ABSTRACT

Title of Dissertation: ROLE OF HUMAN PARIETAL AND PREMOTOR CORTICAL AREAS IN COMPLEX HAND MOVEMENTS

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The need to understand our ability to plan and successfully execute movement is a core aspect of clinical neurophysiology. Studies in humans are particularly valuable and can have direct application to neurological disorders. While most studies have focused on the physiological characteristics of relatively simple movements (e.g., finger flexion, extension), the aim of the current studies is to determine the mechanisms involved in producing meaningful, complex movements that better represent natural movements. Electroencephalography (EEG) measures such as movement-related cortical potentials, coherence, and event-related synchronization and desynchronization allow investigators to determine the functions of specific areas and coherent networks before and during movement. Patients with ideomotor apraxia, who produce abnormal movements with spatial and/or temporal errors during pantomime of praxis movements (e.g.,

using a hammer, waving good-bye), were compared to normal subjects. It is our hypothesis that performance of complex movements involves early preparatory activity seen localized in the left parietal and premotor cortical areas. Additionally, we hypothesize that the activity seen in the parietal and premotor cortices is coherent and part of a functional network for such movements. Stroke patients with parietal and premotor lesions with apraxia will show a decrease in function of these areas, as well as reduced communication of the network as a result of their anatomical damage. Our studies revealed widespread and early activity of the parietal cortex for praxis movements in normal subjects. This early activity was also seen in the inferior temporal cortex. The distribution and timing of this activity was different when comparing it to simple movements, which generally had activity confined to the premotor cortex. Moreover, an active functional network was seen between the parietal and premotor cortices of the left hemisphere for praxis movements. This network differed from that seen in patients with ideomotor apraxia, where activity in the right hemisphere parietal and premotor areas became predominant. These studies provide evidence of distinct and early parietal activity before praxis and a functional network that is involved in planning and execution, which can be modified in the event of brain injury.

ROLE OF HUMAN PARIETAL AND PREMOTOR CORTICAL AREAS IN COMPLEX HAND MOVEMENTS

by

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This dissertation is dedicated to 4 special people who helped me develop my scientific curiosity at an early age;

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LIST OF ABBREVIATIONS

AIP – anterior inferior parietal area

APB – abductor pollicus previs

BP – Bereitschaftspotential

CBD – corticobasal degeneration

CCZ – caudal cingulate zone

CMAd – dorsal cingulate motor area

CMAr – rostral cingulate motor area

CMAv – ventral cingulate motor area

CNV – contingent negative variation

ECOG – electrocorticography

EEG – electroencephalography

EMG – electromyography

ERD – event related desynchronization

ERS – event related synchronization

FCU – flexor carpi ulnaris

fMRI – functional magnetic resonance imaging

IPL – Inferior parietal lobule

LSM – left sensorimotor area

LSPL – left superior parietal lobe

LIP- Lateral intraparietal area

LIPL – left inferior parietal lobe

M1 – Primary motor cortex

MES – mesial cortex

MRCP – movement related cortical potentials

NS' – Negative slope

PMdc – dorsal premotor cortex, caudal part

PMv – ventral premotor area

PPC – posterior parietal cortex

PPN – posterior parietal negativity

PRR-Parietal Reach Region

RCZ – rostral cingulate zone

RIPL - right inferior parietal lobe

RSM – right sensorimotor area

RSPL – right superior parietal lobe

SMA – supplementary motor area

STS – Superior temporal sulcus

TMS – transcranial magnetic stimulation

VIP – ventral intraparietal area

Chapter 1 Introduction

Knowledge of the functions of different areas of the brain has evolved for hundreds of years. Early investigators wanted to know not only how the normal brain worked, but sought to understand how lesions affect certain faculties. An early investigation by Everard Home to "…procure accurate information respecting the functions that belonged to individual portions of the human brain…" (Home 1814) highlights early understanding of the brain as a structure that has different parts with a variety of functions. Later investigations revealed that these different parts are interconnected which could result in the transmittance of information relevant to a task from one area of the brain to another. We now know that there are many connections from single areas of one cortical region to various, and sometimes very precise regions of the brain.

The function of complex cortical circuitry is thought to be one of many important mechanisms of the brain. In principal, for tasks involving multiple processing levels, there must be communication between distinctly different brain areas that are involved in processing information relevant to the task. This is hypothesized to be the case for some types of complex motor control tasks, where object features and meanings are constructed by one area of the brain, and preparing the hand for the appropriate motor performance of that object is dominated by yet another. Praxis hand movements are a type of complex motor task that is of interest in this body of work. These are movements that are aimed at performing

the goal of operating a tool or performing a gesture. Specifically, the studies described here are aimed at understanding several basic features of activation and integration of distinctly separate cortical areas critical to praxis performance. Under consideration here are the activation and integration of the parietal and premotor cortices. These two cortical areas have been extensively studied in both human and non-human primates, and models have been proposed for their activity guiding complex movement. First, studies were performed specifically to determine the temporal activation of these cortical areas in planning and execution phases of hand praxis. Following the knowledge gained in those studies, analysis was performed to understand the activation of cortico-cortical networks in planning and executing praxis. This provides a novel understanding of functional connectivity involved in complex motor control. Studies in patients who are impaired at performing such complex praxis movements provide a model of cortico-cortical network dysfunction that allows us to better understand the importance of this dynamic property of the brain. The above-mentioned studies provide a framework for further studies on cortical networks and integration of processes of different areas of the brain. Additionally, these studies provide insight on the mechanisms involved in altering the normal function of the brain after lesions. Our studies show the functional relevance of the models and raise further research questions about cortical function for motor control. It is fitting to review the work related to these cortical areas to establish a proper framework for these studies.

Posterior Parietal Cortex

The parietal cortex has been extensively explored in recent years. Particular attention is focused on the posterior parietal cortex, consisting of the superior and inferior parietal lobules. Both areas have components related to motor control, perhaps in the formulation of higher-level motor plans. These areas are thought to play a role in tasks such as reach and grasp movements. In the macaque monkey, a specific region known as the parietal reach region, found along the intraparietal sulcus, has been shown to be involved in planning and executing a reach movement to specific targets (Batista and Andersen 2001). A similar region has been shown in the macaque to encode information about preparation for reach and location of a remembered target for either a saccade or reach (Calton et al. 2002). There are many areas in the primate posterior parietal cortex involved in directing and controlling hand, eye, head and arm movements (as reviewed below, and in (Rizzolatti et al. 1997)).

In human fMRI studies, preparing and performing imagined prehension activates areas of the intraparietal sulcus and the superior parietal lobule (Johnson et al. 2002). This activation leads researchers to believe that such areas may be involved in tool use, as well as other similarly complex hand movements. Activity in the posterior parietal cortex has been shown during tool use movements, gestures, and other complex movements, including imagination of such movements (Ochipa et al. 1997; Moll et al. 1998; Choi et al. 2001). Defining the anatomical and functional properties of the many parietal regions has

been done, primarily in the macaque monkey. Specific regions are active, during preparation and/or execution of active touch, reaching, pantomime of observed action, planning arm and leg movements based on sensorimotor activity, and monitoring/controlling arm movements (as reviewed in (Rizzolatti et al. 1998b)). It is often thought that the motor roles of the parietal cortex are movement preparation and motor intention. Actually, much of the posterior parietal cortex has some function in controlling movement (Andersen and Buneo 2002). During a visuospatial attention task when no arm or hand movement is required, a very small area of posterior parietal cortex is activated (Rushworth et al. 2001b); and this activity is thought to be the human homologue of an area in the monkey concerned mainly with attention to visual targets with no motor involvement (Snyder et al. 2000). In the previously mentioned Rushworth et al. (2001) study, during hand movements to a fixated target, activation is seen across much of the posterior parietal cortex, in regions along the intraparietal and parieto-occipital sulci and an area adjacent to the intraparietal sulcus, similar to an area in monkeys active during hand manipulation (Hyvarinen 1981).

While these studies suggest predominant left parietal area activity, the right posterior parietal cortex must not be ignored. Right hemispheric predominance has been shown when subjects are orienting to stimuli (Nobre 2001; Corbetta and Shulman 2002). However, these studies mostly reflect eye-motor activity. During motor attention paradigms involving subjects covertly planning hand movements using positron emission tomography (PET), posterior parietal cortical

activation is clearly seen in both hemispheres (Deiber et al. 1996; Krams et al. 1998). Studies still suggest that motor attention involving the right hand generally activates the left posterior parietal cortex predominantly (Rushworth et al. 2001a).

While there are many anatomical divisions of the posterior parietal lobe, much of the investigation in monkeys has focused on three main areas. First is the parietal reach region (PRR), which is mainly involved in reach-to-grasp actions. Second is the anterior intraparietal region (AIP), which is considered to be mainly involved in grasping. Third, is the lateral intraparietal area (LIP), which is largely concerned with eye movement planning. Studies of the function of these regions suggest that they are each actively involved in types of complex movements, similar to praxis. These areas and their involvement in complex movement are reviewed in the following paragraphs.

The PRR is a region that has been extensively studied. It is an amalgam of multiple anatomically defined regions of the PPC; yet, the area has been shown to have neurons that are specific for a particular task. As the name suggests, reach-related activity dominates this area, but its pattern of activation may be implicated in various types of complex movement. Neurons in the PRR are active during a planned reach (Batista and Andersen 2001). Specifically, activity of the PRR does not code for any possible reach, but only for the next planned reach. This indicates that this area may be involved in information processing only for a

movement that is to be executed immediately, while ignoring all other possible and future movements. It has been proposed that the PPC is involved in a complex network to eliminate all other possible options for movement, only selecting the one that is most appropriate to perform immediately (Bartolo et al. 2003). While this proposal is based on human data, the human homologue of PRR may invoke similar mechanisms for praxis-type movements, which are best studied in humans. Most praxis movements have multiple ways to perform them correctly. For example, one may use a hammer for hitting or removing a nail. Additionally, there are many different tool-object configurations involved in this type of movement that will change the posture of the hand. It is possible that selection of hitting a nail into wood requires that all other possible movements be eliminated from the motor program. This would involve both parietal and premotor/prefrontal cortices, as will be discussed further in the next section of this chapter and is a point of emphasis in the results and discussion of Chapter 5. Additionally, such tool use requires reaching for and grasping a tool to perform the movement, which would certainly involve a human homologue of the PRR. The PRR has been shown in human fMRI studies to have preferential activity when pointing to a target versus making a saccade to the same target, indicating its activity is specific for hand motor intent (Connolly et al. 2003). In a primate study, monkeys were instructed to reach or saccade to a fixation point based on the presentation of a flash of light. In this study, the PRR was active preferentially for reach (Snyder et al. 2000). Additionally, if a saccade was instructed, then just before movement the cue was changed to indicate a reach, the

PRR became maximally active. Thus, the PRR can also respond to changes in the type of motor plan. These studies provide evidence regarding the dynamics of parietal activity.

Area AIP has shown to have considerable potential in the studies of limb motor control. This region of the IPL is involved mainly in hand manipulation and grasping movements. One study identified several neurons in this area that are active depending on the type of object to be manipulated, suggesting that coding of shape and orientation occur in this area (Sakata et al. 1995). Additional evidence suggests that the AIP may have an even more complex role. Recordings of neurons in the macaque showed that neurons in this area are visual-dominant and visuo-motor in function (Murata et al. 2000). Additionally, the investigators in this report found that activity could be further classified in to object (ex. tools) or non-object (primitive shapes) classifications with varying selectivity. This complex classification system provides a rationale for the consideration of complex cortical relationships that provide the posterior parietal cortex with many types of information. Neurons in this area are also selective for size (Ito et al. 1995) and orientation (Taira et al. 1990) of objects that are to be grasped. This area does not appear to have neurons that respond exclusively to tactile input or bimodal visual-somatosensory input. Thus, it is largely related to processing visual input and recognizing motion (Andersen et al. 1997), likely for motor control. It has been suggested that this area has another critical function for

processing motor commands, e.g. processing the efferent copy of the motor command created by the premotor cortex (Andersen et al. 1997).

The LIP is thought to have a role in planning eye movements (Dickinson et al. 2003; Zhang and Barash 2004), but may also be involved in activity related to the hand in a secondary, but critical fashion. While studies have revealed that the LIP is also involved in coding three-dimensional information of objects (Gallese et al. 1994), it has been hypothesized that it also plays a significant role in properly executing grasping 3-D objects. Studies are beginning to show that this area relays object dynamics to more motor relevant areas of the PPC (perhaps the AIP or PRR). This area is related to the function of intention (Snyder et al. 1997) and visuospatial behavior (Colby and Duhamel 1996). Neurons in this area are also involved in motor aspects of grasping behavior (Gallese et al. 1994). While saccade control seems to dominate the literature to date, certainly more investigation is required to show the dynamics of LIP's interaction in limb motor control.

Lesions of the left parietal cortex can show a multiplicity of gross deficits in motor control. Because lesions in humans are rarely seen in strict anatomical borders (such as confined only to the AIP), human investigations must describe these lesions in broader terms. Redirecting motor attention is severely impaired in patients with damage to the left parietal area, much more so than right parietal lesions (Rushworth et al. 1997). Ideomotor apraxia, a deficit of normal tool-use

pantomime and gesture performance, is most often associated with left parietal and/or premotor lesions (De Renzi and Lucchelli 1988; Haaland et al. 2000). Motor sequence generation can also be affected (Haaland and Harrington 1996; Hermsdorfer et al. 2001). This deficit of motor sequence generation could emerge from processes devoted to attention, since continuing a motor sequence requires constant redirection of motor attention from one movement to the next (Rushworth et al. 2003). If a patient cannot continually progress through a motor plan as it is evolving, regardless of knowledge of movement, the motor task may become more degraded as it proceeds.

While movements such as pantomime are done without direct object control, there is research based on object-directed action that is clearly relevant to pantomime and the posterior parietal cortex. Visuomotor systems have been long studied, and findings illustrated that their pathways dealt predominately with spatial location ("where") and qualities ("what") of the intended object. The proposition is one of a ventral stream that reaches the inferotemporal cortex and a dorsal stream that passes through the posterior parietal cortex. Data showed that monkeys with lesions in inferotemporal cortex had significant trouble with visual pattern recognition, whereas monkeys with posterior parietal lesions had problems determining spatial locations of a rewarded visual cue (Ungerleider and Brody 1977). Thus, based on these data, the dorsal stream is specified for spatial perception (where) while the ventral stream is specified for identification of objects (what). However, later evidence places more importance on a

predominately motor function of these areas as the eventual goal of the activity seen in these streams. If there are two separable streams for processing, it is likely that they are somewhat specialized for different motor control mechanisms. Because they arise from the visual cortex, it is certainly likely that they are involved in visual perception and action processes. On the basis of the eventual output of the areas, it is proposed that the role of the streams is not "what" versus "where", but "what" versus "how" (Goodale and Milner 1992). This implies less of a perceptive role, but more of a motor role of these pathways.

In a study of visually-guided grasp, patients with bilateral parietal lesions could recognize line drawings of common objects, however picking up objects was severely impaired (Jakobson et al. 1991). Based on the hand posture of the subjects in this study, it is clear that they could not use information about size and shape of the tool to conform their hand to the appropriate object size. Such a motor deficit extends beyond the borders of a purely spatial perception deficit. If a spatial perception problem was the main culprit, hand configuration should not be affected, but perhaps only the ability to get into proximity of the target. Patients with lesions in the inferotemporal cortex having visual agnosia have been studied and show that object recognition is largely impaired, while hand and finger movements to the same objects are normal (Goodale et al. 1991a; Goodale et al. 1991b; Milner et al. 1991). Such patients cannot clearly discern the different sizes of comparable shapes, and cannot estimate or perceive the size of objects clearly. Thus, the deficits seen here mostly correspond to the visual

knowledge of objects. Therefore, the dichotomy may be best explained as a dorsal "how" and a ventral "what" system. However such a dichotomy may not be fully complete due to the heavy interconnections between these areas (Goodale and Milner 1992). These interconnections may allow for the bridging of brain signals related to understanding what an object is and how it is to be used. Clear separation of the processes of cognitive perception and motor prehension have been shown (Goodale et al. 1994b). It should be pointed out that this is complex because identification of an object must precede functional understanding. Therefore, there must be a complex network to bridge these signals together.

Premotor Cortex

In monkeys, it has been shown that area 6 on the medial wall of the brain consists of two distinct areas: the supplementary motor area (SMA) and the pre-SMA (Picard and Strick 1996). The SMA is the area considered to have more of a direct motor function because of its connectivity with the primary motor area (M1) and spinal cord (Luppino et al. 1993a). Neurons in the SMA are known to discharge in correlation to movement onset or to specific types of movement (Rizzolatti et al. 1998a). It is considered that the SMA (F3 in primates) together with its connection in the parietal lobe (area PFG, corresponds to BA 7) plays an important role in movement onset and specific sequences of multiple joint movements (Tanji et al. 1996). The pre-SMA (F6 in primates) receives a modest connection from the parietal lobe. It has been postulated that this area plays a role in controlling actions encoded in lateral parietofrontal circuits gated by

motivational factors or that it is directly involved in the cognitive aspects of a task (Rizzolatti et al. 1998a; Picard 2001). The cingulate motor areas found on the medial wall of the brain can generally be divided into the rostral cingulate (CMAr), caudal cingulate in the ventral bank of the cingulate sulcus (CMAv), and caudal cingulate in the dorsal bank (CMAd) in primates. These areas also have suspected human homologues: the rostral and caudal cingulate zones (RCZ and CCZ). Finger movements can activate different sites along the CCZ (possible homologue of primate CMAd) as well as the SMA (Petit et al. 1998). The RCZ (which may be a homologue of monkey CMAr) may have more of a cognitive role in selecting action (Picard and Strick 1996; Carter et al. 2000; MacDonald et al. 2000; Picard 2001).

Divisions of the lateral premotor cortex have been found to have a role in movement planning. Specifically, the dorsal part of the lateral premotor cortex, caudal portion (PMdc, F2 in primates), has been shown to have much in common with the SMA in that they both project to the spinal cord and both are involved in the control of movements (Geyer et al. 2000b). Cells having connections from the parietal cortex to the PMdc have been demonstrated to be more active during a limb movement task opposed to visual saccades, making a case for it being involved with motor control (Boussaoud 2001). However, the rostral PMd (F7 in primates) seems to have more of a role in cognitive processes (reviewed in Picard and Strick, 2001).

One fascinating function of the left premotor cortex is its role in movement selection, action recognition, and imitation (Kalaska et al. 1997; Thoenissen et al. 2002). PMd, for example, appears to be preferential for selecting movements based on learning and experience (Toni et al. 2001). Most research on action recognition and imitation has focused on the activity seen in Broca's area. Neurons able to recognize actions have been recorded in primates in area F5 (area PMv) (Murata et al. 1997; Rizzolatti and Arbib 1998). These "mirror neurons", as they are called, are highly active when the monkey manipulates an object and when viewing grasping and manipulation. Additional evidence has revealed that these neurons are highly selective for representing sounds and visual input of particular actions, such as breaking of a peanut or tearing a piece of paper (Kohler et al. 2002; Keysers et al. 2003). The proposed human homologue of area F5 is Broca's area. Transcranial magnetic stimulation (TMS) and fMRI studies have revealed that Broca's area is active during action recognition and imitation of object use (Hamzei et al. 2003; Heiser et al. 2003). This is of particular interest for studies of praxis, since two ways to assess apraxia in patients are to determine the ability to imitate or recognize an action. While damage to the parietal cortex may begin to explain deficits of imitation or recognition, lesions to Broca's area may provide an additional rationale for such deficits.

The premotor cortex is active when planning a movement to an intended target. In this case, information about target location, and hand position must be integrated to form an appropriate movement. In a primate study of motor control,

monkeys were cued to reach for a left or right target with the cued left or right arm, while recording from neurons in the lateral premotor area. This study found that visual information of the selected target and somatosensory information of the hand that is to be moved are gathered together in the premotor cortex to allow for a subsequent reach (Hoshi and Tanji 2000). Additionally, this study revealed that neurons in this area are also selective for instruction: if a left target was cued, action with the left hand was performed most compared to the right hand whether target or hand instruction came first. However, if the right hand was cued then the left target was cued, activity for the left cue was substantially smaller. In this particular neuron, left targets along with motor action with the left hand is preferred. This finding illustrates a role for the premotor cortex in task selection. This is related to the mechanisms of selection of appropriate movements that may occur in the parietal cortex as well, as discussed in the preceding section. Since there are many ways to perform most movements, the brain must select the appropriate type for each task. The premotor cortex has very selective activity based on task type. It has a very clear role in motor programming, specifically in determining the specific motor parameters that are to occur (Kurata and Wise 1988b; Kurata and Wise 1988a; Kurata 1993). The precise coding seen in the above-mentioned Hoshi and Tanji (2000) study for visual and somatosensory information provides a hypothesis for complex movement, as reach mechanisms are likely similar to complex movement. This form of selection may be also involved in, for example, appropriate use of a hammer, where a very small target (the nail) must be hit accurately. Similarly, very specific activity of the premotor

cortex must be required. It is possible that the premotor cortex has some role in selecting specified motor parameters that help drive precise hand movements accurately to a specified target.

Parietal and premotor connectivity

Special circuits between the parietal and frontal cortices have been postulated to control certain aspects of movement. Figure 1 shows the multiple specific connectivity of the parietal and premotor cortex of monkeys. The proposed purpose of the anatomical connections between these areas is to transform useful sensory and cognitive information into an appropriate action. Based on this hypothesis, the function of the network is to integrate the knowledge of the task, contained in the parietal lobe, with the proper motor representations of the specific task in the premotor cortex. Naturally, the motor plan would be executed when the task planning is sent to the motor cortex. Since these connections serve a very specific role to plan and coordinate precise movements, it is inferred that damage to the cortical areas themselves or to white matter fascicles connecting these structures can cause impairment in normal function. One such anatomical connectivity is between the anterior intraparietal cortex and the ventrorostral part of the premotor cortex which has been shown to play a role in guiding appropriate movements of the distal arm (Matelli et al. 1993).

Circuits from a variety of parietal and premotor areas that connect with primary motor cortex tend to be involved in executing hand movements and controlling

independent finger movements, which is key for the proper development of complex, goal-oriented movements such as praxis (Rizzolatti et al. 1998a). Many other circuits have been investigated and shown to be involved in motor control. One circuit is formed with parietal area PF (in BA 7) and premotor area F5 (PMv). It is proposed that the "mirror neurons" of area F5 are supplied with visual information from part of the ventral stream (superior temporal sulcus, or STS) from area PF. Because there are no known direct projections from the STS to the premotor area, established connections from the STS to area PF may supply F5 with its mirror properties (Matelli et al. 1986). It is worthy to note that the STS has been shown to have similar mirror neuron properties and is critical in observation and imitation. Anatomical connectivity with SPL area PE and mesial premotor area F3 may be involved in postural adjustments and general motor readiness preceding voluntary movement sequences (Massion 1992; Tanji et al. 1996). Connections with area IPL area VIP and lateral premotor area F4 are hypothesized to play a role in encoding proper movements in response to visual targets (Bremmer et al. 1997a; Bremmer et al. 1997b). This area F4 is the same area that shows motor and target selectivity in primates (Hoshi and Tanji 2000). Some of these circuits are important for complex movements, such as praxis, and are, therefore, integral in research studies of apraxia. In Chapter 3, research devoted to understanding the role of parietal-premotor networks in humans will be further discussed.

