Cortical Sensorimotor Mechanisms for

Neural Control of Skilled Manipulation

by

Patrick M. McGurrin

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Graduate Supervisory Committee:

Marco Santello, Chair
Jeffrey Kleim
Stephen Helms-Tillery
Marco Davare

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ABSTRACT

The human hand is a complex biological system. Humans have evolved a unique ability to use the hand for a wide range of tasks, including activities of daily living such as successfully grasping and manipulating objects, i.e., lifting a cup of coffee without spilling. Despite the ubiquitous nature of hand use in everyday activities involving object manipulations, there is currently an incomplete understanding of the cortical sensorimotor mechanisms underlying this important behavior. One critical aspect of natural object grasping is the coordination of where the fingers make contact with an object and how much force is applied following contact. Such force-to-position modulation is critical for successful manipulation. However, the neural mechanisms underlying these motor processes remain less understood, as previous experiments have utilized protocols with fixed contact points which likely rely on different neural mechanisms from those involved in grasping at unconstrained contacts. To address this gap in the motor neuroscience field, transcranial magnetic stimulation (TMS) and electroencephalography (EEG) were used to investigate the role of primary motor cortex (M1), as well as other important cortical regions in the grasping network, during the planning and execution of object grasping and manipulation. The results of virtual lesions induced by TMS and EEG revealed grasp context-specific cortical mechanisms underlying digit force-to-position coordination, as well as the spatial and temporal dynamics of cortical activity during planning and execution. Together, the present findings provide the foundation for a novel framework accounting for how the central nervous system controls dexterous manipulation. This new knowledge can potentially benefit research in neuroprosthetics and improve the efficacy of neurorehabilitation techniques for patients affected by sensorimotor impairments.

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TABLE OF CONTENTS

APPENDIX

LIST OF FIGURES

Figure Page

CHAPTER 1

MECHANISMS UNDERLYING OBJECT GRASP AND MANIPULATION

The human hand is a remarkable biological system due to its versatility and complex mechanical and neural architecture. The interplay between these factors enables humans to interact with physical objects via a variety of different grasp types and in numerous contexts. We perform these actions every day when we tie our shoelaces, drink from a full cup of coffee, or use tools during tasks of daily living. These tasks, while appearing effortless upon their planning and execution, require a series of complex visuomotor transformations to ensure their success (Jeannerod et al. 1995; Flanagan et al., 2006; for review see Castiello, 2005 and Wolpert et al., 2011).

When grasping to manipulate an object, two events must occur. The finger(s) must contact the object in a way that enable the subsequent manipulation, and consequently each digit contacting the object must then generate a given amount of force required to manipulate the object according to the task requirement, i.e., lift the object while preventing object slip, rotation, or damage that might occur by exerting excessive force. Accurate finger (i.e. digit) position and corresponding digit force generation are therefore part of a functional continuum and crucial for performing object manipulation according to task constraints. I begin by exploring these two fundamental mechanisms.

DIGIT PLACEMENT AND HAND SHAPING

During preparation for object grasp, the brain integrates information from visual cues concerning object properties. This might include object shape, density, weight, and size. Gordon and colleagues have shown that a person can use visual information of such properties to generate an anticipatory motor plan (Gordon et al., 1993). Visual information is also used to shape the grip aperture to object size or the whole-hand to object shape (Jeannerod, 1986; Jakobson and Goodale, 1991; Melmoth et al., 2012; Schettino et al., 2013), grip aperture (Jeannerod, 1981; Soechting and Santello, 1998), and placement of individual digits (Ansuini et al., 2007; Sartori et al., 2011) based on these properties. In general, finger span linearly scales to object size and reaches a peak aperture roughly at mid-reach (Goodale and Jakobson, 1991). In contrast, the correspondence between hand and object shape increase monotonically during the reach (Santello and Soechting 1998).

Additionally, the decision of where to place the fingers on an object is also influenced by the subsequent task requirement during the manipulation phase (Crajé et al., 2011). Crajé and colleagues demonstrated this in an everyday task, where participants were asked to either lift a bottle containing liquid or to lift that same bottle and pour the contents into a cup. Notably, digit placement differed according to the task following grasping (Craje et al., 2011; Rosenbaum and Jorgensen, 1992).

With regard to two-digit grasping, there are many theories of how the coordination between the index finger and thumb occur. Smeets and Brenner have proposed that grasping can be understood largely as independent movements of these two digits (Smeets and Brenner, 2001), with each having its own movement properties. Movements of the thumb tend to be more variable than those of the index finger, which was reflected by a larger deviation in space earlier in the movement. Alternatively, later in the movement the thumb has been shown to show significantly less variability along the trajectory during object reach-to-grasp when compared to the index finger (Melmoth et al., 2012). In this case the thumb and index finger move relative to each other as a functional grasping unit during the execution of a precision grasp. The index finger position changes as a function of the object properties to control the opening and closing of the fingers around an object, thus showing larger deviations from its trajectory to fit the grasp to that particular object (Melmoth et al., 2012). This latter work is supported by Schettino and colleagues, who have shown that when grasping an object with a simple shape and grasp surfaces for both digits (e.g. a rectangle), the thumb tends to make first contact (Schettino et al., 2013).

While thumb flexion can occur independently of other digits due to the structure of the hand, humans demonstrate a tendency for the movement of adjacent digits to be correlated (Schieber and Santello, 2004). It is worth noting that while during whole-hand grasping these correlations may be beneficial to the task, as they may simplify the control required to simultaneously control a large number of degrees of freedom (Santello et al., 1995; for review see

Santello et al., 2013).

In contrast, this organization may interfere with the production of highly individuated finger movement, which may require additional control due to the mechanical coupling between adjacent digits and the anatomical organization of the tendons and muscles in the hand and forearm. For example, stabilizing contractions must be employed to better enable the movement of only a single digit and minimize unintended motion of the others (Schieber and Santello, 2004).

Dexterous control of both the index finger and thumb, e.g., precision grips, is largely mediated via the CST, both to generate intended and suppress unintended movements. This is supported by the correlation between the number of direct connections between cortex and motor neurons and the level of manual dexterity (Lemon et al, 2011).

DIGIT FORCE GENERATION

Regardless of distinct timing of contact of the index finger and thumb on an object to be grasped, humans show a remarkable temporal coordination of digit force scaling (Johansson and Westling, 1984; Burstedt et al., 1997). Namely, subjects tend to synchronize the application of normal and tangential forces (also known as grip and load forces, respectively) at different digits involved in a lifting task. The subsequent application of digit forces during object manipulation can be broken down in to a series of action phases, delineated by mechanical events associated with specific task phases (Johansson and Flanagan, 2009). These action phases are as follows: preload, load, transitional, static, replacement, delay, and unloading (Johansson and Westling, 1984). More recently, these have been re-termed in a slightly different manner as reach, load, lift, hold, replace, and unload (Johansson and Flanagan, 2009). Here I outline these mechanisms, starting from the moment of object contact.

Load Phase. Grip and load forces increase in parallel to ensure that adequate forces are applied to prevent object slip at the time of object lift (Johansson and Westling, 1984b).

Lift Phase. Completion of the load phase is marked by the breaking of contact between the object base and the table surface, marking the moment of object lift-off. Here grip and load forces peak and then stabilize.

Hold Phase. Completion of the lift phase is marked by the object being lifted to the intended height. Here grip and load forces remain steady to ensure that the object is static at the target height.

Replace Phase. Completion of the hold phase, where the object is lowered while maintaining consistent digit forces to ensure grasp stability.

Unload Phase. Completion of the replace phase is marked by the object re-contacting the table surface. Once re-contact is confirmed, digit grip and load forces decrease in parallel until the digits fully release the object and are no longer contacting the grip surfaces.

The coordination between digit grip and load forces must be carefully balanced to prevent slip. Subjects smoothly increase load forces to a magnitude just above the weight of the object, with the peak rate of load force generation proportional to object weight, a feature that manifests as a single bell-shaped peak for load force rate (Johansson and Westling, 1988b). Grip force modulates in phase with load forces to ensure grasp stability, with the magnitude of grip force dependent on the friction between the surface and involved digits (Johansson and Westling, 1984). To maintain stability and prevent slip, grip force must *exceed* the minimum level of force as determined by 1) the friction between the skin and the object and 2) the vertical lifting force (Westling and Johansson, 1984). These authors proposed the concept of “safety margin”, which is the difference between the minimum force required to prevent object slip and that employed during object lift. Although the magnitude of this safety margin can be idiosyncratic, it is a ubiquitous property of object manipulation (Westling and Johansson, 1984).

SENSORIMOTOR PROCESSING – ANTICIPATORY AND FEEDBACK CONTROL MECHANISMS

Together, grasp kinematics and kinetics are part of a continuum that together enable successful dexterous manipulation. Prior to and during the reach, visual (Jeannerod, 1984; Gordon et al., 1991; Jenmalm and Johansson, 1997; Jenmalm et al., 2000, Salimi et al., 2003) and proprioceptive (Proske and Gandevia, 2012) information provide feedback as the hand approach the object to be grasped. At object contact, the brain receives additional sensory information to update the motor plan in real-time to ensure successful object manipulation (Johansson and Westling, 1984; Johansson and Cole, 1992; Johansson and Flanagan, 2009). Upon contact, tactile information is likely the main sensory modality guiding the development of digit forces and their coordination with arm movements. Action phases are normally planned in an anticipatory manner to ensure a smooth transition, as a pure reliance on sensory feedback would generate delays between action phases due to the time required for sensory processing of visual, tactile, and proprioceptive information.

In general, unfamiliar objects only require a few lifts to establish proper force scaling, after which digit force magnitude (Gordon et al., 1993, 1994) and rate of force generation (Flanagan and Johansson, 2002) are learned and consistently reproduced. After learning, subjects can then recall previously used digit forces during future interactions with same or similar objects (Johansson and Westling, 1984, 1988a; Gordon et al., 1993, 1994; Quaney et al., 2003; Nowak et al., 2005). This stored knowledge, termed "sensorimotor memory" (Johansson and Westling (1988a), enables the generation of digit forces in an anticipatory manner (Johansson et al., 1984, 1988; Gordon et al., 1991; Salimi et al., 2000).

Despite the retrieval of sensorimotor memories to enable accurate predictions about object properties, subsequent comparisons between actual and expected feedback during action phases enable online assessment of task performance and corrections when a mismatch is perceived. This online monitoring of observed vs. expected feedback is associated with mechanical events during execution (Johansson and Flanagan, 2009).

Evidence for the role of tactile afferents for grasping and manipulation was provided by microneurographic recordings. This technique, first introduced by Hagbarth and Vallbo in the late 1960s, enables the recording of single peripheral nerve impulses, making it possible to analyze how tactile afferents respond to task mechanical events. Johansson and Vallbo first applied this technique to study sensory coding in the hand in 1983 (Johansson and Vallbo, 1983), and subsequent work applied the same technique to understand peripheral mechanisms that enable feedback control during object grasping (Westling and Johansson, 1987). This work led to the characterization of different types of mechanoreceptors and their specific roles for grasping and manipulation. Specifically, tactile mechanoreceptors can be broadly defined as fast and slow adapting (FA, SA, respectively).

Fifty-six percent of mechanoreceptors in the hand are fast adapting (Johansson and Vallbo, 1983). They respond at the onset/offset of a stimulus and have small, well defined receptive fields.

FAI units. Meissner endings tend to be recruited earlier than other tactile mechanoreceptors by up to 15 ms and show less latency variability in their firing properties (Johansson and Birznieks, 2004). The relative timing of these first spikes contain reliable information about both direction of fingertip forces as well as object shape, suggesting FAI units to be important for encoding information of these properties.

FAII units. Pascinian endings respond at initial touch, start of movement, end of movement, and object release (Westling and Johansson, 1987; Johansson and Flanagan, 2009). FAII units respond most distinctly during object lift-off and touch-down, suggesting that these units may serve to trigger the parallel changes in grip and load forces during the loading and unloading phases. Because FAII units can be found throughout the hand, it would explain why the unloading (i.e. decreased parallel grip-load forces) phase is unaffected by anesthesia to the fingertips (Westling and Johansson, 1987). Lastly, FAII units may play a direct role in adjustment to friction because a topical anesthesia diminishes these responses (Johansson and Westling, 1987).

Forty-four percent of hand afferents in the hand are slow adapting (Johansson and Vallbo, 1983). They respond with a sustained discharge of activity in response to a stimulus, and have wider receptive fields with obscure borders.

SAI units. Merkel endings fire continuously during contact and likely provide continuously updated spatial details to the central nervous system during both dynamic and static phases of object manipulation (Westling and Johansson, 1987). The shape and size of objects touching the hand are encoded by populations of SAI units. When pressed to the fingertip, smaller diameter objects induce faster firing rates due to activation of a smaller population of mechanoreceptors. Alternatively, larger diameter objects will excite more neurons, but the firing rates are lower because the force is spread out over a larger area of skin (Goodwin et al., 1995). Additionally, the firing rate of SAI units are proportional to the curvature of each probe, whereby the weakest responses are evoked by flat or gently rounded probes and become proportionally stronger by smaller probes (Srinivasan and LaMotte, 1991).

SAII units. Ruffini endings are more evenly distributed on the hand and have larger receptive fields (Birznieks et al., 2001) and discharge in response to finger deformation caused by grip *and* load forces. They seemed to be most sensitive to changes in lateral skin stretch, suggesting they may be important for shear forces between the skin and hand-held objects (Vallbo and Johansson, 1983). SAII units also show tonic activity during the static and replacement phases, suggesting that they may demonstrate proprioceptive features (Johansson and Flanagan, 2009), playing a role in registering real-time information about the balance between grip and other manipulation forces, serving to regulate force coordination (Westling and Johansson, 1984).

SAIII units. Lastly, microneurography of the radial nerve that afferents innervating the hairy skin on the back of the hand show profound and consistent dynamic sensitivity to skin stretch (Edin, 2004). These afferent responses come from a sub-group of the slow-adapting units, namely SAIII, which show omnidirectional stretch sensitivity. These units enable kinesthesia at both proximal (Edin, 2004; Edin and Johansson, 1995) and distal (Collins et al., 2005) joints.

Tactile afferents relay important tactile information, including object size perceived through skin stretch on the volar aspect of the hand (Gordon et al., 1991), surface orientation (Jenmalm et al., 1997), and surface texture (Johansson and Westling, 1987; Buckingham et al., 2009; Cole and Rotella, 2002). Additionally, inputs from cutaneous mechanoreceptors enable kinesthesia at both proximal (Collins et al., 2005) and distal joints (Edin and Johansson, 1992; Edin, 2004; Collins et al., 2005) to ensure accurate location of the digits relative to the object and each other. Digit center of pressure on the finger pad is likely to shift as vertical forces increase, causing skin deformation on the finger pads (Shibata et al., 2014), with the resultant activation of

tactile afferents providing additional information about the magnitude, direction, and spatial distribution of digit forces (Johansson and Birznieks, 2004; Birznieks et al., 2001).
Together, these mechanical events triggered by tactile afferents mark the completion of the aforementioned task phases (load, lift, hold, etc.), thus serving as critical “sensorimotor control points” during object manipulation (Johansson and Flanagan, 2009). These control points are maintained via the comparison of predicted and observed tactile signals that link to mechanical events, and together enable the nervous system to evaluate in real-time the completion of action phases during manipulation.

An example of this scenario is the context of lifting an object that is light versus heavy, assuming both have been lifted previously to ensure object properties are familiar. If the motor plan was to manipulate a heavy object and the object’s mass matched the expected mass, object lift-off will occur at the expected time, as indicated by activation of FAII units. Thus, timing of expected and actual sensory information will align. However, either early (lighter than expected) or later (heavier than expected) FAII activation due to unexpected changes in object mass would signal a temporal mismatch between expected and observed sensory information, indicating the motor system to take corrective action to generate an appropriate motor plan based on the updated sensory information (Fig. 1.1). In the event that premature lift-off occurs, a smart reflex activates to terminate the load phase and subsequent corrective motor commands to bring the object to its intended position in space. In the event that lift-off does not occur when expected, corrective action initiates a probing of digit forces. Namely, a slow increase in digit forces until the moment of lift-off occurs and is detected.

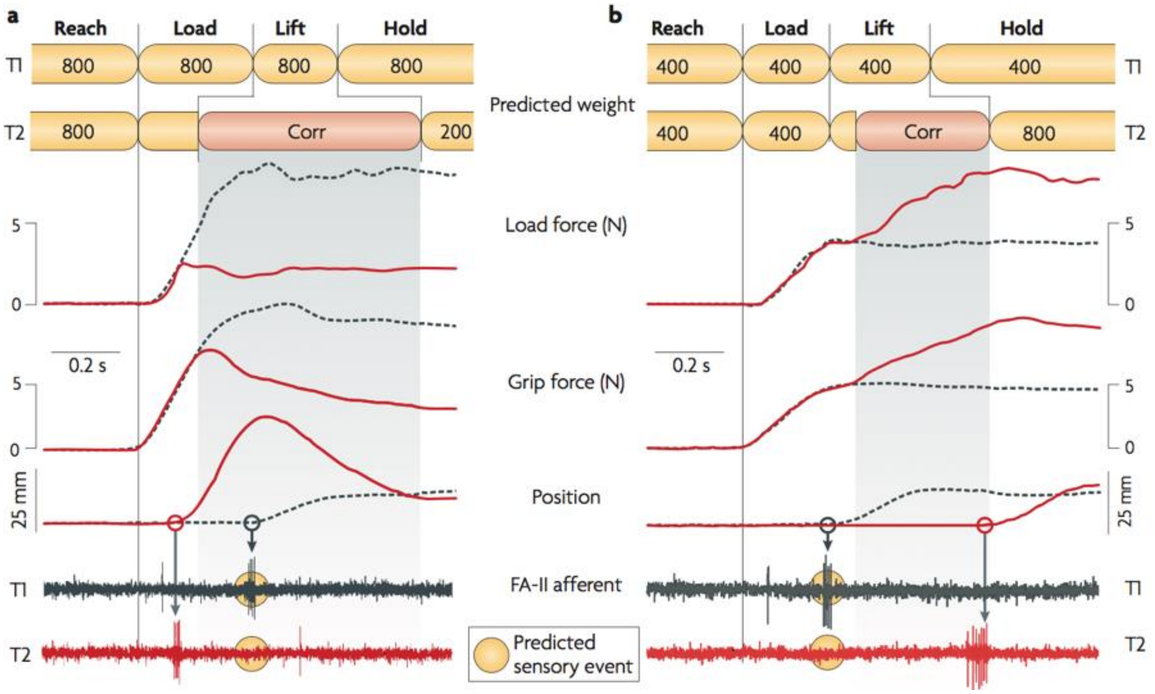


Figure 1.1. Corrective actions triggered by a mismatch between predicted and actual sensory events. The traces in parts a and b show load force, grip force, object position and afferent responses, as a function of time, as a subject grasps, lifts and holds aloft an object. a | Data for when a participant lifted an 800 g object (T1; grey dashed curves) expecting it to weigh 800 g and then lifted a 200 g object (T2; red curves) expecting it to also weigh 800 g. The top diagram represents the predictions that were fed to the action-phase controllers. When the load-phase controller is primed for a weight that is greater than the actual weight of the object (T2), FA-II (fast-adapting type II) afferents signal lift-off before the predicted time (circles behind the nerve traces). This unpredicted sensory event triggers abortion of the implemented controller and execution of a corrective action program (corr) that brings the object back to the intended position. The lift movement becomes faster and higher than intended because the corrective action kicks in after a ~100 ms sensorimotor delay (see position signal, T2). b | The participant also lifted an 800 g object (T2; red curves) while expecting a 400 g weight lifted previously (T1; grey dashed curves). The load phase terminated before the lift-off and the subsequent lift-phase controller was implemented while the object was still standing on its support (T2). In this situation, the absence of an expected sensory event signaling lift-off at the predicted time triggers a corrective action consisting of slow, probing increases in fingertip forces that continue until they are terminated by sensory events signaling lift-off. Legend and caption reprinted from Johansson and Flanagan, 2009.

Predicted and actual tactile signals are thought to be monitored during execution to account for any mismatch and ensure proper grip-load force coupling at the time of object lift-off (Westling and Johansson, 1984; Johansson and Westling, 1987; for review see Johansson and Flanagan, 2009). Importantly, execution errors are used to update a representation of object properties in order to ensure smooth transitions between action phases during subsequent manipulation with the same or similar objects.

MODELS FOR STUDYING OBJECT MANIPULATION

Over the past three decades, research has focused on an experimental model that requires subjects to grasp objects at predetermined contacts (*constrained* grasping). Such an approach is ideal for studying digit force control and isolate it from control of contact points (see below) (Westling and Johansson, 1984, 1988; Gordon et al., 1993; Quaney et al., 2003, 2004). This experimental model has been extensively used and has contributed invaluable knowledge to our understanding of digit force control during object manipulation. However, contact points are rarely identified on everyday objects, and thus understanding how digit placement affects subsequent force application, in addition to object properties, is critical to gaining a full understanding of object grasping during tasks of daily living.

Using an *unconstrained* experimental paradigm, where subjects can self-select digit placement, enables the investigation of both position and force variables during object grasp and manipulation. This more closely resembles performance of everyday tasks, as even lifting the same cup repeatedly over a short period, as one might do when enjoying a morning cup of coffee, would lead to ever-changing shifts in where the digits contact the cup’s surface. In this context, successful manipulation for a given task goal relies on the ability to modulate digit forces based on a given digit placement (Lukos et al., 2007, 2008; Zhang et al., 2010; Fu et al., 2010, 2011). Small errors in digit placement are sensed via the integration of sensory inputs from skin and joint receptors (Johansson and Westling, 1984, 1987; Edin and Johansson, 1995; Edin, 2004) at object contact in order to make any corrective action to the motor plan prior to object lift-off.

It has been recently shown that subjects change digit load force distribution on a trial-to-trial basis to compensate for variability in digit placement (Fu et al., 2010) or object width (Fu et al., 2014), as quantified by an ability to exert the same torque at object lift onset to minimize the roll of an object with asymmetrical mass distribution or to control a virtual cursor, respectively. Interestingly, this phenomenon occurs even after the manipulation has been learned, indicating a functional role for digit force modulation, i.e., ensuring that the manipulation can be performed repeatedly despite small trial-to-trial changes in digit placement.

In addition to enabling a more natural study of object grasp and manipulation, the introduction of an unconstrained grasping paradigm is important for another critical reason. As previously mentioned, unfamiliar objects only require a few lifts to establish proper force scaling, after which digit force magnitude (Gordon et al., 1993, 1994) and rate of force generation (Flanagan and Johansson, 2002) are learned and can then be recalled during subsequent trials (Johansson and Westling, 1984, 1988a; Gordon et al., 1993, 1994; Quaney et al., 2003; Nowak et al., 2005). This means that subjects are more likely to rely on sensorimotor memories, and that the need for modifications to the motor plan due to discrepancies in expected versus observed activity of tactile afferents is less likely during movement execution.

Alternatively, additional sensory feedback is necessary during unconstrained grasping to ensure proper modulation of digit forces based on across-trial variability in digit placement. This would suggest that despite the retrieval of sensorimotor memories based on previous lifts, other mechanisms are likely at play when grasping in this context to ensure proper force-to-position modulation. This has been previously shown via assessment of the timing and intensity of grip force rate profiles during the period between object contact and lift-off. Overall, grip force rate profiles during constrained grasping were better characterized as single bell-shaped peaks, whereas force profiles during unconstrained grasping tended to be multi-peaked (Mojtahedi et al., 2015). This suggests that performance in these contexts required higher weighting of feedforward and feedback control mechanisms, respectively (Johansson and Westling, 1984). This leads to a critical question, that is, are the neural mechanisms underlying the coordination of digit forces to position for dexterous manipulation unique to those during manipulation tasks that are more reliant on the retrieval of previously learned information of digit forces?

NEURAL MECHANISMS UNDERLYING OBJECT GRASP AND MANIPULATION

Primary Motor Cortex. The role of primary motor cortex (M1) in hand motor control has been extensively studied. Within M1, neuronal populations associated with individual digit movements are distributed throughout the total hand area (Schieber and Hibbard, 1993, Beisteiner et al., 2001) and demonstrate a rostral-caudal organization (Strick and Preston, 1978; Rathelot and Strick, 2009). Activation of M1 neurons in non-human primates at both the single-neuron (Muir and Lemon, 1983; Schwartz et al., 1992) and population (Georgopoulos et al, 1992; Schwartz and Anderson, 1990; Baker et al., 1997) level have been shown to encode movement information. Integrity of these neurons are crucial for hand control, as shown by motor deficits caused by damage to M1. Both lesions (Lemon et al., 2012) and reversible inactivation (Fogassi et al., 2001) of M1 in non-human primates impair the control of individual digits for precision grasping. Similarly, human patients with cerebrovascular accidents affecting M1 have difficulties in independently controlling finger movements (Lang and Schieber, 2004) and forces (Kim et al., 2014).

The advent of non-invasive recording techniques has enabled the investigation of M1 in humans and provided significant insights about its functional role. M1 has been identified as critical for storing and retrieving task-relevant information during motor learning and retention (Shadmehr and Holcomb, 1997). Much of this work began with the investigation of learning to reach to a target in the presence of an external perturbation (Richardson et al., 2006) or visuomotor adaptation (Hadipour-Niktarash et al., 2007). Subsequent work utilizing transcranial magnetic stimulation (TMS) methods targeting M1 have been shown to improve (Reis et al., 2009; Galea and Celnik, 2009) or impair (Muelbacher et al., 2002; Baraduc et al., 2004; Iezzi et al., 2010) learning and retention of a simple finger abduction task.

Monkey (Rizzolatti et al., 1988; Murata et al., 1997; Castiello, 2005; Umilta et al., 2007) and human studies (Jeannerod et al., 1995; Lemon et al., 1995; for review see Chouinard and Paus, 2010) suggest that movement planning and execution are mediated by a fronto-parietal network, including cortical regions beyond M1. These include anterior intraparietal sulcus (aIPS) and premotor areas. Activation of this parietal-frontal network is unique based on different grasp types (Begliomini et al., 2007b; Ehrsson et al., 2000), as well as during changes in the requirements of digit force application (Ehrsson et al., 2001; Kutz-Buschbeck et al., 2001).

Anterior Intraparietal Sulcus. Both human (Ehrrson et al., 2000) and monkey (Raos et al., 2006) studies have shown that anterior intraparietal sulcus (aIPS) activation increases in response to task-relevant information. Parietal neurons in monkeys have demonstrated sensitivity to the configuration and orientation of the object to be grasped, suggesting that parietal cortex is involved in the visual guidance of both reaching (Taira et al., 1990) and grasping (Murata et al., 2000), based on object shape, size, and orientation. This activation represents “elemental ‘primitives’ of 3-D shape,” which may then aid in the construction of 3D representations of object to enable successful performance (Sakata et al., 2005). Binkofski and colleagues used functional imaging technology to first demonstrate that human aIPS is the homologue to monkey AIP by studying patients with parietal damage (Binkofski et al., 1998). Damage to this region impairs the control of object grasp (Binkofski et al., 1998), and activation in this region appears to show similar sensitivity to objects of different shape, orientation (Frey et al., 2005). Ample evidence also supports the role of aIPS for encoding high-level information to form an accurate representation of a given object during goal-directed action (Taira et al., 1990; Fagg and Arbib, 1998; Anderson et al., 1997) as well as mediating sensorimotor transformations (Jeannerod, 1995).

