypothesis 2 Reaching movements to targets in the spatial field ipsilateral or contralateral to the effector can be discriminated by the spatial and temporal characteristics of the electromagnetic signals prior to the reach.

The novel finding in the analysis of target location was the lateralization of the power changes in the beta band in the intraparietal sulcus modulated by the spatial field of the target. The right intraparietal sulcus had a stronger beta band power decrease prior to movement for reaches to the right (ipsilateral) target than to the left (contralateral) target. Similarly, in the left intraparietal sulcus, reaches to the contralateral (left) target activated a stronger beta band ERD prior to movement than reaches to the ipsilateral (right) target. Additional evidence came from this analysis that the beta band ERS two seconds prior to S2 that was speculated in the previous analysis to be target-related was in fact modulated by target location. This effect was stronger for reaches to targets on the left field than on the right, adding further support to the view that this event carries information about target location. This effect can be accounted for as a neural correlate to the proximity-to-hand-effect, a well-established behavioral phenomenon (Tipper SP, Lortie C, Baylis GC 1992 Bryden PJ, Roy EA 2006 Meegan DV, Tipper SP 1998 . Welsh TN, Zbinden M. 2009). It holds that due to object proximity cues there is a behavioral preference for objects ipsilateral to the effector (Tipper SP, Lortie C, Baylis GC 1992 Bryden PJ, Roy EA 2006 Meegan DV, Tipper SP 1998 . Welsh TN, Zbinden M. 2009).

Based on the results of this study, I claim that the beta ERS in the intraparietal region prior to reaches to contralateral targets is evidence of an over-ride of the electrophysiological correlate of the proximity-to-hand effect. It is acting as an over-ride of the default preference for the ipsilateral target.

Frontal cortical activation was also modulated by target location. The frontal theta rhythm was stronger in reaches to the left (contralateral) target. Frontal theta rhythms have generally been associated with cognitive functions (Cohen MX, Elger CE, Fell J 2009, Tsujimoto T, Shimazu H, Isomura Y, Sasaki K. 2003), so it is not clear what aspect of the target location could account for this effect. Perhaps a movement that crosses the mid-line requires higher levels of integration across brain regions, supporting the view that the frontal theta rhythm represents a binding of information within a widely distributed spatial and temporal network such as the one involved here.

Hypothesis 3 The characteristics of the temporal and spatial networks of electromagnetic activity prior to imagined reaching movements can be identified in data averaged across subjects.

The unique effect observed in imagined reaches compared with actual reaching movements was a beta band ERS 1.5 seconds prior to the go cue. In previous conditions, the movement-related beta band ERD would be beginning at about this time. Because no actual movement was produced, this event could be associated with the function of blocking a motor program that has been prepared, in essence a frequency-coded braking action. Such a conclusion is based on the widely accepted perspective that in general ERS functions as a “blocking” or “turning off” of active processing of inputs (Pfurtscheller G 1992).

Right frontal cortex produced the same interesting timing-related effects during imagined reaches that were evident in the “all reaches” condition for actual movements. The presence of this effect in just these two conditions likely emerges from the fact that these are the only two conditions that were analyzed time-locked to the S2 ‘go’ cue, thereby increasing the strength of the effects seen due to the stimuli presented. One notable difference between this effect for ‘all reaches’ and for imagined reaches was the difference in the timing of the events themselves. In the ‘all reaches’ condition, the HFO bursts occur 1 second prior to S1 and S2, whereas in the imagined reaches

trials, the HFO bursts occur .5 s prior to S1 and S2. This difference in timing could be accounted for by intrinsic differences in the brain mechanisms for movement and imagined movement or, alternatively, by training effects due to extensive repetition of the task. The imagined reaches trials were recorded after subjects had been performing the actual reaching movements for more than an hour. Training effects, such as shorter reaction times, have been demonstrated in motor tasks (Arito H, Oguri M 1990) following fewer repetitions than those preceding the imagined reaches trials in this experiment, leading to the possibility that training effects could account for the difference in the timing of the bursts of frontal ERS. Actual differences in the timing of covert brain processes associated with moving and thinking about moving could also explain the different timing of the “timing-related” effects in frontal cortex.

Hypothesis 4 Decision-making processes distinguish conditions of movement to a freely-chosen visual target and movement to a visually-instructed target. Differences in the MEG data recorded during these conditions will indicated brain regions and frequencies of activation associated with target selection.

In left superior parietal cortex and middle occipital cortex there appears to be theta-modulated HFO bursts from the presentation of S1 to the end of the beta band posterior ERD S1 response; and then again one second prior to the S2 response until movement onset. This trend did not meet the threshold for statistical significance, although the significantly lower levels of power in the high frequencies compared with low frequencies could lead to the effect being 'swamped' by higher power values in the beta band. Statistical significance might be obtained in additional analysis done solely on the higher frequency range.

Right frontal cortex was the region that distinguished conditions of free choice and instructed reaches. Statistically significant beta band ERD was evident in right frontal cortex in the choice condition from -2 to -1.5s with respect to movement onset but the same effect occurred later, from -1.5 to -1s, in the instructed condition. In addition, the frontal theta rhythms were larger in the choice condition than in the instructed condition. This agrees with previous studies finding this affect associated with decision-making but could also represent a "binding" function of spatially distributed regions.

Hypothesis 5 The location of the target of reaching movements to the spatial field either ipsilateral or contralateral to the effector can be predicted prior to movement onset from single trial MEG data in off-line analysis using a classifier constructed with pattern recognition techniques.