Studies have shown that disrupting these circuits can influence behavior. Using reversible chemical inactivation of the posterior parietal area (specifically area AIP) and premotor (region F5) cortices, primates could not correctly reach a target, often making drastic spatial and temporal grasping errors (Gallese et al. 1994; Fogassi et al. 2001). Additionally, damage of both of these areas and their connections via white matter fascicles has long been implicated in ideomotor apraxia (Geschwind 1965a; Geschwind 1965b; Kertesz and Ferro 1984). As described later, data suggesting disconnection of parietal and premotor areas in apraxia continues to be observed.

Motor cortex

As indicated in the above section, the main idea of the parietofrontal circuitry is to control movements, which is finally done by the motor cortex. It was generally thought that stimulation of the motor cortex causes simple single movements (Penfield and Welch 1951). Stimulation studies have been performed for many years to understand the role of the motor cortex (Fritsch and Hitzig 1870). These experiments provided evidence of a smooth somatotopic organization of the motor cortex with the mouth mapped at the inferior motor cortex and the foot mapped at its superior aspect (Foerster 1936; Fulton 1938; Penfield and Boldrey 1949). However, the clear somatotopy that was thought to exist is now shown to be largely fragmented (Sanes and Schieber 2001). Further studies have generated evidence supporting complex movements from longer duration motor cortex stimulation alone (Graziano et al. 2002b). How these complex movements are

coded is of significant interest. It has been shown that neurons of the motor cortex can respond to varying degrees of a direction of a reach, with broad tuning (Georgopoulos et al. 1986). This broad tuning may be attributed to many other parameters of a movement, such as velocity, position, and force (Caminiti et al. 1990; Georgopoulos et al. 1992; Cabel et al. 2001)). However, longer duration and high-intensity motor stimulation may affect other networks, including the premotor cortices and thalamus, which could be responsible for such complex movements (Bestmann et al. 2003; Bestmann et al. 2004). A map of complex postures may extend into the premotor cortex, which is an area of significant interest to understanding complex movement (see Chapter 1, Premotor cortex) (Graziano et al. 2002a). However, ideomotor apraxia is rarely associated with motor cortex lesions since paresis, which would likely result from motor cortex damage, is a common contraindication (Haaland et al. 2000).

Praxis and Ideomotor Apraxia

In the current studies, praxis relates to movements (customarily performed with the hand) that are purposeful and skilled (Heilman and Gonzalez Rothi 2003). These movements include communicative gestures or demonstration of tool use. It is important to note that demonstration of tool use is different from using the hand as a tool to accomplish a task. For example, using a pair of scissors involves placing the thumb, and generally the index and/or middle finger in the handle of scissors, separating the fingers (open the scissors), and then bringing the fingers back together (closing the scissors to make a cut). However, using your fingers,

as scissors, would involve using extended index and middle fingers to represent blades of scissors. The specific instructions typically described in studies of praxis will demand pretending to hold and manipulate a tool or object. This is also the case in all of the studies presented in this volume.

The most common errors of patients with ideomotor apraxia arise when pantomiming tool use. Because of this, it has been of interest to understand why such a specific deficit occurs, and under what settings could the deficit be manifested. A simplified model of praxis function (as seen in Figure 2) may help explain why the deficit is present and how it can be demonstrated (Cubelli et al. 2000). The remainder of this paragraph refers specifically to the model and its featured elements contained therein. The model takes into account how a patient can be instructed to perform a task. The model distinguishes between a "lexical" route that is responsible for performing meaningful gestures and a "non-lexical" route that is responsible for any type of gesture (whether meaningful or meaningless). In the lexical route, a seen gesture can be matched in a working memory subsystem (the gestural input lexicon) for recognition. If it is recognized, it is identified as a particular type of movement involving a particular tool or way of moving to communicate. The knowledge of this tool or gesture is stored in an "action semantics system".

To allow for correct performance, procedural knowledge of the use of the tool or the purpose of the gesture is stored in a "gestural output lexicon". The

information here relates specifically to instruct on how to perform the movement. Input into this lexical route not only arises from seen gestures, pictures of tools, and cartoons of scenes where a person is about to perform some gesture (all instances where visual clues to hand manipulation are presented), but also from verbal input for performance or written instruction prompting one to perform. Verbal or written cues require the subject specifically to know what a tool or gesture is and to perform it correctly using only their knowledge and internal representations. These word-based cues would bypass matching the seen gestures to stored representations in working memory, but would arrive at the action semantic system for analysis on how the tool pantomimes or gestures are performed. Information is passed on to the gestural output lexicon to allow for correct performance. The last route, the non-lexical route, uses visuomotor conversion to take visual information and convert it into matching motor output. Because of this, the non-lexical route could be employed for meaningless gesture pantomimes, as well as for meaningful gestures. For both routes, the information is stored in a buffer until execution is employed.

Based on this model, one would specifically look for selectively impaired meaningless gestures arising from damage to the non-lexical route (Bartolo et al. 2003). However, if damage to the lexical route was observed, seen meaningful gestures could still be pantomimed via the non-lexical route. It has been proposed that one can, for example, copy written words by either reading the written word with comprehension and copying it, or by a point-by-point copying of the

characters of the written word (Margolin and Binder 1984). One could simply pantomime an act without ever really attempting to understand the action. To eliminate this conflict, if a subject must only rely on their ability to internally generate a motor program based on an instruction command (with no motor visual cues aiding the development of the motor program), then the lexical route must be engaged, specifically using both the action semantics system and the gestural output lexicon. Providing such specific commands can ensure that our testing is aimed specifically at action to command, not imitation to command. If, for example, a patient could not recognize a gesture, they would also have pantomime agnosia, thus having damage to the gestural input lexicon. However, imitation could remain intact via the non-lexical route (Rothi et al. 1985; Rothi et al. 1986; Bartolo et al. 2003). Using pantomime allows better analysis of the anatomical correlates of the lexical route of the model, and the temporal activation of the model as preparation occurs. This specifically addresses the activity of cortical areas involved in meaningful motor processing and execution.

It is proposed that pantomime may involve different neural networks than those seen in direct control of objects. As later explained, patients with deficits in pantomime may regain normal motor control while grasping and manipulating the object. Thus, the addition of tactile cues may help make movements naturally. This is particularly true as long as real mechanical information is conveyed (under conditions of real use) and not just holding objects that are representative of the shapes of tools (Goldenberg et al. 2004). In a kinematic study of normal subjects,

pantomime of a grasp produced a different kinematic signature than actual grasping (Goodale et al. 1994a). This difference in pantomime was seen regardless if the object was removed from the visual field or if it was still there, but the subject was told not to grasp it. It has been proposed that pantomiming involves more ventral stream activity (Westwood et al. 2000). Additionally, the dorsal stream may be involved more in natural actions (Goodale et al. 2004). In patient studies, there is evidence of separate "what" and "how" streams for object and problem-solving knowledge (Hodges et al. 1999). Remarkably, there may be a dichotomy of deficits dependent upon the type of movement to be made. This hypothesis would reinforce the aforementioned "what" versus "how" dichotomy, in part, because it illustrates that natural tool use would demand activation of a system that stores knowledge of how something is to be used, or perhaps compensatory sensory inputs into the parietal cortex, in the case of patient studies (Hodges et al. 1999). However, the ability to successfully pantomime a tool still requires similar motor knowledge. Perhaps all the motor representations of tool use are not stored exclusively in a separate stream, but instead are in cortical areas that are networked between the two streams.

Role of apraxia

Ideomotor apraxia is a cognitive motor disorder characterized by the inability to develop the correct temporal and/or spatial characteristics of a movement in pantomiming object use (Rothi et al. 1985; Rothi et al. 1991). The disorder is further characterized by spatiotemporal errors during pantomime of object-use or

the performance of gestures (Buxbaum 2001). There are other types of apraxia that affect patients differently, but still involve complex movements (Leiguarda and Marsden 2000b). It should be noted that there is intense debate among researchers and clinicians as to the specific clinical picture of each to the following apraxias. The descriptions are meant to provide a general picture of the deficit.

Limb kinetic apraxia is the deficit seen in patients who are unable to make fine precise movements with the fingers of the limb contralateral to the brain lesion. This deficit is typically seen when patients are asked to perform fine manipulation movements (such as picking up a dime or paper clip). Generally, this form of apraxia is seen in patients with lesions in the sensorimotor and premotor areas. However, this is difficult to diagnose since it involves lesions to areas of the brain that generally also cause tone and posture changes which would affect normal grasping and fine finger movements.

Ideational apraxia is a deficit seen in patients with isolated frontal lesions. These patients are often unable to carry out sequenced tasks in an orderly fashion. Patients may, for example, know how to use a knife, but are unable to describe or pantomime its use in making a peanut butter and jelly sandwich. They can, however, use the knife to cut a slice from a loaf of bread. This form of apraxia has been mainly attributed to patients who are in a demented or confused state (Heilman and Gonzalez Rothi 2003).

Conceptual apraxia is a disorder where patients are unable to select the proper use of a tool or object. Different from ideomotor apraxia, where patients have spatial and temporal errors, conceptual apraxics will often make correct movements related to tools or objects that they were not asked to perform. For example, upon command of showing how to use a screwdriver, the ideomotor apraxic patient may make large arcs in the air with the arm. Here, the conceptual apraxic, may pantomime hammer use. This deficit could be related to object agnosia; however, patients with conceptual apraxia can correctly name an object. While there is no determinant locus, the left premotor and parietotemporal areas have been implicated.

Ideomotor apraxia has been studied the most from a clinical perspective. While the linguist Heymann Steinthal first developed a definition of apraxia in 1881, the main early investigators of ideomotor apraxia, specifically, were Hugo Liepmann and Norman Geschwind. Liepmann first reported a patient with apraxia of the right arm only, which led him to exclude agnosia (disorder of recognition) or any elementary motor deficit because the left arm was entirely normal (Liepmann 1900). If the patient had any of the other conditions, apraxia should have been seen bilaterally. Unfortunately, this was a complicated case that was poorly described and the patient had many lesions. In 1905, Liepmann reported the results of 83 right-handed patients with left or right hemisphere lesions. He found that none of the right hemisphere-lesioned patients had apraxia, while half of the

left hemisphere patients had clear deficits (Liepmann 1905). Later investigations revealed a case of a patient with a lesion in the corpus callosum who could not carry out commands with his left hand while having hemiparesis of the right arm (Liepmann 1907). Liepmann explained that this was a deficit of communication between the hemispheres that prevented full use of the left hand. Based on Broca's findings of a left hemisphere center for language, he posited that the left hemisphere was also involved in controlling skilled movements. Additionally, he noted that these deficits usually stem from lesions associated with temporal-pareital regions.

Apraxia was largely ignored until 1965 when Norman Geschwind wrote that apraxia stemmed from a disconnection of Broca's area and the motor cortex (Geschwind 1965b). However, as he pointed out, deficits were not only seen in pantomime to verbal cues, but also to imitation. Geschwind also argued the suggestion of left parietal lesions involved in apraxia, since he had reported left frontal lesions causing apraxia in both hands. He stated that left frontal lesions should not cause apraxia in the left hand since the left parietal cortex was connected with the intact right frontal cortex via the posterior corpus callosum. Many years earlier, Leipmann had suggested that there was a transformation of the motor representations in the parietal lobe that had to occur before the movement could be performed. However, it was unclear as to exactly where this takes place, but was suggested to be in the left premotor cortex (particularly the

SMA), even though there is little evidence to fully substantiate this (Watson et al. 1986).

Because its signs are much less ambiguous, ideomotor apraxia is appropriate disorder to compare to normal cortical function. Ideomotor apraxia is a disorder that was historically considered to be voluntary-automatic in nature (Liepmann 1907). This involves the fact that the patient rarely complains of the deficit outside of the clinical setting where tools and real targets are used for action. However, studies have demonstrated deficits in everyday life, showing that it is worthwhile to understand its physiology and clinical significance (Sundet et al. 1988; Poizner et al. 1990; Foundas et al. 1995; Raymer et al. 1997; Hanna-Pladdy et al. 2003). Errors in pantomiming can be manifested in a vast range from completely unrecognizable pantomime to movements that can be recognized, albeit, somewhat distorted. Overall, transitive movements (i.e. those involving tool/object use) seem to be more affected than intransitive ones (i.e. communicative gestures that would not involve tool/object use) in pantomiming (Leiguarda and Marsden 2000a).

Several possibilities may exist for the extended deficit seen for transitive movements. While tool use movements are much more complex and specified, it could be argued that they require a more focused locus of activation than intransitive gestures. Additionally, tool use pantomime is much less common than intransitive gesturing, which may indicate that neural networks are stronger

for cortical structures involved in preparing and performing these movements, according to Hebbian rules of synaptic plasticity (Fuster 2000). Among elderly normal subjects, gesture production on command and comprehension of correct posture for transitive gestures were more commonly incorrect than for intransitive gestures (Mozaz et al. 2002). This study shows that it is possible for cortical areas related to these transitive and intransitive movements to differ, otherwise, a motor performance deficit and postural comprehension deficit would be comparative for both movement types. If the deficit was purely due to movement complexity, it is more likely that the performance of transitive pantomime would be more typically impaired. Patients with unilateral left hemisphere lesions are diagnosed more commonly as apraxic in pantomiming compared to patients with right hemisphere lesions (Roy et al. 2000a). Hand positioning seems to improve when the patient is provided tactile kinesthetic cues. This could be due to the tool actually helping to establish the correct postural context and the facilitation of formation of the correct hand position for the gesture (Frank and Earl 1990).

There are several diverse clinicoanatomical correlations for the diagnosis of ideomotor apraxia cortically and subcortically. Studies have implicated lesions of the parietal and/or premotor cortex. Damage to the middle frontal gyrus and/or the superior and inferior lobules of the posterior parietal cortex surrounding the intraparietal sulcus has been implicated in a vast majority of patients (Haaland et al. 2000). The rostral portion of PMv (named F5 in primates) and its connection with the lateral bank of the intraparietal sulcus and primary motor area (M1),

which may be related to distal arm movements (Matelli et al. 1985), could play a role in recognizable pantomime. Therefore, damage to the PMv could be involved in a deficit of "motor vocabulary" in the circuit (Leiguarda and Marsden 2000b). Additionally, damage to the dorsal premotor cortex (PMd) could cause breakdown of proximal arm muscles in targeted movements, abnormal arm orientation and trajectory, or deficits in conditional motor learning, all of which can be involved in generating spatial errors (Playford et al. 1993). Involvement of the supplementary motor area (SMA) seems minimal based on studies illustrating no activation of this area during normal subject praxis (Moll et al. 1998). However, in a post-operative study of patients undergoing tumor resection who were left with a SMA syndrome, patients demonstrated difficulties in voluntary arm movements to command (Bannur and Rajshekhar 2000). This is not surprising because the SMA has been shown to be active for voluntary movements (Tanji et al. 1996; Tanji 2001). It has been also proposed and illustrated that the inferior parietal lobe, SMA and motor cortex are all involved in praxis and that breakdown of any of these areas, except the motor cortex, can specifically lead to ideomotor apraxia (Platz et al. 2000). Lesions involving the motor cortex may cause paresis, where loss of limb function would be the more prominent deficit.

Several studies have found that basal ganglia lesions may be involved in ideomotor apraxia. Lesions involving the substantia nigra pars reticulata, globus pallidus, and putamen have been shown to mimic apraxic-like symptoms (Hore et

al. 1977; Kato and Kimura 1992). It is apparent that the possibility exists that different neural systems could be recruited depending on the type of movement sequence that is asked of the patient. By some accounts, it seems that for well-known gesture movements, the SMA and basal ganglia systems would be recruited while tool pantomiming, which is more novel, would involve systems of the prefrontal, premotor, and parietal cortices with the striatum and white matter fascicles (Leiguarda and Marsden 2000b). In this case, tool use pantomime is considered a novel gesture, as it is rarely performed. If so, it would require considerable working memory processes (Bartolo et al. 2003). Generally such movements would involve the tool directly. However, the motor plan requires development of a familiar strategy for motion, and can be considered a well-known gesture. Basal ganglia involvement is certainly possible for either movement type, based on anatomical evidence of connections within the parietal-premotor circuit (Petrides and Pandya 1984; Geyer et al. 2000a; Glickstein 2003).

Purpose of the Studies

It is important to be able to not only understand the spatial relationships of cortical activity for a particular task, but also the temporal relationships. Much information can be gained by determining what brain areas are active in temporal progression leading up to a task. We can gain information about this by utilizing recording methods of electroencephalography (EEG) and electrocorticography (ECOG). In EEG and ECOG, electrodes are placed on the scalp (in EEG) or on the cortical surface (in ECOG), which records the summed voltage from neural

activity of underlying cortical neurons. As will be discussed in the following sections, different analysis methods can be incorporated to describe the function of these cortical areas. Additionally, utilizing coherence methodology allows us to understand the dynamic relationships of spatially distinct cortical regions.

The goal of the research that is contained in this volume is to determine what regions of the brain are active during the preparation and execution of praxis within the left hemisphere. Additionally, knowing when these brain areas are active in relation to each other (i.e. parietal activation occurring before or simultaneous to premotor activation) is of significant interest. Following these studies, we aim to understand if the activity within the parietal and premotor areas is part of a coherent network related to praxis movement. Studies of patients with ideomotor apraxia will be discussed to provide insight on how the mechanisms involved in praxis can change when lesions or degeneration interrupts the normal brain operation. Emphasis will be placed on perilesional areas and homologous areas of the right hemisphere. All these studies help us frame a solid foundation to better understand about praxis and apraxia.

Chapter 2: Cortical Activity Involved in Self-Paced Praxis Movements

Electroencephalography (EEG)

Introduction

The ability to plan and execute a complex motor task is critical in human behavior. Specifically, for tool use and grasp, human studies have suggested that parietal and premotor areas are heavily involved in preparation and execution (Choi et al. 2001; Johnson et al. 2002; Ruby et al. 2002). Similar concepts have been demonstrated in primate experiments (Andersen and Buneo 2002). These studies show patterns of activity in parietal and premotor areas specific to various types of complex motor tasks.

In this study, we sought to improve understanding the roles of these areas in humans to perform complex movements, particularly with regard to their timing. Under consideration, are two types of praxis movements: transitive and intransitive movements. Two studies with functional imaging showed that parietal and premotor areas are involved in praxis movements. Choi et al. (2001) demonstrated that tool use pantomime activated the superior parietal lobule (SPL) and premotor areas. Likewise, a rostrocaudal gradient of activity in the premotor cortex and an inferior-to-superior gradient in the posterior parietal cortex (inferior parietal lobule (IPL) to SPL) were demonstrated during the phases shifting from preparation to execution (Fridman unpublished data). While these studies have good spatial resolution, little is known about the precise temporal activation of

parietal and premotor areas during such tasks. Temporal activation can be assessed in the millisecond range using EEG. Here, we focus on two methods to determine how the cortex prepares for movements: movement-related cortical potentials (MRCPs) and frequency band-specific power change, referred to as event-related desynchronization (ERD) for power decrease and event-related synchronization (ERS) for power increase.

MRCPs have been extensively studied with a wide variety of movement types. The MRCP is an electrophysiological signal of involvement of cortical regions before and during a movement (Deecke and Kornhuber 1978; Deecke et al. 1980; Shibasaki et al. 1980a; Shibasaki et al. 1980b). It reflects the synchronous activity of postsynaptic potentials generated by large pyramidal neurons arranged perpendicularly to the cortical surface. Different periods of the MRCP have been described with simple single movements, generally put into three different periods (Shibasaki et al. 1980b; Kristeva et al. 1990; Tarkka and Hallett 1990; Tarkka et al. 1993). The early period of MRCP, the Bereitschaftspotential (BP), is characterized by a slowly rising negativity characteristically seen beginning about 2 s before a movement. This component is followed by a steeper negative slope (NS′). Following this is the motor potential (MP), which peaks immediately after movement onset.

A second way to assess the temporal sequence of cortical activations is to focus on the power changes in EEG activity in different frequency bands leading up to

and during task performance. These power changes represent activity in ensembles of cortical neurons. There are many ideas as to why such changes occur (Pfurtscheller and Aranibar 1977; Pfurtscheller and Aranibar 1980; Crone et al. 1998; Pfurtscheller and Andrew 1999). Attenuation, or ERD, of a signal in a particular bandwidth before movement onset indicates a decrease of a common cortical oscillation (an idling rhythm), which is blocked, possibly to allow pertinent information transfer. Enhancement, or ERS, of a common cortical oscillation after the movement indicates a return to the idling state.

In the present study, we sought to describe the changes in cortical activity using high-density EEG during praxis movements. Using a self-paced paradigm, we can compare our results to the well-defined MRCP and power change in simple movements. We focused on spatial and temporal activations during preparation and execution of transitive and intransitive movements. All data analyses were meant to be exploratory and to describe the overall activation patterns seen. Based on the concept of hemispheric asymmetry derived from clinical studies of apraxia (Heilman et al. 1997; Heilman et al. 2000), we hypothesized that the left parietal and premotor areas would show ERD and components of the MRCP during the pre-movement period for praxis movements of the right hand.

Methods

Eight healthy right-handed subjects (5 female, 3 male) ranging in age from 22 to 68 years (mean, S.D. = 42.3, 15.3) participated in the experiments. A training session was held before starting the experiments to ensure both proper task

execution and familiarity with the experimental design. The study consisted of a rest period and 6 different types of motor tasks (see below), with a rest condition to start. The movements were performed at a self-paced rate, with no external cues. Subjects sat comfortably in a reclining chair and were instructed to stare at a designated fixation point at a comfortable eye level and to avoid eye blinks and extraneous body movements. They were asked to stay relaxed and only move their right hand during the task.

The experimental session consisted of being asked to make three transitive (hammer-use, scissors-use, and screwdriver-use) pantomimes and three intransitive (wave goodbye, show "peace" and show "ok") gestures with the right hand. A pictorial representation of this is seen in Figure 3. Each transitive movement was to be performed with a rapid onset, and performed twice, or held for about 2 s for the static intransitive gestures. Since some of the movements (particularly transitive movements) require activation of proximal and trunk muscles, subjects were instructed to use only their distal arm to make each movement. Each gesture or pantomime was performed in two blocks of 10 min each. Subjects were to make the movements every 10 – 15 s without counting. After each movement, the subject was to return the arm back to a resting state, resting with the palm facing down on the surface of a pillow. Results from the three transitive movements were averaged together, as were the results from the three intransitive movements. EMG was recorded from the right abductor pollicus brevis (APB) and flexor carpi ulnaris (FCU) muscles. Non-rectified

EMG onset was identified in each trial and marked by investigators as the movement onset; 500 artifact-free trials overall per movement type were averaged offline from a period of 4 s before to 3.5 s after EMG onset. For all analyses, EMG onset was defined as 0 s. Areas of interest (Fig. 4) were defined in the left and right premotor and sensorimotor area (LSM: C3A, C3, C3P; RSM: C4A, C4, C4P), mesial (MES: FZ, CZ, CZA), left and right superior parietal lobule (LSPL: P3, P1; RSPL: P2, P4), and left and right inferior parietal lobule (LIPL: TCP1, P5; RIPL: TCP2, P6).

Data Analysis

MRCP Analysis

All trials containing large drifts, ocular activity, muscle artifact, swallowing, or other artifacts were manually excluded. Epochs were averaged for generating the MRCP. The baseline was corrected on each channel from -4.0 s to -3.5 s before onset. Onset of the MRCP was defined as the first point where the potential consistently deviated from the baseline around a 95% confidence interval. For data analysis of the MRCP, the epoch length was divided into non-overlapping 256ms segments; the average across all time points in each segment was compared between transitive and intransitive movements using a paired t-test. Because this is an initial exploratory study, for this, and all other analyses, an uncorrected $p < 0.05$ was set as the threshold for significance.