Activity in the parietal regions has been shown to connect to dorsal (PMd) and ventral (PMv) premotor regions (Grol et al., 2007; Rizzolatti and Luppini, 2001) and to precede activity in these more frontal regions (Van Shie et al., 2007; Bozzachi et al., 2012; Westerholz et al., 2013). This indicates that aIPS relays goal-directed information about object properties to both PMv (Davare et al., 2010) and PMd (Taubert et al., 2010) for the selection of appropriate digit placement and corresponding force scaling, respectively. This is supported by inhibitory TMS studies showing that unilateral virtual lesions to aIPS disrupt proper grip force scaling during a lifting task (Davare et al., 2007) and eliminates grasp-specific activation of PMv during preparation for a precision vs. whole-hand grasp (Davare et al., 2010).

Ventral and Dorsal Premotor Cortices. Ventral and dorsal premotor regions send task-specific inputs to M1 during goal-directed grasping. In nonhuman primates, electrophysiological recordings from F5 (Umilta et al., 2007; Rizzolatti et al., 1988; Murata et al., 1997) and F2 (Cisek et al., 2003,2005; Raos et al., 2004), the homologues of PMv and PMd, respectively, show grasp-specific tuning properties during movement preparation and execution. In humans, functional imaging studies (Grafton et al., 1998; Ehrsson et al; 2000; Crelier et al., 2000) and transcranial magnetic stimulation studies (TMS; Davare et al., 2006, 2007, 2008) have revealed that PMv appears to encode information about visuomotor transformations required for proper orientation of the fingers during grasp planning. Importantly, neuronal populations in PMv show distinct grasp-specific inputs to M1 when subjects plan (Davare et al., 2009) and execute (Davare et al., 2008) a precision vs. power grasp. This evidence supports a critical role of PMv-M1 connections in conveying information necessary to orient hand posture appropriate for object grasping.

Additionally, PMd appears to send inputs to M1 regarding proper scaling of digit forces. Alternatively, repetitive TMS to left PMd leads to temporal disruption of grip and load force rate production during a constrained grasp task (Davare et al., 2006). Continuous theta burst stimulation delivered to left PMd disrupts the ability to properly downscale digit forces during grasp planning after presentation of competing force-related cues about object weight (Van Nuenen et al., 2012). PMd also has been shown to play a role in using arbitrary force cues for predictive force scaling during visuomotor mapping (Chouinard et al., 2005; Nowak et al., 2009; Taubert et al., 2010). These results support the roles of PMv and PMd in position and force planning for object grasp, respectively.

Cerebellum. Cerebellum has been previously shown to be vital for storing internal models shortly after learning (Shadmehr and Holcomb, 1997; Imamizu et al., 2000, 2003), and updating these models via trial-by-trial learning (Shadmehr and Krakauer, 2008). Patients with cerebellar damage are impaired in such adaptation across many task domains (Diedrichsen et al., 2005) and are unable to use online corrections to improve performance. For example, predictive coupling of grip force is delayed in response to an object being dropped by a subject or experimenter (Nowak et al., 2004) and show a tendency to apply significantly more grip force than a subject without cerebellar damage (Nowak et al., 2009). These findings suggest that the cerebellum utilizes sensory-based error signals (expected vs. observed) to generate a feedforward motor plan to improve performance during subsequent trials (Tseng et al., 2007). In addition, patients show a marked inability to generalize this performance by transferring learned task information to the opposite hand. However, because subjects could still use somatosensory information to scale grip forces (i.e. could still use feedback to scale grip forces) suggests that the cerebellum is important for the transfer of somatosensory information related to an object's mechanical properties to other task-related regions (Nowak et al., 2009). This denotes cerebellum as important for anticipating predictable changes in the environment but not for reacting to unpredictable events (Morton and Bastian 2006).

The output of this forward model information is sent to parietal cortex to compare predicted and observed sensory feedback. Retrograde tracing in cebus monkeys AIP connections demonstrate strong connections with both the cerebellum and basal banglia (Clower et al., 2005). Other neural structures also appear to play a secondary role relevant for context clues during the recall of stored information, including dorsal premotor cortex (Shadmehr and Holcomb, 1997), as well as interactive processing in M1, S1, and SMA (Bursztyn et al., 2006). Functional connectivity during these regions is evident during tool use and becomes greater with increased learning (Imamizu et al., 2000; Tamada et al., 1999). This complex organization of frontal, motor, parietal, and cerebellar regions will require addition work to understand how communication and processing in these other regions occurs during more natural object grasp and manipulation.

Subcortical Networks. The role of Basal Ganglia (BG) has been identified as being important for making corrective sub movements in response to movement errors (Tunik et al., (2009). Activity related to corrective sub-movements tends to occur immediately prior to activity over M1 for initiation of a movement correction (Roy et al., 2003) during tasks utilizing novel dynamic (Tunik et al., 2009) and kinematic (Seidler and Chintalapati, 2006) perturbations. These BG-M1 interactions link to both the timing and magnitude of movement corrections (Houk et al., 2007). In addition, patients who have damage to BG appear less able to rely on sensorimotor memories during object grasp and manipulation, requiring compensatory torque generation (Lukos et al., 2010), supporting the role of both BG and M1 in the retrieval of sensorimotor memories and the subsequent integration of sensory feedback during task execution.

GAPS IN UNDERSTANDING OF NEURAL CONTROL MECHANISMS

While there is a robust literature that movement planning and execution are mediated by a fronto-parietal network (Rizzolatti et al., 1988; Umilta et al., 2007; Jeannerod et al., 1995;

Lemon et al., 1995), this work has not carefully explored how the grasp network enables the coordination of digit forces to position. Therefore, the broad goal of this dissertation was to investigate these cortical mechanisms underlying skilled object manipulation.

The role of primary motor cortex in digit force planning. Modulations of corticospinal excitability (CSE) probed through single-pulse TMS discriminate between planning precision from whole-hand grasping (Cattaneo et al., 2005; Prabhu et al., 2007). Additionally, both TMS (Loh et al., 2010) and functional imaging (Kutz-Buschbeck et al., 2001) studies have identified a relation between M1 activity and force control when the required force magnitude is cued during movement preparation. However, a critical gap in the protocols of the above work (Chouinard et al. 2005; Loh et al. 2010) is that digit placement was not controlled for. Thus, these experiments may not have been suitable to discriminate between planning of digit forces from planning of digit forces *and* positions. Therefore, the aim of experiment #1 (Chapter 2) was to quantify the extent and time course of CSE modulation over M1 during digit force *planning* for precision grasping in humans in a context where digit placement is fixed by the experimenter.

The role of primary motor cortex during the retrieval of learned sensorimotor information. M1 is thought to encode sensorimotor memory of grasp forces. This view is supported by studies showing that a ‘virtual lesion’ over M1 via inhibitory repetitive TMS impairs the ability of subjects to use force information acquired during previous experience when lifting objects of different weights (Chouinard et al., 2005) as well as when performing repeated lifts with the same object (Nowak et al., 2005; Berner et al., 2007; Schabrun et al., 2008). While this previous work was performed in a constrained grasp context, isolating the study to digit force retrieval, the aim of experiment #2 (Chapter 3) was to use inhibitory TMS to investigate the role of M1 in the processing of other grasp-related sensorimotor mechanisms during the execution of a grasping task in an unconstrained grasp context. Specifically, we assessed whether M1 is involved in two critically important functions: (1) storing and retrieving sensorimotor memories of learned digit placement, and (2) enabling the modulation of digit forces in response to natural trial-to-trial variability in digit placement.

As outlined above, previous work suggested that the nervous system uses feedback following object contact to update the motor plan to account for trial-to-trial variability in digit placement during unconstrained grasping to ensure proper force generation at the time of lift off. This consideration prompted us to also investigate the role of primary somatosensory cortex (S1). The main cortical inputs to the primary motor cortex originate from the premotor and somatosensory areas (Dum and Strick, 2005). In addition, it has been shown that neuronal populations in M1 receive feedback via cortico-cortical projections from S1 (Darian-Smith et al. 1993; Stepniewska et al. 1993). Schabrun and colleagues have also shown that cTBS stimulation over S1 causes an increase in preload duration (Schabrun et al., 2008), suggesting that S1 processing is important for proper timing and coordination of action phases during prehensile tasks.

Sensitivity of the brain dynamics underling position and force control during object grasp. Experiments #1 and #2 introduced a novel way to study the role of M1 with regard to dexterous grasp and manipulation. However, monkey (Rizzolatti et al., 1988; Murata et al., 1997; Castiello, 2005; Umilta et al., 2007) and human studies (Jeannerod et al., 1995; Lemon et al., 1995; for review see Chouinard and Paus, 2010) suggest that inputs to M1 during movement planning and execution are mediated by a broad fronto-parietal network. Functional magnetic resonance imaging (fMRI; Ehrsson et al., 2000; Gallivan et al., 2012) and electroencephalographic (EEG) studies have identified unique magnitude and temporal evolution of activity in parietal and frontal regions during both motor planning and execution (Ehrsson et al., 2000; Grol et al., 2007; Bozzacchi et al., 2012; De Sanctis et al., 2013). Activation of parietal-frontal networks is unique based on different grasp types (Begliomini et al., 2007b; Ehrsson et al., 2000), as well as during changes in the requirements of digit force application (Ehrsson et al., 2001; Kutz-Buschbeck et al., 2001). However, the investigation of these cortical mechanisms underlying object grasp have predominantly focused on precision vs. whole hand grasping. Therefore, the aim of experiment #3 (Chapter 4) was to use EEG to investigate whole-brain dynamics in relation to digit position and force control during the preparation phase of constrained and unconstrained grasping.

CHAPTER 2

CORTICOSPINAL EXCITABILITY UNDERLYING DIGIT FORCE PLANNING FOR GRASPING IN HUMANS

INTRODUCTION

Successful object grasping and manipulation rely on the application of grip forces on the object that can be flexibly modulated according to object properties (Johansson and Cole, 1992; Johansson and Westling, 1984; Westling and Johansson, 1984). Due to relatively long delays associated with somatosensory feedback, sensorimotor control of digit forces also relies on planning derived from prior experience with the same or similar objects (Johansson and Flanagan, 2009). Our recent work suggests that digit force scaling is also a function of where the subject grasps the object (Fu et al., 2010).

Although the above studies point to humans' ability to plan digit forces, as well as to correct for erroneously planned forces, the issue of *when* digit force planning within a reach-to-grasp task takes place and the underlying neural mechanisms remain unexplored. Electrophysiological studies in non-human primates have revealed that firing rates of different subsets of primary motor cortex (M1) neurons correlate positively or negatively with grasp force during exertion of active force on the object (Evarts, 1968; Thach, 1978; Cheney and Fetz, 1980; Maier et al., 1993; Ashe, 1997; Hepp-Reymond et al., 1999; Hendrix et al., 2009). More recently, Ebner and colleagues have demonstrated that a subset of corticomotor M1 neurons in rhesus monkeys exhibit digit force-related activity prior to reach onset in preparation for force production on the object using a power grip (Hendrix et al., 2009). Evidence from humans with brain lesions suggests the involvement of the corticospinal tract, parietal and occipital regions of the brain, and cerebellum in planning of digit forces for object grasp and manipulation (Nowak et al., 2003; Rost et al., 2005; Raghavan et al., 2006; Dafotakis et al., 2008a).

Transcranial magnetic stimulation (TMS) studies in neurologically intact individuals demonstrated the role of anterior region of intraparietal sulcus (Davare et al., 2007), corticospinal tract (Loh et al., 2010), and M1 (Chouinard et al., 2005) in planning digit forces to grasp and lift an object based on memory of prior lifts, i.e. s*ensorimotor memory*. However, in addition to *sensorimotor memory*, successful manipulation depends on appropriate digit force modulation to compensate for trial-to-trial variability in digit positioning on the object (Fu et al., 2010). This phenomenon led to the proposition that subjects plan both digit position and force prior to object contact, but adjust forces following contact after sensing a discrepancy, if any, between planned and actual digit positions. This theoretical framework raises the question of whether the design of the above TMS experiments (Chouinard et al., 2005; Loh et al., 2010) might have been suitable to discriminate between planning of digit forces from planning digit forces and positions. Therefore, the extent to which corticospinal excitability (CSE) is modulated with digit force planning for grasping in humans and the time course of CSE modulation deserves further investigation. Another significant gap is the contribution of intracortical M1 circuitry to digit force planning.

To address these issues, the present study was designed to quantify the extent to which M1 is involved with digit force planning associated with a reach-to-grasp task. We pursued this objective by using single-pulse TMS to quantify the excitability of corticospinal tract, whose fibers predominantly originate from M1 (Lemon, 2008), and the role of intracortical circuitry within M1 during digit force planning. For the second objective, we used a paired-pulse TMS approach to assess short intracortical inhibition and facilitation within M1 (Kujirai et al., 1993; Davare et al., 2008; Rothwell et al., 2009). To allow for repeatable trial-to-trial planning of digit position, we studied two reach-to-grasp tasks that differed in terms of whether, following contact on the same points on the object, subjects were asked to exert negligible or significant force on the object without lifting it. This approach was used to isolate the digit force planning component embedded in the reach-to-grasp task, as the only difference between the two tasks was planning of digit force. To quantify the time course of CSE changes associated with digit force planning, we delivered TMS to M1 at different time points within a period starting before reach onset and ending prior to object contact. Based on the above reviewed literature, we hypothesized that force planning-dependent modulation of CSE would occur prior to reach onset.

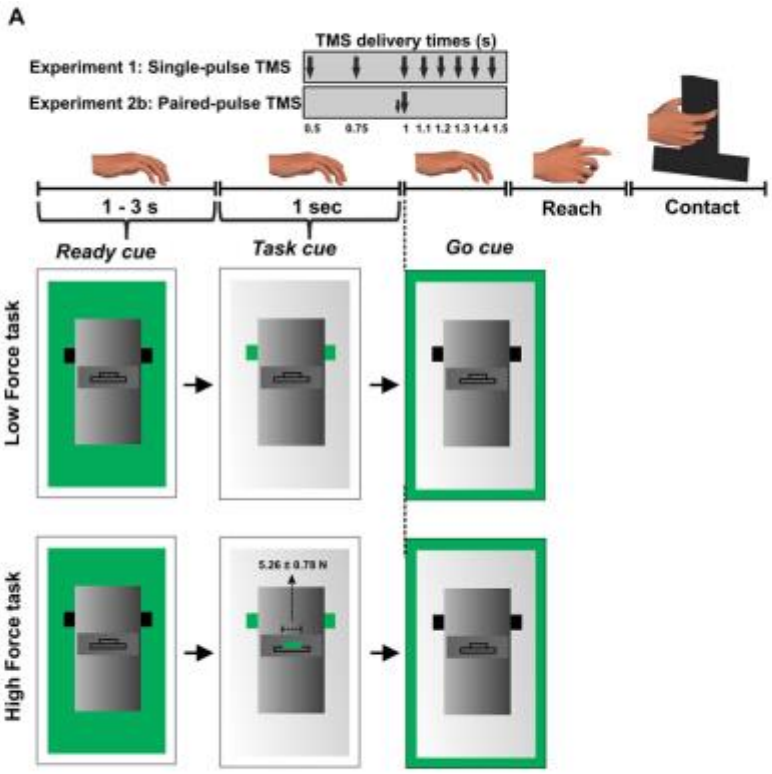
METHODS

Subjects. Twenty-two right-handed volunteers aged between 18 and 33 years (mean ± SD: 22 ± 8 years; 9 females) with normal or corrected-to-normal vision, no history of musculoskeletal disorders, neurological disease, or upper limb injury were recruited to participate in the study. All subjects were naïve to the experimental purpose of the study and gave informed consent to participate in the experiment. Eight subjects participated in Experiment 1. Experiment 2a (paired-pulse validation) was performed on 6 subjects, and Experiment 2b was performed on ten subjects (2 of whom participated in Experiment 2a). Subjects were screened for potential risk of adverse reactions to transcranial magnetic stimulation according to guidelines by Rossi and colleagues (Rossi et al., 2009) using the TMS Adult Safety Screen (Keel et al., 2001). The experimental protocols were approved by the Office of Research Integrity and Assurance at Arizona State University.

***Grip device*.** Force exerted by thumb and index finger perpendicular to each gripping surface were measured by two 6-dimensional force/torque sensors (Fu et al., 2010; Zhang et al., 2010) (Nano-25, ATI Industrial Automation, Garner, NC) mounted on a custom-designed inverted T-shaped grip device (Fig. 1).

***Transcranial magnetic stimulation (TMS)*.** Resting motor threshold (rMT) was estimated using single monophasic TMS pulses delivered by a Magstim model 200 stimulator (Magstim, Whitland, UK). The TMS coil was held tangential to the scalp and perpendicular to the presumed direction of the central sulcus, 45° from the mid-sagittal line, with the handle pointing backward inducing current in postero-anterior direction. Using suprathreshold TMS pulses, we located the region of left M1 that represents the right first dorsal interosseus muscle, which in turn corresponds with the hand ‘knob’ area in M1 (Yousry et al., 1997). The position of the coil was adjusted to optimize the motor-evoked potential (MEP) amplitude in all recorded muscles. Following this procedure, the rMT was determined as the TMS intensity that induced 50 μV peak-to-peak MEPs in 5 of 10 trials in the FDI muscle (Rossini et al., 1994). The rMT was on average 39 ± 4% (mean ± SEM) of the maximal stimulator output. During all experimental procedures following rMT estimation, the TMS coil was stabilized using a coil holder mounted on the TMS chair (Rogue Research Inc., Canada). Following the identification of the optimum coil location in primary motor cortex, the coil was traced on the scalp using a surgical skin marker pen. The location of coil was regularly checked for any displacement that might have occurred during the experimental session.

Tasks. All experiments were performed in a quiet and well-illuminated room. Subjects were seated in a custom-made chair specifically designed for TMS with the head supported in a head-rest (Rogue Research Inc., Canada). The grip device was placed on a table in front of the subject chair. The subjects' dominant hand rested pronated comfortably on the table surface at a distance of 30 cm from the grip device. Subjects were instructed to reach and grasp the grip device using the tips of their thumb and index finger at a self-selected speed, but without lifting it, using their right hand (Fig. 2.1a). They were instructed to keep their non-involved digits, i.e. middle, ring and little finger, extended during the performance of both tasks.



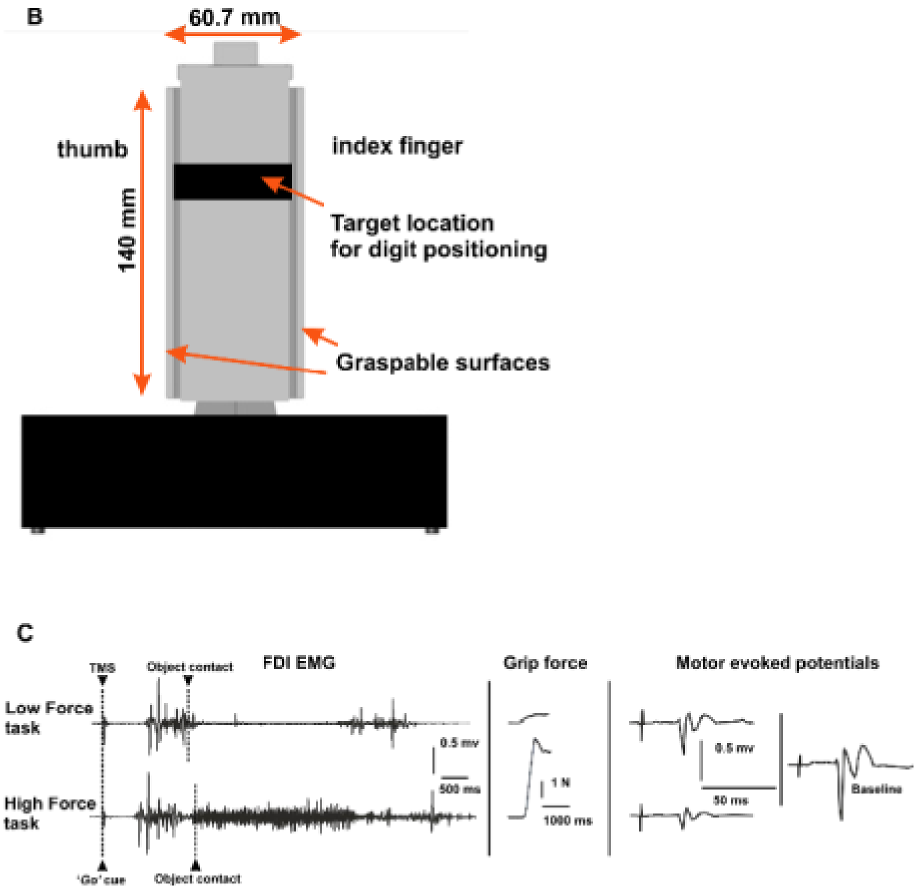


Figure 2.1. Experimental setup, protocol, and representative data. A: Experimental protocol. B: Grip device. C: Electromyographic activity from m. first dorsal interroseus (FDI), grip force exerted by thumb and index finger, and motor evoked potentials elicited by TMS at the instant of the 'go' cue for the "High Force" (HF) and "Low Force" (LF) trials (one representative subject, Experiment 1). The baseline motor evoked potential was obtained by delivering TMS in between trials while the subject was at rest (see text for more details).

We studied two task conditions: a "Low Force" task (*LF*-task) and a "High Force" task (*HF*-task). For the *LF*-task, subjects were instructed to reach and grasp the object at predetermined locations (Fig. 2.1) by exerting minimal force (< 1 N) perpendicular to its gripping surfaces. For the *HF*-task, we instructed subjects to exert 10% of their maximal voluntary force (MVF). MVF was measured for each subject at the beginning of the session by asking subjects to squeeze as hard as possible with thumb and index finger the same grip device used for the experiment. We selected the largest force out of three MVF trials to set the target level for *HF*-task. Subjects were asked to grasp the object at the same locations for both tasks. The location of the instructed digit placement on the grasp surfaces of the grip device was denoted by a colored tape attached on the front panel of the device.

For both tasks, a computer monitor placed behind the grip device presented three sequential visual cues: the first *'ready'* cue signaled the beginning of a trial, and was followed by a *'task'* cue presented at random delays (1-3 s) after the '*ready*' cue. The *'task'* cue consisted of a schematic '*box*' representing the grip device (Fig. 2.1a) and informed the subject about whether the upcoming task was a *LF*- or a *HF*-task. Finally, the *'go'* cue appeared 1 s after the *'task'* cue to instruct subjects to initiate the reach-to-grasp task. Note that both *LF*- and *HF*-task cues showed a force target, the only difference between the targets being the required force magnitude. The experimenter ensured that subject's performance was consistent with the 'task' cue during each trial. Force feedback was provided to the subjects to ensure they would not go beyond a ± 1 N window centered at the target force for each task. For *HF*-task, subjects were instructed to apply force to reach the target shown on the computer monitor during the '*task*' cue presentation (Fig. 2.1a). Subjects were allowed to practice both *LF* and *HF* tasks before data collection started. We should emphasize that *LF* and *HF* tasks were identical in terms of reach distance, cue sequence, and visual display of force feedback, the only difference being that for the *HF*-task subjects were asked to exert a much greater normal force than for the *LF*-task.

Transcranial magnetic stimulation: corticospinal excitability (Experiment 1). To assess the influence of digit force planning on the corticospinal excitability (CSE), we delivered single-pulse TMS at 120% of rMT to left M1 of eight subjects using a 50-mm diameter custom-made figure-of-eight coil at one of eight latencies from the *'task'* cue in a random order: 500, 750, 1000 (coinciding with the *'go'* cue), 1100, 1200, 1300, 1400, and 1500 ms. This procedure was used for both *LF* and *HF* tasks. *LF* and *HF* tasks were presented randomly across 6 blocks of 40 trials each. Each combination of task condition and TMS delivery time was repeated 15 times. During each block, each subject received eight single-pulse TMS interspersed between trials to assess CSE at rest (baseline MEP) for normalization procedure (see below). TMS pulses were spaced at least 5 s apart. As both tasks required digit positioning on the object at same locations, any task-related difference in CSE at one or more TMS delivery times would be due to digit force planning.

Validation of paired-pulse TMS protocol (Experiment 2a). It has been shown that when the interval between the first (conditioning) pulse delivered at sub-threshold intensity and the second (test) pulse delivered at supra-threshold intensity is between 1 and 5 ms (ISI), there is a significant inhibition (short intracortical inhibition, SICI) of the response to the test pulse. However, if the ISI is between 6 and 50 ms, there is a significant facilitation (short intracortical facilitation, SICF) of the response to the test pulse (Kujirai et al., 1993). To validate our paired-pulse TMS protocol, either single pulse (test alone) or two (paired) pulses with inter-stimulus interval (ISI) of 1, 2, 4, 8, 10, 12, and 15 ms randomized across trials were delivered to six subjects using a 70-mm diameter custom-made figure-of-eight coil with subjects at rest. Fifteen trials were delivered per single pulse and each paired-pulse ISI with a total of 120 stimulations. The first (conditioning) pulse was delivered at 80% of rMT followed by another (test) pulse at 120% of rMT (Davare et al., 2008).

Assessment of intracortical inhibition and facilitation (Experiment 2b). We used a paired-pulse TMS approach on 10 subjects to quantify the balance between intracortical inhibitory and facilitatory circuits within M1 during digit force planning. Using the same above-described tasks (*LF* and *HF*), we delivered either single pulse (“test” stimulus) or paired-pulses with inter-stimulus interval (ISI) of 1, 2, 8, 10, and 15 ms randomized across trials at the moment of the *‘go’* cue using a single TMS coil placed over the M1 hand area. We focused on this time only because the results of Experiment 1 revealed that CSE was modulated as a function of task only at the time of the ‘*go*’ cue. Subjects performed 15 trials per task per TMS pulse (single or paired). Each subject performed 6 blocks of 30 trials each. The stimulation intensity was the same as for Experiment 2a. Similar to Experiment 1, subjects received five single-pulse TMS interspersed between trials to assess CSE at rest during each block.

Data Analysis. We recorded electromyographic (EMG) activity using Ag/AgCl bipolar surface electrodes from three intrinsic muscles of the right hand (first dorsal interosseus, FDI; abductor pollicis brevis, APB; abductor digiti minimi, ADM) and one forearm muscle (flexor carpi radialis, FCR). For Experiment 1, ADM and FCR were used as control muscles to determine whether the effects of digit force planning on CSE during movement preparation (if any) were specific to the muscles involved in the execution of the tasks (FDI and APB). For Experiment 2b, we used only ADM as a control muscle as both controls used in the first experiment showed similar but no task-specific effects. The MEP peak-to-peak amplitude was measured to assess the CSE during preparation for each of the two grasp tasks. To avoid any influence of ongoing EMG activity on MEPs, trials with EMG activity greater than two times the standard deviation of the mean background EMG activity occurring 100 ms prior to the TMS pulse were excluded (<10 % of trials). About 40% of trials for TMS elicited at 1400 and 1500 ms after the ‘task’ cue (400 and 500 ms after the ‘go’ cue, respectively) were excluded because the reach was initiated, as indicated by an increase in the EMG activity of one or more muscles, prior to the delivery of the TMS pulse. Therefore, MEPs computed for these two time points were excluded from statistical analysis (Experiment 1).