Classification of the spatial field of the target was possible with 78% -98% accuracy with an alpha of .05 after multiple comparisons correction using single trial data for just more than half of the subjects. Variables that affected the accuracy of classification included: the number of trials available for classification; the width of the frequency bin; the number of features in the model; the number of partial least squares regression components in the model.

The number of trials available to build the model was the single largest factor affecting the accuracy of classification. Data sets that included many trials that had to be discarded due to artifacts or technical malfunctions were not classified with accuracy better than chance. More specifically, datasets with less than 250 events could not be classified. The power analysis done prior to the experiment had suggested that 600 events would be required, however

classification was possible with as low as 250 events.

Two different widths for the frequency bins were tested as features for the classification model, 9 Hz and 18Hz. Better accuracies were obtained with the classifier based on 18 Hz frequency bins.

The number of features used in the classification model affected the accuracy of the classifier. Most models utilized 24 - 32 feature-pairs (frequency bin/MEG sensor). Using more features created a condition of over-fitting. In such a case the model classified the training set nearly perfectly, but did not do well in classifying new inputs. Using too few features also resulted in poor accuracy of classification.

The number of components of the partial least squares regression (PLSR) included in the model affected the accuracy of classification. Classification for most datasets was optimized with 2-3 PLSR components. Each higher component of the regression accounts for additional variance between the two classes, so classification accuracy is increased as more components are added until too many components are included resulting in over-fitting of the data. Just as over-fitting caused the accuracy of the classifier to deteriorate when too many feature-pairs were included, a model constructed with too many PLSR components did not generalize to new inputs.

The features used for classification clustered in areas identified in the studies of the averaged data that were associated with reaching and in particular with target location: parietal, occipital, and frontal. In addition motor sensors were always selected as features by the algorithm.

VIII. A. Cocktail Party, (or Happy Hour) Version of the Findings

Now, to return to Tippy's Taco Shack on the shore in Encinatas. So what *is* the brain doing while we sit at our table at happy hour, arms-length from a basket of chips and a frozen margarita? The signature patterns in the electromagnetic activity of the brain reported in this study shed some light on that question.

Assuming you are right-handed, it is a well-established finding that the left side of your brain processes the signals necessary to evoke movement. This study showed that the lateralized response for motor control also has an effect on the lateralization of brain activity associated with processing sensory aspects of the target of the movement. In particular, immediately after you look at the chips or margarita as a possible treat, in the *left* middle occipital/temporal/parietal junction there is a strong 75-300Hz burst of

ERS followed by a half second of beta ERD that is only weakly present if at all in the right hemisphere. This occurs whether or not the target (the margarita) is on the left or right, suggesting the lateralization is due to the stimulus being processed as a target of a movement rather than as an effect of the stimulus location. To dissociate whether this effect is present for all stimuli processed prior to an upcoming movement or just for the specific target of the movement cannot be determined from this study because all the stimuli tested were targets of upcoming movements. A study comparing sensory processing of more than one stimulus prior to movement in which only one was the target, as well as a study with left-handed subjects in which the modulation would be expected in the right hemisphere, could be done to dissociate those two conclusions. If indeed the lateralized response to visual stimuli in the *left* occipital/temporal/parietal region as seen in this study reflects a modulation of sensory processing due to target status, it would be possible to use the electromagnetic activity of the brain to predict upcoming targets of movement up to two seconds prior to the movement itself. In other words, if a miniature, portable MEG system were available (they are not) to put on your head, the lateralized response of the electromagnetic signal recorded from your brain to

the target stimulus could be used to predict whether you were about to eat a chip or drink your margarita before you even moved a muscle.

In a similar example of “mind-reading” during happy hour, this study also provided evidence of another neural electromagnetic signal recorded at the scalp that could be used to predict whether you were about to reach for the chips or the margarita prior to movement. On the table at Tippy’s Taco Shack, the chips are on your left on the table in front of you and the margarita is on the right. Spatial reasoning theory based on behavioral studies predicts that you will reach for the margarita due to the proximity of the margarita. Such a claim now has electrophysiological support. There is an increase in power in the beta band in the left intraparietal sulcus 2.5 seconds before you move if you’re going for the chips, but not if you’re reaching for the margarita. This finding could be further tested using the same paradigm used here but with left-handed reaches.

IX. Future Studies

The results discussed here suggest future studies to further dissociate components of the electromagnetic activity of the brain involved in reaching to visual targets. First, it was suggested but not determined if there are movement related components in the responses to the S1 cue in occipital cortex. This would be a very early motor component. In this study the left hemisphere of the brain showed stronger activation during the beta band ERD sensory response to S1 in occipital cortex. I speculated that this may be an enhancement or 'response bias' present in the sensory response resulting from the fact that only right handed reaches were being executed, therefore biasing the contralateral dorsal stream of visual processing. This could be tested by running experiments with both right and left handed reaches.

The claim in this study that the beta band ERS in the intraparietal sulcus is a neural correlate of an over-ride of the proximity-to-hand effect could be confirmed with further testing, using the same paradigm used here but with left-handed reaches.

The other interesting effect I think deserves further investigation is the frontal theta rhythm, which was a component in the selection of a target and in the localization of contralateral targets in this study. A

future study utilizing information about the phase of the electrical activity could identify whether phase coupling was present between theta and HFO activity. Such a phenomenon could have a functional role in binding the various brain regions (Doesburg SM, Green JJ, McDonald JJ, Ward LM 2009 Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT 2006 , Tort AB, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ 2008 Jensen O, Colgin L 2007 Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsaki G. 2008) involved in preparing for a reach to a target. Such a finding could contribute to one of the most actively pursued questions in neuroscience today: the “binding problem”. An experiment that requires integration of simple visual and motor components would make a reasonable platform for study of such a phenomenon.

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