Band Specific Power Analysis

The same trials used for MRCP analysis were subjected to power analysis. Activity related to ERD and ERS was calculated both in the alpha (10-12 Hz) and high beta (18-22 Hz) bands since these frequencies have been shown to be relevant in motor tasks. The signal was bandpass filtered (-24 dB/octave) to acquire these frequency bins, rectified, and averaged across trials. The magnitude of power was normalized by expressing the change as a ratio of the absolute power at baseline period from –4.0 s to 3.5 s before movement. Magnitude was expressed as the percentage of increase (positive percentage) or decrease (negative percentage) from baseline, as described previously by Pfurtscheller and Aranibar (1977). Epochs were divided into non-overlapping 256ms segments and analyzed for statistically significant differences between types of movement for each area of interest using a paired t-test.

Hemispheric Predominance

Analysis was performed to determine if there was a significant dominance of left hemisphere activation for praxis movements performed with the right hand. To determine hemispheric predominance, comparisons were made for each movement type separately comparing LIPL versus RIPL, LSPL versus RSPL, and LSM versus RSM for each time bin, using the paired t-test. Comparisons were made for the alpha and beta power change and the MRCP.

Results

MRCP

All movements demonstrated well-defined MRCPs. Figure 5A illustrates the grand average voltage-time plots of the MRCP from the areas of interest previously defined (see Methods section). Full spatial and temporal evolution of the MRCP is shown in the voltage head plots in Figure 5B for transitive and 5C for intransitive movements. The earliest component of the MRCP occurred over left parietal areas, particularly over LSPL beginning 3.3 s before movement onset. The potential then spread to LIPL electrodes around 2.9 s before movement onset. This pattern was similar for both movement types. Then negativity appeared in the bilateral sensorimotor areas, beginning around 2.5 s before both movement types. No significant differences comparing transitive and intransitive movements were seen in any area of interest during preparation.

At movement onset, negativity became maximal over bilateral sensorimotor and MES areas. Significant levels of difference were seen during execution of transitive movements compared to intransitive movements only in the LIPL (time = 0.5-2 s after onset; range of significance values, p=0.01-0.03) and RSM (time = 0.0 - 1.4 s; range of significance values, p=0.02-0.04), with transitive movements showing greater negativity.

Band Specific Power Analysis

Drop in power (ERD) in the alpha (10-12 Hz) band was evident only in the later preparatory phases of the movements. There were no significant differences between transitive and intransitive movements. ERD began over LSM about 1.4 s

before the movement and spread to left parietal areas at about 0.15 s before movement. Alpha ERD appeared greatest over LSM, LSPL, and LIPL. RSM showed ERD only at movement onset.

Power decrease in the beta (18-22 Hz) band was evident early in the preparatory phase of the movements. Figure 6A and 6B displays the head maps of the ERD for transitive and intransitive movements. ERD began early over the mesial areas, at about 3.3 s before movement for both movement types. Together with this, ERD was seen in LSM, LIPL and LSPL areas occurring around 3.2 s before onset. Sustained ERD was also seen in the RSM, RIPL, and RSPL at about 2.3 s before movement. Significantly greater ERD was seen in two periods during preparation of transitive movements compared to intransitive movements at MES areas (first period, time = 2.0 - 1.0 s before onset, range of p values, p = 0.03-0.04; second period, time = 0.5 s before to 1.0 s after onset, range of p values, p = 0.02-0.04). Only one area showed significant ERS differences comparing the two movement types. ERS during transitive movements was significantly greater over LSM (p = 0.04) and at near significance (p=0.08) over MES and RSM.

Hemispheric Predominance

The results for MRCP laterality and power change for transitive and intransitive movements were similar. Therefore, the laterality results for transitive movements are reported.

First, looking at the LSM versus RSM, the MRCP showed no significant laterality. Alpha power change, as well, showed no significant laterality. By contrast, beta power change showed significant laterality with left superiority during preparation from 2.8 to 1.2 s before movement onset (range of p values = 0.01-0.03) and during execution from 1.8 to 3.5 s after movement onset (range of p values = 0.005-0.04).

For LSPL versus RSPL comparisons, the MRCP showed left hemisphere superiority during preparation from 2.5 s to 0.5 s before movement onset (range of p values = 0.015-0.04), and from 2.8 s to 3.5 s after onset (range of p values = 0.001-0.04). For alpha power change, significant left hemisphere superiority was seen from 0.6 s before to 1 s after movement onset. Beta power change revealed left hemisphere superiority during preparation from 2.0 s to 1.2 s before onset (range of p values = 0.015-0.05) and during execution from 2.8 s to 3.5 s after onset (range of p values = 0.01 – 0.05).

For the LIPL versus RIPL comparison, the MRCP showed no significant laterality. There was no significant difference in alpha band power change. In the beta band, left hemispheric superiority was seen from 2.8 s to 3.5 s after movement onset (range of p values = 0.005-0.04).

Discussion

We found that both transitive movements and intransitive gestures produced large activations in parietal, central and premotor areas during movement preparation and execution. Based on findings of the MRCP data, pre-movement negativity was seen earliest in the electrodes over the LSPL about 3 s before onset. During this time period, beta ERD began over the LIPL, LSPL, LSM and MES cortices. Later during the preparatory period, about 2.2 s before onset, MRCP spread to include bilateral posterior parietal and sensorimotor cortices. Beta ERD became greatest over LSPL and LSM areas during this later preparatory period. Alpha ERD began slowly over the LSM during late preparation as well. At motor execution, transitive and intransitive MRCP showed enhanced negativity mainly over bilateral sensorimotor and MES cortices. Alpha ERD was greatest in the LSPL. Beta ERD was greatest over MES, LSM, LSPL and LIPL areas. Pre-movement laterality was present, particularly for MRCP in the LSPL, beta power change in the LSM and the LSPL. After movement onset, laterality was dominant in the MRCP for the LSPL and for the beta power change in the LSM, LSPL and LIPL.

Generators of Activity

These experiments represent evidence of early stages of motor preparation in parietal and premotor MRCP and ERD involved in these complex movements. While we show that activity is present in these areas, the precise generators are unknown. However, such studies cannot be done definitively because of the lack

of uniqueness of the inverse problem (Phillips et al. 2002; Platz et al. 2002; Finke et al. 2003; Ha et al. 2003; Whittingstall et al. 2003).

MRCP and Parietal Cortex

A key finding is the early slow negativity initially appearing over left parietal areas during preparation. For simple repetitive movements, early slow negativity is seen first over the SMA or bilateral sensorimotor areas (Ikeda et al. 1995; Cui et al. 2000; Stancak et al. 2000). This has been related to programming and initiation of a motor task. Combining various neuroimaging studies, early slow negativity is thought to originate chiefly from bilateral regions of the mesial cortex to mediate movement production (MacKinnon 2003). Using dipole source analysis, it is more clearly shown that the bilateral sensorimotor and medial frontocentral cortices (including SMA) share similar temporal activation patterns relating to early slow negativity (Toma and Hallett 2003). However, in the present study, posterior parietal negativity is seen during preparation. Considering the nature of transitive and intransitive movements, parietal areas are critical for task preparation. Patients with ideomotor apraxia, a deficit of tool use or gesture pantomime, can have parietal cortex lesions causing deficits in transitive and intransitive tasks that are not explained by elementary motor deficits (Poizner et al. 1990). Additionally, these areas have been implicated in pre-movement phases of reach and manipulative tasks (Binkofski et al. 1999; Snyder et al. 2000; Sunderland and Sluman 2000). Because of the increased cognitive demand involved in such movements, the parietal cortex may be critical in integrating the high demands of such tasks into a unified and clear movement.

Therefore, early negativity related to preparation in complex, goal-oriented motor tasks could begin in the left parietal cortex. This would be the source of pre-movement signals for more complex movements.

Pre-movement slow negativity for simple motor tasks is hypothesized to originate from surface negativity caused by thalamocortical projection neurons terminating in the superficial layers of the bilateral sensorimotor cortex (Ikeda et al. 1995). There are also thalamocortical projection neurons that synapse in the superficial layers of the posterior parietal cortex, (Avendano et al. 1990; Kakei and Shinoda 1990; Schmahmann and Pandya 1990), and this might be the origin of posterior parietal negativity seen in the present study.

Functional Implication of ERD Findings

Early and increased ERD in mesial frontal sites for transitive movements likely reflects self-initiation of the movements. Stimulus-guided movements tend to engage more lateral premotor areas, while internally initiated complex motor sequences activate more mesial premotor sites (Tanji et al. 1996; Tanji 2001). Similarly, because the motor command is more automated in this task type, the SMA may be recruited and used as a preferential subsystem (Leiguarda and Marsden 2000b). Difference in the mesial ERD for the preparatory phase between transitive and intransitive movements in the beta band is worth considering. The ERD can increase as task complexity increases (Boiten et al. 1992). Transitive movements require more grasp and manipulation than

intransitive movements. This may be why beta ERD in the mesial area is stronger for transitive movements, especially in late movement preparation when motor areas are programming the precise motor plan.

The increase of the transitive beta ERD compared to intransitive movements at the MES recording area may reveal additionally recruited physiological channels required to process preparatory information from the parietal component of the MRCP. Such a difference in the ERD could be related to involvement of a tool directed at a specific and small external target (e.g., hitting a nail at a precise point is a target for hammer pantomime) while performing transitive movements. Gestures, however, are made to persons in a broad spatial area. Waving good-bye to a person several feet away requires less spatial accuracy that hitting a nail with precision. This difference in MES activation may result from the development of the precise motor plans to spatially specific targets devoted to the premotor cortex. Information about body part and target location is known to be integrated in the premotor cortex (Hoshi and Tanji 2000; Fujii et al. 2002).

Post-movement beta ERS was significantly greater for intransitive movements compared to transitive ones in MES, LSM, and RSM areas. ERS possibly indicates that the networks which displayed ERD earlier are now in an inactivated state and are unlikely to process information (Pfurtscheller 1992; Pfurtscheller and Andrew 1999). Beta ERS was shown to coincide with reduced neuronal excitability in the motor cortex (Chen et al. 1998). Processing of tool use may

require greater neuronal computation after movement onset. Because of the increased motor demand of tool use, transitive movements may require a slower return to the inactivated state than gesture movements.

Coupling of ERD and MRCP

In this study, cortical physiological measures of the MRCP, ERD, and ERS were considered to better understand the time course of activity of cortical processing. It is possible that the ERD is much more consistent than the MRCP at detecting differences in these movements. Precise comparisons between ERD and MRCP are difficult. It is likely that because of the differences in onset between the two signals, they are representative of two brain functions, although this does not mean that they are completely unrelated. The first beta ERD changes were seen in the LIPL, LSPL, LSM and MES areas. However, this distribution of beta ERD was present at the same time as the early slow wave negativity in the parietal cortex. The two findings may reflect functionally related processes. ERD could be interpreted as an opening of a physiological channel to permit processing of meaningful neuronal behavior. As the power of the oscillations decreases (ERD), the channel opens more. Such opening may enable information processing that is reflected in the MRCP. As negativity increases in the parietal areas, processing these early signals may begin in the LIPL, LSPL, LSM and MES areas. This would identify activity of these mesial and left hemispheric brain areas early in processing task-relevant information. The flow of information in a proposed parietofrontal network could spread the MRCP to eventually include MES and

bilateral sensorimotor areas. Once the information in the MRCP is used (during and after movement onset), the channel may close, which is represented by increased power of the oscillations (ERS) in these areas. Simultaneously, negativity in these areas decreases because the task has been performed.

Transitive versus Intransitive Movements in Parietal Cortex

Similarities in preparatory parietal ERD (except briefly in the RIPL), as well as MRCP, in transitive and intransitive movements may indicate that processing cognitive information related to the task demands of performing transitive and intransitive movements is similar. In nature, both movements require distinct hand adjustments so that the gesture is properly understood or the tool is manipulated correctly. In addition, both tasks represent motor behavior that is to be performed relative to placing an item in the outside world. Orientation of a pair of scissors, a hammer, and a screwdriver requires proper positioning of the pantomimed tool to some target (e.g., a sheet of paper, nail, or screw) away from the body. Likewise, communicative gestures are oriented toward an external target (the person for whom they are intended). This likeness in the general pre-processing of conceptual knowledge for such movements may explain why parietal ERD and MRCP patterns are similar between the two movement types. The role of the posterior parietal cortex involves general information related to task performance. However, processing the specific motor plan, as done by premotor areas, may still show differences of the ERD or MRCP, as explained earlier.

Laterality of Praxis Movements

Our results indicate that the MRCP, and particularly the beta power change, show significant laterality with left hemisphere predominance for the premotor and parietal cortices. This was seen in both preparation and execution. The left hemisphere may indeed be dominant for praxis, as indicated by the wealth of studies where lesions to left hemisphere parietal and/or premotor areas cause functional deficits (Hanna-Pladdy et al. 2001a).

The LSM was predominant compared to RSM for preparation. If the LSM and MES areas are the main anterior cortical structures that prepare praxis movements, then this left hemispheric predominance is reasonable. There was no time when the right hemisphere activity was significantly greater than the left hemisphere. However, it should be noted that the right hemisphere may have some role as well, and it has been presumed to be of particular interest as a secondary pathway linking the left parietal and bilateral premotor areas via the corpus callosum (Kertesz and Ferro 1984). Right hemisphere activity may prove to be a valuable target for rehabilitation in patients who are unable to make such movements normally.

Network of Left Parietal and Premotor Cortices

The issue of a left parietal-premotor network in praxis has been under investigated in behavioral and imaging studies in primates and humans (see review of Rizzolatti et al. 1998 and Johnson et al. 2002). Our studies illustrate that left

hemispheric parietal and premotor areas are active. However, this analysis does not indicate whether or not such activity of these areas is synchronous. Coherence analysis of the involved cortical areas can show whether there is indeed a left parietofrontal network related to praxis. Studies of patients with ideomotor apraxia have shown that both areas are critical when performing praxis movements. Furthermore, animal studies of reaching and grasping have indicated that lesions in premotor areas and parietal areas cause deficits in performance (Gallese et al. 1994; Fogassi et al. 2001). This evidence reinforces the hypothesis of functionally related parietal and premotor areas. This specific hypothesis will be evaluated in Chapter 4.

Electrocorticography

While EEG provides very useful information about the electrical activity of the brain, its greatest drawback is that it is recording this brain activity with electrodes that are laying on the surface of the scalp. Therefore, the electrodes are a good distance from the brain causing spatial estimates of sources of activity to be blurred because of volume conduction caused by hair, skin, bone, and other structures that cause separation of the electrodes from the cortical surface. However, if one can remove these structures, we can detect brain activity with both optimal temporal and spatial resolution. This is possible in electrocorticography (ECOG). In epilepsy patients who are undergoing routine ECOG monitoring to detect focal epileptic activity, the opportunity exists to do

short-term testing of motor activity recording directly from the surface of the brain. Using this technique, we can determine the location of MRCP onset in various areas of the brain. Because the electrodes are placed in a different location for each patient, results are described on a case-by-case basis.

Based on the results in the previous chapter, we can now speculate that cortical areas involved in praxis hand movements may be different from those seen in simple hand movements. Since we can record directly from the surface of the brain, it is meaningful to explore the brain areas devoted to planning and executing these movements. Additionally, it is of interest to generate further speculation about the differences in cortical areas devoted to processing simple and complex movements.

Because ECOG provides optimal spatial information, we can seek more knowledge of the activity of areas posterior to the motor cortex involved in complex praxis movements. Specifically, looking at the spatial and temporal organization of the MRCP for praxis versus more simple movements, we can begin to better know what cortical areas are involved in praxis. We hypothesize that simple and praxis movements will involve MRCP in premotor and motor cortices; however, praxis movements will also involve MRCP in the temporoparietal cortex.

Methods

All ECOG recording presented in this chapter are recorded in the NIH Clinical Center Surgical Intensive Care Unit. Patients all gave their informed consent for

this study. This study did not compromise the clinical purposes of the corticographic recordings: to determine the epilepogenic cortex. Patients performed the tasks lying on a hospital bed at a 45˚ angle. Electrode grids of varying size (dependant on the size of brain that needed to be monitored for surgical purposes) were implanted onto various parts of the cortical surface. Surface EMG was recorded on the thumb and forearm flexors in order to capture movement onset. Patients were asked to perform a simple thumb flexion for three 6-min blocks. Following this, they were asked to make praxis pantomimes (using a hammer, using a pair of scissors, using a screwdriver) for three 6-min blocks. One patient (OM) performed a grasping pantomime as the praxis movement. Each movement was to be made in a self-paced manner, with a timing of once every 10-15 s. In order to maintain vigilance during the task, the patient was allowed to take a break for as long as needed to rest or to eat a meal between each session.

Patient #1 – EM

EM was a 26 year-old right-handed female who suffered from epileptic seizures. She was implanted with a lateral premotor/motor area 8x8 (64 channel) grid and a 2x4 grid covering the anterior and posterior inferotemporal cortex, all within the left hemisphere. As a surgical requirement, stimulation was done on the 8x8 grid covering the lateral premotor cortex only. Stimulation studies over the inferotemporal cortex were unavailable, because of surgical limitations. Stimulation of the cortical area under electrodes 34, 35, 41, 43, 44, 45 caused movement of the lips and/or tongue. Stimulation of the cortical area under

electrodes 51, 52, 59, 60, 61 caused arm and hand movements. The motor cortex was identified based on the results of the stimulation studies. Based on these results, we determined that she was eligible for our studies. After the third day of implantation, she was rendered stable by the surgeon and was eligible for testing.

Patient #2 – OM

OM was a 21 year-old left handed male who suffered epileptic seizures. He is undergoing his second surgery to remove the epileptogenic cortex, as he still suffers from recurrences. He was implanted with electrodes in a 2x5 grid covering the parietotemporal region, 4x5 grid over the posterior parietal cortex, and a 1x4 strip over the inferotemporal cortex. Stimulation over these areas revealed a complex pattern of auras, motion sensation, along with finger, hand, and limb movements. Based on these findings, we determined that he was eligible for our studies. After the fourth day of implantation, he was deemed ready for testing.

Data analysis

All analysis of the MRCP was done on a Dell PC using Neuroscan (Compumedics, El Paso, TX). The continuous EEG files were bandpass filtered from 0-50 Hz. EEG data were epoched into segments from –4.0 to 1.5 seconds around EMG onset. There was no significant eye-blink artifact that had caused exclusion of data. For each subject, all tool use movement trials were averaged together, as were all simple movement trials. Epochs were visually inspected for

large artifacts that would contaminate. As well, electrodes that were over, or adjacent, to the epileptogenic cortex were removed from analysis. The amplitudes were measured over each electrode. Since ECOG data are recorded from implanted electrodes, and obtained from recording over different areas in different people, analysis is made only on individual subjects. Electrodes with MRCP were visually identified in each subject and marked to indicate the beginning of the potential. Time of onset of the MRCP was determined with a regression line that detected the slope of the potential. The MRCP onset was determined by the first time point where the average potential exceeded the baseline level of activity for 200 ms. Onset of MRCP was compared between simple movement and tool use pantomime.

Results

EM

Direct comparisons were made between the MRCP seen for the simple movement and praxis movement. Figure 7A and Table 2 detail the results for this subject. For the simple movements, MRCP is generally confined to the lateral premotor cortex, closest to the motor cortex. The earliest MRCP onset over the lateral premotor cortex was seen at –2.36 s before movement onset (electrode 51), which was adjacent to the motor cortex. Thumb and hand movements were seen during cortical stimulation under this electrode. Another electrode (52), which showed MRCP beginning at –1.58 s before movement, also generated a thumb movement upon stimulation. There is no MRCP seen on electrodes over the more

anterior half of the 64-channel lateral grid (covering more anterior and ventral premotor cortex) or over the inferotemporal regions. For the praxis movements, there was a much larger distribution of the MRCP to include the more extended lateral premotor cortex, specifically the dorsal premotor cortex and the inferotemporal cortex. Regions around the premotor cortex directly adjacent to the motor cortex showed early MRCP before movement. More anterior and ventral regions of the premotor cortex showed this early MRCP as well. While stimulation did not elicit any motor response, electrodes 31, 32, and 22 showed tool use pantomimes MRCP beginning as early as –3.51 s before onset. These electrodes showed no MRCP for thumb flexion alone. Recordings over the posterior inferotemporal cortex showed early MRCP that began at –3.60 (PIT1), -0.59 (PIT2), and –1.71 (PIT3). These showed no such potentials for thumb movements.

OM

Figure 8 details the result for this subject. During the simple movement, there was no negativity seen over electrodes over the posterior parietal area. However, there were two temporal cortex electrodes (one over the inferotempotal cortex and one adjacent to the superior temporal sulcus) that showed MRCP beginning at -2.20 and –1.5 s before onset, respectively. Stimulation of the cortex under these electrodes caused motion sensation and mild finger agnosia. For the praxis movements, MRCP was seen in two electrodes over the posterior parietal lobe beginning at –1.5 and –1.13s before movement onset. Stimulation of both of

these areas caused visual auras. As well, the MRCP was seen in three electrodes over the temporopareital area beginning –1.8, -1.25, and –2.5 s before movement onset. Stimulation of the cortex under these electrodes caused visual auras, finger agnosia, and mild right/left disorientation, respectively.

Discussion

Activation of lateral premotor areas prior to motor control has been well established in EEG and ECoG (Ikeda et al. 1995; Satow et al. 2003). This is critical because the premotor cortex has anatomical connections with the motor cortex, which will ultimately guide appropriate hand movements. While this is clear for anterior structures, the necessity of activation of higher-level cortical areas should also be considered. Moreover, some of these areas may not participate in steps to generate certain movements. Thus, we sought to understand the role of higher-level areas in different hand movements. Using ECoG, we can determine more precise loci of anatomical activation, compared to EEG, yet still using an optimal temporal domain. Using this technique, we found that the inferotemporal and parietal regions are active during praxis hand movements, whereas it is not for a simple hand movement. This pattern fits our hypothesis and provides some distinct anatomical information regarding possible MRCP generators for complex praxis. Additionally, the premotor cortex was active for both movement types (patient EM); however, the anterior and ventral premotor cortex showed MRCP for praxis but not simple movements.

ECoG recordings are very effective in studying spatial and temporal properties of tasks in humans. While it is a good technique, it is often limited by the differences in individual subjects. This is because it is impossible to record from the exact same brain areas across patients. Therefore, amplitudes, latencies, and anatomical locations of responses can vary between patients. Thus, our results offer a general view of how the brain is active during these tasks. Additionally, using this technique to record from the parietal cortex is a rare opportunity, as parietal lobe epilepsy is exceedingly unusual (from 3 to 10% of tumor and nontumoral patients), although the parietal lobe constitutes about 25% of brain volume (Seigel 2003).

Temporal MRCP

While parietal activity (patient OM) was expected, based on our previous studies and investigations in the literature, activity over the temporal cortex should be discussed. This was a unique opportunity, as it is rare to see epilepsy of parietal origins that would justify placing electrodes over such posterior structures. We know that the temporal cortex and the temporoparietal junction are important in many different types of modalities, including somatosensory, visual, and auditory stimuli (Matsuhashi et al. 2004). We believe our results agree with the notion that the inferotemporal cortex is involved in knowledge of how an object is to be used (Goodale and Milner 1992). In both subjects, we see MRCP activity before movement onset in this region, which could encode higher level processing

demands related to knowledge of how objects are employed or manipulated for proper use. This fits a proposed model that expands a role of the inferotemporal cortex (together with posterior parietal and premotor cortices) to be additionally involved in complex and meaningful movements, such as praxis (Fagg and Arbib 1998). While this may be particularly true for visual cuing of movement (as the above-mentioned paper suggests), we find that subjects generally report imagination of a scene in which they make the movement, which could cause activation of similar structures (Moll et al. 2000; Zacks et al. 2003), even though the task is self-initiated. Inferotemporal cortex activation is seen in fMRI studies of praxis pantomime, in addition to SMA, parietal, and premotor areas (Choi et al. 2001). From this evidence of activity before EMG onset, we propose that the inferotemporal and posterior parietal cortices are two high-level posterior structures (relative to the central sulcus) that are involved in pre-movement praxis activity. Exactly what the contribution of these areas represents is a matter of ongoing debate.