For Experiment 1, we computed the ratio between MEPs elicited at each of the above-described time point and ‘baseline’ MEP recorded between trials to normalize MEP data across subjects. Repeated measures analysis of variance (rmANOVA) was used to determine the effects of within-subject factors of *Task* (2 levels: *LF*, *HF*), *TMS delivery time* (6 levels: 500, 750, 1000, 1100, 1200, and 1300 ms), and *Muscle* (4 levels: FDI, APB, ADM, FCR) on the normalized MEP (*n*MEP) amplitude. To assess potential task-dependent modulation of EMG activity, the amplitude of EMG activity from each muscle was quantified by computing the root-mean-square (RMS) of the EMG signal from “Go” to object contact, and over a period of 1500 ms following object contact on each trial and task, and pooled across different TMS delivery times. For each subject, we computed the ratio of EMG activity during *HF* trials to EMG during *LF* trials.

For Experiment 2a, CSE modulation for 7 different ISIs at rest was analyzed using rmANOVA with *TMS pulse* (8 levels: 1, 2, 4, 8, 10, 12, 15, test alone) as a within-subject factor. We used post-hoc Dunnetts’ test to compare MEP for each ISI with the test alone MEP. For Experiment 2b, paired-pulse MEP data was normalized to single-pulse MEP data to assess the influence of the conditioning stimulus on the test stimulus. We performed rmANOVA with *Task* (2 levels: *LF*, *HF*), *ISI* (5 levels: 1, 2, 8, 10, 15), and *Muscle* (3 levels: FDI, APB, ADM) as within-subject factors on normalized paired-pulse MEPs.

Finally, we performed rmANOVA with *Task* (2 levels: *LF*, *HF*), and *Muscle* (3 levels: FDI, APB, ADM) as within-subject factors on *n*MEPs pooled across subjects from experiments 1a and 2b (single-pulse TMS data; *n* = 18). We applied Huynh-Feldt corrections when sphericity assumption was violated. We performed post-hoc comparisons using paired t-test with Bonferroni corrections. Significance level was set at 0.05.

RESULTS

All subjects complied with the task instructions by exerting significantly greater grip force on the object during the high force than the low force task (*HF*- and *LF*-task, respectively*;* Experiments 1 and 2b; n = 18; paired t-test; $t_{17} = -9.1$; $p < 0.001$). For the *HF*-task, subjects exerted 5.26 ± 0.78 N (10.07 ± 0.36 % of MVF; mean ± SEM) grip force following accurate digit positioning on the object, whereas for the *LF*-task subjects exerted negligible grip force (1.06 ± 0.27 N; mean ± SEM).

Corticospinal excitability during planning "Low Force" versus "High Force" tasks (Experiment 1). We determined whether digit force planning influences CSE during movement preparation and prior to object contact using two grasp tasks. MEP peak-to-peak amplitude elicited during two tasks was reduced when compared with resting state MEP (Figs. 2.2a and 2.2b), which is consistent with previous literature (Cattaneo et al., 2005; Prabhu et al., 2007a). However, this reduction in MEP amplitude was significantly different across single-TMS pulse timings (Figs. 2.2a and 2.2b; significant Task × TMS delivery time interaction; $F_{(5, 35)} = 4.534$; p = 0.003). Furthermore, MEP amplitude for the two tasks was different across four muscles (significant Task × Muscle interaction; $F_{(3, 21)} = 4.351$; p = 0.016). For FDI, greater reduction in MEP amplitude was observed for *HF*-task versus *LF*-task but only at 1000 ms after the *'task'* cue presentation, i.e. at the time of the '*go*' cue (post-hoc paired t-test: $t_7 = 5.457$; p = 0.001; adjusted $\alpha = 0.025$). For APB, this difference was close to, but failed to reach the adjusted α-level of 0.025 ($t_7 = 2.3$; p = 0.053). For ADM and FCR, the difference between the CSE for two tasks at time of the '*go*' cue was not significant (p > 0.1; Fig. 2.2d). Furthermore, the RMS amplitude of EMG during the reach was not significantly different across the two task conditions (No Task × Muscle interaction: $F_{(3,,21)} = 2.1$; $p > 0.1$; No main effect of Task: $F_{(1,,7)} = 3.6$; $p = 0.1$). The lack of task difference in EMG amplitudes of intrinsic and forearm muscles would suggest negligible or no difference in finger kinematics. Thus, as our two tasks differed only in terms of the amount of normal force required following digit positioning at the same locations on the object, our findings suggest that the difference in MEP amplitude observed at the moment of *'go'* cue presentation was associated with digit force planning. Furthermore, the task-specific modulation in CSE was only observed in muscles directly involved in the grasp (Figs. 2.2c and 2.2d). Additionally, we observed that the increase in FDI EMG activity during performance (a 1500-ms window following object contact) of *HF*-task versus *LF*-task (EMG ratio: 7.3 ± 1.95, mean ± SEM) was significantly greater than that for other muscles (APB: 1.74 ± 0.26; ADM: 1.97 ± 0.16; FCR: 1.56 ± 0.06; all p-values < 0.05).

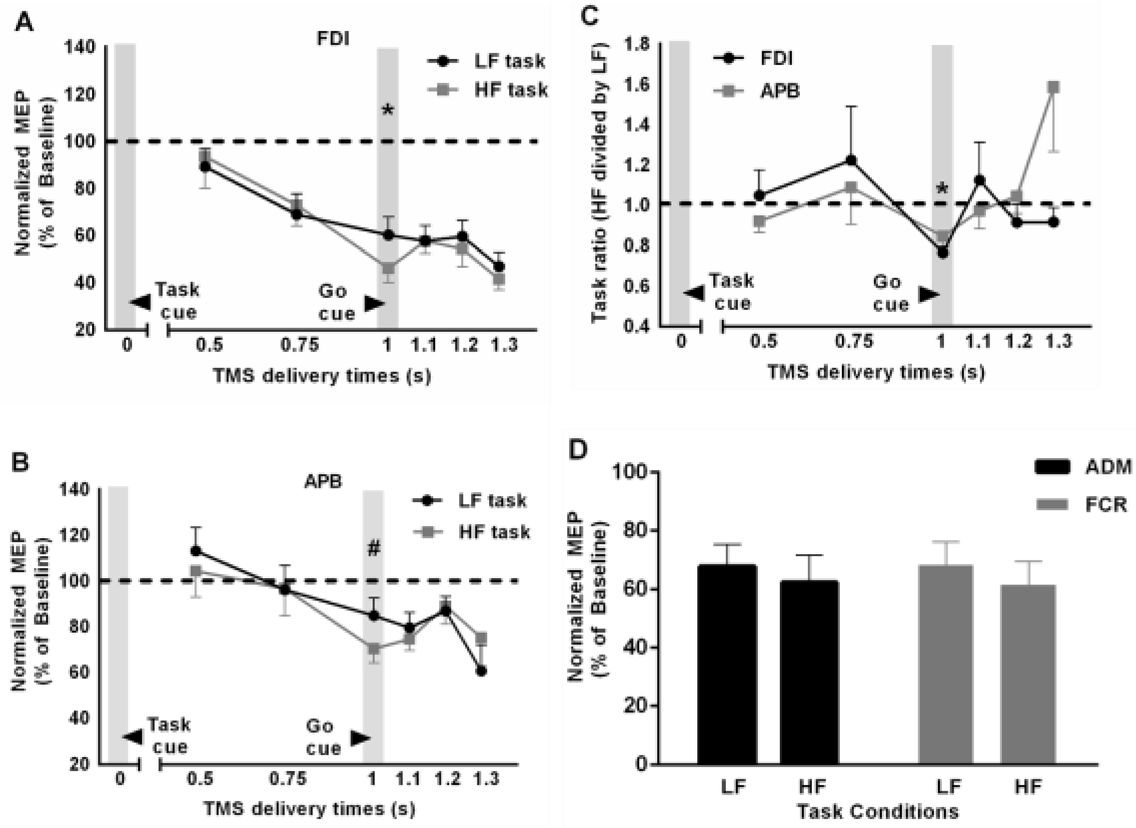


Figure 2.2. Corticospinal excitability as a function of time and task. A and B: Time-course of corticospinal excitability (CSE), denoted by motor evoked potential (MEP) amplitude normalized relative to baseline MEP, for m. first dorsal interosseus (FDI) and m. abductor pollicis brevis

(APB), respectively, as a function of TMS delivery time and task. The asterisk indicates a p-value < 0.01 and # indicates a p-value < 0.1. C: Time course of the ratio between HF-task MEP and LF-task MEP for FDI and APB. Values greater than 1 denote greater CSE for HF-task than LF-task. Data are averages of all subjects (vertical bars denote standard errors of the mean). Asterisks indicate values significantly different than 1 (p < 0.025). D: Normalized MEP amplitude for abductor digiti minimi (ADM) and m. flexor carpi radialis (FCR) at the time of 'go' cue.

Validation of paired-pulse TMS protocol (Experiment 2a).

Using paired-pulse TMS over M1 at rest, we confirmed previous findings (Kujirai et al., 1993; Davare et al., 2008) of reduced MEP amplitude with an inter-stimulus interval ranging between 1 and 5 ms, and larger MEP amplitude with an inter-stimulus interval between 8 and 15 ms (Fig. 2.3a; significant main effect of TMS pulse: $F_{(2.65,\ 13.24)} = 19.8$; $p < 0.0001$). We observed a significant difference between MEP amplitudes elicited using paired-pulse TMS at all ISIs (except 12 ms) and that elicited using single-pulse (test alone) TMS (post-hoc Dunnets' test: all adjusted $p < 0.05$ except 12 ms: $p = 0.09$).

Intracortical inhibition and facilitation (Experiment 2b). We investigated the modulation of intrinsic circuits within M1 when subjects planned for *HF* versus *LF* tasks at the moment of *'go'* cue, i.e., 1000 ms following the *'task'* cue, as this was the only stimulation time at which a task effect was found for MEPs. We failed to observe a difference in intracortical inhibition (ISIs: 1 and 2 ms) or facilitation (ISIs: 8, 10, and 15 ms) between the two tasks (Figs. 3B and C; no Condition × ISI interaction: $F_{(2.03,\ 18.62)} = 1.17$; $p = 0.33$; no main effect of Condition: $F_{(1,\ 9)} = 3.83$; $p = 0.1$).. Furthermore, the amount of suppression in MEP amplitude with shorter ISIs and facilitation in MEP amplitude with longer ISIs for the two tasks were similar across muscles (no Condition × Muscle interaction: $F_{(2,\ 18)} = 1.48$; $p = 0.25$; no main effect of Muscle: $F_{(1.46,\ 13.12)} = 0.52$; $p = 0.55$).We confirmed our findings from experiment 1. Specifically, MEP amplitude for the two tasks was different across three muscles (significant Task × Muscle interaction; $F_{(2,\ 18)} = 4.8$; $p = 0.02$; main effect of Muscle; $F_{(2,\ 18)} = 5.3$; $p = 0.016$). Post-hoc tests showed greater reduction in FDI and APB MEP amplitudes for *HF*-task versus *LF*-task (FDI; $t_9 = 3.69$; $p = 0.005$; APB: $t_9 = 3.26$; $p = 0.01$; adjusted $\alpha = 0.025$). For ADM, the difference between the CSE for two tasks was not significant ($t_9 = -0.75$; $p = 0.45$).

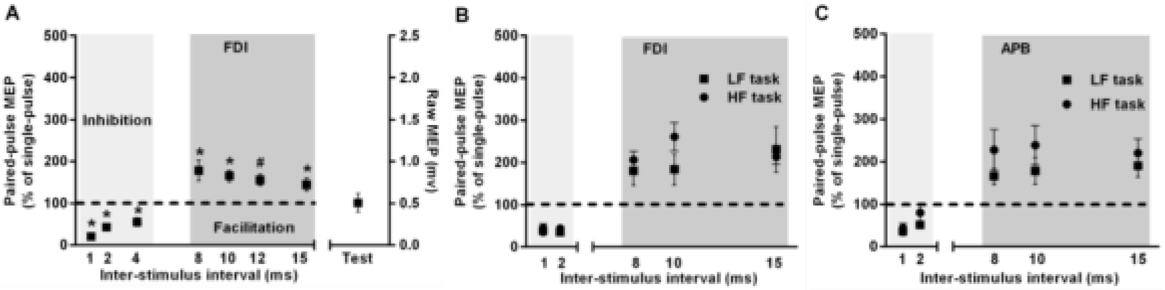


Figure 2.3. Paired-pulse TMS. A: Validation of short-intracortical inhibition and facilitation protocol in the FDI muscle at rest as a function of different TMS inter-stimulus intervals. Test data were obtained by delivering single-pulse TMS. The asterisk indicates an adjusted p-value < 0.05 and # indicates an adjusted p-value < 0.1. B and C: Short-intracortical inhibition and facilitation assessed at the time of 'go' cue, i.e., during preparation but prior to movement onset of HF- and LF-tasks in the FDI and APB muscles, respectively. Data are averages of all subjects (vertical bars denote standard errors of the mean).

After pooling data from subjects from experiment 1 and 2b (*n* = 18), we observed that the reduction in MEP amplitude elicited using single-pulse TMS 1000 ms following the *'task'* cue presentation was again significantly greater when preparing for *HF* versus *LF* tasks (Fig. 2.4; significant Condition × Muscle interaction: $F_{(1.69,\ 28.8)}$ = 5.1; p = 0.016; main effect of Condition: $F_{(1,\ 17)}$ = 14.5; p = 0.001). However, the magnitude of suppression was different across three muscles (main effect of Muscle: $F_{(1.565,\ 26.59)}$ = 8.28; p = 0.003). The MEP amplitudes for FDI and APB, but not ADM, were significantly reduced for *HF* versus *LF* tasks at the moment of '*go*' cue (post-hoc paired t-test: FDI: t_{17} = 5.69; p < 0.001; APB: t_{17} = 3.88; p = 0.001; ADM: t_{17} = -0.173; p = 865; adjusted α level = 0.025).

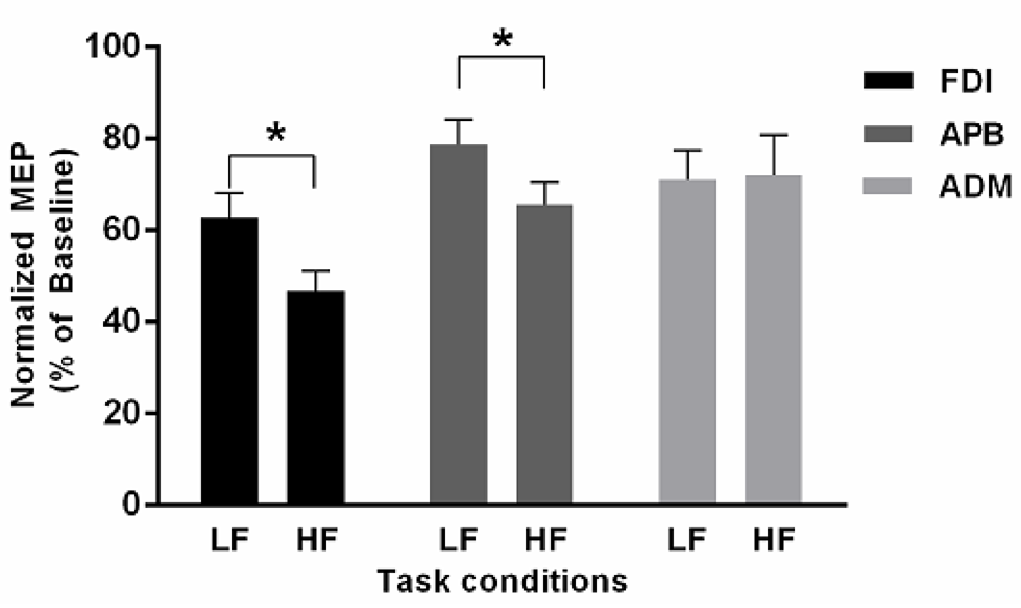


Figure 2.4. MEP data pooled across Experiment 1 and 2b. The figure shows normalized MEP data obtained through single-pulse TMS pooled across Experiment 1 and 2b (n = 18) for the FDI, APB, and ADM muscles at the time of 'go' cue for HF- and LF-tasks. Data are averages of all subjects (vertical bars denote standard errors of the mean). Asterisks indicate significant differences in MEP between HF- and LF-tasks.

DISCUSSION

The neural mechanisms underlying planning and execution of dexterous grasping and manipulation are not well understood. Here we used two reach-to-grasp tasks that differed in terms of whether significant or negligible normal force was exerted on the object following contact. Using single-pulse TMS, we quantified the influence of digit force planning on corticospinal tract excitability (CSE) and its time course. We found differential modulation of CSE when subjects planned digit forces but only when the TMS pulse coincided with the '*go*' cue denoting the time to initiate reach. Furthermore, the results from our paired-pulse TMS experiment demonstrated that the modulation of intracortical inhibitory and facilitatory circuits within M1 was similar when subjects planned either task. Overall, our results suggest that digit force planning influences CSE prior to initiation of reach, and that this task-dependent modulation may be mediated by inputs outside of M1.

CSE suppression during movement preparation. Our single-pulse TMS results showed significant reduction of MEP amplitude, a measure of CSE, during movement preparation but prior to reach onset. It has been suggested that suppression in CSE may represent a 'braking' mechanism to suppress the tendency to initiate reach (Prut and Fetz, 1999; Prabhu et al., 2007b). Consistent with this argument, we observed suppression of CSE in all muscles that we recorded from, i.e., three hand (FDI, APB, and ADM) and one forearm (FCR) muscles. In our study, with the cue to initiate reach (‘*go’* cue), subjects were required to reach and grasp the object, which also results in concurrent pre-shaping of the hand to adopt a posture based on object’s shape (Santello, 2002). Withholding these movements until the time of ‘*go’* cue would thus result in suppression of CSE. Suppression of CSE during movement preparation has also been found when subjects prepared for a reaction time task (Hasbroucq et al., 1997; Touge et al., 1998; Duque et al., 2012), and for a motor task to be performed at a self-selected speed (Cattaneo et al., 2005; Prabhu et al., 2007b). CSE suppression may originate at the level of the spinal cord as suggested by reduction in H-reflex amplitude (Touge et al., 1998), and inhibition of motor neurons through inhibitory spinal interneurons, during movement preparation (Prut and Fetz, 1999). However, the authors of later electrophysiological study in *Macaca* monkeys argued that as the afferent inputs to the spinal cord do not change during rest and movement preparation, the modulation of spinal interneurons resulted from activity in cortical areas during movement preparation (Prut and Fetz, 1999). Recent TMS work in humans has identified the role of premotor dorsal area in sending inhibitory inputs to M1, leading to CSE suppression to control the impulse to initiate movement until the cue to initiate movement occurs (Duque et al., 2012).

In contrast to our findings, other studies have reported an increase in MEP amplitude prior to movement onset (Starr et al., 1988; Chen et al., 1998; Chen and Hallett, 1999). Chen and colleagues (1998) reported that an increase in MEP amplitude begins 100 ms prior to self-paced movement onset. However, these authors used subthreshold TMS, as this is more sensitive than suprathreshold TMS in detecting an increase in MEP amplitude (Chen et al., 1998).

Influence of digit force planning on corticospinal excitability. We found task-dependent modulation of CSE when the TMS pulse coincided with the *‘go’* cue while subjects prepared for the High Force (*HF*) versus the Low Force (*LF*) task. In the *HF* task, subjects were instructed to apply a significant amount of grip force following accurate digit (thumb and index finger) positioning on the object whereas the Low Force task (*LF-task*) required only accurate digit positioning and minimal grip force. As the two tasks differed only in the magnitude of force exerted on the object following digit positioning, the difference in CSE resulted from the planning of digit forces during movement preparation but prior to reach onset. An alternative explanation is that digit force planning occurs prior to reach onset, and that the presentation of the cue to signal reach onset results in the release of the motor plan. Although we cannot distinguish between these two scenarios, our results suggest that the force-dependent modulation of CSE occurs prior to reach onset. The muscle-specificity of the observed task-dependent modulation further supports the notion that digit force planning was related to the muscles that would have been engaged in generating grip force, i.e. FDI and APB, but not ADM and FCR.

The time course of CSE during digit force planning suggests that force planning-related inputs reach (see below) M1 prior to initiation of reach. Specifically, task-dependent modulation of CSE was observed when the TMS pulse coincided with the *'go'* cue but prior to reach onset. This suggests an early involvement of M1 in planning digit forces in humans. Virtual lesions elicited by TMS of M1 in humans have been shown to impair the ability to plan digit forces during gripping and lifting based on prior experience with the same object (Chouinard et al., 2005; Nowak et al., 2005; Berner et al., 2007). However, in these studies, disruption of M1 was performed offline and not while subjects prepared for the grip and lift task. Thus, it was not clear when grip force planning-related information reached M1. Our results suggest that force planning-related information is available to the corticospinal tract long before the hand contacts the object. More recently, CSE assessed prior to initiation of reach during a grasp-to-lift task was shown to reflect the memory representation of object weight (Loh et al., 2010). However, these studies (Chouinard et al., 2005; Loh et al., 2010) might not have been suitable to discriminate planning of digit forces from position (see Introduction).

CSE modulation based on task requirements was observed when the TMS pulse coincided with the signal to initiate the grasp, i.e. '*go*' cue, at 1000 ms after task cue presentation. This observation is consistent with Prabhu and colleagues (2007) who reported significant modulation of CSE when subjects prepared to grasp a handle versus a disc but only when single pulse TMS, coinciding with the cue for initiating a grasp, was delivered 800 ms following object presentation. This task-related modulation in the CSE disappeared when either the TMS pulse and '*go*' signal were dissociated, or the TMS stimulation signaled '*go*' at different time points across trials. Lemon and colleagues (Prabhu et al., 2007a) inferred that the task-related modulation of CSE is significant when TMS probes the system at a predictable grasp onset time, i.e. '*when visuomotor inputs had their greatest anticipatory influence on M1'*. In our study, the '*go*' cue always appeared at the same time following the '*task*' cue during each trial, which would have allowed subjects to predict the onset of reach. Thus, the '*go*' cue in our study appears to be the time at which the effect of force planning-related neural inputs on CSE is strongest. This is consistent with the finding by Loh and colleagues (2010) that grasp planning based on sensorimotor memory is revealed by CSE changes at the time of '*go'* cue. However, based on our proposed theoretical framework (Fu et al., 2010), CSE modulation during preparation to grip and lift an object could be due to both digit position and force planning.

It is plausible that presentation of the anticipated 'go' cue to initiate reach might have induced retrieval of memory related to task-specific characteristics or features (Singhal et al., 2013). However, we do not expect to see a change in magnitude of MEP suppression during *HF*- versus *LF*-tasks if the reach onset would have been internally driven (Thut et al., 2000).
It is somewhat counterintuitive to observe greater suppression in MEP amplitude for the *HF*- rather than *LF*-task. However, electrophysiological studies in rhesus monkeys found that less than 10% of recorded M1 neurons showed significant modulation in their firing rates with respect to baseline activity when the monkeys prepared to reach and grasp objects with different force levels (Hendrix et al., 2009). Thus, if a similar cortical circuitry operates in humans, it could be speculated that such a small subset of M1 neurons might have influenced CSE during digit force planning in our study. Furthermore, a subgroup of M1 neurons has been found to suppress their activity during exertion of large versus small grip force (Maier et al., 1993; Hepp-Reymond et al., 1999). If a similar suppression of M1 neuron firing rates had occurred at the planning stage of the *HF*- task, it would account for the greater CSE suppression associated with digit force planning. Both speculations, however, require further investigation. It should also be noted that CSE modulation may have resulted from force-planning related inputs from higher-level brain areas

(see below). This argument is consistent with the fact that CSE modulation during movement preparation originates from several cortical areas (Prut and Fetz, 1999).

Digit force planning and intracortical M1 circuitry. The findings of Experiment 1 motivated a follow-up experiment to determine the source of changes in excitability in the corticospinal tract during digit force planning. To determine the role of the local M1 circuitry within M1 during digit force planning, we used a paired-pulse TMS approach where a subthreshold TMS stimulus preceded delivery of a suprathreshold TMS pulse. Although SICI and SICF are mediated through separate mechanisms, the modulation of MEP size is due to modulation of neural circuits intrinsic to the site of stimulation, i.e., M1 (Münchau et al., 2002; Chen, 2004). The modulation of MEP size with different inter-stimulus intervals between paired TMS pulses (i.e. SICI and ICF) delivered in synchrony with the *'go'* cue but prior to grasp initiation was similar for *HF* versus *LF* tasks. Our finding of task-dependent modulation of CSE, but an absence of modulation in intracortical inhibitory circuitry (SICI) is not consistent with the recent report from Kouchtir-Devanne and colleagues (Kouchtir-Devanne et al., 2012). These authors reported an increase in CSE, but a decrease in SICI during precision grip using index finger and thumb versus during an abduction of the index finger. The authors suggested that the greater reduction in SICI during precision grip allowed larger corticopsinal volleys during stimulation, thus recruiting greater proportion of α-motoneurons (Kouchtir-Devanne et al., 2012). Interestingly, the modulation in SICI that was observed during the performance of task might have also been influenced by afferent inputs reaching the spinal cord. However, in our study, we assessed SICI at rest (i.e. prior to reach onset), thus making direct comparisons between the two studies inappropriate.

Another difference between the two studies is that both of our experimental conditions consisted of grasping movements (low vs. high force), whereas the above-referenced study compared a two-digit grasping task with a single-digit force production task. Overall, our findings suggest that the local circuitry within M1 did not contribute significantly to planning of digit forces at the cue signaling reach onset found through single-pulse TMS (Experiment 1).

Cortical circuitry involved in digit force planning. In addition to the above described study by Hendrix et al. (2009), parietal, occipital, and subcortical structures (cerebellum and basal ganglia) play a role in grip force planning and control (Murata et al., 1997; Ehrsson et al., 2000, 2001; Chouinard et al., 2005; Nowak et al., 2005; Rost et al., 2005; Berner et al., 2007; Davare et al., 2007; Dafotakis et al., 2008b; Prodoehl et al., 2009). BOLD-related cortical activity was significantly greater in right intraparietal cortex when subjects applied a small versus larger force using a precision grip (Ehrsson et al., 2001). For object manipulation tasks, learning to scale digit forces based on object properties (i.e., weight) also seems to engage a fronto-parietal network (Nowak et al., 2005; Raghavan et al., 2006; Dafotakis et al., 2008a). Virtual lesions of M1 (Chouinard et al., 2005; Bäumer et al., 2009) resulted in disruption of grip force scaling based on memory of prior lifts, and virtual lesion of contralateral aIPS (Davare et al., 2007) led to an overshooting of peak rates of grip and load forces suggesting a possible interference with the internal representation of object weight. Based on these findings, we propose that aIPS and premotor areas may have played an important role in sending force planning-related information to M1. Moreover, this information would reach M1 during movement preparation but prior to reach onset. This theoretical framework is the subject of ongoing investigation.

Digit force control: planning and feedback-driven corrections. The present findings demonstrate that digit force planning-related processing starts well before object contact. This finding is consistent with the theoretical framework we recently proposed that planning of digit forces can occur prior to grasp (Fu et al., 2010). However, it should be noted that early onset of digit force planning as reported here does not preclude corrections to planned digit forces later in the task. According to the sensorimotor control point theory (Johansson and Flanagan, 2009), the central nervous system compares planned and actual development of digit forces across critical mechanical events associated with manipulation, e.g., contact, onset of object lift, and onset of static object hold. If a mismatch is detected, subjects make force adjustments according to the task requirements. For example, in a task where subjects can choose digit placement, planned and actual digit positions may not match. In this case, planned digit forces might have to be changed once the mismatch is detected (Fu et al., 2010). Similarly, when object mass is greater than anticipated, the inability to lift the object at the anticipated time triggers feedback-driven force upgrades to scale digit forces and eventually enable object lifting. Besides being used for online digit force corrections, this feedback information is used to update digit force planning for successive lifts (Johansson and Westling, 1984; Westling and Johansson, 1984; Johansson and Flanagan, 2009).

CONCLUSIONS

The present study provides two new insights about neural mechanisms underlying force planning for grasping in humans. First, CSE was sensitive to the planned magnitude of digit force for grasping before reach onset. Second, the force-dependent modulation of CSE appears to be driven by inputs from areas other than M1.

CHAPTER 3

SKILLED OBJECT MANIPULATION REQUIRES CONTEXT-DEPENDENT CORTICAL INTERACTIONS IN HUMANS

INTRODUCTION

Skilled object manipulation is a hallmark of human evolution. We routinely use our hands to manipulate tools and objects, such as drinking from a glass of water, without realizing how the brain orchestrates these seemingly simple tasks. However, our ability to manipulate objects relies on a complex interaction between a sensorimotor memory of fingertip forces developed based on previous experience with an object and online sensory feedback (Johansson and Cole, 1992; Johansson and Flanagan, 2009). Although the role of fronto-parietal cortices in this sophisticated interplay has been extensively studied (Lemon et al., 1995; Ehrsson et al., 2001; Chouinard et al., 2005; Davare et al., 2006, 2007; Jenmalm et al., 2006; Bensmail et al., 2009; Groppa et al., 2012), this work has drawn an incomplete picture of these cortical mechanisms. Research over the past three decades has focused on the control of digit forces through an experimental model based on grasping objects at predetermined contacts (*constrained* grasping)(Johansson and Cole, 1992; Johansson and Edin, 1993). Although this model has provided significant insights into neural control of object manipulation, the constrained grasping approach neglects a critical component of sensorimotor control that is fundamental to natural hand-object interactions: choice of digit placement.

When individuals can choose where to grasp an object (*unconstrained* grasping), the central nervous system is challenged in a distinct manner from a constrained grasp context (Lukos et al., 2007, 2008, 2010, Fu et al., 2010, 2011; Mojtahedi et al., 2015). Specifically, constraining grasp contact to the same location over consecutive trials allows participants to rely on a sensorimotor memory of digit forces and use sensory feedback upon lifting the object to assess the accuracy of the force plan, e.g., object slip or tilt (Westling and Johansson, 1984; Johansson and Westling, 1988; Johansson and Cole, 1992; Gordon et al., 1993; Johansson and Flanagan, 2009). However, unconstrained grasping is associated with increased trial-to-trial variability of digit position. Therefore, applying the same forces on each trial – but at different contact points – would lead to task failure(Fu et al., 2010, 2011; Mojtahedi et al., 2015). Remarkably, skilled manipulation can still be accurately performed. This occurs by virtue of the fact that participants modulate digit forces as a function of digit position on a trial-to-trial basis (Fu et al., 2010, 2011; Mojtahedi et al., 2015). This implies that the nervous system uses digit position feedback following object contact to scale the force distribution every time a given object is grasped at different contacts. The ability to flexibly modulate digit forces to position can account for humans' unique ability to perform skilled manipulation. However, the underlying neural mechanisms remain to be identified because the dominant research model has been constrained grasping.

In the present work, we chose to focus on the role of primary motor cortex (M1) for the control of grasping and manipulation, as this area has been identified as being critically important for the control of skilled manipulation. Previous studies of constrained grasping in humans using behavioral, imaging, and non-invasive brain stimulation approaches have emphasized the involvement of M1 in building, storing, and retrieving sensorimotor memory of grasp forces (Chouinard et al., 2005; Jenmalm et al., 2006). We hypothesized that a disruption in M1 would disrupt the ability to retrieve stored information obtained during learning and would be grasp context dependent. Namely, during constrained grasping we hypothesized that the disruption of stored information would manifest via a change in load force generation, comparable to findings of previous work (Nowak et al., 2005). In contrast, the disruption in M1 during unconstrained grasping would impair the retrieval of information for digit placement.

Furthermore, as our theoretical framework indicates that the nervous system uses feedback of digit position following object contact for changing force distribution during unconstrained grasping, we also investigated the role of primary somatosensory cortex (S1) in the control of skilled manipulation. We hypothesized that S1 would be critical for digit force-to-position modulation by relaying somatosensory feedback about digit position to M1. Therefore, a virtual lesion to S1 during unconstrained grasping should not impair retrieval of information for digit placement, but rather impair proper digit scaling of digit forces to digit placement.

By combining electroencephalography (EEG), ‘virtual lesions’ through non-invasive transcranial magnetic brain stimulation (TMS), and a novel behavioral paradigm, we uncovered significant differences in brain dynamics over M1 and S1, and their functional roles in constrained and unconstrained grasping. While confirming M1’s role in storing sensorimotor memory of digit forces for constrained grasping, we show for the first time that the role of M1 on skilled manipulation is sensitive to grasp context. Specifically, M1 integrity is critical in unconstrained grasping for both the retrieval of learned digit position, as well as coordinating control of digit forces based on feedback of this digit placement. Lastly, we demonstrate that S1 provides M1 with online feedback of digit position necessary for digit force-to-position modulation. We conclude that sensorimotor cortical areas are differentially engaged according to whether the manipulation task demands predominantly memory- or feedback-based control of digit position and forces.

METHODS

Subjects. Ninety naïve right-handed (Oldfield, 1971) volunteers (23 ±4.12 years [mean ± SD]; 44 females) with normal or corrected-to-normal vision and no history of musculoskeletal disorders or neurological disease participated in this study. Subjects were screened for potential risks of adverse reactions to TMS using the Transcranial Magnetic Stimulation Adult Safety Screen(Keel et al., 2001) and gave their written informed consent according to the declaration of Helsinki. All protocols were approved by the Office of Research Integrity and Assurance at Arizona State University and the Committee for the Protection of Human Participants at the University of Houston.

Grip device. A custom-designed inverted T-shaped object instrumented with two six-dimensional force and torque transducers (Nano 25; ATI Industrial Automation, Garner, NC) (Fig. 3.1a) was used to record forces and torques exerted by the index finger and thumb. Graspable surfaces consisted of two long parallel PVC plates (140 × 22 mm) covered with sandpaper (grit #320), each mounted vertically on one transducer (Fig. 3.1a). The grip device was designed to measure grip and load force (normal and tangential to the graspable surface) exerted in the *x*- and *y*-direction, and each digit’s center of pressure. The transducers’ location relative to the graspable surfaces was blocked from the subject's view to prevent visual cues from biasing the choice of digit placement. The base of the grip device consisted of three compartments (left, center, and right). A 400-g mass was placed in the right (relative to the subject) compartment and was hidden from view to prevent subjects from using visual cues to anticipate the object's mass distribution. The added mass created an asymmetrical mass distribution resulting in an external torque in the frontal *x-y* plane of 255 N•mm (T_{ext}, Fig. 3.1a). The object's total mass, including the additional load, was 790 g. Each end of the object's base was placed on a custom-made, battery-driven switch (lift switch). The release of either switch by upward movement of the object from the table was used to calculate the time of object lift onset. We used a wireless inertial measurement unit (IMU, Emerald, APDM, Portland, OR) fastened to the top of the object to measure object tilt during the lifting phase.

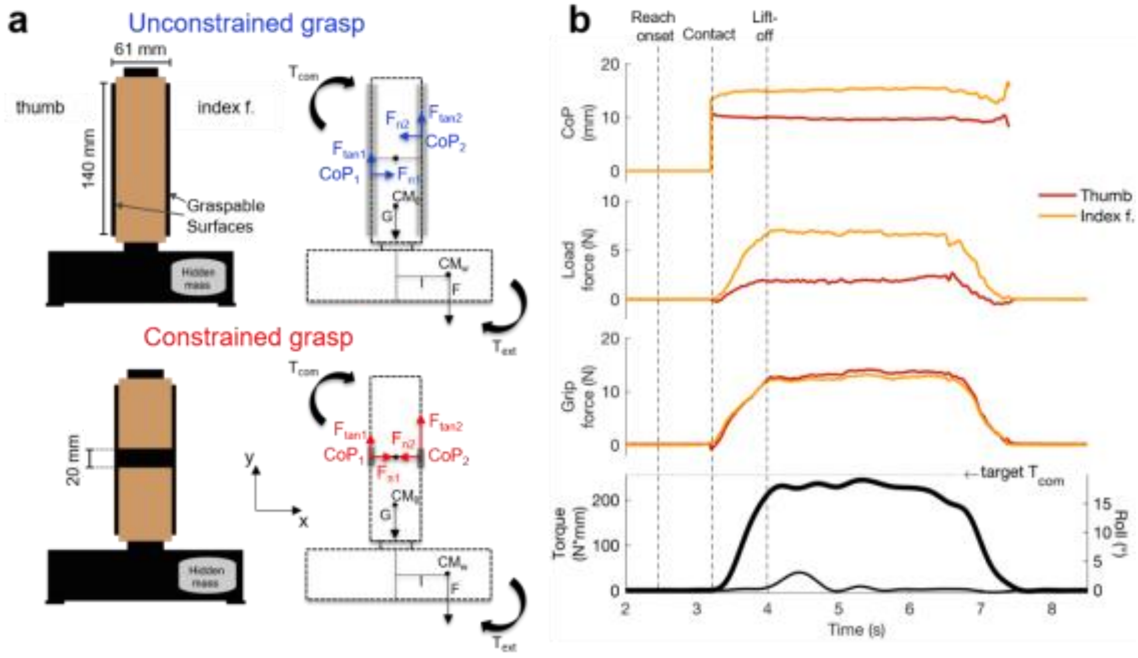


Figure 3.1. Grip device, experimental conditions, and experimental variables. (a) Schematic and free-body diagrams of the custom-built grip device for the unconstrained and constrained grasp conditions. (b) Experimental variables are shown for one representative trial of the manipulation task performed using an unconstrained grasp. From top to bottom, traces are the output of mechanical switch signaling lift onset, thumb and index finger (index f.) center of pressure (CoP), load and grip forces, actual and target compensatory torque (Tcom) (thick line), and object roll (thin line), respectively. The sign of Tcom has been inverted for graphical purposes. At object contact, the index finger is placed higher than the thumb and exerts larger load force. Similar grip force is exerted by each digit. Between contact and lift onset, subjects generate a Tcom that

approaches the target Tcom at object lift onset, thus minimizing object roll (thin line; peak value < 5°).

Experimental Protocol. Subjects sat comfortably in a custom TMS chair (Rogue Research Inc., Canada), with right hand pronated and rested on the hand switch. Subjects were asked to perform a dexterous manipulation task. This task consisted of reaching and grasping the grip device placed on a table 15 cm in front of them using the thumb and index fingertips at a self-selected speed, lifting the object vertically to a height of 5–10 cm above the table while trying to minimize object tilt, holding the object for 2–3 seconds, replacing the object on the table, and finally returning to the start position on hand switch and remain at rest until the next trial. During each trial, subjects were asked to lift the object as straight as possible, i.e., to prevent the object from rotating on the frontal plane due to the right-sided asymmetrical mass distribution (Fig. 3.1a). Successful performance of our manipulation task requires subjects to exert a compensatory torque (T_{com}) of the same magnitude but in the opposite direction of the external torque (T_{ext}) in an anticipatory fashion, i.e., at object lift onset (Fu et al., 2010).

We elicited different force control mechanisms (see Introduction) by either allowing subjects to freely choose grasp contact locations (unconstrained grasping condition, *uncon*) or constraining contact locations by visually cueing grasp points on the object (constrained grasping condition, *con*) (top and bottom objects, respectively, in Fig. 3.1a). The neural mechanisms underlying control of *con* and *uncon* grasping were investigated in two separate experiments using electroencephalography EEG or TMS.

For the *uncon* grasping condition in both EEG and TMS experiments, subjects were instructed that they could grasp anywhere along the vertical plates to perform the task. For the *con* grasping condition in the EEG experiment, the grasp point of each digit was visually cued using two LEDs (14 mm apart) on each side of the object within which the fingertip had to be placed. The EEG study addressed the question of to what extent do source activation of primary motor and sensory cortices (M1 and S1, respectively) differs during execution of *con* versus *uncon* grasping. We expected these differences to reflect a greater involvement of feedback- vs. sensorimotor-based control of forces in *uncon* than in *con* grasping (Mojtahedi et al., 2015). We asked subjects to perform a learning block of 10 *uncon* trials. As the largest performance improvements (i.e., minimization of peak object roll) occurs within the first three trials(Fu et al., 2010, 2011), we used the mean of subjects' preferred digit placement at object lift onset in trials 6-10 of this learning block to set the location of the LED boundary locations for the *con* context. This procedure ensured that average digit position and force distributions would be statistically indistinguishable across *con* and *uncon* trials, while leaving intact the trial-to-trial force position modulation which only occurs in the *uncon* grasping condition. Thus, EEG activation differences that might occur when comparing *con* versus *uncon* grasping conditions would only be attributable to processes associated with digit force-to-position modulation occurring between contact and object lift-onset. After the learning block, subjects performed 60 experimental trials that were used for EEG analysis. Specifically, half of the subjects performed a block of 30 *uncon* trials followed by a block of 30 *con* trials, whereas the other half performed these two blocks of trials in the opposite order. This design controlled for potential order effects of block presentation. Statistical analysis confirmed lack of significant differences in T_{com} and related variables (see equation 1) within each grasping condition regardless of the order of presentation.

Unlike the EEG study, the *con* grasping condition in the TMS experiment was designed to address the question of whether the control of digit force and position differed following a virtual lesion to M1, thus ruling out a need to statistically match digit force and position across *con* and *uncon* grasping conditions*.* To allow comparison with previous studies of *con* grasping, subjects were instructed to grip the object at fixed collinear locations indicated by a horizontal marker placed across the front of the object (vertical length: 20 mm; see Fig. 3.1a). The *uncon* grasping condition was identical to the EEG study. A computer monitor placed behind the object presented two visual cues to the subject to guide each trial. The first 'ready' cue signaled the beginning of a trial, and after a random delay (1-3 s) subjects were shown a 'go' cue to initiate the reach. To allow subjects to learn the dynamics of the object, they were asked to perform 10 practice trials (*"Learn"* block). Following this block, subjects then performed two blocks (*"Pre"* block, *"Post"* block) of 15 trials each (Fig. 3.2). TMS was delivered between the *Pre* and *Post* block (see below). Each block was separated by a rest time of 5 minutes, during which subjects were asked to sit quietly.

Electroencephalography. Scalp EEG was recorded from 22 subjects using a 64-channel Acticap system (BrainVision, Morrisville, NC) at a sampling rate of 1 kHz, with resolution 0.1 µV and bandpass filter of 0.1-100 Hz. Impedances were kept < 10kΩ 3-D electrode locations were recorded using a Captrak camera system (BrainVision, Morrisville, NC).

EEGLAB was used to perform EEG pre-processing steps (Delorme and Makeig, 2004). Continuous data were first high-pass filtered (0.5 Hz). Eye movement and blink artifacts were removed using Independent Components Analysis (Extended INFOMAX algorithm;(Makeig et al., 1996; Lee et al., 1999). On average, 4.46 (± 3.33) components were removed per participant.

Source localization and analysis was performed using a combination of the Brainstorm toolbox (Tadel et al., 2011) and Brainsuite (Shattuck and Leahy, 2002) for cortical parcellation of individual subject structural T1-weighted MRIs (3T, Philips). The cortical surfaces for each subject were reconstructed from the MRIs using Brainsuite. MRIs were co-registered with EEG electrode locations, and used to create a boundary element model (BEM) of scalp, outer skull, and inner skull before source estimation. Source cortical activity from each trial was estimated using distributed source imaging based on a depth-weighted (L2 Norm) minimum-norm estimation (MNE) that estimated an orientation constrained dipole at each parcellated location from the BEM (total of 15,000 dipoles). This is one of the most widely used methods for inverse electrophysiological source model estimation (Michel et al., 2004; Grech et al., 2008). These estimates were converted to current density maps (Hämäläinen and Ilmoniemi, 1994). Our subsequent analysis focused on two regions of interest (ROI): precentral and postcentral gyrus, corresponding to M1 and S1, respectively. These ROIs were identified through automatic neuroanatomical labeling in Brainsuite.

Transcranial magnetic stimulation. We delivered single-pulse TMS (spTMS) to primary motor cortex (M1) of 68 subjects using a Rapid^2 stimulator (Magstim, 70-mm figure-of-eight coil, Whitland, UK). To estimate resting motor threshold (rMT) using suprathreshold TMS pulses, we located the region of contralateral (left) M1 representing the right first dorsal interosseus muscle

(FDI) (Boroojerdi et al., 1999). The position of the coil was adjusted to optimize motor evoked potentials (MEP) amplitudes. rMT was defined as the TMS intensity that induced 50 µV peak-to-peak MEPs in 5 of 10 trials in the first dorsal interosseus (FDI) muscle. To assess corticospinal excitability (CSE), we delivered single-pulse TMS (*sp*TMS) over the region of M1 representing the FDI muscle with the intensity set at 120% of rMT.

We delivered continuous theta burst stimulation (cTBS) to M1 and primary sensory cortex (S1) using the 70-mm coil at an intensity of 80% of active motor threshold (aMT) to transiently disrupt neural activity. aMT was estimated by stimulating M1 at the same site used for rMT while the subject maintained a static contraction using the thumb and index finger on the object at approximately 20% of maximum voluntary contraction (MVC), defined as the average of three trials. We defined aMT as the TMS intensity that induced 200 µV peak-to-peak MEPs in 5 of 10 trials in the FDI muscle. Repetitive pulses were delivered in the form of 3 pulses at 50 Hz repeated every 200 ms for 40 s (600 pulses) (Huang et al., 2005; Parikh and Santello, 2016). As cTBS over M1 has been shown to decrease the size of MEPs, we measured CSE assessed using spTMS to verify the effects of cTBS over M1 (Huang et al., 2005) and S1 (Jacobs et al., 2012).

For M1 stimulation, the TMS coil was positioned over the region of the left cerebral hemisphere representing the right FDI muscle, as identified during rMT estimation. For S1 stimulation, we obtained a high-resolution T1-weighted MRI scan (3T Philips Ingenia scanner) prior to the experiment for each subject. A three-dimensional brain was reconstructed from the MRI slices to display the cortical surface (Brainsight software, Rogue Research Inc., Canada). The TMS coil was positioned over the region of postcentral gyrus posterior to the M1 FDI hotspot (Ni et al., 2009; Torta et al., 2013). The mean Montreal Neurological Institute (MNI) coordinates of the stimulation sites for left S1 were -35.86 ±9.84, –31.6 ±5.59, 55.01 ±4.34 (x, y, z, mean ±SD; *n* = 10). For vertex stimulation (see *Experimental Groups*), the TMS coil was positioned over Cz, based on the 10-20 international system (Jasper, 1958) with the TMS handle oriented posteriorly in alignment with the interhemispheric fissure (Legon et al., 2013). The coil position for the S1 and vertex stimulations was confirmed by the delivery of single TMS pulses at 120% of RMT to ensure that there was no MEP in the FDI muscle.

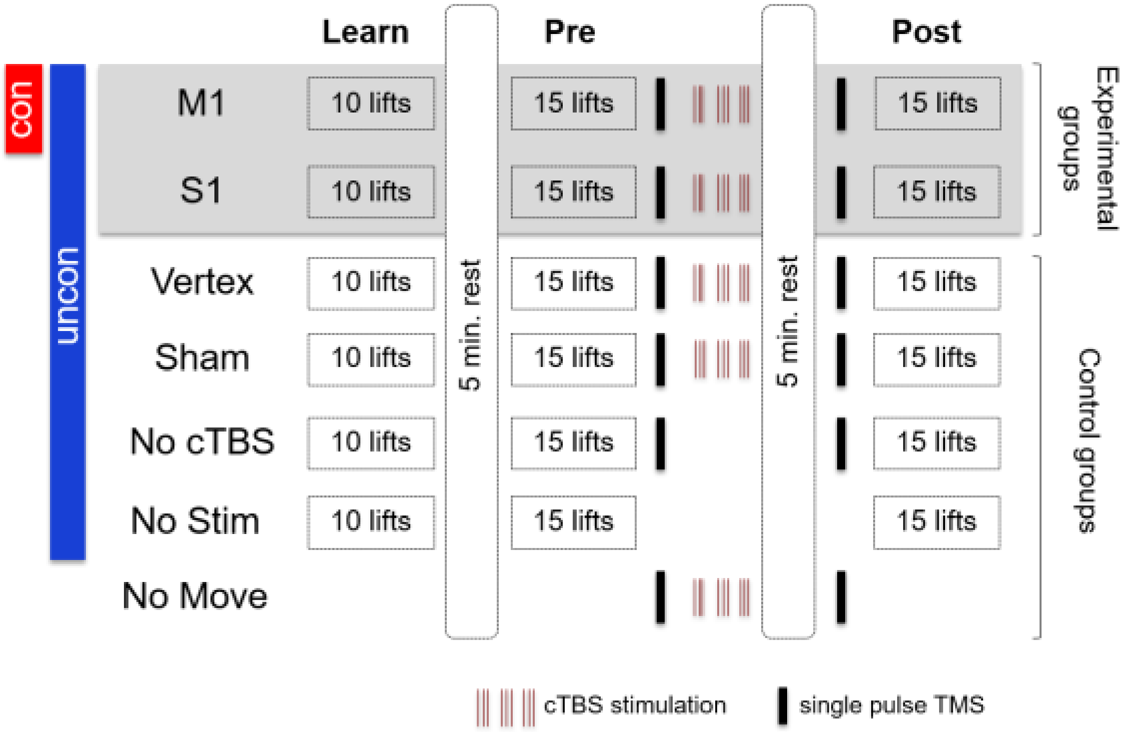


Figure 3.2. Experimental protocols: single pulse TMS and cTBS. We delivered single pulse transcranial magnetic stimulation (TMS) and continuous theta burst stimulation (cTBS). For the experimental conditions, the constrained grasp group (con) received cTBS over M1, whereas the unconstrained grasp group (uncon) received cTBS over M1 and S1. For all control conditions with the exception of No Move, subject were tested in the uncon grasp condition. All groups with the exception of No Stim received single pulse TMS before and after cTBS. All groups with the exception of the No Move group performed 10 repetitions of the manipulation task during the Learn block and 15 repetitions each during the Pre and Post blocks.

TMS experiment: Experimental groups. We delivered cTBS to three groups of subjects. We stimulated M1 of subjects performing the *con* grasping condition (*M1 con*; *n* = 10) and stimulated M1 and S1 of subjects performing the *uncon* grasping condition (M1 *uncon* and S1 *uncon*, respectively; *n* = 10 in each group). Subjects performing the manipulation task under the *con* or *uncon* grasping condition received cTBS over contralateral (left) M1 between the *Pre* and *Post* blocks. CSE was assessed using spTMS immediately after the *Pre* block and before the *Post* block, corresponding to the time immediately before and 5 minutes after cTBS (Fig. 3.2). The same procedures were used for the *uncon* group that received cTBS to S1.

TMS experiment: Control groups. We performed five control experiments to assess the specificity of cTBS effects to the cortical area targeted by TMS and the efficacy of the cTBS protocol: *Vertex* (*n* = 10), *Sham* (*n* = 10), *No cTBS* (*n* = 6), *No Stim* (*n* = 6), and *No Move* (*n* = 6) **(**Fig. 3**)**. All control groups with the exception of the *No Move* group performed the manipulation task in the *uncon* grasping condition.

Subjects in the *Vertex* group received cTBS over vertex between the *Pre* and *Post* blocks. CSE was assessed using spTMS over M1 immediately after the *Pre* block and before the *Post* block, corresponding to the time immediately before and 5 minutes after cTBS (Fig. 3.2). We selected the vertex as a neutral control site to assess the specificity of cTBS-induced effects observed in the M1 and S1 groups.

In the *Sham* group, cTBS was delivered using a second coil placed directly behind the TMS chair's headrest with current directed away from the scalp while the coil over contralateral (left) M1 remained in place. CSE was assessed over contralateral (left) M1 region immediately after the *Pre* block and before the *Post* block, corresponding to the time immediately before and 5 minutes after cTBS (Fig. 3.2). This group was used to control for any somatosensory effects caused by the auditory cue of cTBS on the control of object manipulation (Duecker et al., 2009).

For the *No cTBS* group, CSE was assessed using spTMS over contralateral (left) M1 immediately after the *Pre* block and before the *Post* block (Fig. 3.2). This control was performed to quantify the potential effects of MEP-induced movements on the control of object manipulation. Muscle twitches caused by spTMS over M1 have been shown to affect grasping behavior in subsequent lifts(Flanagan and Johansson, 2002)

The *No Stim* group received neither spTMS nor cTBS (Fig. 3). This group was used to control for any somatosensory effects caused by the auditory cue of spTMS and cTBS on the control of object manipulation (Duecker et al., 2009).

Subjects in the *No Move* group saw the same visual cues as those presented to all other groups, but were asked to remain at rest when seeing the 'go' cue rather than reaching, grasping, and lifting the object. Subjects received cTBS over contralateral (left) M1 between the *Pre* and *Post* blocks. CSE was assessed immediately after the *Pre* block and before the *Post* block, corresponding to the time immediately before and 5 minutes after cTBS (Fig. 3.2). This control group was used to validate the effects of cTBS over M1 on MEP size that was previously reported in the literature (Huang et al., 2005).

For additional details and rationale for the control conditions, please refer to Supplementary Material (Appendix B).

EEG data analysis. Dipole moments (pA*m) were used to quantify neural activity. Source maps were projected to a default brain (Lancaster et al., 2007) and subsequently decibel (dB)-normalized to a baseline period (average of −500 to −250 ms before a 'ready' cue). After baseline normalization, data recorded between contact and object lift onset were averaged within subjects for each condition prior to statistical analysis.

TMS data analysis. Electromyography (EMG) signals were recorded from the right FDI muscle using bipolar surface electrodes (Delsys Bagnoli system, Boston, MA) and digitized at 5 kHz (Power 1401 Cambridge Electronic Design, Cambridge, UK). Peak-to-peak MEP amplitudes (mV) were measured and extracted using a custom written Spike2 script and analyzed using Matlab. EMG signals were screened online and recorded during cTBS stimulation to verify that cTBS did not evoke MEPs.