Ventral Premotor Cortex MRCP

Differential activation of the ventral premotor area is worthy of discussion. This area is thought to be involved in activity related to three dimensional objects and to "mirror neurons", which are active during movement observation (Picard and Strick 2001). It is possible that the additional MRCP seen in these electrodes is due to early processing of the movements that would be required for the task (grasping and operating a tool). These electrodes only display the early slow

wave activity (Fig 7B), possibly indicating that they have a role in pre-processing and less in the actual performance of the movement. This was not observed in patient OM, since no recordings were made in the premotor cortex. Further evaluation of this in patients with similar electrode placements is valuable to clearly understand this activity.

Based on the ECoG findings in this chapter, we can reliably show that parietal and premotor areas are involved in praxis movements, whereas the premotor cortex is involved in simple and praxis movements. We know that this differs from the general idea of MRCPs for simpler movements that has been reliably shown in the previous literature. Our ECoG data provide a demonstration that simple and praxis movements may have different anatomical structures that generate potentials leading up to actual movements. This idea is further explored in the next chapter.

Chapter 3: Verification of Movement Related Potentials in Praxis Movement

Introduction

Simple self-paced movements have been studied using EEG where the BP of the MRCP has been seen beginning approximately 2 s before onset of movement in the bilateral sensorimotor area (Shibasaki et al. 1980a; Shibasaki et al. 1980b; Kristeva-Feige et al. 1997; Toma and Hallett 2003). Looking at the onset of this slow negative component in the previous chapter, left posterior parietal negativity was the earliest EEG event prior to self-paced praxis movements (complex movements such as tool use and communicative gestures). If true, this suggests early posterior parietal cortex activity for praxis movements. Additionally, the ECoG studies from the previous chapter illustrate that preparing praxis movements has different activity than preparing simple movements.

It is possible that the posterior parietal cortex is the generator for praxis movement preparation. Human and primate studies have shown that for praxis and other types of complex movements, the posterior parietal cortex is active during both preparation and execution (Moll et al. 1998; Rizzolatti et al. 1998b; Binkofski et al. 1999; Batista and Andersen 2001; Calton et al. 2002; Fridman et al. submitted). This premovement parietal activity may be due to the complexity of the movement and the mechanisms needed to generate such movements (Gallese et al. 1994; Burnod et al. 1999; Haaland et al. 2000; Batista and

Andersen 2001; Andersen and Buneo 2002; Hamzei et al. 2002; Bartolo et al. 2003). Movement generation mechanisms may include imaging the execution of such movements; the goal of the movement; determining the natural position and setting required for proper performance; sequence of motor acts, and comprehension of the task.

In the current study, we aim to prove that early posterior parietal negativity (PPN) is seen for praxis hand movements compared with a simpler movement.

Methods

Subjects

Nine right-handed normal volunteers (24-57 years of age, mean=35.1, S.D.=17.4) participated in the studies. All subjects gave their informed consent.

Procedure

A training session was performed to ensure familiarity with the experimental design. The experimental tasks took place in six 15-min blocks. Subjects sat comfortably in a reclining chair and were asked to make the motor tasks with the right hand only and avoid extraneous body movements. The motor tasks were made in a self-paced manner.

Experimental sessions consisted of the subjects executing a simple movement (adducting their right thumb) for three blocks. For the remaining three blocks,

they were asked to make a tool use movement (pantomime hammer, scissors, or screwdriver use). Subjects were instructed to make each movement once, followed by a 10-15 s interval between each movement. The tool-use movements were made by only using the distal limb. Blocks of simple movements and tool-use movements were alternated during each recording. Each simple movement was averaged together, as was each tool-use movement. Analysis was made on the differences in preparatory activity of each movement type. High-density (64-channel) EEG was recorded using a linked ear reference. Surface EMG was recorded from the flexor carpi ulnaris and flexor pollicus brevis muscles. EEG was recorded at 1 kHz sampling rate with a DC-100 Hz bandpass filter. EMG was recorded from the right APB and FCU at a bandpass of 5-200 Hz. EMG onset was identified in each trial; and epochs were made from 4.0 s before movement onset to 1.5 s after movement onset. A total of 650 artifact-free trials per condition were collected. For analysis, the signal from electrodes over the left hemisphere posterior parietal area was chosen as our area of interest (electrodes TCP1, C3P, P5, P3, P3P). Additionally, the signal from electrodes over the left premotor area was chosen for further analysis to compare parietal and premotor negativity onset for the two tasks (electrodes C3, C1, C3A, C1A, CZ).

Data Analysis

Analysis of the MRCP was made on a Micron PC workstation using Neuroscan (Compumedics, El Paso, TX) and MATLAB (Mathworks, Inc., Natick, MA). All trials containing large drifts, ocular activity, muscle artifact, swallowing, or other

artifacts were manually excluded. Epochs were averaged together to generate the MRCP. Baseline was corrected on each channel from –4.0 s to –3.5 s before onset. Amplitudes were measured over the cortical regions. Analysis was done on four consecutive 500 ms time bins of the EEG signal; -3.5s to -3.0s (BP1), -3.0 to -2.5s (BP2), -2.5s to -2.0s (BP3), and –2.0 to -1.5s (BP4), comparing the simple versus tool-use movements. Division of the BP into four components is arbitrary and not a scientific distinction. Analysis was also done to detect the time of onset of the first negativity of the MRCP. MRCP onset was defined as the time point where the signal extended beyond a 95% confidence interval from baseline. Multivariate ANOVA was performed to assess the influence of the movement type on the time bin of BP over the posterior parietal area and the premotor cortex. Where appropriate, a post-hoc Bonferroni corrected t-test was done to measure the significance of the effect. Analysis was made to detect significant differences between simple and tool-use movements across homologous time bins (e.g. simple movement BP1 versus tool use movement BP1).

Results

Parietal and premotor early negativity

Multivariate ANOVA with type of movement and segment of BP over the posterior parietal area as factors revealed a significant effect of type of movement ($F=13.5$, $p=0.0005$), time bin of BP analysis ($F=5.11$, $p=0.003$), and interaction effect ($F=4.8$, $p=.004$). Post-hoc analysis was made comparing each movement type for all four time bins. In the BP1 period, there was no statistically significant

difference in the potentials (p=0.08). However, during BP2 and BP3 (between -3.0 to -2.5s and -2.5s to -2.0s before movement onset), significant differences were seen where tool pantomime had greater negativity than thumb adduction (BP2, p=0.0002; BP3, p=0.0020). There was no longer a corrected significant difference by BP4 (p=0.0205). This effect was not seen for analysis of the type of movement and segment of MRCP over the premotor cortex, where the multivariate ANOVA revealed an insignificant effect on type of movement (F=0.69, p=0.41), or time bin of BP analysis (F=0.26, p=0.87).

Effect of type of movement

To assess if there was a difference in the negativity recorded over the premotor and parietal areas for each task, multivariate ANOVA was performed with location of recording and time bin of BP analysis as factors. For simple movements, there was no effect for location (F=2.09, p=0.15) or for time bin of BP analysis (F=0.55, p=0.64). However, looking at the tool-use pantomime, there was an effect for location of recording (F=10.79, p=0.0017) and for time bin of BP (F=3.41, p=0.024). Post-hoc analysis revealed significant differences for the negativity seen over the parietal compared to the premotor during BP1 (p=0.009), BP2, (p=0.001), BP3 (p=0.012), and BP4 (p=0.011) for tool-use pantomime.

Average onset of negativity for tool-use movements was 2.8 s before movement onset, while for simple movements onset was 1.7s, which was significantly different (p=0.0001). Figure 9A displays the waveforms recorded over the

posterior parietal cortex. The topography of these potentials differed as well. Looking at the spatial plots in Figure 9B, the beginning of the BP for thumb adduction is best seen occurring over bilateral sensorimotor areas, while the distribution for tool pantomime was more posterior, beginning over the left parietal area. For tool pantomime, negativity continued to be focused in the posterior parietal areas, extending into bilateral sensory and motor areas continually as movement onset approached. Contrary to this, the simple movement had more anteriorly placed negativity which extended into the motor areas in a fashion similar to tool pantomime. At movement onset, distribution of the movement-related negativity for tool use extended to include parietal areas, whereas the simple movement was more focused over bilateral sensorimotor areas.

Discussion

Pre-movement negative potentials preceding self-paced movements have been studied extensively for various types of movements. However, these movements are generally limited to simple movements (e.g., finger flexion or tonic extension), which are less typical in everyday application than using objects in the environment. In the present study, we sought to compare of the traditional MRCP paradigm using a simple movement with the complex tool-use movements to better determine differences from more simple forms of movement. We found that self-paced praxis movements give rise to negativity 2.8 s before EMG onset, originating in the left posterior parietal area, while the simpler thumb adduction

gives rise to negativity 1.7 s before EMG onset with a central distribution. The early PPN seen in this study may reflect early preparatory processes for complex movement planning. These early parietal processes are hypothesized to be critical for normal planning and executing of praxis hand movements, and when disrupted, may produce ideomotor apraxia (Haaland et al. 2000). Lesions of the left hemisphere posterior parietal cortex are often responsible for this disorder (Hanna-Pladdy et al. 2001a; Heilman and Gonzalez Rothi 2003).

Early Negativity

It is worth considering why activity involved in preparing these movements is seen so early. Experiments comparing simple and complex bimanual sequence hand movements have shown earlier negativity for the latter (Cui et al. 2000). It is possible that the complexity of the movement (e.g., multiple joint movements and the coordination between them) requires greater neuronal computation. A site of this computational demand, particularly for more skillful movements, is the parietal lobe (Wise et al. 1997). Pre-movement activity confined to sensorimotor areas may occur for simple movements because they are generally fairly limited in the joint configurations required to fully carry them out and driven by more automatic mechanisms that may be stored in more anterior sensorimotor structures. It is possible that the relative simplicity of thumb adduction requires less computational strategy, reflected in later slow negativity than the pantomimes. Additionally, the left parietal area is thought to be involved in motor attention and covert preparation (Rushworth et al. 2003). Selecting the

appropriate motor formulas for a complex praxis task may require longer times of covert planning than simple movements.

While differences in time of MRCP onset have been seen when comparing the MRCP of "simple" versus "complex" movements, spatial differences have not been identified (Simonetta et al. 1991; Cui and Deecke 1999a; Cui and Deecke 1999b; Cui et al. 1999). In our comparison, both spatial and temporal differences were seen. Thus, the spatial differences are not due to one movement being simply "more complex" (i.e., involving more musculature) than another. Rather, they are more likely due to additional cortical mechanisms related to normal praxis movements not present for simple movements.

Right hemisphere activity

Although data analysis focused on the left hemisphere, we do not intend to completely ignore contributions from the right hemisphere. Negativity also was present in the right hemisphere (Fig. 9B). While there is little evidence that lesions of the right hemisphere posterior parietal area produce deficits in normal performance mostly for tool-use pantomime (Heilman and Gonzalez Rothi 2003), it does not mean that this area of the brain is not involved in praxis tasks. Studies have suggested that recovery of motor function may involve enhanced motor-related right hemisphere cortical function (Miyai et al. 2003; Luft et al. 2004). Further investigations are needed to evaluate the importance of right hemisphere activation in normal and patient populations.

This study proves statistically what was suspected previously and supports the role of the parietal cortex in planning praxis movements. Determining exactly what the parietal cortex is contributing will require further experiments. The data presented thus far show that parietal and premotor structures are active in preparing and executing praxis movements. This is useful, but does not address whether this activity is functionally related (as part of a network) or not. This is explored in the next chapter.

Chapter 4: Cortical Networks for Self-paced Praxis Movement

Distributed parietofrontal networks appear to be involved in some goal-based movements (Wise et al. 1997; Burnod et al. 1999). Evidence supports the presence of such networks based on studies of anatomical connectivity between various parietal and frontal areas using neuronal tracers and lesion studies in non-human primates (Petrides and Pandya 1984; Cavada and Goldman-Rakic 1989b; Cavada and Goldman-Rakic 1989a; Rizzolatti et al. 1998b; Luppino et al. 1999; Geyer et al. 2000a). For transitive and intransitive pantomimes, such networks have been hypothesized to play a significant role in humans. In our previous EEG study of self-paced praxis hand movements described in Chapter 2, left hemisphere parietal and mesial premotor areas were highly active during preparation and early execution. Additionally, Chapter 3 further defined the timing of activity of the posterior parietal cortex in preparatory activity related to praxis.

Corticocortical connectivity studies to determine anatomical networks are difficult to perform in humans. However, coherence studies using EEG can be implemented to assess functional connectivity utilizing the optimal temporal resolution EEG provides. Coherence between two EEG signals is defined as the spectral cross-correlation between two channels normalized by their individual spectral power. This normalization makes coherence resistant to fluctuations in power of the frequency band of interest in the signal. If a signal in a particular

frequency band is coherent between multiple regions, one can determine how strongly coupled they are based on the magnitude of the interaction. Paradigms studying self-paced movements (Andrew and Pfurtscheller 1995; Leocani et al. 1997; Ohara et al. 2001), visuomotor tracking (Classen et al. 1998), object recognition (Mima et al. 2001), associative learning (Miltner et al. 1999), and perception (Rodriguez et al. 1999) have utilized similar coherence methods as a measure to infer cortical connectivity and functional relatedness. With this analysis technique, we also can infer functional connectivity between parietal and premotor areas at many time points during our task.

In the present study, we sought to understand the dynamics of parietofrontal networks during praxis movements. Based on our previous findings of left hemisphere activity (Chapter 2), we hypothesized that left hemisphere parietal and premotor areas will be highly coherent during the pre-movement period, indicative of a planning phase for these complex and meaningful movements. We also expect increased coherence between the premotor and motor cortices for movement execution. The coherent activity of these networks should fall away in the post-movement periods because the movement has been accomplished.

Methods

Subjects and data collection procedure are the same as described in Chapter 3. Therefore, the procedure will be only briefly summarized. Eight healthy right-handed normal volunteers (5 females, 3 males) ranging in ages from 22 to 68

years (mean, S.D. = 42.3, 15.3) participated in the experiment. Subjects sat comfortably in a reclining chair for the entire study.

The study was divided into 7 blocks, with a rest condition as the first block. The movements were to be performed in a self-paced manner, without the assistance of external cues. Subjects were instructed to stare at a designated fixation point straight ahead and avoid eye blinks and extraneous body movements. The experimental session consisted of being asked to make three transitive (tool use movements: hammer-use, scissors-use, and screwdriver-use) pantomimes and three intransitive (communicative gestures: wave goodbye, show "peace" and show "ok") gestures. Each movement was made with the distal right arm. Movements were divided into 6 blocks of 10 minutes each. Subjects made the movements every 10 – 15 s without counting. 64-channel EEG was recorded at 1 kHz sampling rate using linked ear reference and a bandpass of DC to 100 Hz. EMG was recorded from abductor pollicus brevis (APB) and flexor carpi ulnaris (FCU) muscles of the right upper limb with a bandpass of 5 to 200 Hz. EMG onset (0 s) was identified in each trial, with 250 artifact-free trials per condition, averaged offline from a period of 4 s before to 3 s after EMG onset.

Data Analysis

Coherence Analysis

The magnitude of coherence was calculated based on values relative to baseline to reduce the intersubject variability of absolute coherence. We limited our analysis to the beta band (18-22 Hz) because it was the most reactive band in our electrophysiological studies of praxis movements. Beta band coherence was expressed in non-overlapping 256 ms time windows across the time interval of the entire epoch. Baseline of coherence measures was relative to the first 3 time windows (the first 768 msec of the epoch).

Coherence is a measure of the linear dependency of two signals at a specific frequency. In its formal definition, we regard the time courses of two signals, $x_i(t)$ and $x_j(t)$, respectively, as random numbers whose statistical properties we want to estimate. In the context of this paper, the indices i and j refer to EEG channels. If $z_i(\omega)$ and $z_j(\omega)$ are the respective (complex valued) Fourier transforms, then the cross-spectrum $B_{ij}(\omega)$ is defined as

$$B_{ij}(\omega) = \langle z_i(\omega) z_j^*(\omega) \rangle$$

(1)

where * denotes complex conjugation and $\langle\ \rangle$ denotes 'expected value', i.e., the hypothetical average over an infinite number of samples. The complex valued 'Coherency' $\mathbf{C_{ij}(\omega)}$ is now simply the normalized cross-spectrum

$$C_{ij}(\omega) = \frac{B_{ij}(\omega)}{\left(B_{ii}(\omega) B_{jj}(\omega)\right)^{1/2}}$$

(2)

Being a complex number, coherency contains two pieces of information: the magnitude and phase. In many applications (including the present study), one is only interested in how large the dependence between two signals is, and 'coherence' can be defined as the absolute value of $\mathbf{C_{ij}(\omega)}$.

In practice, coherency/coherence can only be estimated. In the case of event-related coherency, as done here, each epoch is divided into a sequence of time windows, with a Hanning window characterized by the time t of its center. If we denote by $\mathbf{z_i(\omega, t, n)}$ the Fourier transform at frequency $\boldsymbol{\omega}$ of the time series of the $\mathbf{n}^{th}$ epoch in the time window **t,** then we estimate the cross-spectrum as

$$B_{ij}(\omega,t) \approx \frac{1}{N}\sum_{n} z_i(\omega,t,n) z_j^*(\omega,t,n) \qquad (3)$$

Coherency is now estimated with (2) using this estimated cross-spectrum (3). The absolute value of coherency (coherence) is always between 0 and 1. If a baseline is subtracted, coherence has values from –1 to +1, with increases in coherence being positive and decreases being negative. For the purposes of this study, only the magnitude of coherence increases or decreases is considered. The phase of coherence may be analyzed; however, its meaning may be arbitrary to the analysis because we are analyzing a specific frequency band and making no hypotheses about a delay in coherent activity in one location with respect to another. Therefore, it is not included in this analysis because of its difficult interpretation.

In order to assess the dynamics of coherence in the network, coherence of pairs of electrodes over parietal, premotor, and motor areas in the left hemisphere were

chosen since we are particularly interested in intrahemispheric connectivity patterns contralateral to the involved limb. This judgment was based on previous descriptions of left parietal and premotor areas being especially critical to right hand praxis movements and other complex gestures and tasks. Such descriptions have not been made for the right hemisphere. Electrodes over the left parietal (superior posterior parietal area: P1 and inferior parietal area: P5, TCP1); left premotor (C3A and F5); motor (C3); and mesial supplementary motor (CZA) areas were considered in the analysis. Choosing coherent pairs between electrodes were assessed from the above electrodes of interest within the hypothesized network for performance of praxis; for example, parietal-premotor coherence defined by coherent values for C3A-P1 and parietal-motor by P1-C3. Coherence values at each of the 256 ms time windows were compared between homologous electrode pairs for transitive and intransitive movements and assessed for significance (e.g., significant differences between P1-C3 transitive versus P1-C3 intransitive). Comparisons of interest were between electrodes of parietal-premotor, premotor-motor, parietal-motor, parietal-supplementary motor, premotor-supplementary motor, and supplementary motor-motor areas. Coherence values at each time window were normalized using the inverse hyperbolic tangent ($\tanh^{-1}$) (Rosenberg et al. 1989; Farmer et al. 1993). Only values significantly ($p=0.05$) above the first 768 ms of the epoch (the baseline, as explained earlier in the Data Analysis section), as computed by the two-tailed t-statistic, are displayed in head plots to avoid considering spurious interactions. The significant baseline level above zero in magnitude was calculated by

establishing the limits that were ±2 standard deviations above and below the baseline period. Values exceeding these limits are considered significantly above baseline. This value was found to be in the range of ±0.09 in magnitude for each comparison. Values within this range were considered equal to zero in magnitude for plotting and analysis purposes. Thus, all values exceeding +0.09 and below -0.09 are considered to be significantly above or below baseline, respectively.

In addition to the above-described analysis of the magnitude of coherence, additional analysis was done on the imaginary part of coherency (Nolte et al. 2004). This analysis sought to reveal coherent interactions that are void of volume conduction artifacts. If signals in two channels come from a single source, the relative phase is either zero (if the electric potential induced by this source has the same sign at the two electrodes) or $\pm\pi$ (if the electric potential induced by this source has an opposite sign). In either case, coherence is a real number. Coherence can only have a non-vanishing imaginary component if the activities of two sources are time-lagged. Since the activity of a single source is never time-lagged to itself, the imaginary part of coherence does not detect 'self-interaction'.

Results

There were no significant differences in coherence between the same electrode pairs tested between transitive and intransitive movements; therefore, results are

described together. Time and magnitude of coherence reported are representative values that are significantly above baseline ($p<.05$, above +0.09 in magnitude) for the average of a particular coherent network across all electrodes of comparison.

Relative to baseline, significant coherence increases involving C3 (motor cortex) first began in premotor/mesial areas at about 2.5 s before the movement. The area of coherence increase during this time was greatest at premotor (magnitude = 0.18) and mesial (0.20) areas. Soon after this increase, coherence values fell back to baseline, but quickly rose to peak just after movement onset (t = 0.8s, magnitude = 0.35, supplementary motor; magnitude = 0.30, premotor). During this second peak, C3 coherence to the premotor and mesial areas reached a maximum. After this movement onset increase, coherence began to fall during motor task execution. By about 1.0 s after movement onset, coherence was back to baseline and fell below baseline in premotor areas. There was no coherence increase seen between the motor area and left parietal electrodes in either the preparation or execution stages.

Coherence increases to the mesial areas began above baseline to the left parietal (magnitude = 0.18) and motor area (0.20) at 2.5 s before movement. Increases of CZA coherence to the parietal area were present throughout the task preparatory period. Initial increases in coherence during preparation between mesial and

motor areas fell below baseline (magnitude = 0.08). However, coherence levels rose quickly to peak at movement onset. At movement onset, the magnitude of the coherence values at parietal areas (0.3) peaked and remained high. During movement execution, coherence increases from CZA to the parietal area slowly fell below baseline approximately 1.2 s after movement onset. Similarly, coherence increases to the motor cortex began to rise above baseline at about 2.3 s before movement (magnitude = 0.2). This coherence increase then peaked at movement onset (magnitude = 0.32) and fell back below baseline by about 2 s after movement onset. Lateral premotor areas displayed little sustained coherence with the SMA region during the preparatory periods. At 1.5 s (magnitude = 0.1) and about 0.8 s before onset (0.15), SMA-premotor coherence increased slightly (see Fig 10F).

Coherence increases to the premotor area began 2.5 s before movement in the motor (magnitude = 0.18) and parietal (0.12) areas. This became more sustained within 1 s of movement onset; however, values remained low (just above 0.15 in magnitude until about 0.5 s before onset). At 0.8 s before onset, coherence was considerably higher in the motor area (magnitude = 0.30) and posterior parietal areas (0.26), and then began to diminish at movement onset. There was also a small increase in coherence to mesial electrodes (previously described). By about 1.5 s after movement began, coherence values fell well below baseline.

Early coherence increases to the parietal area were seen primarily in lateral and mesial premotor electrodes, and continued to rise until 0.8 s before movement onset. Similar to other findings, coherence values quickly returned back to at or near baseline by 1.5 s after onset. A small coherence increase was seen between motor and parietal areas 2.5 s before movement (magnitude = 0.12). This peak quickly fell below baseline. There was no coherence increase between parietal and motor areas during the remainder of the epoch.

The imaginary part of coherence was analyzed in the same way as the magnitude. This analysis yielded no consistent result in any of our pairs of interest for either transitive or intransitive movements.

Discussion

Corticocortical coherence allows us to address questions related to coupling of distant brain regions to integrate information relevant to some task. It is crucial for distant areas of the brain that must integrate information for a task to be able to communicate as a network to allow for correct processing (perception, movement, etc.). This is nicely demonstrated where coherence increases between the bilateral occipitotemporal lobes resulted when a recognized image was presented in the center of the visual field (Mima et al. 2001). Presenting an object in the center of the visual field requires binding of the object between both visual hemifields, which are processed separately in the bilateral occipital hemispheres.

This binding could be accomplished by coherent activation, as seen between the occipitotemporal lobes. Using a similar approach, we can assess the temporal evolution of coherence as it relates to the hypothesized functional connectivity of a parietofrontal circuit during preparation of praxis.

Scalp recorded EEG is particularly useful to assess changes in temporal activity over cortical areas; however, it lacks the spatial accuracy of neuroimaging methods. Here, we compared coherence for electrode pairs that overlie cortical regions. However, there is no guarantee that we are recording specifically from that region because the distance of the electrode from the actual cortical area created by the scalp and skull. There is also the concern that recordings from mesial electrodes may not only record from the SMA, but also from bilateral premotor sources. We infer that the results are representative of areas related to praxis function (including parietal, lateral premotor, and mesial premotor areas), based on previous imaging studies of preparation and execution of praxis (Fridman et al. unpublished data), and the cortical function and anatomical connectivity seen in the posterior parietal and premotor cortices (Rizzolatti et al. 1998b). It would be preferable to analyze fluctuations of coherence between individual EEG sources of oscillatory activity as determined by source localization; however, such methods are not well developed.

Coupling of distant brain regions

Our study indicates that parietal and premotor areas are not acting individually, but rather in a coupled manner. Figure 10 summarizes the results. Briefly, coherence increases related to preparation were seen across parietal, premotor, supplementary motor and motor areas during preparation and execution. Specifically, the parietal cortex showed escalating coherence with the SMA and premotor cortices, while only a small significant increase was seen between the motor and parietal cortices during the pre-movement period. Premotor areas showed large coherence increases to parietal and motor areas. There was little increase in coherence between premotor area and the SMA region relative to baseline. SMA showed high coherence with parietal and motor areas. The first coherence increases were generally seen about 2.5 s before movement onset.

Principles of coherence analysis

Determining the meaning of coherence is critical to the discussion of the results. A coherence value of +1 means that the first signal is a scaled and/or time-delayed copy of the second signal at a particular frequency band for all epochs. In this case the first, (or second) signal completely determines the second (or first) one: the 'interaction' between them is maximal. It should be noted here that 'interaction' means 'observable relation' – whether this is a true physical interaction or rather the effect of a common source is, mathematically speaking, beyond the scope of the analysis. EEG channels do not interact directly. Whether an observed 'interaction' reflects interaction of brain sources is a difficult

question. In most cases one has to resort to arguments for, rather than proofs of, the claims made.

The coherence between two processes can be zero although the processes are strongly related, e.g., if one time series is the square of the other. In general, coherency misses all nonlinear dynamical relations. However, showing that EEG contains anything that is inconsistent with the assumption of linear dynamics has proven to be unfounded, and we believe that linear measures contain most of the relation between brain sources (Theiler and Rapp 1996; Stam et al. 1999).

Studies of coherence must carefully determine whether interactions of two channels are the result of 'self-interacting' sources. Coherence between channels arising from activity volume conducted to several electrodes must be regarded as artifactual. Unfortunately, there is no clear method to exclude such an effect because, formally speaking, any coherence matrix is consistent with non-interacting sources.

Paradigms

Utilization of the self-paced paradigm is important to consider. Source analysis of activity related to self-paced movements tends to be related to lateral premotor areas predominantly (Toma and Hallett 2003). Mesial and lateral premotor activity was shown in physiological parameters (movement-related cortical potentials and power analysis) reflected in the EEG in preparation and execution

(Chapter 2). The mesial areas are also ascribed an important role in developing and executing complex movements (Tanji 2001). A similar effect was seen in the present study. Coherence increases for mesial areas (parietal-mesial and mesial-motor) help to further demonstrate its importance in the type of movements performed here.

Coherence and anatomical pathways

Parietal and lateral premotor areas have numerous corticocortical connections. Coherence between these areas was present; however, parietal-SMA coherence was also highly increased. The SMA has been shown to be the recipient of posterior parietal axons both directly and via the basal ganglia (Petrides and Pandya 1984; Geyer et al. 2000a; Glickstein 2003). Based on the anatomical findings and our main hypothesis, it is not surprising to see functional coherence between these areas; however, this coherence could be mediated through cortical or subcortical relationships. The distinct coherence patterns between the parietal, mesial and lateral premotor areas could be accomplished through corticocortical connectivity or connections with the basal ganglia. It is possible that between coherent electrode pairs, coherence can be maintained across polysynaptic pathways if the activity at the synapse does not interfere with the oscillatory activities of the original signal. This can be explained by stating: if A is coherent with B, and B is coherent with C, A and C might be coherent if B maintains the properties of A causing it to be coherent with C. In this example B (e.g., basal ganglia) must maintain the phasic properties the signal from A

(parietal cortex) so that A remains coherent with C (premotor cortex). In theory, this could be problematic for a polysynaptic structure such as the basal ganglia to accomplish. Thus, the coherent relationships seen here may be easiest to explain by considering direct corticocortical relationships. Patients with Huntington's disease with damage to corticostriate projections and the basal ganglia showed signs of ideomotor apraxia (Hamilton et al. 2003). However, the study also reported that ideomotor apraxia was not present in patients with lesions limited to the basal ganglia itself.

Afferents to the SMA region originate mainly from premotor, somatosensory, and parietal areas (Luppino et al. 1993b). SMA coherence to parietal areas (Fig. 10C) is prominent; however, there is little premotor-SMA coherence (Fig. 10F). The lack of coherence between these areas is puzzling. One explanation may be based on the strong parietal-SMA coherence (Fig 10C). Because it is a self-paced complex hand movement, the contribution of mesial areas to the task is expected to be higher than the lateral premotor areas. Additional contributions of the lateral premotor areas to the SMA may be negligible in task preparation. If this is true, the SMA may be the main anterior cortical area driving preparation of the task, needing less support from other premotor structures. In this analysis, all increases in coherence are relative to an early baseline (4.00 to 3.25 s before movement). Additionally, if coherence increases are not seen, this might be explained by unchanging high coherence values relative to the baseline. Alternatively, lateral premotor coherence to the motor area could represent a

secondary path in the preparation period. If the lateral and mesial premotor areas are part of two different paths, and one is secondary to the other, the two may not need to be coherent with each other. Thus, coherence between premotor areas and SMA would be low, but not affecting any coherence increases seen in premotor-motor paths (Fig 10B).

A result of note was the lack of coherence between the motor and parietal cortex (Fig 10A). Motor cortex has been reported to receive cortical input mainly from the SMA, followed by smaller contributions from the lateral premotor and sensory cortices (Ghosh et al. 1987). Rizzolatti and colleagues (1998) show that monkey parietal area PE has the only parietal projections to the primary motor area and is hypothesized to function in directing the primary motor area to the location of the limb in space for control of precise movements. Such coherence does not exist in our study design. In principle, it may seem that if three areas are part of a coherent network, each individual area must be coherent with each area within the network. However, while coherence was seen for the parietal and premotor areas, as well as the premotor and motor areas, it is not essential that the parietal and motor areas be coherent as well. Using the form of an earlier argument: if A is coherent to B, and B is coherent to C, A is not necessarily coherent with C. In this case, the activity of the parietal and motor cortices (A and C respectively, from the stated example) can be independent of each other, while the activity of the premotor areas (B, from the stated example) could have a linear dependency of both the parietal and motor areas. This being the case, there would be no

strong uniform coherence arising from measures comparing the coherence of parietal and motor cortical areas. This coherence pattern strengthens our results by making coherence increases purely from volume conduction less likely. The motor cortex is closer than the premotor cortex to the parietal cortex. If increased parietal – premotor coherence was caused mainly by volume conduction, this effect should also be seen in increased parietal – motor coherence values.

This analysis reveals another relationship for coherence increases over time. Figures 10 B, C, D, and E show bimodal increases in coherence. The first increase occurs early during preparation, and the second is centered on movement onset. This may convey two distinct coherent increases related to separate processes. The first increase could be related to preparing the motor plan. The second could be directly related to the motor program needed to execute the task. Determining the onset of preparatory activity for self-paced movements is unclear since there is no cue to signal pre-processing of the task. However, cortical mechanisms may initiate and drive these preparatory processes without external cues. This early coherence increase could represent such processing. Further studies of such a bimodal relationship for coherence should be done to assess its significance.

Many studies have described functional associations between parietal and premotor areas related to motor control in primates. Inactivation of a premotor area shown to be heavily connected with the posterior parietal cortex (region AIP)

and motor cortex demonstrated significant deficits in hand grasping (Fogassi et al. 2001). This deficit in hand grasping was also demonstrated after reversible inactivation of AIP (Gallese et al. 1994). In humans, such networks are hypothesized to play a role in motor control. Imagined grip selection activated a parietofrontal circuit in fMRI that is similar to a reach circuit that has been defined in monkeys (Johnson et al. 2002). Lesions of the left parietal lobe have been heavily implicated in contributing to spatial and temporal errors (Weiss et al. 2001). As well, the left premotor cortex has been implicated in motor control related to both hands (Hlustik et al. 2002). Studies have shown that the SMA is also critical for praxis (Watson et al. 1986; Marchetti and Della Sala 1997). Decreased uptake in premotor, SMA, and parietal regions was seen in a patient with ideomotor apraxia using positron emission tomography (Kareken et al. 1998). The fact that lesions in multiple cortical loci lead to ideomotor apraxia contributes more to the idea that praxis involves a distributed modular network involving each of these areas (Hanna-Pladdy et al. 2001b). One such example of a distributed network that matches visuo-somatic, sensorimotor, and position-direction information into a unified command has been proposed for reach and tracking (Burnod et al. 1999). Such a network theory could also explain praxis.

Our studies help expand a theory of unified parietal – premotor networks for praxis. With the activation patterns seen, we can illustrate functional connectivity in at least two paths. There is a parietal-lateral premotor-motor path (Figs. 10 D, B) and a parietal-supplementary motor-motor path (Figs. 10 C, E). Understanding

the roles of these two different functional paths deserves further study. Since there is a lack of coherence between parietal and motor cortices directly, we infer that the premotor cortical areas (lateral and/or mesial) are critical in further development of the plan of such complex motor tasks (also demonstrated in (Fridman et al. unpublished data)). Each path is in agreement with proposed underlying neuroanatomy and physiology of areas related to the preparation and execution of complex, meaningful movements. This study demonstrates that coherent parieto-premotor-motor functional networks exist for planning and executing praxis hand movements, allowing us to test specific hypotheses of parietofrontal networks more carefully in future studies.

Chapter 5: Coherence Using a Cued Praxis Paradigm

Introduction

Coherence analysis is helpful in determining functional relationships between brain areas. However, it is possible that activity seen in a single EEG channel is observable in multiple channels due to volume conduction of sources (Sarvas 1987). Such volume conduction may be reflected in erroneous coherence increases between channels that reflect activity of a single source. A measure of connectivity that is robust to artifacts of volume conduction can be given by the imaginary part of coherency (Nolte et al. 2004). The magnitude of coherence, which is generally reported, includes a part that has a zero phase delay. It is possible that the zero phase component of coherence between two signals has some volume-conducted information. The imaginary part only looks at time-lagged relations, and is therefore, not contaminated with artifactual interactions arising from the relation of an activity with itself. By analyzing only the imaginary part, we can test for only true interactions between parietal and premotor areas.

The purpose of this study is to further analyze parieto-premotor networks during praxis preparation and execution. To detect distinct preparatory and execution-related activity, the Go/No Go paradigm can be used. In this paradigm, a task instruction is given to a subject followed by a time interval where they are instructed to think about the task. This is the planning/preparation phase. At

"Go", execution is triggered, leading to a rapid motor response of the task. The "No Go" cue would lead to inhibition of the motor command. By discerning coherency related to preparation and execution more clearly than for self-paced movements, we can better evaluate the role of coherent changes seen in a parietal-premotor network. We hypothesize that during preparation, there will be increased coherency between left hemisphere parietal and premotor areas. After presentation of "Go", we hypothesize that there will be a coherency increase related to execution. However, after presentation of "No Go", we hypothesize that greater coherency increases will be seen related to inhibition of the motor program, based on earlier findings of increased parietofrontal coherence just after a NoGo cue (Shibata et al. 1998).

Methods

Subjects

Nine normal volunteers (4 males, 5 females) from 22 to 68 years of age (45.8 ±19.4) were studied.

Experimental Procedure

The paradigm used in this study is similar to that used in an fMRI study of parietal and premotor activation related to praxis movements (Fridman et al. submitted). The current study consisted of one training session of approximately 5 min to ensure familiarization with the task followed by four 18-minute experimental sessions. Subjects sat comfortably in a reclining chair and were

presented instructional word cues related to each task. The cues were presented on a 16-inch LCD monitor. The monitor was positioned 12 inches away from the face in the center of their visual field. The first cue (S1) was an instruction sentence (e.g., “Show me how to use a hammer”), which is displayed on the screen for 2 s. The S1 instructions were developed from a list of 20 tool-use movements and 20 communicative gestures. After presentation of this cue, a blue cross was positioned in the middle of the screen for 6 s. The subject was informed that this served as a time to think about and plan the movement that was presented in the S1 cue. Following this, a variable “Go” or “No Go” command cue (S2) was presented for 2 s. If “Go”, subjects were instructed to perform the movement with their right hand as quickly as possible until a “Rest” cue was presented 3 s later. The movement was to be made repetitiously for the entire 3 s period. If “No Go”, the subjects were instructed to rest until presentation of the next S1. Presentation of “Go” and “No Go” were randomized and each accounted for 50% of all trials. Experimental sessions were conducted with a 5-min rest condition between each session.

Data acquisition

High density (64-channel) EEG was recorded using SynAmps (Compumedics; El Paso, Texas) with a linked ear reference. EEG was recorded at a 1 kHz sampling rate and a bandpass range of DC to 100Hz. To ensure proper performance based on the S2, surface EMG was recorded at the abductor pollicus brevis (APB) and flexor carpi ulnaris (FCU) muscles in the right upper limb with a bandpass range

of 5-200 Hz. For each trial, onset of S2 served as time = 0, and epochs from 8.5 s before S2 onset to 3.0 s after were collected. For quantitative analysis of parietal and premotor functional connectivity, imaginary coherency between premotor electrode C3A and parietal electrode TCP1 was chosen to assess the circuit.

Data Analysis

Because the purpose of the study is to determine the network for praxis, tool-use pantomime and communicative gesture movements were analyzed together. "Go" and "No Go" trials were analyzed separately. The epochs were analyzed in non-overlapping 512 ms segments. For event-related coherence analysis, the baseline was corrected for the first segment of the dataset.

For each segment, channel and epoch, we calculated the Fourier-transform of the Hanning-windowed data. We denote the result as $x(f,t,i,k)$, where **f** is frequency, **t** the time of the center of the segment, **i** the channel and **k** the epoch. The cross-spectrum (**S**) is the product of the Fourier amplitudes for all pairs of channels and for all segments averaged over all epochs:

$$S(i,j,f,t) = \frac{1}{K}\sum_{k=1}^{K} x(f,t,i,k)\, x^{*}(f,t,j,k)$$

where * denotes complex conjugation. Coherency (**C**) between two channels **i** and **j** at a frequency **f** at time **t** is simply the normalized cross-spectrum:

$$C(i,j,f,t) = \frac{S(i,j,f,t)}{\left(S(i,i,f,t)S(j,j,f,t)\right)^{1/2}}$$

Coherency is a complex number with absolute value smaller or equal to one. If the signals in two channels are unrelated their relative phase is random: the terms in the sum tend to cancel each other out and the coherency converges to zero (with increasing number of epochs). If the signals in the two channels come from a single source the relative phase is either zero (if the electric potential induced by this source has the same sign at the two electrodes) or $\pm\pi$ (if the electric potential induced by this source has opposite sign). In either case, coherency is a real number. Coherency can only have a non-vanishing imaginary component if the activities of two sources are time-lagged. Since the activity of a single source is never time-lagged to itself, the imaginary part of coherency does not detect 'self-interaction'. As such, analysis was made on the real part of coherency to determine if there was any effect seen. The real part of coherency reflects the zero-phased components ignored by the imaginary part. The magnitude of the total coherence is a measure including both real and imaginary parts, and thus may be contaminated with volume-conducted information. We can compare the results of the magnitude of coherence, real part, and the imaginary part of coherency to determine if we can see an effect outside of volume-conducted artifacts.

To determine significant differences between "Go" and "No Go" trials, analysis was made on four 512 ms time segments of the data. Two adjacent periods occurred during preparation, at 4.7-3.6 s before S2 stimuli onset, and two adjacent periods from 0.4-1.5 s after S2 stimuli onset. The preparation time was selected

as it is roughly between S1 and S2 and the subject should have time to consider the command by that time. If the time was too early, it is possible that the activity could relate to reading or internal re-verbalizations of the command. If too late, it is perhaps too close to motor related activity. The execution time was chosen as it would be activity directly attributed to the decision based on S2 and motor activity. To ensure that the variances of the preparation and execution in "Go" and "No Go" trials were equal, an F test for variances was performed. Upon accepting the null hypothesis the variances were the same (preparation, $F = 1.05$, $p = 0.45$; execution, $F = 0.72$, $p=0.25$), a Bonferroni corrected t-test for $\mathbf{n} = 4$ comparisons at $\alpha = 0.05$ was performed. The corrected α value (α_c), calculated by $\alpha_c = \alpha / \mathbf{n}$, was 0.0125.

Results

Magnitude of Total Coherence

Analysis of the magnitude of total coherence in this study produced no clear interactions within the parietofrontal network during preparation. After presentation of the S2 stimulus, there was a small increase in the magnitude of the "Go" coherence ($t = 0.4$ s) while the "NoGo" coherence remained low, but this was not significant ($p=0.46$). While there are no consistent increases or decreases seen in this coherence measure, we can look to the individual parts (real and imaginary) to see if an interaction exists.

Real Part of Coherency

Analysis was done on the real part of coherency for both preparation and execution. The real part of coherency presents no evidence of increases of event-related coherence within the parietofrontal network; therefore, we looked at the imaginary part to determine if our hypothesized coherent network is best explained looking at time-delayed information.

Imaginary Coherency

Coherency increases were seen between the parietal and premotor areas during the preparation period for both the "Go" and "No Go" conditions. General patterns of coherency can be seen in Figure 11 for "Go" and "No Go" conditions. Initial increases were seen within the parietal-premotor network from the presentation of the S1 cue. Increases were seen until a peak was seen at about 2.7 s before onset of S2. During the preparatory period, imaginary coherency measures between TCP1 and C3A from 4.7 to 3.6 s before onset of S2 showed no statistical difference between the "Go" and "No Go" condition (first bin, $p=0.42$; second bin, 0.07). Following this initial increase, a rapid decrease of coherency was seen about 0.8 s before S2 for both conditions. Upon presentation of S2, initially the "No Go" condition showed no corrected statistically significant coherency increase compared to the "Go" condition ($p =0.028$). However, in the second time bin analyzed after onset of the S2 cue, the "No Go" condition showed a significant difference ($p = 0.001$). The increase of coherency during the "No Go" condition remained steady for the duration of the analysis window. The

pattern of magnitude of the imaginary part of coherency across time can be seen in Figure 12.

Discussion

Anatomical parietofrontal networks are critical for performing many different complex hand movements in non-human primates (Rizzolatti et al. 1998b; Rizzolatti and Luppino 2001). If these anatomical networks are present in humans, it is possible that they help to guide complex hand movements, a characteristic of our everyday motor control (Johnson-Frey 2003). Earlier studies of parietofrontal networks in praxis have been shown during pre-movement and at movement onset for self-paced movements looking at the magnitude of coherent activity (Chapter 4). In this previous study, a parietofrontal functional circuit was demonstrated. However; because it was a self-paced movement study, there was no clearly distinct onset of preparation. In the current study, preparation occurs after S1. Subjects generally report thinking about the type of movement that must be made to carry out the command in the S1. Moreover, looking at the magnitude of coherent activity between the two channels analyzes, in part, zero phase lag components between the two signals that may have activity related to a single volume conducted source. To increase our confidence in our hypothesis, we focused primarily on the imaginary part of coherency in the current study. In doing this, we see increased coherency between parietal and premotor networks increasing during preparation of praxis hand movements. There is no significant

difference between “Go” and “No Go” conditions. However, after presentation of S2 (Go or No Go), there was a significant difference in the magnitude of the imaginary coherency, with “No Go” conditions being greater than “Go” conditions. This effect was not seen for the real part or the magnitude of coherence.

Principles of imaginary coherence

Coherency between two channels at a specific frequency is a complex number (geometrically, a 2-dimensional vector), which characterizes the linear relationship between the signals at a particular frequency. This quantity is usually studied in polar coordinates: the absolute value (length of the vector) is called coherence and is a measure of the strength of the relationship between the two signals; phase (the angle of the vector to the positive x-axis) measures the relative time-lag. In contrast, here we studied the same quantity in Cartesian coordinates, i.e., the real and imaginary part of coherency (the x- and y-components of the vector).

In this analysis, there were increases and decreases in coherent parietal and premotor relationships. However, one must be cautious, since these “increases” or “decreases” can arise under two conditions. One is simply that the magnitude of the imaginary part increases relative to the other condition. Secondly, however; if there is an increase in a time lag of the two signals, this would also cause an increase in the size of the imaginary part. In the case of our analysis, by

focusing on Cartesian coordinates, if the phase were to decrease, this would cause a shift in the coordinates where the real part (on the x-axis) would increase, while the imaginary part (on the y-axis) decreases, assuming the magnitude remains relatively unchanged. The opposite would occur if the phase lag increased. However, since the magnitude of coherence consists of the real and the imaginary parts of coherency, is a mathematical necessity that if the imaginary part increases, the magnitude of coherence must also increase. While we see no increases in the real part or the magnitude of coherence, we are left to wonder how this can be. It is plausible that in this network we are studying, much of the coherence has a time delay by nature. This means that the real part would remain very small constantly; thus an increase in the imaginary part would not affect the real part, but could play a role in the magnitude of coherence. If the increase of the imaginary part is relatively small and there was little to no increase in the real part, the magnitude of coherence would only increase by a small fraction that may be undetectable in our analysis. Another possibility is that the real part is just too noisy to see an effect. Thus, a noisy real part and an increasing imaginary part yield a magnitude of coherence that is additionally unstable. Therefore, any increases in the real part or the magnitude would not be deemed significant. This is likely the case in these data as the real part showed a high amount of noise and the magnitude showed an insignificant increase during the tested conditions.

It can be hypothesized that time delay relationships between signals from brain areas are relatively consistent (Tallon-Baudry et al. 2001). Theoretically, this

would be the case in our analysis of the period before S2, which is the same in both “Go” and “No Go” conditions. However, S2 should initiate different brain mechanisms for the two conditions, which could account for a change in phase. Because we see no effect after evaluating the real part of coherency at preparation and execution, we speculate that the increase in imaginary coherency represents a consistent shift in phase of the parietal-premotor signals, which is similar during the preparation stage and different during the execution stage. If there is a small increase in the real part, mathematically, its influence on the magnitude of total coherence would be negligible. This is why we only see increases in the imaginary coherence. The differences during the stage after S2 would be attributed to activity of a network now responsible for inhibiting a motor plan in the “No Go” stage, but having a negligible function in the “Go” stage. This inhibitory network is likely anatomically similar, yet functionally distinct, from the preparation network.