Behavioral data analysis. Force and torque data were acquired by 12-bit A/D analog-to-digital data acquisition boards (DAQ 6701 and 6023E; National Instruments, Austin, TX). The IMU sensor data was sampled at 128 Hz with a 14-bit resolution, and the gyroscope had a range of ±2000º/s, and noise density of 0.05 rad/s/√Hz.

Force, torque, and object roll data were analyzed offline using custom MATLAB scripts (Mathworks, Natick, MA) to compute the following variables (Fig. 3.1b): (1) *Digit forces*: Digit tangential force (F_{tan}) is the vertical force component parallel to the grip surface produced by each digit to lift the object. Digit load force data exerted by each digit was used to compute the difference between thumb and index finger load forces ($F_{tan1} – F_{tan2} = d_{LF}$). Digit normal force ($F_n$) is the force component normal to the grip surface produced by each digit. Digit grip force was defined as the average of the thumb and index finger normal forces ($[F_{n1} + F_{n2}]/2 = F_{GF}$). (2) *Digit center of pressure*: The center of pressure of thumb and index finger (CoP_1 and CoP_1, respectively) was computed using the force and torque output of each sensor (Fu et al., 2010; Zhang et al., 2010). CoP data were then used to compute the vertical distance between the CoP on the thumb and finger side of the grip device ($CoP_1 - CoP_2 = d_y$). We computed the compensatory torque exerted on the object (T_{com}) using the following equation:

$$T_{com} = d_{LF} \cdot \frac{w}{2} + d_y \cdot F_{GF} \qquad (1)$$

where 'w' denotes the width of the object. (3) *Peak object roll*: We have earlier noted that peak object roll is negatively correlated with the magnitude of T_{com} (Fu and Santello, 2015). Therefore, peak object roll was used to quantify the behavioral consequence of T_{com} for each experimental and control condition. We defined peak object roll as the maximum roll occurring ~150 ms after object lift-off.

All of the above variables, with the exception of peak object roll, were computed at the time of object lift onset to quantify anticipatory control of manipulation (Lukos et al., 2007; Fu et al., 2010). Object lift onset was defined as the time at which the first of the two object switches was released from the object switch plate and remained open for 50 ms.

Statistical analysis. For the EEG experiment, baseline normalized dipole moments averaged within subjects for each grasping condition (30 trials each) were compared using t-tests with Bonferroni corrections.

For the TMS experiment, we assessed subjects' ability to perform the manipulation task by comparing the first trial with the average of the last five trials of each block (*Learn, Pre, Post*) within and across experimental groups (Fig. 3.2). Our previous work using the same manipulation task has found that subjects quickly learn to generate the necessary T_{com} (Fig. 3.4) within the first three trials so as to minimize object roll(Salimi et al., 2000, 2003; Fu et al., 2010). Analysis of the first trial of each block thus allowed the assessment of subjects' performance without any previous experience (*learn1*), and recall of stored sensorimotor memory of grasp position and forces acquired after learning the manipulation task (*pre1*, *post1*). Subsequently, averaging the last trials of each block (*learn5*, *pre5*, *post5*) was performed to obtain a measure of stable performance for each block.

To assess learning-related changes in behavior, we performed a 4 x 2 between-within repeated measures (rm) ANOVA with *Group* (4 levels: M1 *uncon*, M1 *con*, S1, Vertex) as the between-subject factor, and *Block* (2 levels: learn1 learn5) as the within-subject factor. To confirm that subjects' performance remained stable during trials after learning and prior to cTBS, we performed a 4 x 3 between-within rmANOVA with *Group* (4 levels: M1 *uncon*, M1 *con*, S1 *uncon*, *Vertex*) as the between-subject factor, and *Block* (3 levels: *learn5*, *pre1*, *pre5*) as the within-subject factor. A similar statistical design was used to assess performance in the remaining control groups (for details see Supplementary Material*).*

To assess the effects of cTBS on T_{com} and object roll, we performed a 4 x 3 between-within rmANOVA with *Group* (4 levels: M1 *uncon*, M1 *con*, S1, Vertex) as the between-subject factor, and *Block* (3 levels: pre5, post1, post5) as the within-subject factor. Post-hoc t-tests and one-way ANOVAs were used to compare between- and within-group differences, respectively. We performed separate one-way rmANOVA to assess the effects of cTBS on individual variables (d_{LF}, d_y, and F_{GF}). We opted to perform only within-group analyses for individual position and force data because subjects could have selected different magnitude of the components of T_{com} giving rise to spurious between-group differences, although the overall goal of T_{com} generation is the same. Finally, we used one-sample t-tests to assess the changes in MEP data. We applied Huynh-Feldt corrections when sphericity assumption was violated. Appropriate Bonferroni alpha corrections were used for post-hoc t-tests.

RESULTS

Sensorimotor cortical activity is sensitive to grasp context. To determine the extent to which the involvement of M1 and S1 is grasp-context dependent, we recorded scalp EEG and quantified source current density power over precentral and postcentral regions, which served as representative regions for M1 and S1, respectively (see Methods). Source current density power was computed from contact to object lift for both constrained and unconstrained grasping (*con* and *uncon*, respectively). For both grasp contexts, the task consisted of grasping and lifting a sensorized object. The task's goal was to minimize the object roll after lift. This was achieved by participants exerting a compensatory (opposite) torque (T_{com}) on the object to counteract the object's external torque (T_{ext}), caused by its asymmetrical mass distribution (Fig. 3.1a). The two grasp contexts differed only in terms of whether object contact locations were visually cued or could be chosen by the subject. Specifically, the experimental design aimed at removing significant differences in digit position, forces, and torques at object lift onset across the two grasp contexts (see Methods). This was confirmed by statistical analyses revealing that digit force and position distributions at object lift-off were statistically indistinguishable in *con* versus *uncon* grasping (all $P > 0.62$).

Consistent with previous work, we found that although subjects in *con* and *uncon* groups were able to quickly learn T_{com}, digit load forces were significantly correlated with trial-to-trial changes in digit position only for *uncon* grasping (see Supplementary Material; a detailed description of behavioral results is presented below for the 'virtual lesion' experiments). Importantly, EEG source power was significantly larger during *uncon* than *con* grasping over both M1 and S1 (main effect of *Group:* $F_{1,21} = 379.6$ and 22.69, respectively; both $P < 0.0001$; Fig. 3.3).

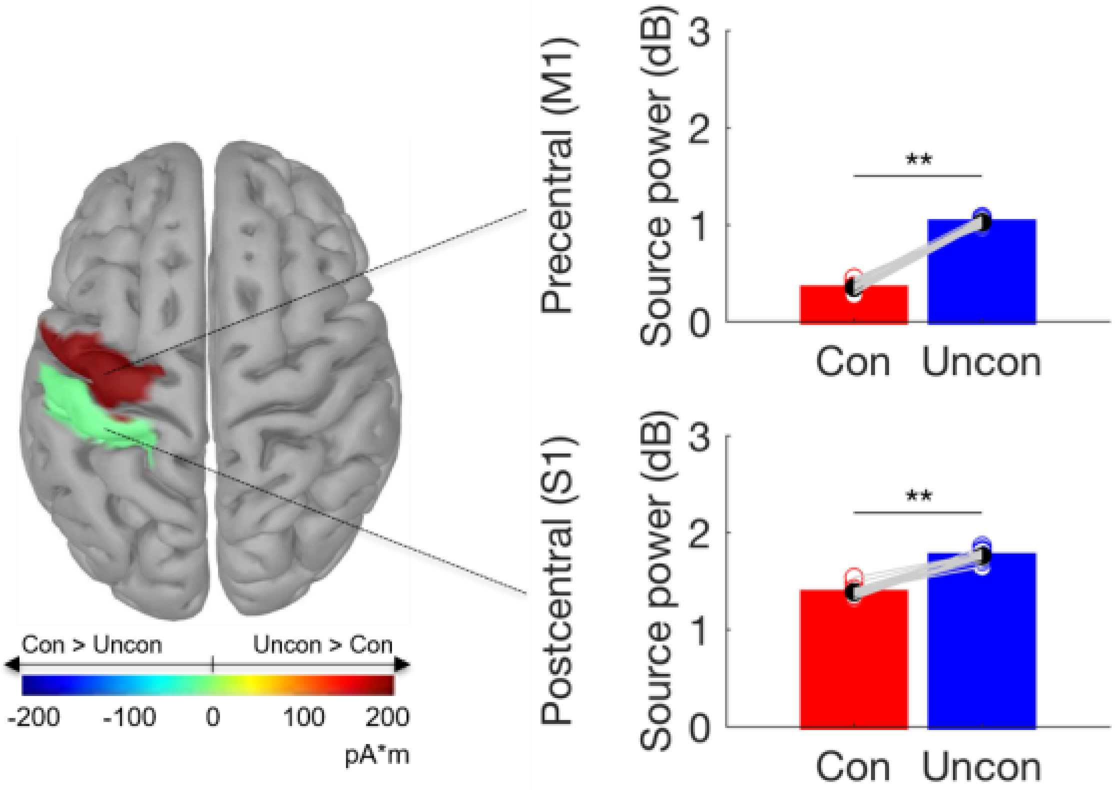


*Figure 3.3. EEG source current density power. Color-coded brain areas denote statistically significant source power differences (pA*m) between constrained and unconstrained grasping over left precentral and postcentral regions. Bar plots show mean normalized source power (decibel) for each grasp context measured from object contact to lift. Overlaid gray lines show condition differences for individual subjects (n = 22). ** denotes P < 0.0125. Data are averages (± SE) of all subjects.*

This finding supports our hypothesis that activation of M1 and S1 is modulated by grasp context, while raising the question of their functional roles. To address this question, we performed virtual lesions to M1 and S1 using transcranial magnetic stimulation, TMS (continuous theta burst, cTBS) (Fig. 3.2).

A virtual lesion of M1 and S1 impairs execution of learned manipulation in a grasp context-specific fashion. On the first trial of the *Learn* block, subjects were unaware of the object's mass distribution as the object is visually symmetrical and therefore exerted no or negligible T_{com} (Fig. 3.4). Therefore, the first object lift was characterized by large object roll (Fig. B.3). However, consistent with previous work(Salimi et al., 2000; Fu et al., 2010; Zhang et al., 2010), subjects quickly learned to compensate for the object's mass distribution and generate the necessary T_{com} over the remaining trials of the *Learn* block (main effect of *Block*: $F_{1,36} = 359.6$, $P < 0.0001$) similarly across groups (no significant *Group* × *Block* interaction: $F_{1,36} = 2.365$ or main effect of *Group:* $F_{1,36} = 0.553$, both $P > 0.16$). As a result, subjects learned to reduce object roll over the remaining trials of the *Learn* block (main effect of *Block*: $F_{1,36} = 67.05$, $P < 0.0001$; no *Group* × *Block* interaction: $F_{1,36} = 0.706$, $P = 0.613$). Following learning, all subjects exhibited a stable T_{com} and object roll over the remaining *Learn* and *Pre* block trials (no main effect of *Block* or significant interaction, both *P*-values > 0.83; Fig. 3.4; see Supplementary Material for details (Appendix B).

We delivered cTBS to the M1 *con*, M1 *uncon*, S1 *uncon*, and *Vertex* groups immediately following the *Pre* block, but prior to the beginning of the *Post* block. We verified the effectiveness of our cTBS protocol using single-pulse TMS to measure changes in corticospinal excitability in all groups (Fig. 3.2 and Fig. B.1; for details see Supplementary Material (Appendix B). We selected the vertex as a neutral control site to assess the specificity of cTBS-induced effects on the control of our manipulation task following stimulation of M1 and S1.

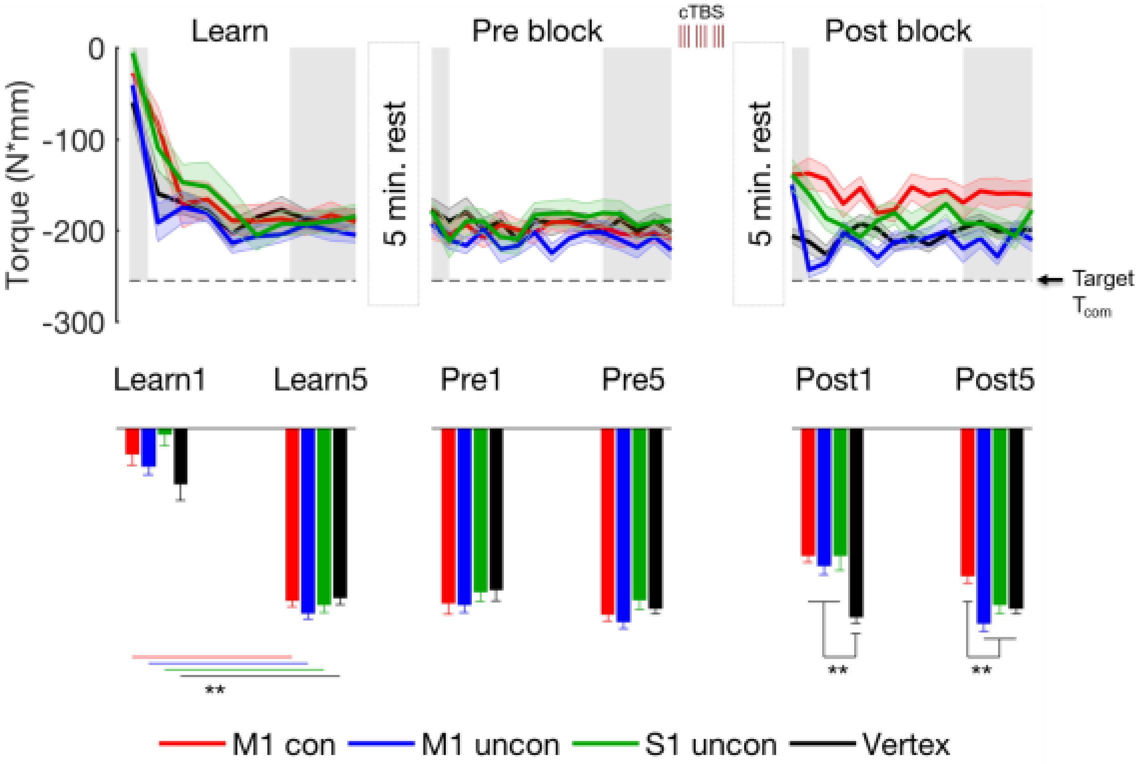


*Figure 3.4. Compensatory torque: Experimental groups and control condition (Vertex). The top plots show compensatory torque (T_{com}) during the Learn, Pre, and Post blocks in the M1 uncon, M1 con, S1 uncon, and Vertex groups. Shaded data denote trials used for analysis. The horizontal dashed line denotes the external torque induced by the added mass at the bottom of the object (Target T_{com}) that should be compensated for by a compensatory torque (T_{com}). Bottom bar plots show T_{com} on the first trial and the average of the last 5 trials for each block. ** denotes $P < 0.0125$. Data are averages (± SE) of all subjects.*

Following cTBS over M1 and S1, but not vertex, subjects were unable to exert the previously-learned T_{com} (significant *Group* × *Block* interaction: $F_{2,72} = 25.14$, $P < 0.0001$; main effect of *Block*: $F_{2,72} = 6.339$, $P < 0.0001$) (Fig. 3.4). Specifically, on the first trial following cTBS (Post1), subjects in the three experimental groups exerted significantly smaller T_{com} than those in the *Vertex* group, although T_{com} reduction was not significantly different across experimental groups (all *P*-values > 0.42). However, the persistence of the cTBS effect on T_{com} during the *Post* block was dependent on whether subjects performed the manipulation task in the *con* or *uncon* condition. For the M1 *uncon* and S1 *uncon* groups, T_{com} impairment was short lived, returning to the same magnitude as T_{com} exerted by the *Vertex* group at the end of the *Post* block (all *P*-values > 0.15; Fig. 4). In contrast, the drop in T_{com} for the M1 *con* group persisted through the end of the *Post* block, as revealed by significantly smaller T_{com} relative to the *Vertex* group ($t_{(9)}$ = 6.286, *P* = 0.0023).

Peak object roll results after cTBS paralleled those of T_{com}, i.e., peak object roll was larger in the *Post* than *Pre* block in the three experimental groups but not in the *Vertex* group (main effect of *Block* ($F_{2,72}$ = 15.94, *P* < 0.0001) and significant *Group* × *Block* interaction ($F_{2,72}$ = 6.38, *P* < 0.0001) (see Fig. B.3 and Supplementary Material (Appendix B). Similar to the *Vertex* group, no difference in object manipulation performance was found in all other control groups when comparing *Pre* and *Post* blocks (see Fig. B.2 and Supplementary Material (Appendix B).

As T_{com} results from the coordination of digit position (d_y) and forces (d_{LF}, F_{GF}) (equation 1, Methods), we analyzed the extent to which virtual lesions affected each of these variables for the M1 *con*, M1 *uncon* and *S1 uncon* groups using the same subsets of trials as those used for the above T_{com} analysis.

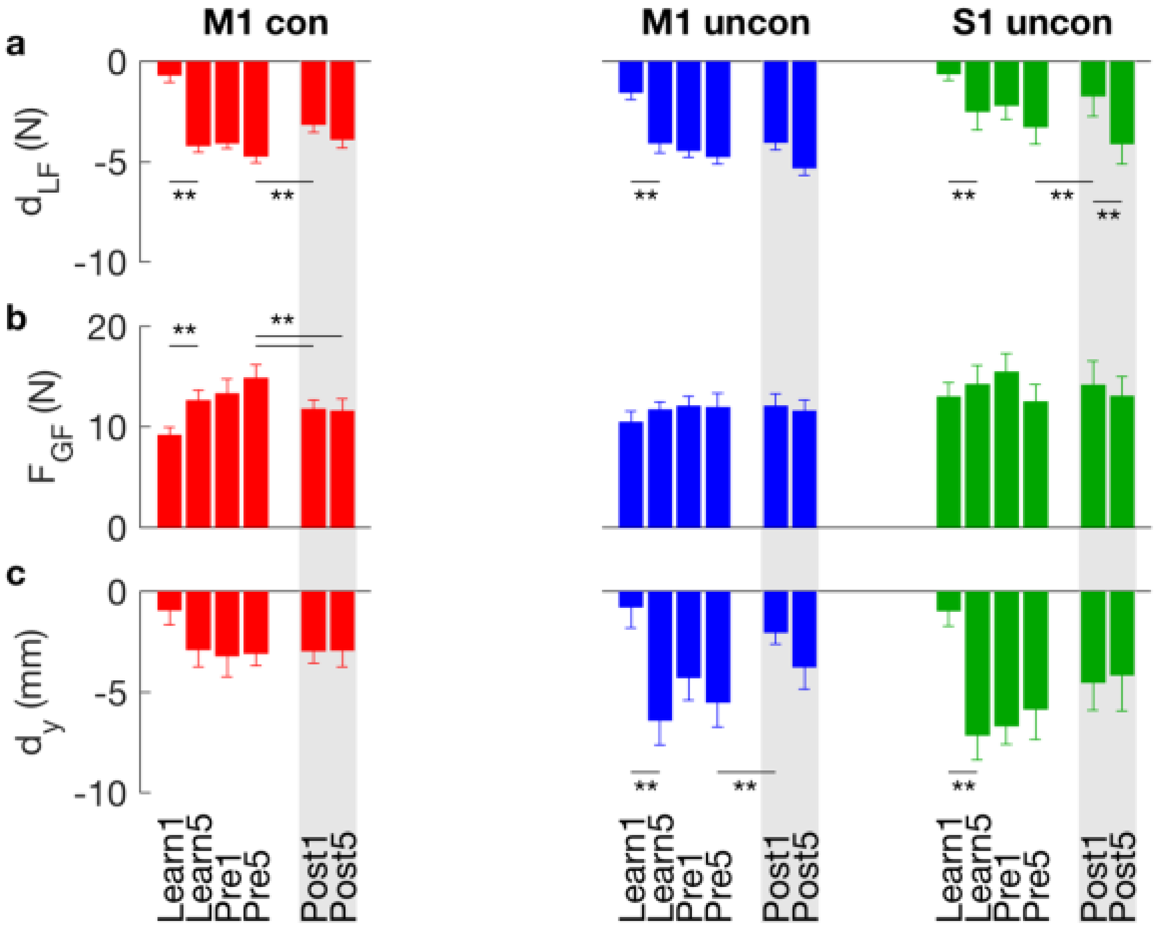


*Figure 3.5. Modulation of digit placement, digit load and grip force: Experimental groups. (a), (b), and (c) are vertical distance between thumb and index finger center of pressure (dy), difference between index finger and thumb load force (dLF), and average grip force (FGF), respectively, for each block of trials. Bars within the shaded regions denote data after cTBS. ** denotes P < 0.0125. Data are averages (± SE) of all subjects.*

Constrained grasping: Disruption of M1 impairs retrieval of learned grip and load forces. In *con* grasping, the target T_{com} can only be attained by digit force modulation because digit placement is constrained to be collinear (Fig. 3.1a; equation 1). As expected from previous work(Fu et al., 2010), grip (F_{GF}) and load force (d_{LF}) modulation occurred early during the *Learn* block until a consistent force distribution was attained (F_{GF}, main effect of *Block*: $F_{1,9} = 26.98$, $P < 0.001$; d_{LF}, $F_{1,9} = 46.53$, $P < 0.0001$; Figs. 3.5a,b). As grasp contact points are constrained by visual cues, the vertical distance between the thumb and index fingertip (d_y) did not significantly change across trials of *Learn* and *Pre* blocks ($P = 0.683$; Fig. 3.5c).

Following cTBS to the M1 *con* group, participants were unable to retrieve and use the same digit forces used in previous trials, such retrieval being a key feature of *con* grasping(Johansson and Westling, 1984, 1988). Specifically, both F_{GF} and d_{LF} significantly decreased (main effect of *Block*: $F_{2,18} = 13.76$ and 14.30, respectively; both $P < 0.0001$). F_{GF} and d_{LF} on the first *Post* block trial were significantly smaller than on the late *Pre* block trials (post1 vs pre5: $t_9 = 3.936$ and -7.081, respectively; both $P < .003$; Figs. 3.5a,b). The cTBS effect on F_{GF} was also present at the end of the *Post* block (post5 vs pre5: $t_9 = 6.880$, $P < 0.0001$). Importantly, and in contrast to digit forces, d_y was unaffected by cTBS (no main effect of *Block*, $F_{2,18} = 0.045$, $P = 0.956$; Fig. 3.5c). These results indicate that the effect of cTBS on T_{com} in *con* grasping (Fig. 3.4) was due to selective disruption of the retrieval of learned digit forces, while sparing the control of visually-cued digit position.

Unconstrained grasping: Disruption of M1 impairs control of learned digit placement and modulation of load force. In *uncon* grasping, changing the vertical distance between thumb and index fingertip (d_y), together with subsequent digit force modulation, contributes to attaining the target T_{com} required to minimize object roll (Fig. 3.1a; equation 1). Consistent with previous work (Fu et al., 2010; Zhang et al., 2010), after experiencing a large object roll on trial 1 subjects increased d_y, i.e., placed the index fingertip higher than the thumb, during the *Learn* block (learn5 versus learn1, main effect of *Block*: $F_{1,9}$ = 12.07, P = 0.007) (Fig. 3.5c). After learning to generate the correct T_{com}, subjects maintained similar d_y across *Pre* block trials (no main effect of *Block*, $F_{2,18}$ = 0.045, P > .05). Whereas F_{GF} did not significantly change during *Learn* or *Pre* blocks (P > 0.05), digit load force distribution (d_{LF}) was concurrently modulated as subjects exerted larger index finger load force relative to the thumb (Figs. 3.5a,b) during late versus early *Learn* block trials (main effect of *Block*: $F_{1,9}$ = 28.13 , P < 0.001). Parallel modulation of d_y and d_{LF} ensures the attainment of the target T_{com}(Fu et al., 2010). Once the manipulation task was learned, subjects used similar d_{LF} across *Pre* block trials (no main effect of *Block*, $F_{2,18}$ = 0.045, P > .05).

cTBS to M1 impaired subjects' ability to use the same digit positions learned in previous *uncon* trials (main effect of *Block*: $F_{2,18}$ = 7.30, P = 0.005). Specifically, we found a decrease in d_y on the first *Post* block trial compared with the late *Pre* block trials (post1 vs pre5: t_9 = –3.684, P = 0.005; Fig. 5c). However, this d_y impairment did not persist over the remaining *Post* block trials (post5 vs. pre5: t_9 = -2.00, P = 0.076; Fig. 3.5c). Interestingly, the large change in d_y caused by cTBS was not accompanied by a significant modulation of d_{LF} or F_{GF} (no main effect of *Block*: $F_{2,18}$ = 5.27 and 0.106, both P > 0.07; Figs. 3.5a,b). Thus, the effects of cTBS during *uncon* grasping were opposite to those found for *con* grasping, such that virtual lesion to M1 impaired the control of digit placement but not digit forces. Thus, in *uncon* grasping the lack of co-modulation of d_{LF} to the cTBS-induced change in d_y caused the underlying reduction in T_{com} (Fig. 3.4; equation 1).

Unconstrained grasping: Disruption of S1 impairs the modulation of load force distribution. Similar to the M1 *uncon* group, subjects in the S1 *uncon* group modulated both d_{LF} and d_y as they learned to exert T_{com}. During late versus early *Learn* block trials, subjects exerted larger load force with the index finger and placed it higher than the thumb (main effect of *Block* on d_{LF} and d_y: $F_{1,9}$ = 5.04 and $F_{1,9}$ = 6.71, both P < 0.0029; Fig. 3.5a,c). Once the manipulation task was learned, d_{LF} and d_y remained stable across *Pre* block trials (all P-values > 0.10). In contrast, F_{GF} was not modulated during the *Lean* and *Pre* blocks (P > 0.05).

Of all T_{com} components, cTBS over S1 affected only digit load force distribution. d_{LF} was significantly reduced relative to *Pre* block trials (main effect of *Block*: $F_{2,18} = 16.50$, $P < 0.0001$; post1 vs pre5: $t_9 = –4.187$, $P = 0.002$; Fig. 3.5a). However, this cTBS-induced effect on d_{LF} did not persist over the remaining *Post* block trials (post5 vs. pre5: $t_9 = 2.059$, $P = 0.070$; Fig. 3.5a). In contrast, F_{GF} and d_y and were statistically indistinguishable from trials preceding cTBS (no main effect of *Block*: $F_{2,18} = 0.867$ and 2.34, respectively; both $P > 0.13$; Fig. 3.5b,c).

DISCUSSION

Our study was designed to test the overarching hypothesis that constrained and unconstrained grasping are mediated by different neural mechanisms. Our results obtained from EEG and cTBS experiments support this hypothesis by revealing differential activation of sensorimotor cortices and a grasp context-dependent role of M1 and S1 during skilled object manipulation. Here we demonstrate for the first time that digit force-to-position modulation – a phenomenon associated with more natural, unconstrained grasping – critically depends on both M1 and S1 to ensure successful manipulation. Importantly, integrity of S1 alone is not sufficient to mediate digit force-to-position modulation, as indicated by disruption of digit position control and failure to modulate forces to position following cTBS over M1. Lastly, when digit placement is constrained to be repeatable and predictable across trials, we confirmed previous work pointing to M1 as involved in mediating a memory-based control of manipulative forces. These findings suggest a flexible and context-dependent organization of the sensorimotor cortical network involved with the control of skilled manipulation.