Additionally, the analysis may also reveal information about which waveform occurs first, since we are analyzing time-delayed signals only. From a computational perspective, timing may be difficult to prove. The analysis suggests that the direction of the imaginary coherency is from parietal to premotor areas (Fig 11). However, direction of the coherent relationship is arbitrary. For example, at 20 Hz, the parietal signal could be occurring 5 ms before the premotor signal. Conversely, it could also be 45 ms after the premotor signal. Generally, because of the speed of neuronal transmission, one can accept the shorter time

latency as the actual value but there is no clear mathematical basis for this argument. Therefore, the imaginary coherent relationships are expressed as positive or negative, without regard to directionality.

From a biological perspective determining if the parietal signal is leading the premotor signal, or vice versa, is also ambiguous. It is very possible that multiple, bi-directional brain processes are being used in this paradigm. Upon presentation of a cue (e.g. Show me how to use a hammer), processing occurs in parietal areas to define hammer usage. One may use a hammer to hit a nail in or to pry a nail out. Moreover, there are an infinite number of hand configurations and angles to drive in, or remove the nail. Ultimately, one must select the appropriate movement to make. This may be done by working memory processes of recent movements or based on task and instruction information (Bartolo et al. 2003). This selection would involve premotor/prefrontal networks to select a specific hand configuration (Fagg and Arbib 1998; Grafton et al. 1998). Thus, a network from parietal to premotor structures is implemented in this step. After selection of the appropriate movement by premotor structures, this information is relayed to parietal structures to block the unselected movements and continue to update the specifics of the movement as needed. Premotor areas would be the driving structures to accurately plan the movement parameters, and would involve a network from premotor to parietal structures. In our analysis, these direction changes would be identified as positive (parietal to premotor) and negative (premotor to parietal) coherency values. Equivalent and simultaneous bi-

directional coherency values may be cancelled out. However, if one coherent direction is stronger, this one would be emphasized. Based on the above-described mechanisms, initial increases in the imaginary coherency until about 2.7 s before S2 onset reflect processing of various types of ways to perform the movement instructed in the S1 signal in a parietal to premotor direction. The drop in imaginary coherency could result from a decision being made about the proper movement, just before onset of the S2 in the premotor to parietal pathway. If both pathways are active at the same time at a similar magnitude, this would result in net coherency levels falling to or at near zero, as seen in this situation (Fig 12). Eventually, the parietal to premotor path would become more dominant again and involved in inhibitory processes, as will be discussed later. Thus, computationally and biologically, the direction of the coherent relationship should be left to further investigation. The result of this study is best described as illustrating a genuine coherent relationship between parietal and premotor areas, void of possible volume-conducted interactions.

Unequivocal parietal-premotor coherence

The presence of genuine coherent activity between parietal and premotor areas further underscores the importance of networks between these areas in performance of praxis. It has been considered that coherent networks exist that can integrate activity related to various aspects of planning a complex motor task to actual performance of the task (Wise et al. 1997; Burnod et al. 1999). For praxis movements, this could involve knowledge of tools (or gestures), the normal

motor parameters in situations performing the associated task, and then developing a motor pattern based on this information. Coherency during preparation is particularly important. In this study, there was no difference in the coherency related to preparation movements between “Go” or “No Go” trials. This is logical, becuse the subjects were told to plan the movements that they were instructed to, which happens regardless of the type of S2 that will be presented. This allows us to know that such coherency values are related solely to preparation, and are not contaminated with any motor activity.

However, after S2 presentation, there is a difference between trials. After presentation of “No-Go”, it is possible that there is an inhibitory process involving similar areas that are also present in preparatory processes. It has been known that motor inhibition is related to parietal-premotor networks, which could relate to the increased coherence after presentation of “No Go” (Shibata et al. 1998). Conjunction analysis in functional magnetic resonance imaging (fMRI) found inhibitory processes related to “Stop” and “No-Go” tasks in mesial, medial, and inferior frontal and parietal areas (Rubia et al. 2001). Additionally, during a “No Go” decision in fMRI, activation included bilateral premotor areas, left dorsal premotor areas, and left inferior parietal sulcus (Watanabe et al. 2002). Sources of inhibitory activity have been seen in premotor areas (Sasaki et al. 1989; Sasaki et al. 1993).

Decrease of coherency during the Go trials should be discussed. During self-paced praxis movements, coherence increases relating to early pre-movement preparation and just before and during execution of praxis are clear (Chapter 4). It could be that in a self-paced paradigm, three phases of activity are seen in two discrete time periods. The first is an unconscious planning period, which allows for an initial peak of coherency, followed by conscious awareness of planning a movement and execution that could occur in a small time window around the onset of the movement. Thus, we cannot be completely sure that coherence increases close to execution contain only preparatory coherent activity, but mechanisms related to relatively immediate task performance. In the present paradigm, overt planning occurs as soon as presentation of the S1 happens. This is the advantage of the paradigm. Additionally, parieto-premotor coherency may not be as required at the onset of a movement, since there is an extensive planning period in the task.

If the purpose of parieto-premotor networks is to generate an appropriate plan for a complex hand movement such as praxis, the findings fit the hypothesis. It has been hypothesized that parietal and premotor areas, and possibly networks between the structures, can be involved in online control of movement (Wise et al. 1997; Cunnington et al. 2002; Johnson et al. 2002; Hanakawa et al. 2003). However, this is not generally seen in response selection studies, where mainly the premotor area selects the appropriate motor response (Bunge et al. 2002). In similar Go/No-Go studies, only sensorimotor, mesial frontal, thalamic and

cerebellar activity is seen during execution (Watanabe et al. 2002). In our paradigm, normal subjects have an extensive planning period and are able to formulate a clear motor program, which is a function of the left hemisphere network for praxis movements.

The studies in the present and previous chapters illustrate the functional networks seen for praxis pantomime. While these are studies of normal subjects, we have a robust baseline dataset to form hypotheses about the possibilities of changes in cortical dynamics for praxis hand movements and for patients with IMA. This is explored in the next chapter.

Chapter 6: Cortical Networks in Patients with Ideomotor Apraxia

Introduction

The inability to properly pantomime tasks seen in apraxia is not only a clinical curiosity, but also affects the lives of patients. Generally, two types of patients are thought to suffer from ideomotor apraxia: patients with a degenerative disease called corticobasal degeneration (CBD) and stroke patients. CBD patients typically have degeneration of frontal cortices and of the subcortical structures, including basal ganglia (Boeve et al. 1999; Lang 2003). A multitude of motor deficits are seen in these patients together with ideomotor apraxia. This typically makes identification of apraxia much more difficult. These patients often complain of being unable to perform a category of movements often referred to as "activities of daily living". These include difficulty brushing teeth, using a spoon, or combing hair. Largely the case in CBD, movement disorders (e.g., tremor, myoclonus, or dystonia) may impact the performance of these tasks, patients will still report, or will be observed, having difficulty in the proper orientation of using a toothbrush and perhaps use exaggerated movements more characteristic of apraxia (e.g., using a toothbrush by making large circular arcs in the air moving the entire arm). Stroke patients with left hemisphere lesions suffering from apraxia will have the same types of errors.

Because damage to the brain and its networks has likely caused these deficits, we can study the activity of cortical networks to see how they have changed in order to properly perform the tasks. Using coherence analysis in EEG (Chapters 4 and

5), we have seen evidence of the networks responsible for praxis. We have seen that normal self-paced praxis activates a network of the left hemisphere parietal and premotor areas (Ch. 4). However, in stroke and CBD patient populations, left hemisphere damage is seen. Therefore, we hypothesize that for patients this network involves more coherence within the right hemisphere or a change in the left hemisphere coherence patterns to account for the damaged cortex. This is evidence of a dynamic change of cortical networks involved in cortical reorganization related to re-establishing praxis.

Methods

Patients

Three right-handed CBD and two stroke patients were acquired to participate in this study. The patients were acquired from the Human Motor Control Section Clinic and the Stroke Clinic, both of NINDS, NIH (Bethesda, MD) and National Rehabilitation Hospital (Washington, DC). Table 3 lists the area of lesion for the patients. Both the CBD and stroke patients underwent rigorous evaluation to ensure that movement disorders would not interfere with normal praxis function or be confused with apraxia. These subjects were instructed to perform self-paced tool-use pantomimes (hammer, scissors, screwdriver) with the distal left hand (distal to the elbow), according to the same self-paced paradigm followed in Chapter 2. All patients had ideomotor apraxia that affected both hands equally. However, since right-hand paresis was seen in each patient, the left hand was tested. A more rigorous training session was performed in the apraxia patients.

They were instructed to perform the tasks repeatedly over a one-half day training session. This was done to ensure that they could learn to perform the task correctly, with performance similar to that of the normal subjects. This is important since comparing normal movements with severely disordered movements would not make for a good comparison. It was also important that the patients be able to feel as though they were able to make the movements and have the same motivation as normal subjects. Once this was achieved, the EEG study began.

Normal subjects

Right-handed normal subjects, age-matched to the patient population, were studied for this portion for the experiment. A short training session was held to begin the tasks to ensure proper performance. The left hand was used in the normal subjects to match patient studies. Each type of praxis movement was performed for 2 - 6 min blocks, for a total of 6 blocks. Praxis movements were averaged together to acquire a symbolic characteristic for transitive movements.

Data acquisition and analysis

64-channel EEG (DC-100 Hz, 1 kHz sampling rate) was recorded using Synamps and NeuroScan 4.2 Acquisition Software (Compumedics, El Paso, TX) with surface EMG (5-200 Hz) from the left APB and FCU to signal approximate onset of the movement. EEG signal was bandpass filtered offline to DC-50 Hz and marked to indicate EMG onset. Epochs were made from 3 s before movement

onset to 1.5 s after movement onset. Approximately 150-artifact free trials were acquired for each participant and analyzed for coherence using in-house functions in Matlab (Mathworks, Natick, MA). Coherence was analyzed in non-overlapping 256 ms segments for coherence using the same equations and method as stated in Chapter 2. Coherence values, relative to a 512 ms baseline, are reported in magnitude from –1 (decreases) to +1 (increases in coherence). Analysis was done on the pre-movement time periods only, because there might be remaining kinematic differences in the movements that we could not account for that may affect the coherence results.

Results

Figure 13 represents the comparison of each subject group with each comparison of coherent pathways analyzed.

Normal Subjects

Coherence increases were assessed during both the preparation and execution time periods. Results show that beginning about 2.5 s before EMG onset, coherence increases were seen between the left parietal- left premotor (Fig 13). These coherences continued to increase until a peak (magnitude = 0.021) just before movement onset began. This represents a similar pattern to that which was seen for the normal right-hand praxis movements. No other stable coherence patterns were seen.

Patients

In the patient populations, differences were compared to what was seen in the normal subjects. The data from the CBD patients were grouped together, as they had matching lesion profiles and similar results. In the CBD patients, the result shows a coherence pattern that involves coherence increases between the left parietal-right parietal (maximal magnitude = 0.18 at movement onset), left parietal-right premotor (maximal magnitude = 0.22, 0.5s before movement onset) and right parietal-right premotor (maximal magnitude = 0.16, 1.5s before movement onset) areas of interest. The first coherence increases were seen between the left parietal-right premotor areas by 2.7 s before movement onset. Coherence increases were seen between the bilateral parietal areas beginning about 2.7 s before movement onset. Coherence increases were also seen between the right parietal-right premotor area by 2.5 s before onset. These increases all remained consistently high during the duration of the pre-movement period into movement execution.

In our stroke patients, there was a difference compared to the normal subjects as well. In the first stroke patient (with left parietal lesions), coherence increases were seen between the right parietal-left premotor areas that peaked just before movement onset (magnitude = 0.23). Just before movement onset, coherence was seen between the left parietal-right parietal areas (0.15), and the bilateral premotor areas (maximal magnitude = 0.22 at 1.0 s before movement onset). In the second stroke patient (left premotor and subcortical lesion), The greatest coherence

increase was seen between the right parietal-right premotor areas just before movement onset (magnitude = 0.23). This patient showed decreases in baseline coherence, particularly in the bilateral premotor areas (magnitude = -0.22) and the left parietal-left premotor areas (-0.30) just before movement onset.

Discussion

fMRI findings have shown that compensation of function can occur in patients with stroke over time, with training strategies (Luft et al. 2004). Training strategies are important in regaining the ability to operate normally. In this study, this cortical compensation was assessed in a different way: Do corticocortical networks in the brain change? Here, we are not only looking for differences in the activity of the brain, but dynamic relationships between anatomically distinct areas of the brain as it is possible for two areas of the brain to be active, yet not coherent in function (Pfurtscheller and Andrew 1999). Of specific interest is the connection between parietal and premotor cortices. It is known that the left parietal cortex has connections with the left premotor (Rizzolatti et al. 1998b) and right premotor cortices (McGuire et al. 1991). In the current study of coherence in normal subjects, saw no evidence of left parietal-right premotor coherence increases. However, in patients with left premotor lesions, we expect that the right premotor cortex would play a large compensatory role in planning/preparing praxis. In this study, normal volunteers showed coherence increases between left parietal-premotor areas. The patients showed a largely different coherent network, now involving the right hemisphere parietal and premotor cortices.

Thus, the right hemisphere has become a major part of the network for praxis movement.

Hemispheric reorganization

The right parietal area has been considered by some to store copies of the same information relevant to praxis that is seen in the left hemisphere. In a study of apraxia patients with left and right hemisphere lesions, patients performed equally poorly on intransitive movement (Roy et al. 2000b). It is not typical to see right hemisphere stroke patients with apraxia (Halsband et al. 2001). Because of this, there is little confirmation that the right parietal area has any motor representations for praxis. Studies have suggested that learning (or re-learning) of playing a stringed instrument leads to an experience-based reorganization of left parietal and premotor cortices (Kim et al. 2004). Activity related to spatial processing has been shown to switch from the left to right parietal lobe suggesting plasticity of higher-level processes as well (Zacks et al. 2004). If this were possible, it would account for apraxia patients being able to perform these praxis tasks with reorganization of high-level representations for these movements. In this study, it is clearly possible that coherence patterns are now changing, representative of reorganized connections devoted to recovery of normal performance using parts of the brain that are not damaged by lesions or degeneration. Coherence between bilateral homologous areas (left and right parietal, left and right premotor) could represent a network where information is shared or moved to another intact hemisphere for processing. For example, there

are coherence increases between the bilateral parietal cortices for CBD patients, but no significant increases for the bilateral premotor cortices. While the left premotor cortex was largely damaged in these patients, which could impair left hemisphere parietal-premotor functional pathways, a new network is established that involves bilateral parietal coherence and between right parietal-right premotor areas.

Functional principle of left parietal-right premotor coherence

A network of principal interest is the left parietal-right premotor pathway, which uses connections via the corpus callosum. While there is adequate anatomical evidence to support the existence of this pathway, there is little to suggest that it has a large role in normal function. It was postulated that a left parietal – right premotor network could be established when lesions cause degeneration of left hemisphere parietofrontal white matter tracts, which was thought to be the main factor in apraxia (Kertesz and Ferro 1984). While functional coupling has not been fully demonstrated, fMRI evidence supports this hypothesis in patients with left premotor lesions which establish right premotor activity (Luft et al. 2004; Schaechter 2004). The result in this chapter indicates that there is a functional recovery that is also coherent. Further analysis of other patients with ideomotor apraxia is worthwhile to establish how the network changes. These data provide early evidence of reorganization of functional pathways due to brain damage.

Chapter 8: Conclusions

Insights

The research described in this volume provides several thoughts on ideomotor apraxia and the overall function of the brain. First, we could determine and verify that there is early activity related to pre-processing motor commands in the parietal lobe that spreads to the premotor cortex by analyzing MRCP and frequency-dependent power changes. This is not seen for simpler movements, which likely have greater premotor activity associated with them, or need less complex planning. We also see this early activity in the parietal and inferior temporal cortices for praxis but not for simple movements using ECoG which provides highly accurate spatial and temporal information. Additionally, we know that distinct brain areas work as a functional network to perform these tasks based on our coherence findings in normal subjects.

A highlight of this coherence study indicates that there is a necessity in parieto-premotor networks, and not just parieto-motor networks, which show no functional activity in this task. This is a result that is supported by intensive anatomical studies of parieto-premotor networks in non-human primates, which are largely assumed to exist in humans. The resulting coherence is probably due to direct cortico-cortical coherence, since it is likely that multisynaptic projections would not allow us to see these phasic relationships. To date, there has been no other investigation to illustrate a functional association of these to brain areas to suggest that there is direct anatomical connectivity between the parietal and

premotor cortices. When there is damage to those networks that cause ideomotor apraxia, there is a functional reorganization of the circuitry to include the right hemisphere, which is not involved in coherent networks in normal subjects. While these are relevant to apraxia research, it is also important to neuroscience. This work has given some insight into overall brain functions. We can now confidently state that there are functional networks devoted to planning and executing movement, which can change in the event of brain injury. The analysis reveals the first evidence of what has been speculated for more than 100 years.

Research has suggested many hypotheses to explain brain functions. Historically, it was thought that specific connectivity between neurons could not account for brain functions because "All behavior seems to be determined by masses of excitation… , without regard to particular nerve cells" (Lashley 1942). Connectivity in the brain has been challenged, yet coherence, and similar measures, have provided insight into the possibility that the brain operates as a network. Specifically for praxis, we can see in these studies that cortical function to generate behavior is not confined to local areas, but rather requires broad networks of activation in very specific routes. This is substantiated by our results in Chapter 6, where there is no longer coherence within the left hemisphere parietofrontal network for patients with lesions that cause damage to left hemisphere structures. This further confirms the notion that there is not only reorganization of activity in local areas after brain injury, but also to large scale networks, so that restoration of function can occur.

While EEG has limited the analysis to cortical structures, it is hypothesized that extracortical components may be involved in praxis and apraxia. This is an issue of serious debate in the literature. Unfortunately, it is also difficult to assess the physiology of these areas in humans. Basal ganglia lesions are seen in patients with apraxia. Quantitative evidence suggests that there is significant error in learned, skilled movements in patients with left basal ganglia ischemic lesions (Hanna-Pladdy et al. 2001b). Generally, the left basal ganglia is involved in spatial and temporal features of learned movements, sequence learning, and response inhibition (Boyd and Winstein 2003; Seiss and Praamstra 2004). While degraded spatial and temporal features of movements are clear highlights of ideomotor apraxia, movement disorders may be present which would prevent a clear diagnosis. While avoiding these confounding motor deficits, ideomotor apraxia was seen in diverse patient groups with mixed cortical and basal ganglia damage (Leiguarda et al. 1997).

A case study suggests ideomotor and ideational apraxia involvement in basal ganglia damage leading to CBD (Chainay and Humphreys 2003). Another patient with a basal ganglia and external capsule lesions showed normal production of transitive and intransitive gestures on command and imitation, but low scores in performing gestures in situations shown in a set of cartoons (Bartolo et al. 2003). However, ideomotor apraxia is not seen in patients with damage strictly to the basal ganglia in Huntington's disease unless it is present with corticostriate

damage (Hamilton et al. 2003). Additionally, administration of dopaminergic medication does not help Parkinson's disease patients perform motor tasks better on an initial attempt, but does assist in incremental learning of a motor command over time (Hanna-Pladdy and Heilman 2002). It is possible that the basal ganglia are involved in motor learning, but may not be as involved in performance of learned praxis movements. This casts some doubt on the relevance of the basal ganglia exclusively to apraxia. The cerebellum is also involved in motor learning, yet has never been implicated as playing any role in apraxia (van Mier et al. 1993; Petersen et al. 1998; van Mier et al. 2004). There is continued reluctance to consider basal ganglia damage as a cause of ideomotor apraxia.

The thalamus is of considerable interest as well. It has been long known that there are corticothalamic projections originating in the posterior parietal, superior temporal, and premotor cortices of rhesus monkeys (Yeterian and Pandya 1985; Yeterian and Pandya 1989; Yeterian and Pandya 1993), all areas thought to be involved in praxis. Thus, it seems possible for parieto-thalamic-premotor circuits to exist which may become damaged at the thalamic level and cause ideomotor apraxia. One study indicated the presence of apraxia in patients with lesions limited to the thalamus and/or basal ganglia (Agostoni et al. 1983). Yet, the apraxia test that they developed revealed very mild ideomotor apraxia, with a more prominent deficit of copying three-dimensional line drawings (constructional apraxia). A case study of a patient with an infarct of the dominant thalamus showed severe ideomotor apraxia (Nadeau et al. 1994). However, in a

study of 9 patients with lateral thalamic infarcts, no patients had ideomotor apraxia (Annoni et al. 2003). Ideomotor apraxia was seen in 7 of 10 non-aphasic apraxic patients with subcortical damage, yet this also involved the white matter (Papagno et al. 1993), which may have more implications on cortico-cortical circuitry (Kertesz and Ferro 1984). Additionally, a case study reported a patient with a pulvinar infarct who had severe ideomotor apraxia (Shuren et al. 1994), however; this patient also had left occipital and inferior temporal lesions.

While these areas have not been directly associated with apraxia, it is clear that the inferior temporal area has a major role in complex movement (Goodale and Milner 1992; Fagg and Arbib 1998; Choi et al. 2001). One possibility of thalamic involvement is apraxia resulting from diaschisis where, in this case, a focal injury to a thalamic area could affect a cortical area that it is anatomically connected to. This occurs because of deafferentation. Whether diaschisis-invoked parietal or premotor deficits are seen in thalamic lesion patients is important to pursue. Although there are no clear cases of apraxia as a result of diaschisis, evaluation of this phenomenon in thalamic stroke cases is worth considering.

Future investigations

There are many important avenues for research in praxis and apraxia. As was discussed in the Introduction, one important aspect to be studied is how and where the motor representations are transformed into movements. Ideally, this occurs in the premotor cortex, but there is no tangible evidence how this is performed.

Clearly describing the structures involved in this transformation will assist in better understanding the deficit. It is rational to suggest, based on the model (Fig 2, and Praxis and Ideomotor Apraxia section of Introduction) that premotor lesions mainly impair performance and not recognition while parietal lesions could affect both. This is because premotor lesions do not impair the motor representations stored in the parietal lobe which would still be maintained to allow for a match between the seen gesture and its cortical representation. This is theoretically clear, yet has not been systematically evaluated. One way in which this could be evaluated is by performing transcranial magnetic stimulation (TMS) studies in normal subjects to cause anatomically precise "virtual lesions" in various areas of the premotor and parietal cortices to assess what the behavior effect is for praxis. Which premotor areas correspond mostly to performance-based praxis deficits will be the best indicators to evaluate this issue.

In accordance with this, a clear systematic evaluation of the deficit is important. There are many clinical batteries that are used to test ideomotor apraxia, and different ones evaluate different features of the deficit (pantomime to command, performance with the tool, and recognition). If research can develop a standard measure to test the deficit, we can begin to clearly evaluate the role lesions play in the deficit. To date, there is a noticeable lack of this in the literature. Since there are more reports that substantiate the idea that apraxia affects people in daily living and not just as a clinical phenomenon, research can now focus on longitudinal studies of different patients with apraxia to assess how cortical

dynamics change during spontaneous rehabilitation. In addition, what the best rehabilitative strategies are must be better evaluated. This is a very new field to consider, since ideomotor apraxia has traditionally been thought of as purely a clinical manifestation. Since the deficit in apraxia patients is more complicated than loss-of-use deficits seen in paresis, for example, more precise strategies must be employed that involve specific types of movement.