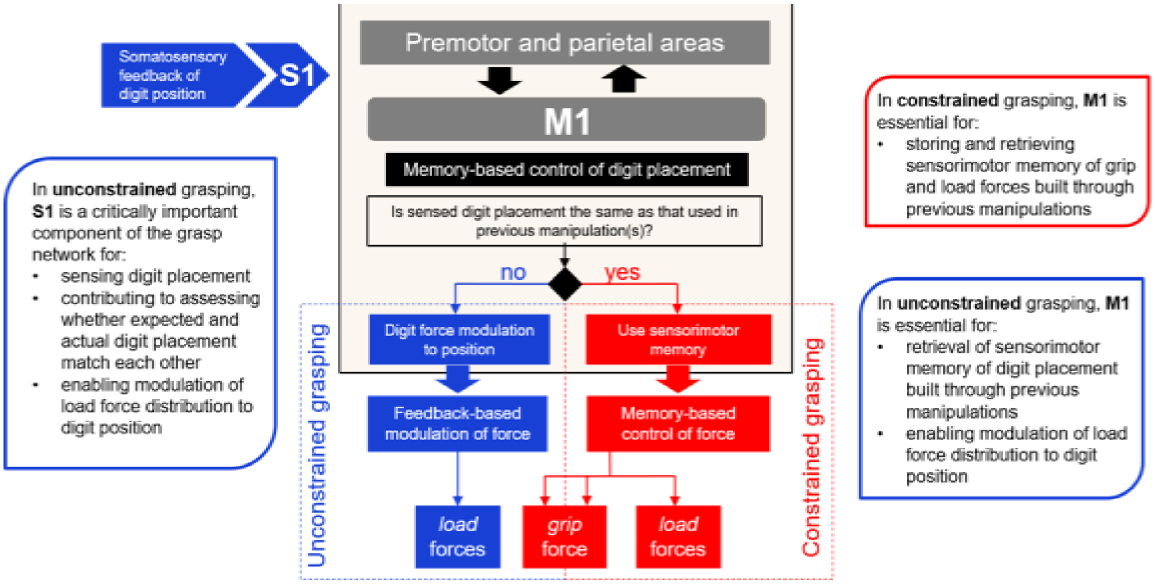
In most every day, natural hand-object interactions, digit placement is not cued or constrained by object geometrical features. Nevertheless, humans are exquisitely skilled at manipulating a given object or tool despite the fact that grasping may occur at different points on the object across repeated manipulations. In these circumstances, subjects exhibit trial-to-trial variability in digit placement, even after the object's dynamic properties have been learned(Fu et al., 2010). Such variability could be caused by errors in sensorimotor transformations responsible for controlling multi-joint torques to bring the hand in the proximity of the object, despite the fact that reaching movements are usually visually guided. In a series of behavioral studies, we found that variability of digit position that may naturally occur from trial to trial is compensated for by modulating digit forces prior to onset of manipulation, i.e., before object lift-off (Fu et al., 2010, 2011). This digit force-to-position modulation is a phenomenon that is critically important for ensuring that the goal of the manipulation task is accurately accomplished when digit position is not constrained. Behavioral evidence points to the involvement of a feedback-based control of digit forces, such that sensed digit placement would be used to modulate digit forces accordingly on a trial-to-trial basis. From a neural control perspective, we had proposed that being certain or uncertain of contact points challenges the nervous system in very different ways. Specifically, constraining contact enables the retrieval and use of grasp forces used in previous manipulations, as subjects are certain that the forces used in previous trials and applied to the same contact points will generate the same behavioral outcome on future trials. In contrast, uncertainty of contact points limits the extent to which subjects can confidently rely on such memory-based control of grasp forces, and thus must involve an alternative or complementary force control mechanism. The results of the present study specifically suggest that cortical sensorimotor activation (Fig. 3.3) and the functional role of sensorimotor areas (Fig. 3.5) are sensitive to whether grasp force control is dominated by memory- versus feedback-based mechanisms.

Previous work combining TMS-induced virtual lesions and a constrained grasping task identified M1 as being implicated in storage and retrieval of sensorimotor memory of grasp forces (Chouinard et al., 2005; Nowak et al., 2005; Jenmalm et al., 2006). Our results confirm such a role, while extending these observations in important ways. When contact points were predictable, virtual lesions to M1 prevented retrieval of learned digit forces for an extended period of time (M1 *con*, Fig. 3.5a,b). In contrast, when contact points were not predictable, virtual lesions to M1 elicited two inter-related phenomena that were short lived: subjects could not implement digit placement similar to that before delivery of cTBS (M1 *uncon*, Fig. 3.5c), and digit forces were not modulated as a function of the new digit placement (M1 *uncon*, Fig. 3.5a,b). Together, these findings suggest that M1 plays two important roles for the control of dexterous manipulation. First, if contact points are not visually cued or constrained by object geometry, M1 appears to be involved in a memory-based control of digit placement based on previous manipulations. Second, integrity of M1 is necessary for ensuring that forces can be modulated as a function of position.

Based on the above results, the question arises as to whether the neural mechanisms responsible for digit force-to-position modulation entirely reside within M1 or, conversely, might involve other brain areas. One of the assumptions of our theoretical framework is that sensory feedback of digit placement is required to modulate digit forces to placement from contact to object lift onset. If so, one would predict that (1) a differential level of cortical activation in S1 for *con* versus *uncon* grasping, and (2) virtual lesion to S1 should impair subjects' ability to modulate digit force to position in *uncon* grasping. Both of these predictions were confirmed by our EEG and cTBS results (Fig. 3.3 and Fig. 3.5, respectively). Therefore, M1 and S1 appear to play synergistic yet distinct functional roles. Specifically, while integrity of both areas is necessary to ensure that digit forces are modulated to position, each area is associated with distinct functions: M1 can flexibly retrieve a sensorimotor memory of digit forces or implement modulation of digit forces depending on the grasp context while being responsible for a memory-based control of digit position, whereas S1 would utilize sensory feedback of digit placement to enable digit force modulation to position. We speculate that such information flow might occur through recurrent loops between M1 and S1 (Thompson et al., 2017), as suggested by the step-like force corrections that occur only in *uncon* grasping (Mojtahedi et al., 2015).

We should note that S1's role in digit force-to-position modulation is not obligatory. Specifically, one might have conceived force planning arising prior to contact when digit placement is visible shortly before contact. While such vision-based force planning is still possible and likely to occur, contact detection through visual, proprioceptive, and tactile feedback is likely to be a critical event for verifying that planned and actual digit position match. We further propose that this feedback is also instrumental for estimating the relative position of the digits involved in the grasp. Importantly, the S1 cTBS results also indicate that visual feedback of the hand trajectory and contact points – available throughout the task – does not seem to play a significant role in digit force-to-position modulation. Thus, our findings not only support the notion of a feedback component of digit position underlying dexterous manipulation at unconstrained contacts, but also rules out a predominantly vision- or feedforward-based mechanism for grasp force control.

It is well known that the cortical network involved with grasp control, which has been defined primarily based on research on constrained grasping, comprises several areas. For example, the anterior region of intraparietal sulcus (aIPS) and premotor ventral (PMv) participate in the accurate shaping of hand prior to object contact (Ehrsson et al., 2000; Begliomini et al., 2007), whereas aIPS, premotor dorsal area (PMd), and M1 play a role in the storage and/or retrieval of finger force scaling appropriate for the hand shape used in the grasp (Ehrsson et al., 2001). Work on patients with posterior parietal cortex lesions revealed that they experience difficulties in shaping the fingers according to intrinsic object features (Jeannerod et al., 1994) and impaired predictive scaling of grip forces during self-induced modulation of load forces (Nowak et al., 2003). In able-bodied individuals, transient reversible TMS disruption of PMv and bilateral aIPS areas prior to object lift-off leads to increased variability in hand shaping (Grafton et al., 1998; Tunik et al., 2005; Davare et al., 2007; Schettino et al., 2015), whereas TMS disruption of contralateral aIPS, PMd and M1 results in disruption of grip force and load force scaling (Chouinard et al., 2005; Olivier et al., 2007; van Nuenen et al., 2012). S1 appears to be involved in sensing of predictable (Schabrun et al., 2008) and unpredictable (Jenmalm et al., 2006) contact events occurring at the fingertips during skilled manipulation. Finally, skilled manipulation relies on interactions among posterior parietal areas, such as aIPS and S1, and frontal areas such as PMv, PMd, and M1 (Olivier et al., 2007; Grafton, 2010; Vesia and Davare, 2011). However, none of these studies examined the grasp-context dependency of M1 and S1 introduced by choice of digit placement. The present findings significantly extend our understanding of neural mechanisms underlying skilled manipulation and provide the foundations for a new theoretical framework (Fig. 3.6).



In **unconstrained** grasping, **S1** is a critically important component of the grasp network for:
- sensing digit placement
- contributing to assessing whether expected and actual digit placement match each other
- enabling modulation of load force distribution to digit position

In **constrained** grasping, **M1** is essential for:
- storing and retrieving sensorimotor memory of grip and load forces built through previous manipulations

In **unconstrained** grasping, **M1** is essential for:
- retrieval of sensorimotor memory of digit placement built through previous manipulations
- enabling modulation of load force distribution to digit position

Figure 3.6. Cortical sensorimotor mechanisms for neural control of skilled manipulation. The diagram shows a new model describing the roles of M1 and S1 for the control of skilled manipulation for constrained and unconstrained grasping contexts.

Our framework posits that the above-described interactions between M1 and premotor-parietal cortical areas lead to hand shaping (Grol et al., 2007; Cavina-Pratesi et al., 2017), which culminates with positioning the digits at remembered locations used in previous manipulations. Throughout this process, somatosensory inputs to S1 and visual inputs contribute to guiding the hand towards the planned contact points on the object (Fig. 3.6). Following contact, our cTBS results suggest that whether sensed digit positions are the same or different from those used in previous manipulations dictates whether digit forces can be controlled by retrieving sensorimotor memory of digit forces or, conversely, by modulating them to the sensed digit positions (red and blue tracks, respectively; Fig. 3.6). Note that load force distribution is typically scaled to digit positions (Fu et al., 2010, 2011) and, as noted above, load force modulation requires both integrity of M1 and S1. In contrast, grip force appears to be insensitive to whether grasp contacts are constrained or unconstrained (Fu et al., 2010), and therefore its control is likely to be driven by sensorimotor memory (Fig. 3.6).

Our work underscores the context-dependent roles of primary motor and somatosensory cortices for the control of skilled manipulation by revealing the dual role of M1 and its synergistic interactions with S1 for the trial-to-trial modulation of digit force to position. Future work should examine the contribution of higher-order frontal and parietal cortical areas to building high-level task representations required to drive the coordination of digit position and forces to attain a given task goal, i.e., preventing the object from slipping or tilting during manipulation.

CHAPTER 4

CONTEXT-DEPENDENT BRAIN DYNAMICS DURING GRASPING AND OBJECT MANIPULATION

INTRODUCTION

A hallmark of human grasping is that it can be performed in many different contexts, including changes in object weight (Quaney et al., 2003), number of digits (Fu et al., 2011), object size (Gordon et al., 1991), and object center of mass (Salimi et al., 2003). Our previous work has more recently focused on another critical dimension: the ability to modulate digit force to position by studying a context where digit placement is self-selected (Fu et al., 2010). This paradigm introduced a novel aspect of grasp control relative to previous work that focused on constrained digit placement (for review see Johansson and Flanagan, 2009). In the context where digit placement is fixed (constrained grasping), subjects rely more heavily on the retrieval of previously used information to execute a near-identical motor plan across multiple lifts (Jenmalm and R. S. Johansson, 1997; Gordon et al., 1993; Johansson and Westling, 1988). In contrast, when digit placement can be self-selected (unconstrained grasping), real-time control becomes necessary for the modulation of digit forces to compensate for across-trial variability in digit placement (Fu et al., 2010, 2011; see Chapter 1).

To date, the control mechanisms underlying constrained versus unconstrained grasping have been measured during the movement execution phase, quantified via variability in digit placement and force rate profiles measured between object contact and lift-off (Fu et al., 2010; Mojtahedi et al., 2015). While these metrics provide a clear distinction between control mechanisms underlying constrained and unconstrained grasp contexts, they cannot provide information concerning the neural mechanisms during the movement planning phase. This is an important question, as it remains to be established whether the different force control mechanisms elicited by the two grasp contexts emerges from object contact onwards, or earlier.

While there is a robust literature reporting changes in brain activity for hand-object interactions that utilize devices requiring different hand postures (Cattaneo et al., 2005; Prabhu et al., 2007b; Gallivan et al., 2011) or different force magnitude requirements (Ehrrson et al., 2001;

Jenmalm et al., 2006; Hendrix et al., 2009; Loh et al., 2010), this work is unable to discriminate brain dynamics related to the more subtle, yet critical aspect of control explored in our previous work. That is, how does the nervous system prepare for a task with similar control requirements with regard to position and force parameters, but the need for unique sensorimotor control mechanisms? It may be the case that during movement planning, the nervous system implements a default motor plan that is insensitive to the sensorimotor requirements of the upcoming grasp context. In this scenario, sensory feedback occurring at and following object contact would then drive force control based on feedback of digit position or memory in unconstrained or constrained grasping, respectively. Alternatively, during movement preparation the brain may plan for these grasp contexts in wholly distinct ways to accommodate the different sensorimotor requirements associated with the execution phase.

The goal of the present experiment was to use electroencephalography (EEG) to assess changes in cortical activation during planning constrained versus unconstrained grasping. We asked subjects to perform a manipulation task while controlling for digit placement and corresponding digit forces. We hypothesized that top-down mechanisms active during movement preparation would be sensitive to the anticipated extent of forthcoming grasp feedback during execution of constrained versus unconstrained grasping. Specifically, we proposed that during movement preparation, neural oscillations in the medial frontal theta band would predict grasp-type dependent behavioral changes during the subsequent execution phase. Medial frontal theta activity has been associated with high-level cognitive processes (Cavanagh et al., 2012; Cavanagh and Frank, 2014), including memory encoding and retrieval (Rizzuto et al., 2006; Hasselmo and Stern, 2014), working memory (Jensen and Tesche, 2002; Jacobs et al., 2006), and top-down control for action selection (Johnston et al., 2007; Womelsdorf et al., 2010). These changes have been linked to availability of sensory information, and affect subsequent modulation of reaction times during task performance (Cavanagh and Frank, 2014). While less explored, medial frontal theta oscillations have been related to performance beyond traditional memory paradigms (Hsieh and Ranganath, 2015), and thus we suspect that modulations in this frequency band will also link to the retrieval of sensorimotor information when preparing for constrained grasping.

A second prediction was that beta power would also demonstrate grasp-dependent modulation, as it has been associated with integrating information related to task requirements (Zaepffel et al., 2013; Turella et al., 2016), including uncertainty in feedforward estimations (Tan et al., 2014), as well as the temporal prediction of sensorimotor events (Saleh et al., 2010). Based on this information, we hypothesized that reduction in beta power would be greater for unconstrained than constrained grasping due to its greater reliance on online feedback of digit position. In addition, we speculated that this context-dependent beta modulation would remain present during the execution phase as well, as the monitoring of sensorimotor events is necessary for successful object grasp and manipulation (Johannsson and Flanagan, 2009).

We tested our hypotheses by asking subjects to perform a manipulation task whereby constrained and unconstrained grasp trials were presented either in a blocked or randomized fashion. A third hypothesis was that differences in beta and theta power modulation across grasp contexts would occur during movement planning and execution regardless of trial presentation.

METHODS

Subjects. Twenty-two naïve right-handed (Oldfield et al., 1971) volunteers (27 ± 3.51 years [mean ± SD]; 9 females) with normal or corrected-to-normal vision and no history of musculoskeletal disorders or neurological disease participated in this study. Subjects gave their written informed consent according to the declaration of Helsinki. All protocols were approved by the Office of Research Integrity and Assurance at Arizona State University.

Grip device. A custom-designed inverted T-shaped object instrumented with two six-dimensional force and torque transducers (Nano 25; ATI Industrial Automation, Garner, NC) was used to record forces and torques exerted by the index finger and thumb. Graspable surfaces consisted of two long parallel PVC plates (140 × 22 mm) covered with sandpaper (grit #320), each mounted vertically on one transducer. The grip device was designed to measure grip and load force (normal and tangential to the graspable surface) exerted in the *x*- and *y*-direction, and each digit's center of pressure. The transducers' location relative to the graspable surfaces was blocked from the subject's view to prevent visual cues from biasing the choice of digit placement. An LED display was fitted to the front of the object's frontal plane, with one column of 25 LEDs running along the inner edge of each graspable surface (see Fig. 4.1b). This display provided visual cues to guide performance (see below).

The base of the grip device consisted of three compartments (left, center, and right). A 400-g mass was placed in the right (relative to the subject) compartment, creating an asymmetrical mass distribution resulting in an external torque in the frontal *x-y* plane of 255 N•mm (T_{ext}). The object's total mass, including the additional load, was 790 g. Each end of the object's base was placed on a custom-made, battery-driven switch (lift switch). The release of either switch by upward movement of the object from the table was used to calculate the time of object lift off.

Force and torque data were acquired by 12-bit A/D analog-to-digital data acquisition boards (DAQ 6701 and 6023E; National Instruments, Austin, TX) and subsequently analyzed offline using custom MATLAB scripts (Mathworks, Natick, MA) to compute the following variables: (1) *Digit forces*: Digit tangential force (F_{tan}) is the vertical force component parallel to the grip surface produced by each digit to lift the object. Digit load force data exerted by each digit was used to compute the difference between thumb and index finger load forces (d_{LF}). Digit normal force (F_n) is the force component normal to the grip surface produced by each digit. Digit grip force was defined as the average of the thumb and index finger normal forces (F_{GF}). (2) *Digit center of pressure*: The center of pressure (CoP) of thumb and index finger was computed using the force and torque output of each sensor (Fu et al. 2010; Zhang et al., 2010). CoP data were then used to compute the vertical distance between the CoP on the thumb and finger side of the grip device (d_y) and defined as thumb CoP minus index finger CoP. We computed the compensatory torque exerted on the object (T_{com}) using the following equation:

$$T_{com} = d_{LF} \cdot \frac{w}{2} + d_y \cdot F_{GF} \qquad (1)$$

where 'w' denotes the width of the object.

All of the above variables were computed at the time of object lift off to quantify anticipatory control of manipulation (Lukos et al., 2007; Fu et al., 2010). In addition, we fitted a Gaussian function to the time course of grip force rate data between object contact and lift off to quantify the extent to which its shape resembled a bell shape profile. To do this, we amplitude-normalized grip force rate data and subsequently computed the root mean square error (RMSE) between the best-fitted Gaussian function and the normalized grip force rate data (GF_{RMSE}) on a per-trial basis. The "Fit" command from the model-based calibration toolbox of MATLAB software to perform the curve fitting analysis step.

Reach Kinematics. During the experiment subjects sat comfortably with their right hand pronated and rested on a custom-made, battery-driven switch (hand switch), which served as the start and end location for the hand during each trial. Release of this switch with an upward movement of the hand from the table was used to determine reaction time.

Experimental Protocol. Subjects were asked to reach and grasp the grip device placed on the table 15 cm in front of them using the thumb and index fingertips at a self-selected speed, lift the object vertically to a height of 5–10 cm above the table while trying to minimize object tilt, hold the object for 2–3 seconds, replace the object on the table, and finally return to the start position on the hand switch and remain at rest until the next trial. During each trial, subjects were asked to lift the object as straight as possible to prevent it from rotating on the frontal plane due to the right-sided asymmetrical mass distribution. Successful performance, i.e. roll minimization, required subjects to exert a compensatory torque (T_{com}) of the same magnitude but in the opposite direction of T_{ext} at the time of object lift off (Fu et al., 2010).

LEDs on the object's frontal plane (Fig 4.1b) presented two visual cues to guide performance during each trial. The first 'ready' cue, designated by all LEDs flashing on for 250 ms, signaled the beginning of the trial. After a fixed delay of 1 s., subjects were shown a 'go' cue, signaling subjects to execute the task. We calculated reaction time (RT) as the difference between the moment the 'go' cue illuminated and the subsequent release of the hand switch. The 'go' cue, which remained on for the duration of the trial, also indicated the required placement of subject's thumb and index fingertips on the object. Here two LEDs served as an upper and lower bound on each side of the graspable surface (Fig 4.1b), between which subjects were asked to contact the object. The boundary for placement could either be large (140 mm) or small (14.1 mm), and served the purpose to either allow digit placement to be self-selected (*uncon*) or to be constrained by the experimenter (*con)*, respectively. We assessed individual CoP components for thumb and index finger in the con condition for each trial to ensure that subjects placed their digits within the LED boundaries, and subsequently removed these trials (< 5%) from further analysis.

Subjects first performed a learning blocked of 10 *uncon* trials. As learning occurs within the first three trials (Fu et al., 2010, 2011), we used the mean of subjects' preferred digit placement (d_y) in trials 6-10 of this learning block to set the location of the LED boundary locations for the *con* context. This procedure ensured that digit position and force distributions would be statistically indistinguishable across *con* and *uncon* trials (Fig 4.1c). After the learning block, subjects performed four experimental blocks of 30 trials. In the first two blocks, subjects performed a block of 30 *uncon* and 30 *con* trials, with order counterbalanced across subjects to control for potential order effect of block presentation. After these blocks, all subjects performed two additional blocks of 30 trials, during which *uncon* and *con* trials were delivered randomly (Fig 4.1a).

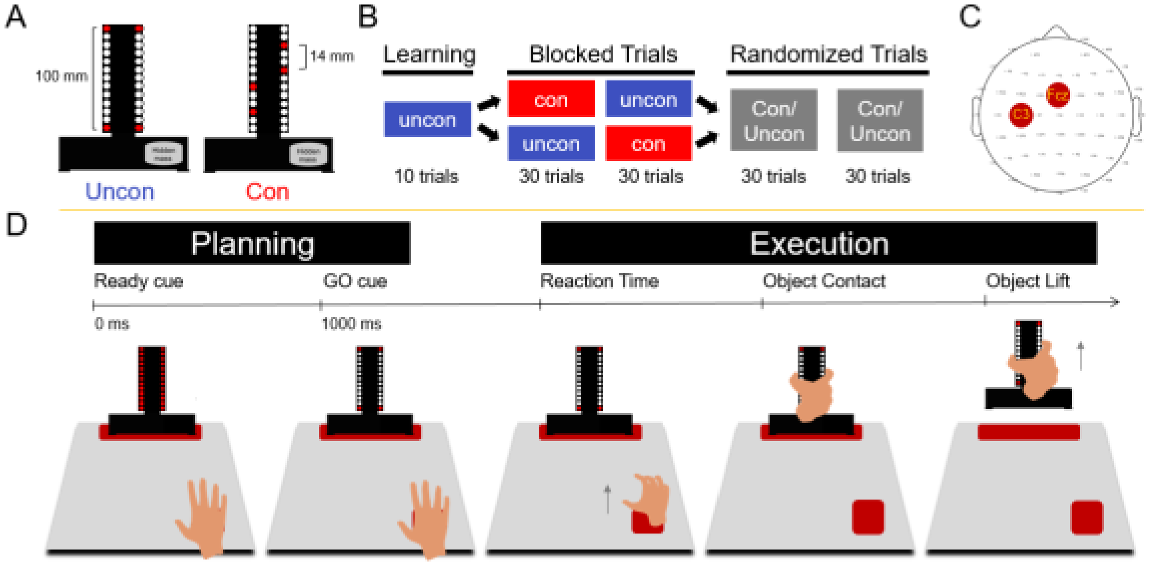


Figure 4.1. Experimental Conditions and Analysis. A. Subjects were cued via LEDs on the objects frontal plane where to grasp the object. LEDs signaled either large (uncon) or small (con)

boundaries on each graspable surface of the object. B. All subjects performed a learning blocking using an uncon grasp context. Subjects then performed 2 sets of blocked trials, one of uncon and another of con trials, with order counterbalanced across subjects. All subjects then performed 2 sets of randomized blocks, whereby uncon and con trials were delivered within the same set of trials. All groups performed 10 repetitions of the manipulation task during the Learning block and 30 repetitions each during the blocked and randomized trial sets, for a total of 130 trials. C. Location of electrodes C3 and Fcz, those included in EEG analysis. D. EEG data was analyzed across 5 epochs during both planning and execution. Example cues are shown for an uncon trial.

EEG data analysis. Scalp electroencephalography (EEG) was recorded using a 64-channel Acticap system (BrainVision, Morrisville, NC) at a sampling rate of 1 kHz, with resolution 0.1 µV and bandpass filter of 0.1-100 Hz and impedances kept below 10kΩ. EEG was recorded by 60 channels from the scalp with ground placed at AFz and a left mastoid reference. Four scalp electrodes removed from positions FT9, FT10, PO9, and PO10 and subsequently positioned to record activity due to eye movements (electrooculogram, EOG). The two electrodes for recording horizontal eye movements were placed at the canthus of each eye. Two additional electrodes were placed above and below the left eye to record vertical movements.

Continuous EEG data was processed using EEGLAB (Delorme and Makeig, 2004). Data were first high-pass filtered (0.5 Hz) to remove any drift, and were then parsed into epochs for further processing. Five epochs were selected based on the experimental question, including time of ready cue, time of go cue, reaction time, object contact, and object lift-off. Each epoch was a window of length of −1000 ms before and 1000 ms after these events, with the window size of each epoch large enough that it contained enough padding to minimize edge artifacts from time-frequency transforms (Cohen 2014). After parsing data into epochs, all trials were visually inspected to check for large scalp EMG or other events that introduced noise. Trial removal was performed uniformly across all epochs, such that each epoch contained the same number of trials from each subject. Subsequently, EOG artifacts related to eye movements and blinks were removed using Independent Components Analysis (ICA; Makeig et al., 1996). We used the Extended INFOMAX algorithm to obtain components (Palmer, Kreutz-Delgado, and Makeig, 2012). On average, 4.46 (± 3.33) components were removed per participant. Following artifact removal, we applied a current-source density spatial filter (Kayser and Tenke, 2006) to reduce the spatial spread of activity due to volume-conduction.

Time-frequency transforms of each trial in each epoch were extracted using wavelet convolution in the frequency domain. Specifically, the EEG power spectrum from concatenated single-trial epochs was obtained using a Fast Fourier Transform (FFT), and then multiplied by the power spectrum of a complex Morlet wavelet ($e^{-i2\pi tf} e^{-t^{\wedge}2/(2\sigma^2)}$). In this equation, *t* is time and *f* represents frequency (Hz). The frequency was scaled in 55 linear spaced steps from 2 to 60 Hz, and the bandwidth (σ) of each wavelet was defined as $\sigma = n/2\pi f$, with *n* equaling the number of wavelet cycles. The number of cycles specifies the tradeoff between time and frequency resolution of the wavelet, with larger number of cycles increasing frequency resolution (Cohen, 2014). The number of cycles was set to increase from 4 to 20 in linear steps with increasing frequency. The inverse FFT was applied after multiplying both spectra. These operations yield a complex time series that is transformed into an estimate of power at each frequency by taking the squared magnitude at each time point. Power values were log transformed to correct for non-normality (Kiebel, Tallon-Baudry, and Friston, 2005).