Testing patients using imaging and physiology in different types of rehabilitation is of interest. Our studies have largely suggested cortical activity is related to praxis; however, structures such as the basal ganglia and thalamus may also have input into a praxis network. This is particularly true for the basal ganglia, which may become more active as the patient is trained to make the movements again. As previously mentioned, exploring the possibility that diaschisis induces apraxia in subcortical stroke patients is worthwhile. This can be studied by evaluating hypometabolic changes in parietal and premotor cortices after subcortical stroke. While there are reports of apraxia with subcortical lesions, there is no insight on the exact mechanism involved. It is possible that diaschisis is the mechanism of interest. Understanding the physiology of extracortical structures related to praxis and apraxia is additionally important. With the emergence of more invasive monitoring capabilities in certain patient groups (using electrodes that can record deeper in the brain) we can begin to directly record from these subcortical areas and better hypothesize about their function. fMRI studies can also be valuable in this investigation. Additionally, related apraxias, such as limb-kinetic and

conceptual apraxia are interesting since they possibly represent lower and higher levels of complex motor dysfunction respectively. Investigations in the cortical networks in these apraxias can generate further hypotheses regarding higher-level processes in the brain.

As we learn more about the cortical mechanisms of apraxia in patient groups, evaluation of stroke and CBD patients without apraxia is of interest. Additionally, some patients with apraxia have deficits in tool-use movements only and not gestures. We know very little about why these gradations exist in apraxia. We do know that some patients that have left parietal lobe damage that still have the motor representations for praxis movement in tact. It is theoretically possible to clearly determine the localization of these representations contrasting normal subjects, patients with, and patients without apraxia. Using multiple modalities (TMS, EEG, fMRI and other imaging modalities) and analysis techniques can help further our knowledge of these brain areas, hopefully advancing the field of motor control research into issues that accelerate our knowledge to include higher-level aspects of movement.

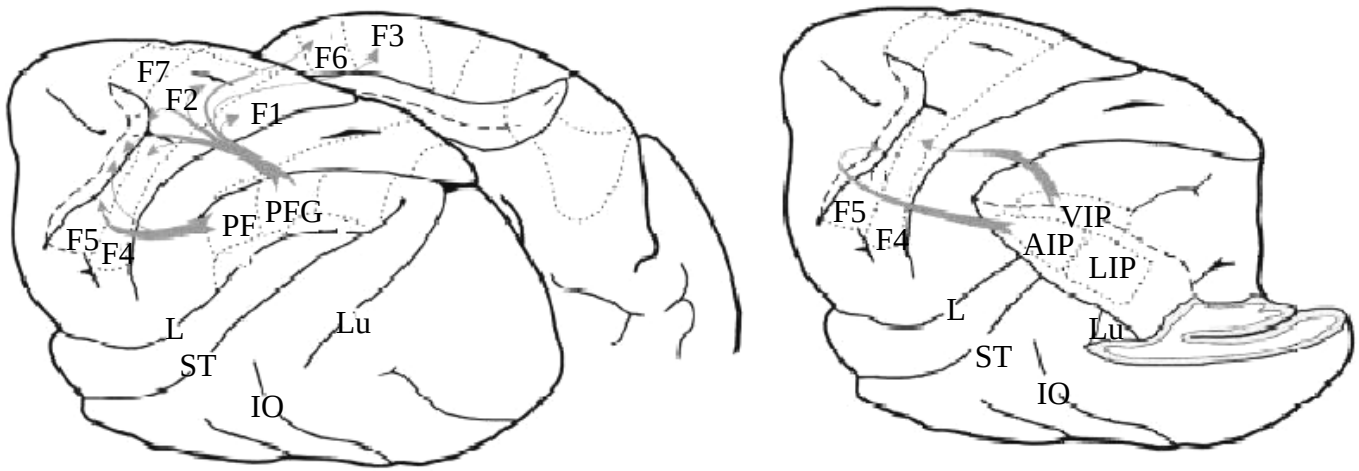

Figure 1 Anatomical pathways (arrows) to identify some connections between the parietal and premotor cortex in monkeys. Premotor and motor areas (F1, primary motor cortex ; F2 caudal segment of dorsal premotor cortex; F3, supplementary motor area; F4, ventral premotor cortex, causal segment; F5, ventral premotor cortex, rostral segment; F6, pre-supplementary motor area; F7, rostral segment of the dorsal premotor cortex) are defined according to Matelli et al. (1995). F1 corresponds to Brodmann area (BA) 4, while F1-7 correspond to BA 6. Parietal areas are defined according to Pandya and Seltzer (1982). PF and PFG are a part of BA 7. Abbreviations: AIP, anterior intraparietal; LIP, lateral intraparietal; VIP, ventral intraparietal; L, lateral fissure; ST, superior temporal sulcus; Lu, lunate sulcus; IO, inferior occipital sulcus; (Reprinted, with permission, from Rizzolatti et al, 1998). See also Table 1.

Brodmann Area	Name	Primate areas that correspond
5	Superior parietal lobule	PE, PEci
7	Inferior parietal lobule	PF, PFG, PFop, PG, PGm, PGop
4	Primary motor cortex	F1
6	Premotor cortex	F1-7

Table 1 Anatomical areas that are discussed in the text. Primate areas are based on the findings of Matelli et al. (1995) for the premotor cortex and based on von Bonin and Bailey used by Pandya and Seltzer (1982) for the parietal cortex.

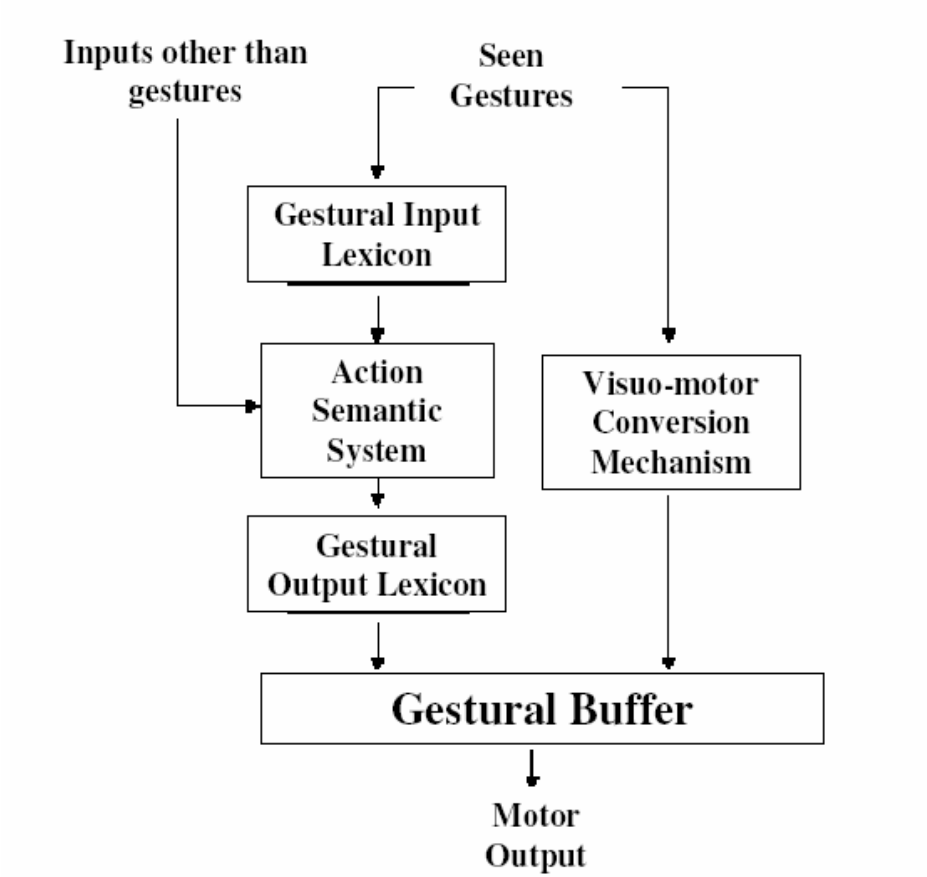

Figure 2 Current model of performance of praxis movements (reprinted with modifications, with permission, from Bartolo et al, 2003)

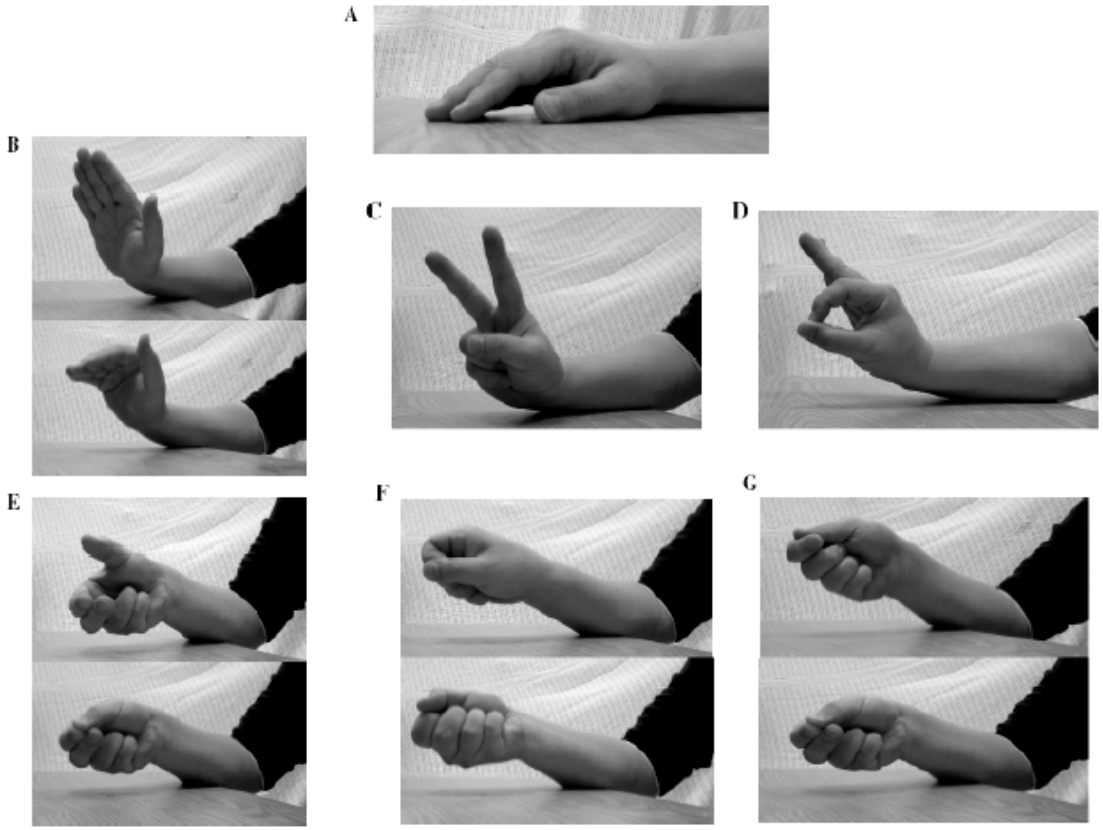

Figure 3 Pictures of the various praxis movements tested in the studies contained in this volume. All movements were starting from rest (A). Intransitive movements (waving goodbye, indicating “peace”, and indicating “ok”) are seen in the second row (B-D). Transitive movements (using a pair of scissors, using a screwdriver, using a hammer) are seen in the third row (E-G). Two of the intransitive movements (C, D) are static postures while the others (B, E, F, G) have two phases: initiating the action (top) and ending the action (bottom).

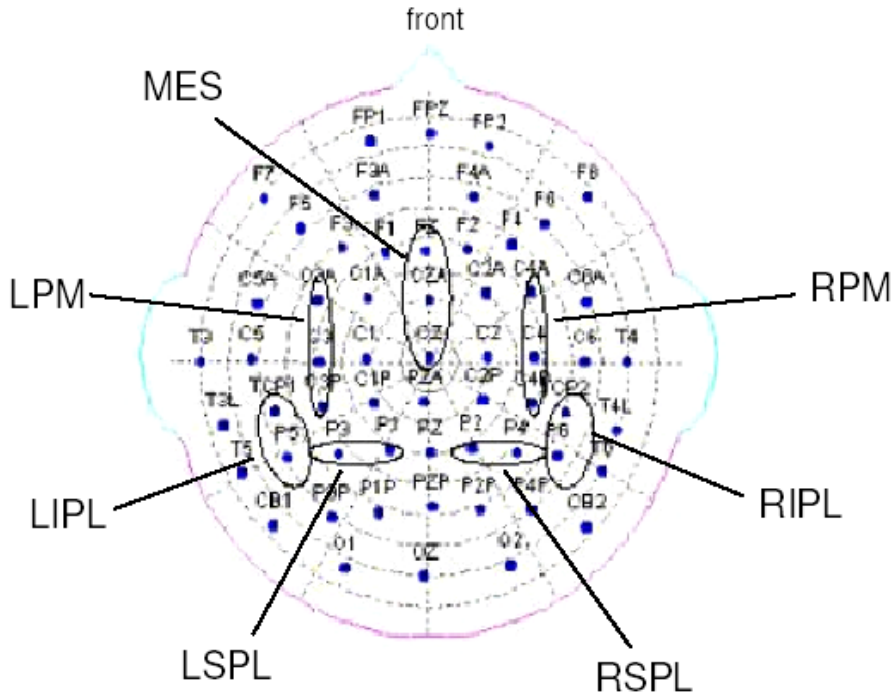

Figure 4 Image of the EEG cap on the surface of the head. Labeled electrodes (black dots) are placed on the scalp surface and lie above specific areas of the brain. Abbreviations indicate the regions of interest in the studies (see text for details).

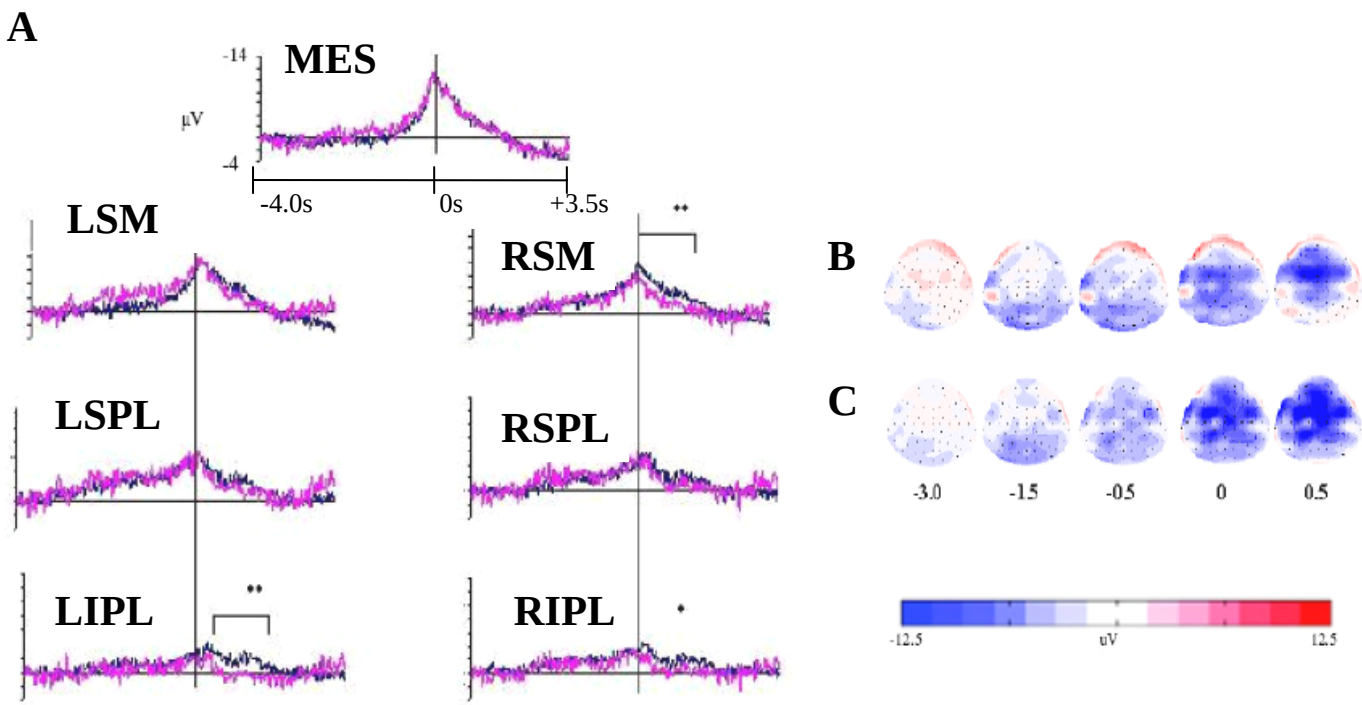

Figure 5 (A) Average of the MRCP seen over the 7 areas of interest across all subjects. Transitive movements are in purple, intransitive movements are in blue. Movement onset is defined by the vertical line through each waveform. Asterisks indicate areas that are significantly different at $p<0.05$ (**) and at $0.10>p<0.05$ (*). Surface head plots to determine the spatial aspect of the average MRCP of all subjects for intransitive (B) and transitive (C) movements are shown. Times (in s) displayed are relative to movement onset (t = 0s).

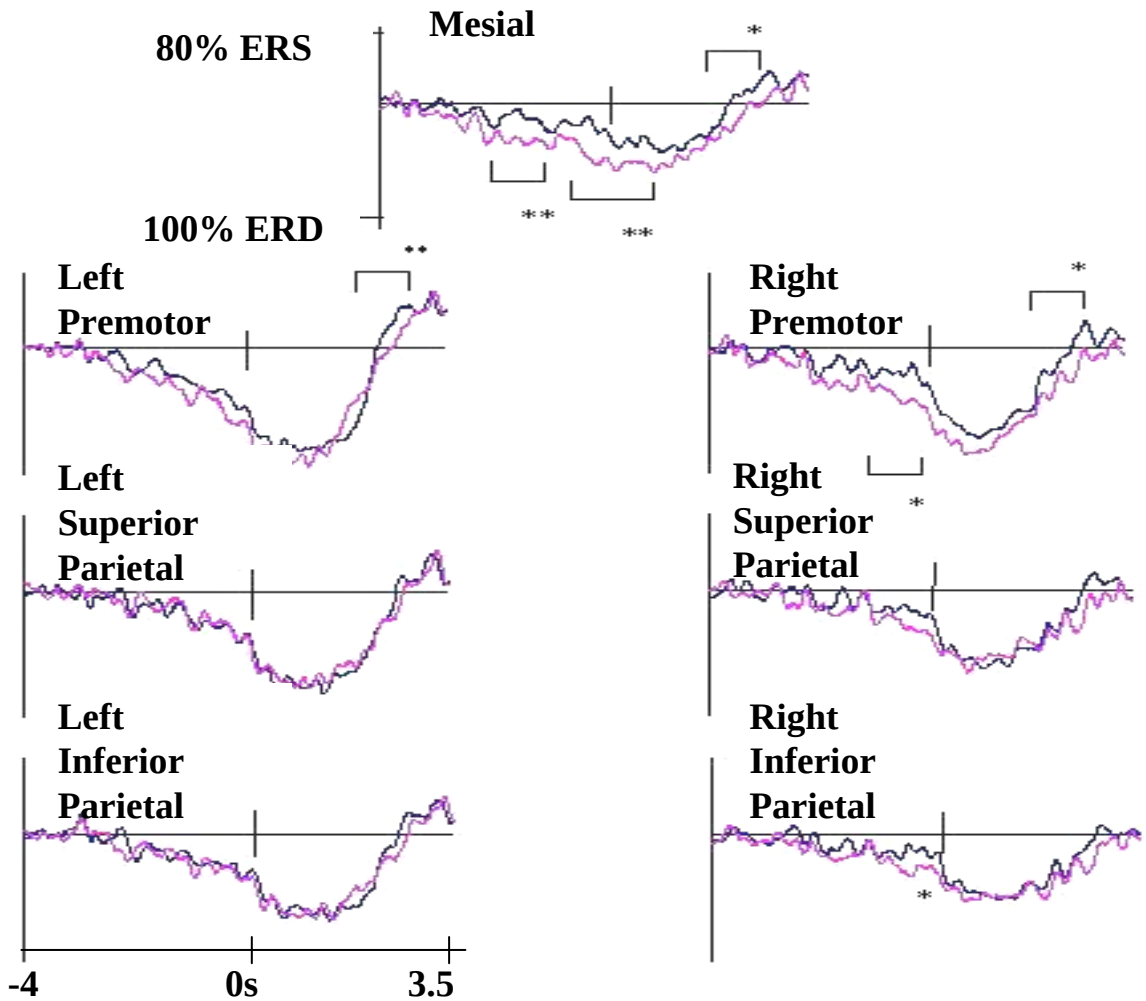

Figure 6 Grand average time-magnitude plots of the beta band ERD seen for transitive (light purple trace) and intransitive (dark blue trace) movements.

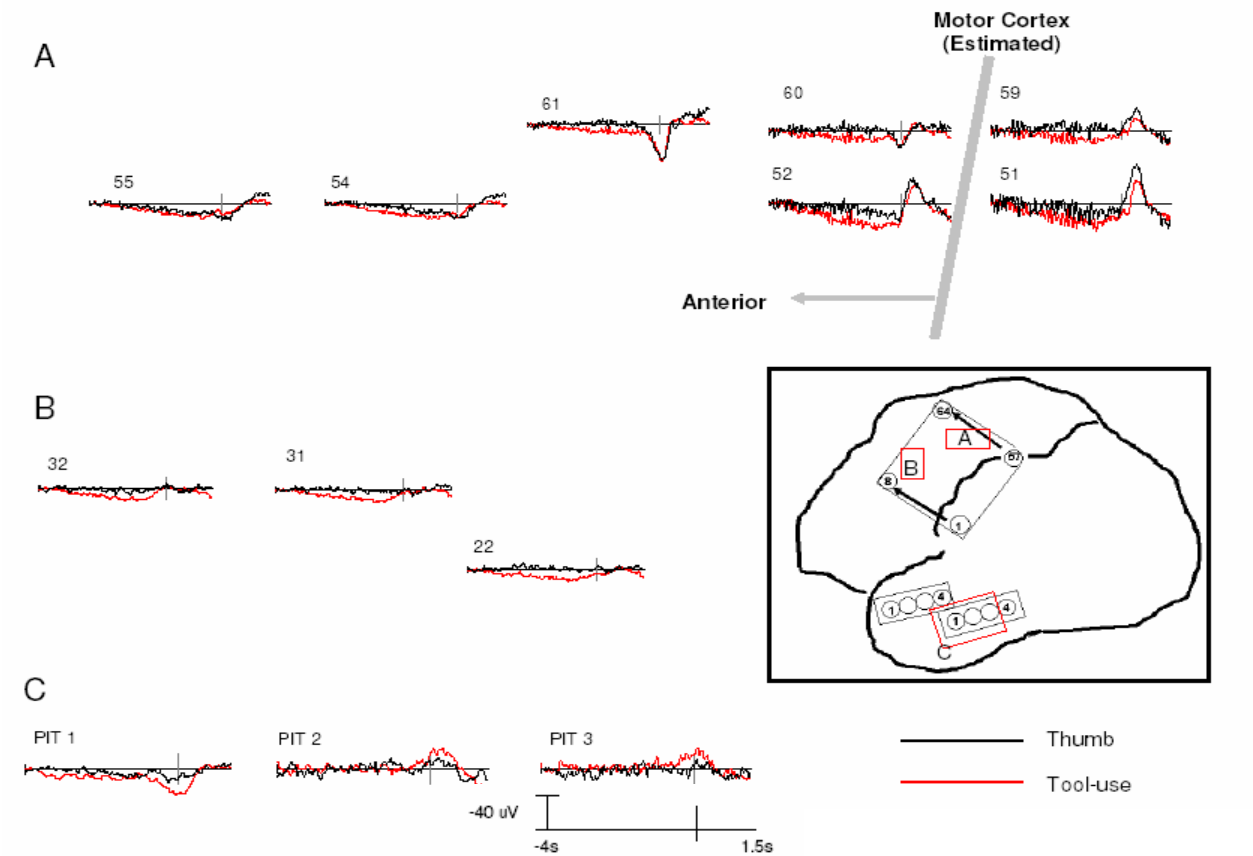

Figure 7 ECOG result from patient EM. Inset figure displays the approximate location of the electrode grids and location of the data in the figure. (A) is the MRCP from the dorsal premotor cortex, adjacent to the central sulcus. (B) is the MRCP from the anterior-ventral premotor cortex. (C) is the MRCP from the posterior inferotemporal cortex.