Time-frequency power values were normalized to the average baseline power at that frequency. Baseline power was calculated from all trials in the experimental session, with a window spanning from −500 to −250 ms before the ‘ready’ cue. This converts EEG power into event-related desynchronization (or synchronization; ERD/ERS; Pfurtscheller & Da silva, 1999), and normalizing to one baseline (pre-ready) allowed a uniform visual and quantitative analysis of ERD/ERS across epochs during both the planning an execution phases. Data points for analysis were obtained from 300-ms windows from five different epochs. We included three epochs that we considered to occur during movement preparation, including time of ready cue, time of go cue, and reaction time. In addition, we included two additional epochs during the movement execution phase, including object contact, and object lift-off. For each epoch, our EEG analyses focused on two frequency bands: theta (4-8 Hz) and beta (16-28 Hz). We provide the rationale for this choice in the Statistical Analysis section.

Given the focus of our experiment is on spectral EEG changes across planning and execution of a task requiring unique sensorimotor control, we chose to constrain our analysis to regions of interest that included contralateral sensorimotor areas and medial-frontal areas

(Pfurtscheller & Da silva, 1999; Tan et al., 2014). Specifically, we analyzed time-frequency data from electrodes C3 and Fcz (Fig 4.1c), averaged across all subjects for *con* and *uncon* contexts. We assessed frequencies in the sensorimotor β and medial frontal θ range to examine EEG power modulation involved in both cognitive and sensorimotor control of object grasping (Cavanagh et al., 2010; Cohen and Donner, 2013; Tan et al., 2016; Tzargarkis et al., 2010), respectively. Our main EEG analysis focused on power change (%) during each of the aforementioned epochs.

Diffusion Model. We used the HDDM python package (Wiecki et al., 2013) to perform a Bayesian diffusion model to explore the relation between medial frontal θ activity and reaction time for constrained and unconstrained grasping. This is a widely-used tool for modeling the relation between decision making and RT (Ratcliff, 1978; Ratcliff & McKoon, 2008). Modeling RT data in a diffusion model allows a full analysis of the distribution of RT values across trials and conditions, and thus provides more meaningful information that simply comparing mean data for this metric. The basic assumptions of the diffusion model are that information accumulates continuously during a binary decision and that this accumulation is characterized by a constant systematic component, termed drift (Voss et al., 2013; Wiecki et al., 2013). We considered two parameters of the diffusion model, each of which has been linked to task difficulty and uncertainty (Voss et al., 2013): (1) drift rate (v), which represents the speed and direction of information accumulation and is quantified as a slope, and (2) separation threshold (a), which represents the amount of information used for a decision.

We ran a series of models, each with unique parameters, and compared the deviance information criterion (DIC) values across all models to optimize model selection. This value is an effective metric for determining model fit (Wiecki et al., 2013), and thus allowed to quantitatively determine which model to use based on our data. The best fitting model was set up such that medial frontal θ was a predictor of separation threshold (a) for *con* versus *uncon* trials. As the DIC values were nearly identical (and notable smaller than the other DIC values), we opted to run an additional model, one in which medial frontal θ was a predictor of drift rate (v) for *con* versus *uncon* trials.

Statistical Analysis. Our initial behavioral analyses focused on participants' ability to generate correct T_{com} during the learn block, and subsequently to apply similar T_{com} values throughout the remainder of the experiment. Our previous work using the same manipulation task has found that subjects quickly learn to generate the necessary T_{com} within the first three trials (Salimi et al., 2000, 2003; Fu et al., 2010), and thus we assessed subjects' ability to learn the manipulation task by comparing the first trial with the average of the last five trials of the *Learning* block. We did this using a repeated measures ANOVA (rmANOVA) with *Block* (2 levels: *Learn1, Learn5*) as the within-subject factor. We performed an additional rmANOVA to assess whether performance was similar at the start of the first block of the experiment as well, with *Block* (2 levels: *Learn5, Block1*) as the within-subject factor and *Order* (2 levels: *Uncon first, Con first*) as the between-subject factor. This also served to confirm that performance was similar irrespective of whether the first experimental block was performed using a *con* or *uncon* grasp context.

A critical check for our protocol's success was to assess whether digit placement (d_y) and digit forces (d_{LF}, F_{GF}) were similar in both the *uncon* and *con* grasp contexts (see Fig 2). A key premise of our experiment was that EEG data would be unique when grasping in these contexts due to their unique sensorimotor requirements, rather than due to differences due to these underlying performance parameters at object lift-off. To compare these position and force variables, we performed a 2 x 2 rmANOVA with *Grasp* (2 levels: *uncon*, *con*) as within-subject factor and *Block* (2 levels: *blocked, randomized*) as the between-subject factor. We performed this analysis for each of the aforementioned position and force variables, as well as T_{com}, d_y variability, RT, and GF_{RMSE}.

The primary goal of the experiment was to assess differences in brain activity during the planning and execution phases of *con* versus *uncon* grasping. To best capture these differences, we opted to focus on trials during the randomized blocks. Assessing data in this context served to rule out any effect of retrieval of previously learned information, habitual task performance, or other potentially spurious effects due to performing repeated trials in the same grasp context, as occurred in the blocked trials. If subjects truly rely on two different control mechanisms, then we expected to see both behavioral and neural differences persist even when the trial context was delivered randomly.

An additional consideration for only including the randomized block trials in the EEG analysis was block order effects. While our initial behavioral analysis, i.e. the mean of blocked trial data irrespective of order, suggested that overall trial performance was similar irrespective of block type (blocked or randomized), the calculation of these means did not take in to account block order, i.e. whether con block was first or second. When we compared mean data for *con* and *uncon* blocked trials while taking order in to account their order, we identified subtle, yet distinct, differences in performance in subsequent analyses (see Appendix C). We argue that these trial order differences are beyond the scope of this research question, i.e. investigating the EEG dynamics that differentiate constrained versus unconstrained grasping. Nonetheless, we opted to include block order in the linear mixed model when analyzing the randomized trial EEG data to account for any possible effect this order may have had on EEG data in the randomized blocks. This would inform us whether any of our reported results were influenced by block order (see below).

To quantify the modulation of cortical activity in the sensorimotor β (Figure C.1) and medial frontal θ (Fig 4.3) frequency bands, we analyzed EEG time-frequency data using linear mixed-effects modeling (West, Welch, and Galecki, 2007), an approach that allowed us to perform single-trial analysis of EEG data. All mixed models were analyzed by first including a full model, and subsequently removing terms from the mixed model until only significant predictors remained, a standard practice of model reduction when using this type of statistical model (West, Welch and Galecki 2007).

To properly model the within-participant residual (co-) variation, block order was included as a random factor. We also specified the models to have a compound symmetry variance-covariance structure specified as using block type and trial number within each block (1-30) as repeated factors. We chose this statistical approach because it enabled us to focus on changes in beta and theta power across grasp context during randomized trials while allowing us to properly model variation arising from block order and trial progression. We note that for all analyses performed via the linear mixed models we report no main effect of block order. This suggests that reported differences in EEG activity during the randomized blocks were not influenced by the previous order of the blocked trial sets.

RESULTS

Learning and Experiment Validation

We first assessed performance during the *Learn* block to confirm that subjects learned to generate the correct torque (T_{com}) to lift with object while minimizing roll. On the first learning block trial, subjects were unaware of the object's mass distribution, as the object is visually symmetrical, but quickly learned to anticipate the object's mass distribution and generate the necessary T_{com} (main effect of *Grasp:* $F_{(1,20)} = 105.8$, $p < 0.05$). After the learning block, subjects generated similar T_{com} at the beginning of the first experiment block (no significant main effect of *Grasp:* $F_{(1,20)} = 2.703$, $p > 0.05$), regardless of whether subjects began with the *uncon* or *con* block of trials (Fig 4.1a) (significant *Grasp* × *Order* interaction*:* $F_{(1,20)} = 0.072$, $p > 0.05$).

During the experimental blocks, subjects generated similar T_{com} during *uncon* or *con* trials regardless of whether consecutive trials of the same grasp type were delivered (blocked trials) or randomly presented (randomized trials) (no significant main effect of *Grasp:* $F_{(1,42)} = 0.745$, $p > 0.05$ or significant *Grasp* × *Block* interaction*:* $F_{(1,42)} = 0.009$, $p > 0.05$). This validated that subjects performed the manipulation task similarly, regardless of trial presentation or grasp type. In addition, we confirmed that subjects demonstrated similar digit placement and corresponding force generation, an expected outcome due to the task design (see Methods). We found that digit placement (d_y), as well as digit grip (F_{GF}) and load (d_{LF}) forces were similar across both blocked and random trial sets (no significant main effect of *Grasp* or significant *Grasp* × *Block* interaction*:* all comparisons, $p > 0.05$) (see Fig 4.2). This was a critical validation step for our subsequent EEG analysis, as we argue that differences in cortical activity distinguishing grasping in a *con* versus *uncon* context would be due solely to unique sensorimotor control mechanisms rather than any other behavioral differences.

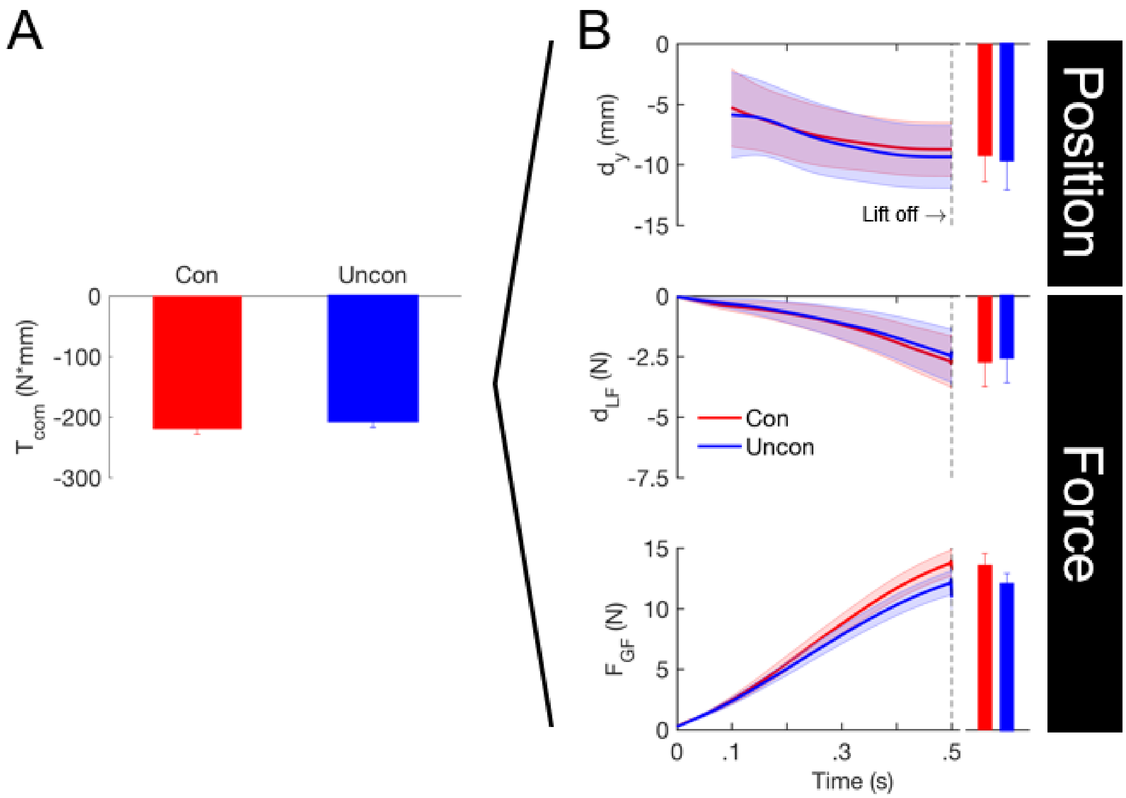


Figure 4.2. Behavioral Data for Constrained and Unconstrained Grasp Contexts. A. Subjects learned to generate compensatory torque (T_{com}) to prevent the object from rotating due to an asymmetrical mass distribution (left). B. T_{com} was generated via the coordination of position and force variables (right). From top to bottom (right), traces denote time course of the vertical distance between thumb and index finger center of pressure (d_y), difference between thumb and index finger load force (d_{LF}), and grip force averaged across thumb and index finger (F_{GF}), from contact to object lift. Each data are plotted from the time at which they can be accurately estimated using the force and torque sensors. Bar plots (far right) show mean data for each variable, measured at the time of object lift off.

Underlying variables enabling successful object manipulation

Despite similar ability to generate T_{com}, grasping in an *uncon* versus *con* context can be distinguished using other behavioral metrics, including increased trial-to-trial variability in d_y for *uncon*, as well as modulations in grip force rate between object contact and lift (Mojtahedi et al., 2015). Our results align with previous work in our lab, that d_y variability (main effect of *Grasp*: $F_{(1,42)} = 28.86$, $p < 0.05$) and grip force RMSE values (main effect of Grasp: $F_{(1,42)} = 12.17$, $p < 0.05$) were larger during *uncon* trials. In addition, neither of these differences were sensitive to block type (no *Grasp* × *Block* interaction: both p values, $p > 0.05$). These results support our underlying premise that *con* and *uncon* grasping require unique sensorimotor mechanisms, and served as the foundation for our subsequent analysis of the movement preparation phase.

Planning-Related differences in Uncon versus Con grasping

The aforementioned differences in d_y variability and grip force RMSE validate previous work from our lab describing the unique behavioral features when grasping in a *con* versus *uncon* context. However, each of these measures is quantified at or after contact. As the main goal of the experiment was to assess differences in sensorimotor control mechanisms when *planning* for an upcoming grasp in these two contexts, we also assessed reaction time (RT). We selected this metric due to its previously reported relation to decision making and response selection (Donders, 1968; Cisek, 2007; Dmochowski and Norcia, 2015; Michelet and Cisek, 2010). We applied EEG analysis based on literature associating RT to medial frontal θ modulation (see Fig 4.3) during movement preparation (Cavanagh et al., 2012, 2014; Jacobs et al., 2006; Womelsdorf et al., 2010; Cohen and Donner, 2013).

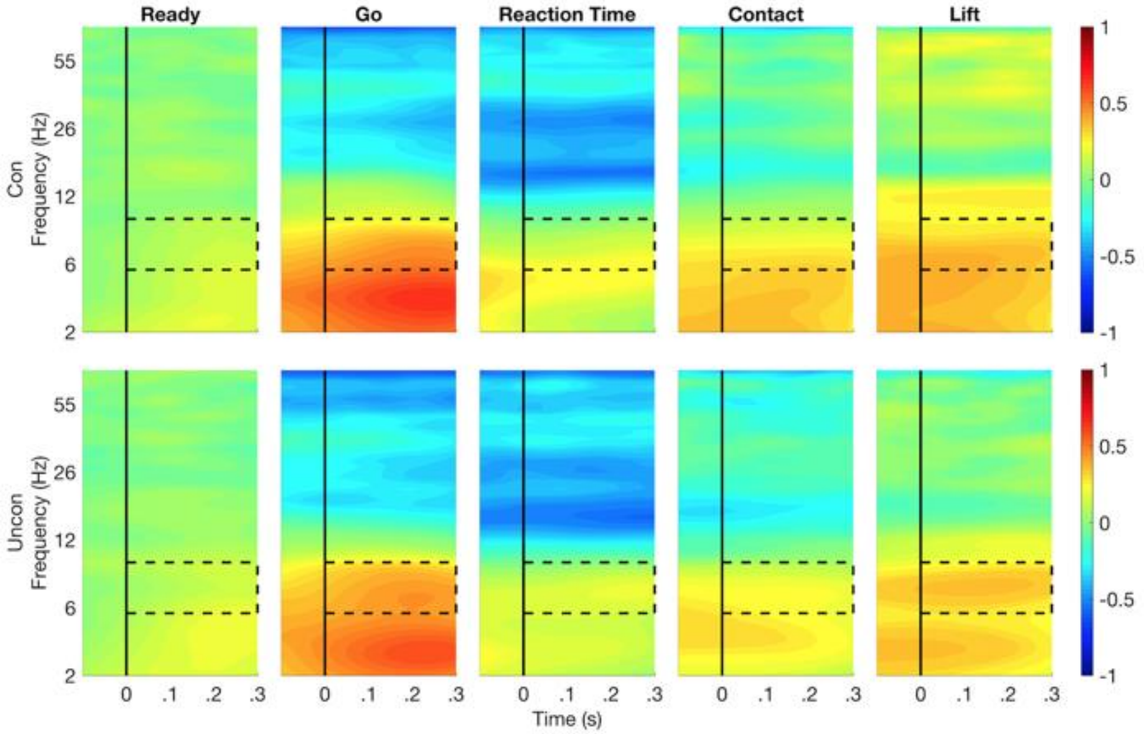


Figure 4.3. Mean EEG time frequency data from electrode Fcz across all time epochs for both con and uncon trials. All data is normalized to a baseline period prior to the ready cue. The black dotted box represents the window used for analysis of theta band activity (4-8 Hz). The vertical black line represents the zero point of the epoch, which either represents the timing of a cue (ready, go) or the onset of a behavioral event (reaction time, contact, lift).

We found that RT was longer for *uncon* than *con* trials (main effect of Grasp: $F_{(1,42)} = 14.17$, $p < 0.05$), and was not sensitive to block type (no *Grasp* × *Block* interaction: $F_{(1,42)} = 0.778$,

$p > 0.05$) (Fig 4.4a). Subsequent EEG analysis of the RT epoch revealed that medial frontal θ activity was not significantly different for grasp type ($F_{(1,1168.73)} = 0.521$, $p = .471$), but did demonstrate an overall main effect of RT at this time epoch ($F_{(1,48.773)} = 12.79$, $p = .001$) (Fig 4b,c). The significant difference in medial frontal θ activity to changes in RT without specificity to the grasp type likely indicates the general positive relationship of RT to medial frontal θ activity, but without a grasp type interaction. This was confirmed by correlating frontal θ and RT data, reporting a significant positive correlation for both *uncon* ($r = 0.655$, $p < .001$) and *con* ($r = 0.512$, $p = .01$).

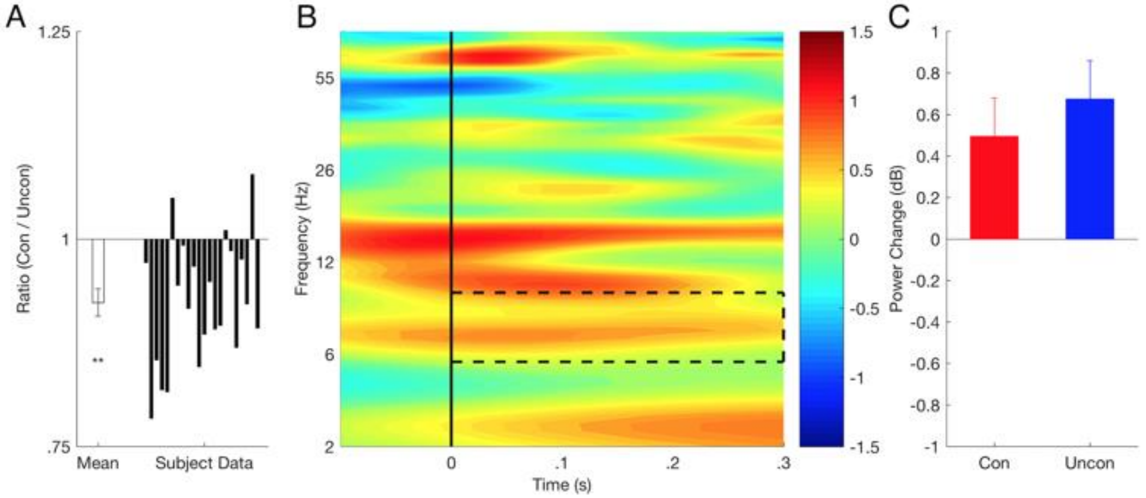


Figure 4.4. Mean reaction time and EEG data at the reaction time epoch for electrode Fcz. A. Individual subject and mean ratio reaction time data (Con / Uncon). Ratio used for graphical purposes and not used for statistical analyses. B. Difference map (Uncon - Con) of time frequency data for electrode Fcz. The black vertical line at time zero represents the time when the hand left the reach switch, cueing reaction time. The black dotted box represents the window used for analysis of theta band activity (4-8 Hz). C. Estimated marginal means for mean power in the theta band for Con and Uncon trials, as generated via the mixed model analysis.

We used a drift diffusion model (DDM) to further assess the relation between medial frontal θ activity and RT. The DDM model provided a more in-depth analysis of the RT data in that it allowed us to assess the distribution of RT values characterized by standard deviations and skewness (Ratcliff, 1978; Ratcliff & McKoon, 2008; Voss et al., 2013) (Fig 4.5a). While we selected this analysis a priori due to its utility in analyzing reaction time data, the decision was also supported by the data in that we found a significantly larger standard deviation of RT values during *uncon* versus *con* trials (main effect of *Grasp*: $F_{(1,42)} = 30.22$, $p < 0.05$), regardless of block type (no significant *Block* × *Grasp:* $F_{(1,42)} = 0.169$, $p > 0.05$). In addition, an analysis of the RT distributions themselves demonstrated differences in the mean (main effect of *Grasp*: $F_{(1,21)} = 21.17$, $p < 0.05$) and standard deviation (main effect of *Grasp*: $F_{(1,42)} = 9.148$, $p < 0.05$) for *con* and *uncon* trials.

Because the HDDM package uses Bayesian estimation, we were able to directly compare the posterior distributions from the DDM model, namely drift rate and separation threshold. Results from models with the two lowest DIC values (see Methods) demonstrated that medial frontal θ activity predicted different separation thresholds and drift rates values for *con* versus *uncon* grasp types. Overall, we found that there was a 98.47% chance that the drift rate was larger for the *con* context and a 98.26% chance that separation threshold was larger in the *uncon* grasp context, (see Fig 4.5b and 4.5c, respectively). Because these differences are based on the distribution of beta coefficients generated by the DDM model, this suggested that the relationship between medial frontal θ activity and RT was significantly different for *con* versus *uncon* grasping (Fig 4.5b,c).

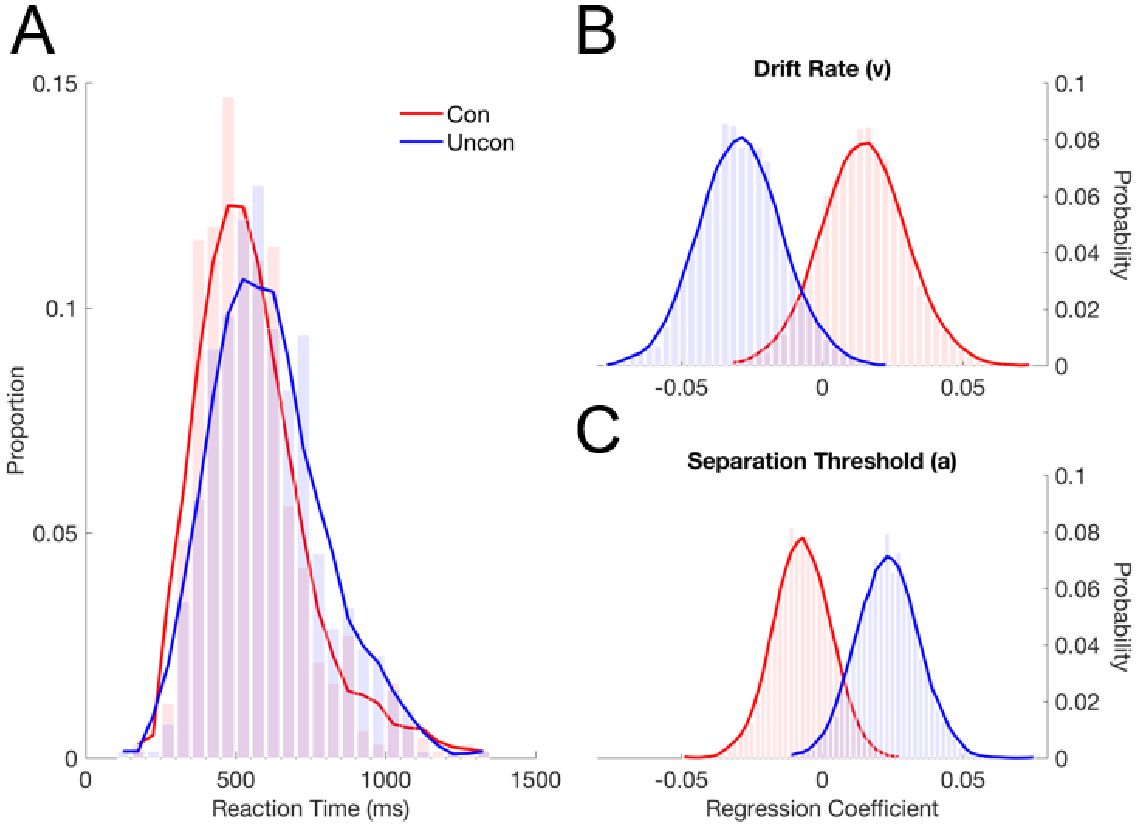


Figure 4.5. Reaction time distributions and Drift Diffusion Model results. A. Reaction time distributions for all trials across all subjects for uncon and con trials. B and C. Distribution of beta coefficients for drift rate (B) and separation thresholds (C) for modeling how medial frontal theta data predicts reaction time for con and uncon grasp types.

Lastly, we were interested in whether medial frontal θ activity during planning would link to behavior during the execution phase. To do this, we assessed the correlation of mean d_y variability and medial frontal θ during the RT epoch, demonstrating a significant positive correlation for the *uncon* (r = 0.4716, p = .027), but not *con* (r = -0.158, p > .05) grasp context. We performed a similar analysis for the mean values of all grasp variables used to calculate T_{com}, including d_y, d_{LF}, and F_{GF}. However, we report no other significant correlations, likely due to the fact that our experimental protocol fixed position and force variables for both grasp contexts.

The role of sensorimotor beta activity during movement planning and execution

We assessed sensorimotor β activity over C3 (Figure C.1), hypothesizing that the underlying sensorimotor requirements required for *uncon* versus *con* grasping would reflect unique activity over this region. This is due to the previously reported modulation of sensorimotor β in response to uncertainty in feedforward estimations for upcoming sensorimotor events (Saleh et al., 2010; Tan et al., 2013). Overall we found that grasp- dependent activity over C3 began to differentiate during movement preparation, at the time of the 'go' epoch ($F_{(1,1165.82)} = 7.157$, $p = .001$). This difference in sensorimotor β power remained until the lift onset ($F_{(1,1161.38)} = 6.955$, $p = .008$), indicating grasp-context specific modulation of EEG power in this frequency band over sensorimotor regions during both planning and execution phases (Fig 4.6). In addition, we found a main effect of RT during these epochs as well (all comparisons, p < .012), with the exception of contact (p = .137). This suggests that EEG power modulation in beta power is sensitive to both grasp type and RT.