Electrode	*Stimulation Result*	*Type of Movement*	*Latency (s)*
Lateral Grid (motor cortex and adjacent PMd)			
51	Thumb and index finger movement	Tool	-3.21
51		Thumb	-2.36
52	Thumb tremor	Tool	-3.24
52		Thumb	-1.58
59	Middle finger twitch	Tool	-2.22
59		Thumb	-0.15
60	Thumb and index finger twitch	Tool	-3.28
60		Thumb	-0.45
61	Arm raising	Tool	-3.41
61		Thumb	-0.65
55	N/A	Tool	-3.36
55		Thumb	-3.04
54	N/A	Tool	3.41
54		Thumb	2.26
Inferotemporal cortex			
PIT1	N/A	Tool	-3.60
PIT1		Thumb	None
PIT2	N/A	Tool	-0.59
PIT2		Thumb	-0.22
PIT3	N/A	Tool	-1.71
PIT3		Thumb	None
Ventral premotor cortex			
32	N/A	Tool	-3.34
32		Thumb	None
31	N/A	Tool	-3.32
31		Thumb	None
22	N/A	Tool	-3.51
22		Thumb	None

Table 2 MRCP onset latency for electrodes analyzed for the ECOG in patient EM. "N/A" under the stimulation result denotes stimulation was not done for clinical reasons (inferotemporal cortex) or no movement was elicited from stimulation (lateral grid). "None" under the latency means that there was no MRCP seen based on the analysis methods used to detect it.

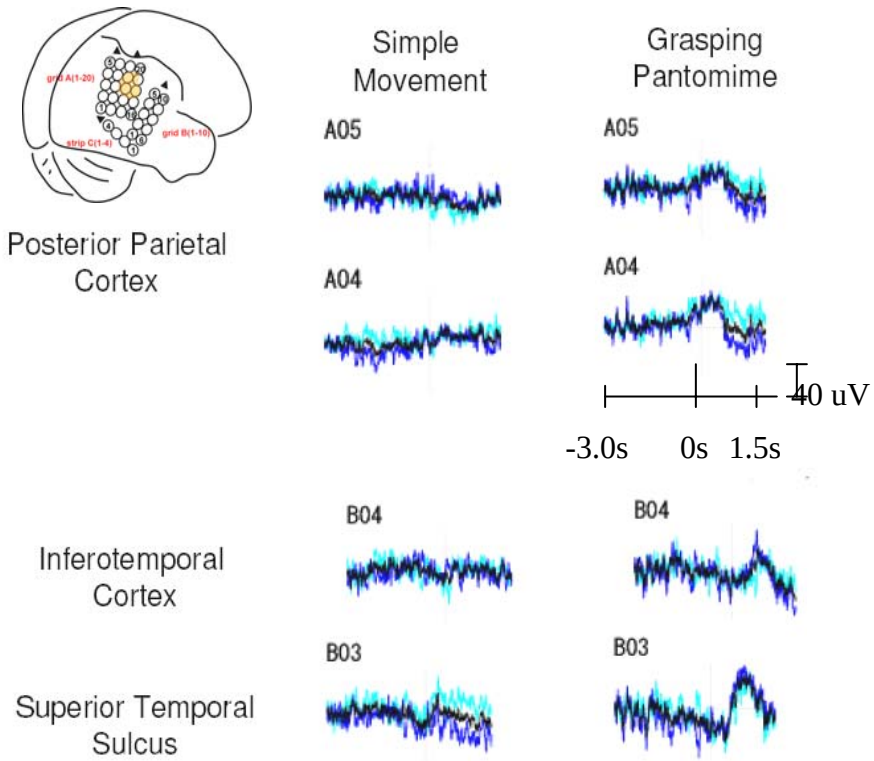

Figure 8 ECOG result from patient OM. Results for 4 electrodes (two from the posterior parietal cortex, two from the temporal cortex) are displayed based on the movement type that was performed. Black traces indicate the total average MRCP, while the blue lines indicate sub-averages of the first (light blue) and last (dark blue) halves of the datasets.

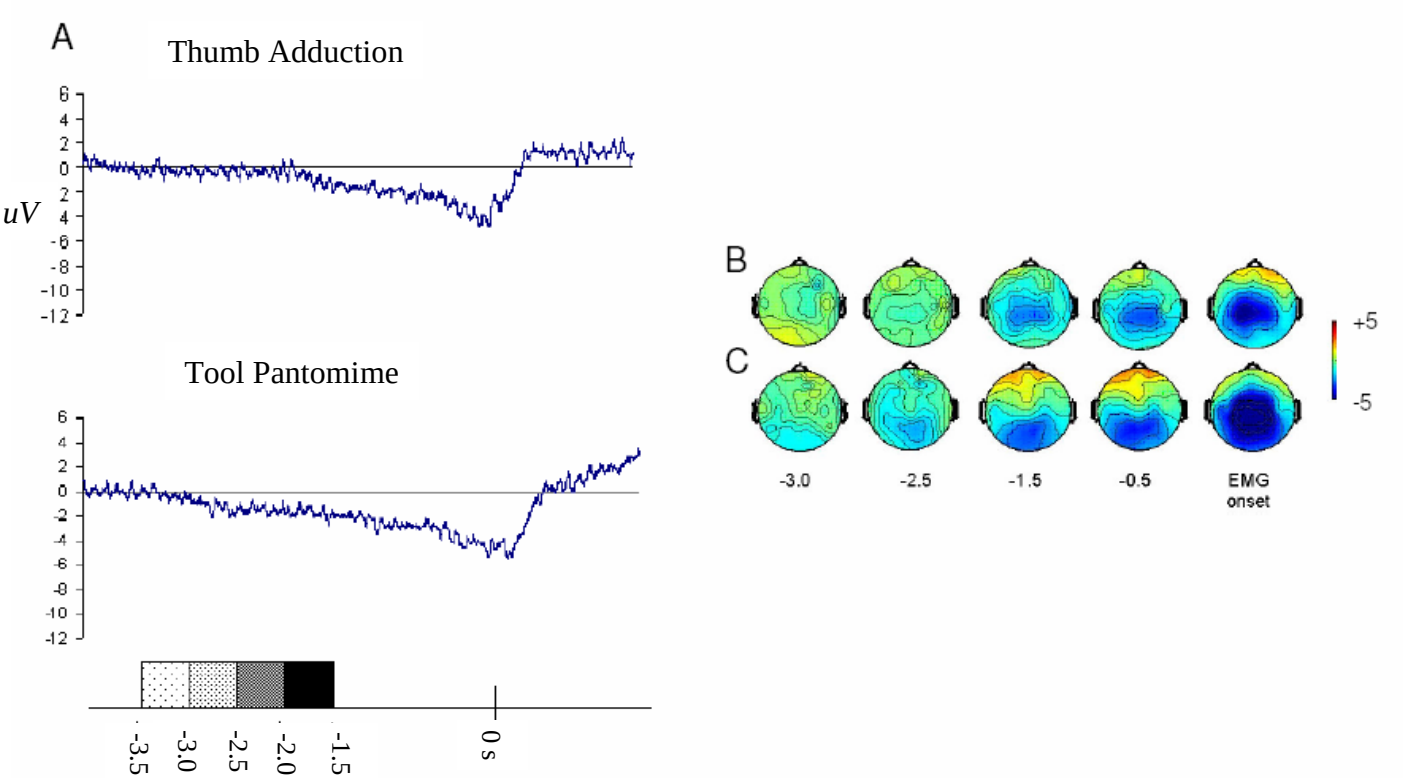

Figure 9 (A) Grand average waveforms of the MRCP for thumb movements and for tool use pantomime recorded in the posterior parietal cortex. Shaded regions indicate the segments that were used in the analysis: BP1 (light stippling), BP2 (medium stippling), BP3 (heavy stippling), BP4 (black). Grand average spatial head plots for the MRCP for thumb movements (B) and tool use pantomime (C) are shown, with times relative to movement onset.

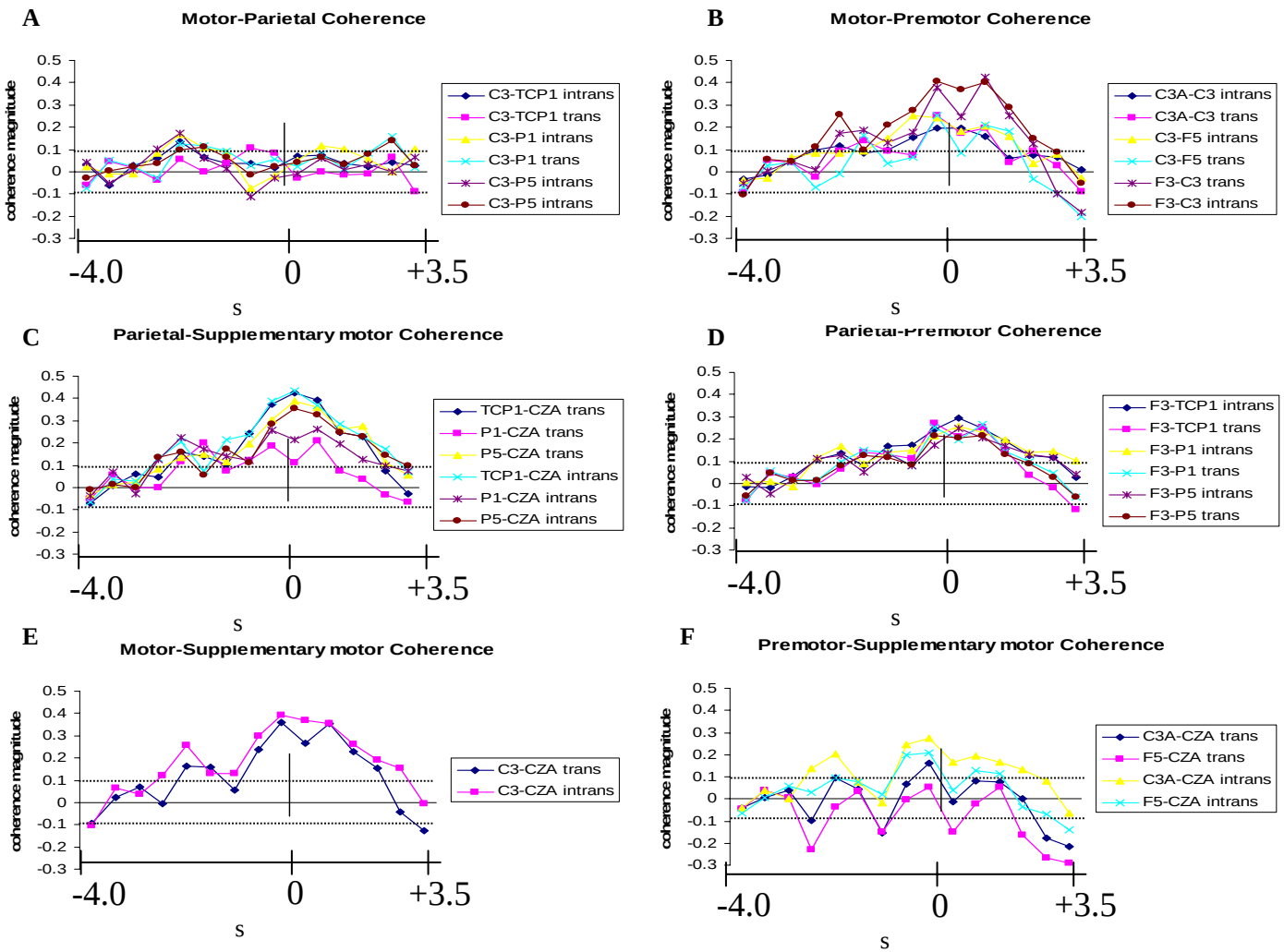

Figure 10 Grand average coherence increases for transitive and intransitive movements across a series of six comparisons. Dotted horizontal line in each figure represents a line of significance relative to baseline ($p<0.05$).

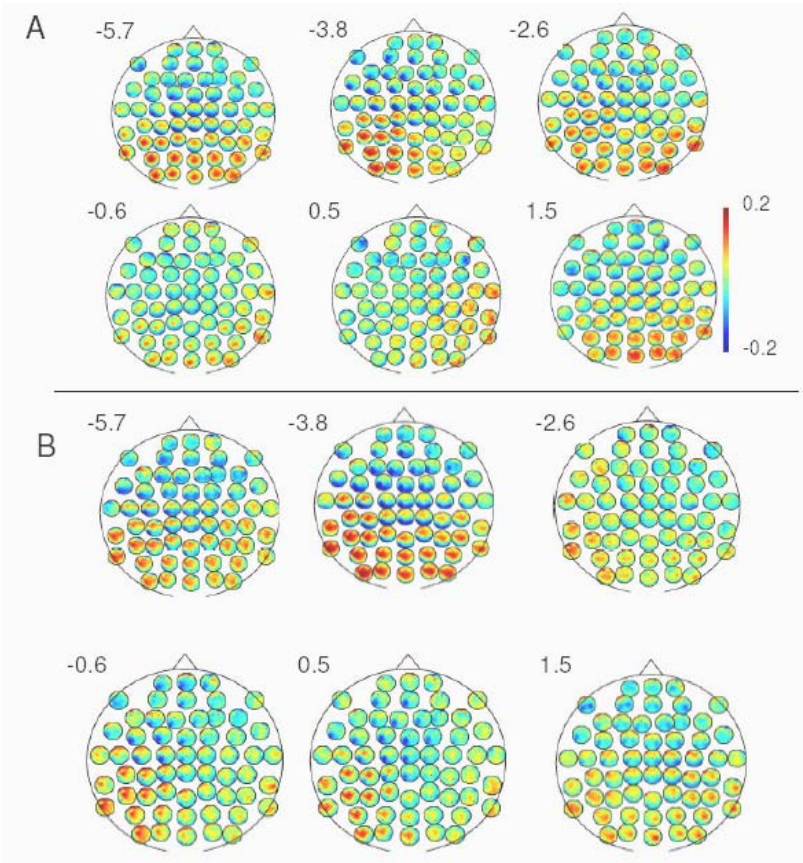

Figure 11 Grand average imaginary coherency expressed in color contour head-in-head plots for the “Go” presentation (A) and the “NoGo” presentation (B). There are 6 heads representative of preparation periods (4) and after the “Go” or “NoGo” cue (2). In this analysis, each large head is filled with smaller heads representative of the EEG channels. Each small head contains the coherency relative to that electrode position (black dot in smaller head). Primarily, the colors represent the respective coherency value, however directionality is implied. For example; in the circle representing frontal electrode F3, if there is a blue color over parietal electrode P3 that means that the imaginary part of the coherency between F3 and C4 is negative, which indicates that F3 is earlier than P3. If the color over P3 is red, the imaginary part of coherency between F3 and P3 is positive, indicating that P3 is earlier than F3. This interpretation of directionality is potentially ambiguous (see Discussion of this chapter). Beside each of the 6 large heads is time (s) relative to presentation of S2.

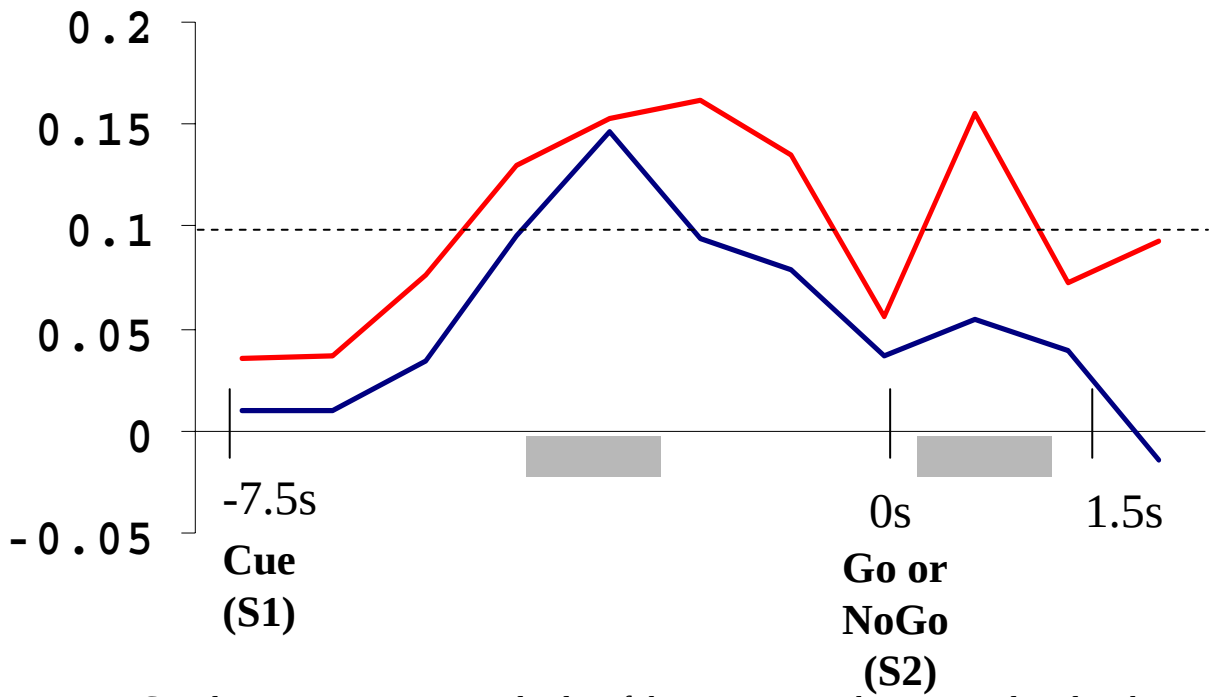

Figure 12 Grand average time-magnitude plot of the imaginary coherency analyzed in the results. The y-axis expresses the magnitude of the change of imaginary coherency during the task. The x-axis represents the time-course of the epoch, with the relative occurrence of the presentation of the visual cues. The area above the shaded rectangles on the x-axis denotes regions used in the statistical analysis. “Go” is in blue and “NoGo” is in red. Significance (2 st. dev. above baseline) is determined by the dashed line, and is similar for both conditions.

Patient	Dx	Description of Lesion	Apraxia	Motor Deficits	Duration
SG	CBD	mild left frontal cerebral atrophy, scattered lesions of bilateral frontal, periventricular and pontine white matter (with left hemisphere emphasis)	Bilateral	Mild disturbances in walking, right hand hemiparesis	2 years
AH	CBD	left hemisphere cerebral atrophy, mostly involving the left frontal lobe and mild atrophy of left temporal lobe	Bilateral	Right hand hemiparesis	5 years
JR	CBD	Mild left frontal atrophy	Bilateral	Right arm hemiparesis	4 months
MK	CVA	ischemic stroke in left MCA distribution, involving the left frontal lobe, inferior left parietal and temporal cortices, mildly affecting left insula and basal ganglia	Bilateral	Right arm hemiparesis	5 years
JS	CVA	Hemorrhagic stroke in left MCA distribution, involving ventral white matter, temporal and parietal cortices, as well as basal ganglia	Left hand (right hand was not testable)	Right arm paresis, shuffling gait, mild oral apraxia	3 months

Table 3 Lesion location chart for patients undergoing EEG coherence analysis. Diagnosis (Dx) indicates corticobasal degeneration (CBD) or stroke (CVA). Stroke patients had lesions commonly in the middle cerebral artery (MCA) distrubution.

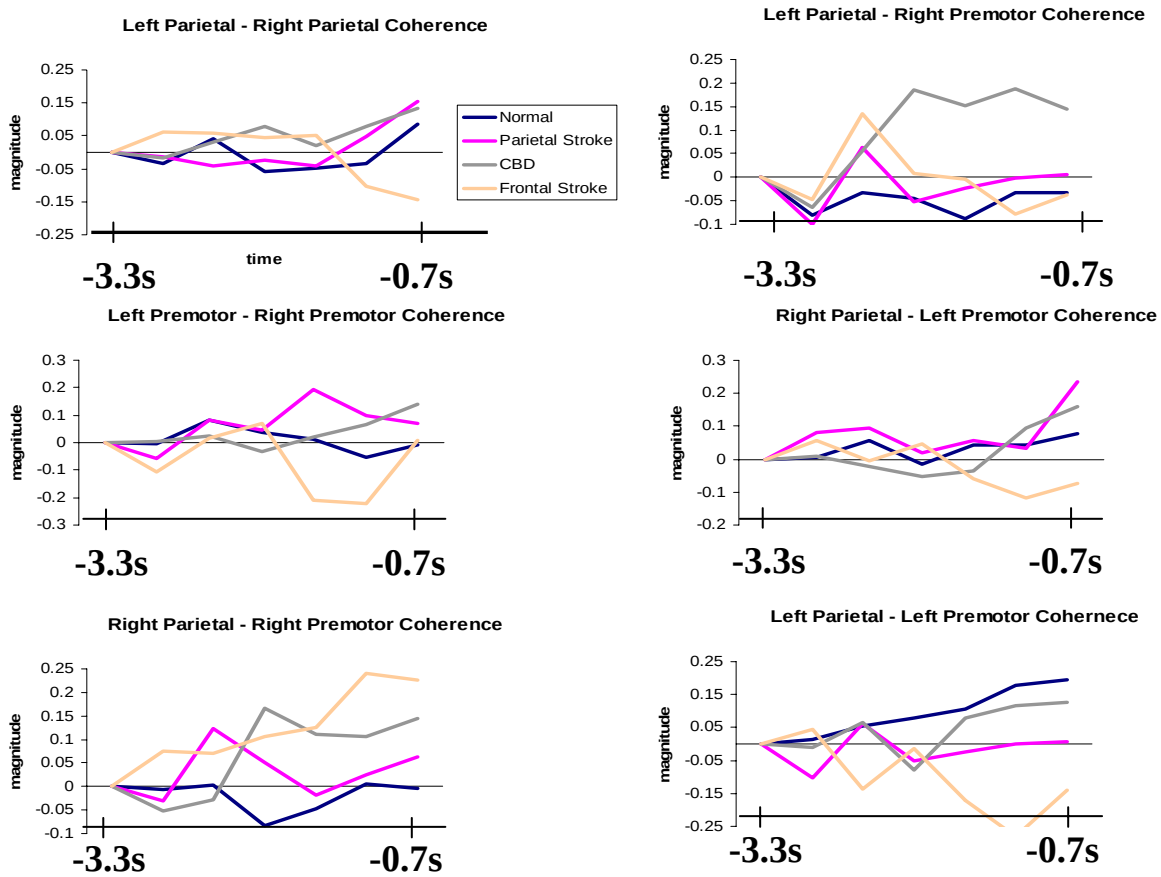

Figure 13 Time-magnitude coherence plots for transitive movements for each patient group divided into the six different coherence paths analyzed.

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