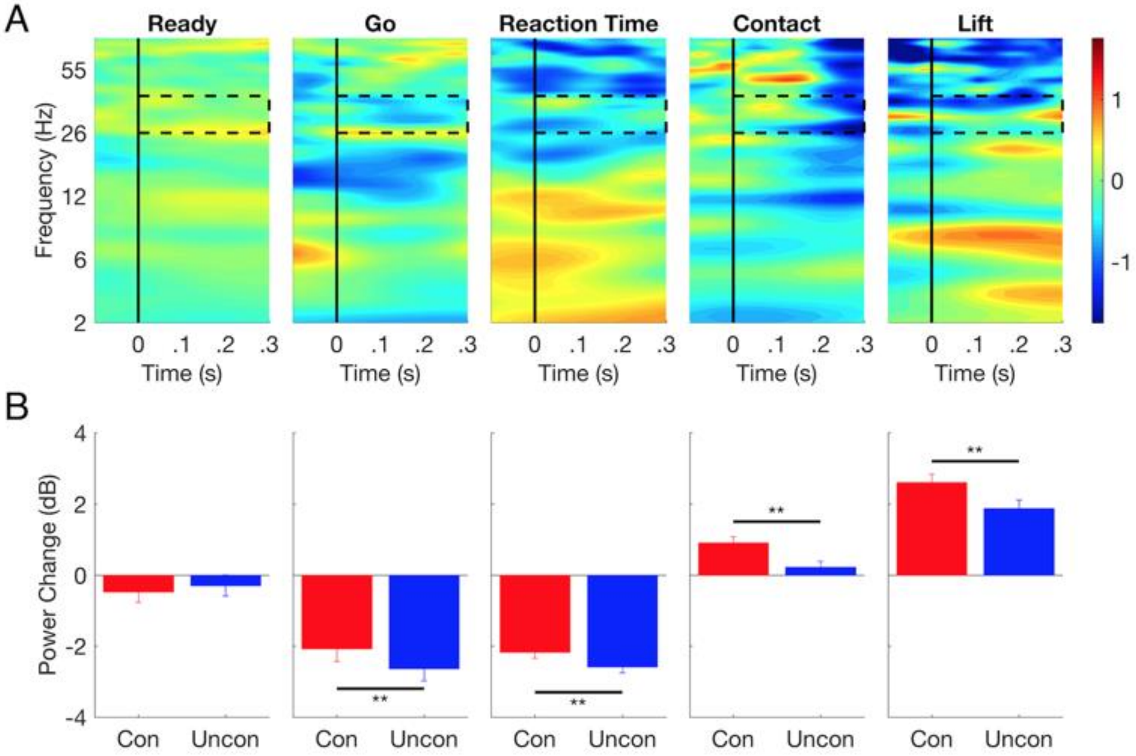


Figure 4.6. EEG data for electrode C3 for all epochs. Difference maps (Uncon minus Con) of time frequency data for electrode C3. Uncon and Con time frequency data are normalized to a baseline period prior to the ready cue. The black dotted box represents the window used for analysis of beta band activity (17-28 Hz). The vertical black line represents the zero point of the epoch, which either represents the timing of a cue (ready, go) or a temporal moment when a behavioral event occurred (reaction time, contact, lift). B. Estimated marginal means for mean power in the beta band for Con and Uncon trials, as generated via the mixed model analysis.

DISCUSSION

In our experiment, we used EEG to explore the neural mechanisms underlying grasp and manipulation across contexts utilizing unique sensorimotor requirements. Overall, we report distinct cortical activation over frontal and sensorimotor regions during both planning and execution. This suggests that rather than implementing a default motor plan that is insensitive to the sensorimotor requirements of the upcoming action, the nervous system prepares for each grasp context differently to accommodate distinct sensorimotor requirements required during the execution phase. Previous work from our lab (refer to Chapters 1,3) has shown that sensory feedback occurring at and following object contact drives force control based on feedback of digit position or memory in unconstrained or constrained grasping, respectively. Here we expand on this work by demonstrating, for the first time, that during movement preparation the brain also demonstrates context-dependent modulations based on the upcoming requirements of memory versus feedback control.

Sensorimotor Mechanisms Underlying Grasp and Manipulation

Neural mechanisms related to hand control have been previously studied, demonstrating that differences during simple thumb abduction and more complex tool use (Wheaton et al., 2005), as well as when planning for a reach-to-grasp task (Bozzacchi et al., 2012) to grasp a small (precision) or large (whole hand) sphere (De Sanctis et al., 2013). However, while previous work has outlined the spatio-temporal properties of cortical activation related to object grasping, this work has focused on different grasp types (e.g. whole hand grasp versus precision grasp). This leaves an open question as to the neural mechanisms underlying grasp and manipulation requiring more subtle differences in performance across repeated lifts. For example, in daily life we often are not tasked with utilizing discrete hand shapes, but rather are required to perform a similar task in somewhat different contexts. This may include changes in task goal (e.g. picking up a glass to hand over or drink from), or due to varying consistency in where the hand contacts the object across repeated lifts.

Consideration to more subtle features of object grasp has led to subsequent work investigating planning-related cortical changes in brain activity in response to different action goals. For example, Westerholtz and colleagues used trial cues to indicate either grasp orientation on the object or final location for the object to be moved to. Here the planning component focused either on the immediate goal or final task goal (Westerholtz et al., 2013). In this context, both the preparation and execution of a power grasp via these unique goal indicators were found to be controlled by distinct temporal patterns of activity over fronto-parietal regions. Van Shie and colleagues generated similar results when cueing immediate and final action during precision and power grasping (van Shie et al., 2007). Together, this work highlights the brain’s sensitivity to goal-directed features of object grasping. However, these results remain unable to clarify how changes in hand posture and orientation interact with planning-related activity for the completion of action goals. This is a critical gap, as object size, shape, and type have been shown to modulate neural activity during a reach to grasp task (de Sanctis et al., 2013). Our novel design, requiring similar grasp parameters for digit placement and force generation, isolates changes in brain dynamics to sensorimotor control mechanisms underlying these shared goals.

Feedforward Estimation and Frontal Theta Modulation

Much of the previous work mentioned above explored the general role of fronto-parietal regions with regard to movement planning and execution. The inclusion of parietal regions is likely due to its noted role in the grasp network (Ehrsson et al., 2000, 2001; Kutz-Buschbeck et al., 2001) for encoding an accurate representation of a given object during goal-directed action (Taira et al., 1990; Fagg and Arbib, 1998; Anderson et al., 1997), based on properties such as object location, shape, and orientation. In contrast, our analysis opted to focus on modulations in medial frontal θ. As our task required similar reach and grasp components, but unique components underlying control mechanisms, we argue that successful performance would require unique processing to prepare the appropriate memory-based versus flexible motor plan. These two control mechanisms are largely distinct due to their level of certainty in feedforward estimations, a property shown to modulate medial frontal θ activity in a variety of motor and cognitive tasks (for review see Cavanagh and Frank, 2014; Cavanagh and Shackman, 2015). These include error monitoring (van de Vijver et al., 2011), random dot motion task (Dmochowski and Norcia, 2015), working memory, (Jensen and Tesche, 2002; Jacobs et al., 2006), and conflict (Zavala et al., 2016). More generally, increased online control during a grasping task has also been shown to induce larger activity in frontal regions (de Sanctis et al., 2013). Based on this role of medial frontal θ with regard to feedforward estimations and online control, we speculated that activity in this frequency band would be sensitive to planning in a *con* versus *uncon* grasp context. Our hypothesis turned out to be correct, as we found larger medial frontal θ activity when grasping in an *uncon* context, that of which has more uncertainty during the movement execution phase due to across-trial variability in digit placement (Fu et al., 2010; Mojtajedi et al., 2015).

We further supported our hypothesis that the movement preparation phase is sensitive to certainty in feedforward estimations by comparing reaction time (RT) across grasp contexts, as the latency of motor responses have been linked to the degree of uncertainty (Pellizzer and Hedges, 2003; Churchland et al., 2008; Tzargarkis et al., 2010). While noting that uncertainty in the context of our task is quite different from that addressed by previous work, our findings were similar in that RT values were consistently larger in a grasp context requiring increased weighting on feedback control during movement execution (Mojtahedi et al., 2015). This expands the consideration of uncertainty beyond the number of possible reach targets or directions in visual space (Tzargarkis et al., 2010), and suggests that uncertainty may also be associated with more subtle aspects of control. Specifically, in our experiment, increases in RT occurred given the same object properties and location, with the only difference being the specified region size for digit placement on the object's graspable surfaces.

Lastly, the results of our drift diffusion model further support the presence of unique context-dependent planning during movement preparation, aligning with previous work demonstrating that changes in available sensory evidence influences medial frontal θ modulations and subsequently influences time to movement onset (Cisek, 2007; Cavanagh and Frank, 2014). Specifically, when grasping in a context allowing increased weighting on previously-learned information, less information is required prior to movement execution due to strong reliance on previously learned and stored information (Jenmalm and R. S. Johansson, 1997; Gordon et al., 1993; Johansson and Westling, 1988). In contrast, a longer preparation phase for the *uncon* context is due to the need for more information prior to movement onset, perhaps due to the need to prepare for increased weighting on real-time control during execution. This transition from feedforward to feedback control may increase cognitive load, and subsequently increase cognitive processing time (Ratcliff et al. 2003; Smith & Ratcliff 2004), that of which is supported by our differences in separation threshold (Fig 4.5).

One unexpected result of our experiment was the finding that medial frontal θ power was not sensitive to grasp type (see Fig 4.4). Nevertheless, the drift diffusion model allowed us to clarify the relation between medial frontal θ, RT, and grasp type. Thus, we speculated that the lack of sensitivity of medial frontal θ power to grasp type may be due to the sensitivity of medial frontal θ power to task difficulty or performance error, but less so to behavioral adjustments required for successful task performance (Chase et al., 2010). In our experiment, this would suggest that frontal regions recognize the need for changes in the action plan based on the required grasp context, but in turn may be less involved in implementing the underlying changes to the motor plan. This may be supported via our finding that the only time epoch where we report distinguishable (albeit non-statistically significant) medial frontal θ activity is the RT epoch. Frontal regions may thus serve to signal the time with which sufficient information is available to initiate movement, and communicate with other cortical and subcortical regions to coordinate the required preparation.

Relating Brain Activity to Behavior - Beta Modulations over Sensorimotor Regions

To better understand how the nervous system prepares for a task requiring unique sensorimotor requirements, we also investigated activity over contralateral sensorimotor regions via the C3 electrode. Beta modulations over sensorimotor regions during object grasp and manipulation have been linked to many different motor and cognitive factors (Tzargarkis et al., 2010; Zaepfel et al., 2013; Jenkinson and Brown, 2011). In addition, sensorimotor regions have been shown to be crucial for object grasp and manipulation (Cattaneo et al., 2005; Nowak et al., 2010; Prabhu et al., 2007; Loh et al., 2010). Our findings align with previous work in that we saw event related β desynchronization during movement preparation (Pfurtscheller and Lopes da Silva, 1999), with peak modulations occurring at the time of the cue signaling task requirements (Saleh et al., 2010). Namely, we see the largest decrease in β power at the time of the GO cue, the cue which informs what grasp type is required for that trial.

We observed a shift from β desynchronization to synchronization across trial epochs, a transition previously reported between the planning and execution phases of a motor task (Zaepffel et al., 2013). Increases in planning-related desynchronization and subsequent post-movement β synchronization (PMBS) have been shown to have a link to certainty in feedforward estimations (Knill and Pouget, 2004; Todorov, 2004; Faisal et al., 2008; Tzargarkis et al., 2010; Tan et al., 2016). Our findings align with previously reported changes in that PMBS is larger for *con,* suggesting more certainty in feedforward estimations in this grasp context (Tan et al., 2016). We note that the timing of β synchronization in our task is not post-movement, but rather begins during execution. However, β synchronization has also been reported during the holding phase of a motor task (Baker et al., 2007; Sanes and Donoghue, 1993), supporting the presence of this phenomenon during movement execution.

We believe that the presence of β synchronization over sensorimotor regions during movement execution in our task elucidates a gap concerning the behavioral mechanisms inducing this modulation in β power. Despite PMBS being inversely correlated with uncertainty in feedforward estimations, it has been linked to tasks which either 1) induce a perturbation during task execution (Tan et al., 2016), or utilize a scenario where uncertainty remains in place only until the moment of the cue to initiate movement is shown, for example when showing a number of targets and then illuminating only one as the final target (Tzargarkis et al., 2010). Here we provide a model of β modulation that is more generalizable to common motor tasks, that is: not only does the object shape, size, orientation remain the same, but uncertainty in feedforward estimations remains present through task performance without change in the task goal or unexpected perturbation. Perhaps more importantly, we demonstrate for the first time how β modulation changes as a function of task performance, rather than only during movement onset or termination. In fact, the shift from desynchronization to synchronization we see during movement execution may be informative of how and when sensorimotor information is used and updated on a trial-to-trial basis.

The fact that we see significant differences during planning suggests that preparing for a motor task characterized by certainty in feedforward estimation entails a unique motor plan than simply retrieving the previously-learned motor plan. Subsequently, the sustained differences during the execution phase support that the motor system is likely incorporating varying degrees of online control to ensure successful task performance. If these differences were simply due to response competition (Michelet and Cisek, 2010) or differences in decision-making (Jacobs et al., 2006) we would expect that similar activity would be present at the time of movement onset. However, differences during the execution phases suggest that differences during planning were linked to specific preparatory processes, and not due to the spatial layout of the LEDs for large and small boundaries at the time of the go cue.

Conclusions and Future Work

The results of our work utilize behavioral and neural data to elucidate the role of grasp-dependent brain dynamics underlying the planning of a grasp and manipulation task, and for the first time demonstrates that the nervous system prepares for an object manipulation task requiring unique sensorimotor requirements prior to movement initiation. In addition, we demonstrate that modulations in β activity over sensorimotor regions are sensitive to uncertainty in sensory predictions during both the movement preparation and execution phases.

While we chose to use two grasp types to distinguish the underlying sensorimotor control mechanisms during object grasp and manipulation, future work should examine ways to modulate uncertainty with regard to feedforward estimations in a more controlled way to explore a link between planning and the relative uncertainty in digit placement. This will allow us to assess whether differences in medial frontal θ and sensorimotor β modulations are due to the more general properties of memory-driven versus flexible control, or whether the brain scales activity when the extent of uncertainty in digit placement is modulated in steps, as has been shown in previous work in non-grasping tasks (Tzargarkis et al., 2010).

More broadly, future work will also explore how the nervous system stores task-relevant information for memory-driven versus more flexible, online control. Previous reports suggest that sensory information is used to specify representations of action selection (Cisek 2006, 2007). In our context, this raises a critical question as to whether the brain stores different representations based on the required weighting of feedforward and feedback control mechanisms, or rather a more centralized internal representation for a given task regardless such requirements. This question addresses whether the nervous system stores goal-related high-level information related to a given task, e.g. required torque to prevent object rotation at the time of object lift-off that may be independent of the end effectors or sensory requirements (Grafton et al., 1998; Rijintes et al., 1999; Wing 2000), or rather stores unique representations for similar tasks (Ingram et al., 2010). The fact that movement onset occurs later in the *uncon* grasp context suggests that despite the need for additional feedback during movement execution, the motor system still prepares for this task in a way that differs from simply retrieving the previously-learned sensorimotor memory to implement the motor plan. However, these results cannot determine whether these temporal differences occur due to information retrieval from a unique stored representation versus preparing for a motor task based on a shared representation of the task goal.

CHAPTER 5

SUMMARY AND CONCLUSIONS

SUMMARY OF MAIN FINDINGS

To date, the human cortical networks representing grasp control have been defined primarily based on research addressing digit position *or* force control, while neglecting the control mechanisms underlying the coordination of these two variables – a phenomenon we refer to as *digit force-to-position modulation* (*Chapter 1*). The overarching goal of this dissertation was to address this gap by assessing the extent to which choice of contact points may involve different neural mechanisms relative to grasping at constrained contacts. This work was designed to improve the understanding of how the brain mediates the ability to grasp and manipulate objects by using an experimental task that shares features with those encountered in activities of daily living.

The advent of non-invasive recording and neuromodulation has enabled a more detailed study of the role of M1 during the preparation phase of more complex hand movements in humans (e.g., Cattaneo et al., 2005; Prabhu et al., 2007; Loh et al., 2010; Kutz-Buschbeck et al., 2001). However, despite the insight provided by these studies, this work was not designed to discriminate planning of digit forces from planning of digit forces (Nowak et al., 2005; Chouinard et al., 2005) *and* position (Classen et al., 1998; Lawrence and Kuypers, 1968; Fogassi et al., 2001; Muir and Lemon, 1983; Lang and Schieber, 2004). This is a critical gap, given the hand muscle representations in M1 are active both during hand opening/closing during the reach leading to positioning of the fingers on the object, as well as exerting forces after contact. Experiment 1 (*Chapter 2*) addressed this gap by exploring whether planning-related changes in M1 were linked specifically to force planning in a context where digit placement was controlled for. The results of this work demonstrated that force planning-related modulation of corticospinal excitability (CSE), quantified via motor evoked potentials (MEPs), occurs much earlier than object contact (i.e., at reach onset) and is sensitive to the magnitude of force production. In addition, these changes in CSE did not result in modulation of M1 intracortical inhibitory and facilitatory circuitry, suggesting that planning of digit forces appears to be driven by inputs from fronto-parietal areas other than M1.

Besides grasping objects at constrained contacts (*Chapter 2*), often humans choose where to grasp an object based on a variety of factors, including implicit knowledge of object's properties and task requirements – we have referred to this type of grasping as *unconstrained*. However, the vast majority of previous work on manipulation has focused on an experimental model that requires subjects to grasp objects at predetermined contacts – *constrained* grasping. This grasp context allows the use of sensorimotor memories (Johansson and Westling (1988a) to generate digit forces in an anticipatory manner (Johansson et al., 1984, 1988; Gordon et al., 1991; Salimi et al., 2000) across repeated lifts with the same object. The extent to which neural mechanisms identified for constrained grasping may be involved with unconstrained grasping remained to be determined. In particular, previous work from the Santello laboratory had proposed that feedback of digit placement would play a greater role in unconstrained than constrained grasping to modulated digit forces to compensate – on a trial-to-trial basis – for digit position variability (Fu et al. 2010).

Experiment 2 (*Chapter 3*) was designed to determine the role of M1 for both planning and execution of digit placement, as well as the coordination of position *and* force variables during object grasp and manipulation. Specifically, we asked subject to perform either constrained or unconstrained grasping, and compared grasp execution pre- versus post continuous theta burst stimulation to M1. The inclusion of a grasp context requiring additional feedback control mechanisms (unconstrained grasping) also prompted the study of primary somatosensory cortex (S1), a novel addition to previous work examining the role of cortical mechanisms underlying object grasp and manipulation. The results of this experiment confirmed the role of M1 in the retrieval of previously learned digit forces, but also identified a novel role of M1 and S1 for digit force-to-position modulation.

Based on the fact that M1 is sensitive to both force planning and the larger context-dependent interactions of M1 and S1 to enable successful performance, the goal of Experiment 3

(*Chapter 4*) was to tie these two studies together to further address the neural mechanisms underlying object grasp and manipulation. This was done by using electroencephalography (EEG) to record real-time brain dynamics during the planning and execution phases of unconstrained grasping.

Experiment 3 is the first study to reveal differences at the planning level between constrained and unconstrained grasping. While previous work has shown that the grasp network is sensitive to planning grasps requiring different hand shapes (Cattaneo et al., 2005; Prabhu et al., 2007; van Shie et al., 2007; Westerholtz et al., 2013) and forces (Ehrsson et al., 2001; Kutz-Buschbeck et al., 2001; Jenmalm et al., 2006), the results of Experiment 3 revealed that cortical activation is modulated to sensorimotor requirements, rather than individual differences in these grasp-related components.

The results of Experiment 3 (*Chapter 4*) provide, for the first time, evidence to support differences in sensorimotor control of object grasp and manipulation at the planning level, demonstrating modulation in medial frontal theta and beta cortical oscillations over frontal and sensorimotor regions, respectively. These findings provide insight into not only about how the cortical grasp network differentially reflects different grasp contexts (memory- vs. feedback based digit force control), but more generally how the brain prepares and executes tasks with varying certainty in feedforward estimation. Lastly, and perhaps most importantly, these results demonstrate that modulation during movement planning reflects subsequent task parameters during both movement initiation and execution.

SYNTHESIS AND INTERPRETATION OF RESULTS FROM ALL STUDIES

While the results of each study provide novel information about the cortical mechanisms underlying object grasp and manipulation within their own context and constraints of the experimental design, this section attempts to discuss all findings within a unified framework.

Planning. Planning-related changes in brain activity were found through two different approaches: CSE and EEG. Despite significant differences in experimental setups (TMS vs. EEG) and experimental protocols (planning force of different magnitudes vs. grasping at constrained or unconstrained contacts), we report two commonalities in the evidence for grasp planning-related modulation of brain activity. First, the motor system starts to take into account upcoming grasp requirements (*force magnitude* and *grasp-specific motor processes*, respectively) before movement onset, as indicated by modulation of CSE and EEG beta power occurring over sensorimotor regions (M1 and M1/S1, respectively). Second, we found evidence for a gating mechanism mediating release of a motor plan, as indicated by a difference in CSE or theta activity from baseline, both starting at the time of the "Go" cue and continuing until movement onset. In both experiments, the moment of the "Go" cue was important because it was a predictable indicator signaling movement initiation, i.e., ".. when visuomotor inputs had their greatest anticipatory influence on M1" (Prabhu et al., 2007; see Chapter 2). In *Experiment 1*, this gating mechanism was associated with a decrease in CSE (see Figure 2.2a,b) before movement onset and is consistent with previous literature (Duque et al., 2012; Hasbroueq et al., 1997; Touge et al., 1998). Furthermore, paired-pulse results (no differences in SICI or ICF) indicate that the inhibitory influence to M1 originated from other cortical site(s), rather than within M1. In *Experiment 3,* this gating mechanism was associated with an increase in theta power over frontal regions (see Figure 4.3). This activity has been shown to encode information related to the task requirements (Botvinick et al., 2001; Shenhav et al., 2013), signaling when appropriate information is available and subsequently organizing the flow of task-related information to complete a motor task (Lopes da Silva, 2013; Cohen, 2014).

It is worth speculating that the gating mechanisms occurring - the suppression of CSE and increases in theta power- underlying both Experiments 1 and 3, respectively, may reflect a similar mechanism. The 'motor braking' process to prevent premature movement onset, manifesting as a suppression of MEPs (Prabhu et al. 2007; Prut and Fetz 1999), has been previously explored by Duque and colleagues, who used TMS to investigate the role of dorsal premotor cortex and prefrontal regions in top-down control of M1 (Duque et al., 2012). In the EEG literature, increases in theta power over these same prefrontal regions appear to be involved with signaling movement initiation based on the upcoming grasp context (Lopes da Silva, 2013). Given that the reported increases in theta in our experiment is located in the same cortical region as that probed by Duque and colleagues (i.e. (pre)frontal regions), we note the possibility that theta modulations may be signaling the release of the motor plan in both Experiments 1 and 3.

Previous work has identified theta modulations as a low-frequency carrier of information, facilitating transmission of information across cortical and subcortical regions (Lopes da Silva, 2013; Cohen, 2014). As the results of the paired pulse experiment in Experiment 1 suggest that information concerning digit force planning is likely sent to M1 from other region(s) of brain, and only arrives to M1 just before movement onset (Cattaneo et al., 2005; Prabhu et al., 2007), the presence of theta modulation at the time of the "Go" cue could be interpreted as a mechanism influencing M1 excitability. Specifically, theta modulation over frontal regions may serve to directly release inhibition on M1. It may also facilitate the transmission of the motor plan to M1, or mediate this process through another region via phase or cross frequency coupling (Cohen, 2014). While it is possible that frontal regions send task-related information (e.g. force plan) to M1, the fact that we see similar changes in theta power in Experiment 3 when subjects plan for similar forces and torques suggests that task-related information is likely coming from another region of brain, whereas frontal regions may function as a more high-level gating mechanism that is insensitive to the specific force and/or position requirements of the task.

Together, the results of Experiments 1 and 3 demonstrate task-related changes in the brain during movement preparation. One notable difference we do report that places our Experiments 1 and 3 data at odds is the direction of change in the CSE and beta power data. While in both experiments we see planning-related differences, we find a decrease in both CSE and beta power (i.e. increase in beta desynchronization). Previous literature suggests that decreases in CSE represent suppression of M1 activity, while increases in beta desynchronization represent a shift toward increased M1 activity (Tzargarkis et al., 2010; Pfurscheller and Lopes da Silva, 1999). In addition, TMS-EEG experiments have demonstrated a positive relation between beta desynchronization and MEP size (Aono et al., 2013; Rau et al., 2003; Takemi et al., 2013). We do note that these studies assessed MEP size and beta desynchronization during *imagined movements* of the wrist (Takemi et al., 2013) or whole-hand (Aono et al., 2013) as well as self-paced finger movements (Rau et al., 2003). Thus, due to the use of different tasks and protocols, we cannot determine the reason for the discrepancy between our results and previous work. Similarly, our tasks in Experiments 1 and 3 are also different, which could perhaps lead to the unique planning-related changes we report (see Chapter 2).

More generally, we also note the challenge in comparing changes in CSE and EEG modulation. From a timing perspective, it has already been noted above that CSE probed excitability of cortex at a finite time point, whereas EEG probed a predetermined window of time. Specifically, CSE was probed at a discrete time point, while changes in both beta and theta power were reported as the mean power over a 300 ms window. In addition, from an anatomical standpoint it is also possible that EEG recordings and CSE may represent different activity in brain. While EEG represents a summation of post-synaptic activity from a large population of neurons under a given electrode, CSE quantifies the excitability of only those neurons projecting to the target muscle (Takemi et al., 2013). Thus, the probed activity from each of these populations may differ based on the neurons sampled using EEG and TMS. This, combined with the fact that we also compared our MEP and EEG data to two different baseline times, i.e. after and before a trial, respectively, may also explain the differences in reported activity over M1 during movement preparation in each of these two experiments.

A conclusive way to assess whether changes in CSE and EEG modulations align would be to repeat Experiment 1, but we would also record EEG activity in addition to using TMS. This would enable a thorough investigation into the relationship between CSE suppression and beta/theta modulations during movement preparation within a given grasp task.

Execution. While cTBS identified a dissociation of the functional roles of M1 and S1, it was perhaps less informative with regard to the temporal dynamics of the reported behavioral disruptions to position and force processing (see Chapter 3), i.e. whether these disruptions affected mostly grasp execution, or both planning and execution. However, the finding that planning-related neural activity modulation is influenced by areas connecting to M1 (Experiment 1) may suggest that execution, rather than planning-related processes, were directly affected by cTBS. This speculation is also supported by the known effects of cTBS on neural activity, which are associated with greater GABA concentration and intracortical inhibition within M1 (Stagg et al., 2009). In addition, to date no reports we are aware of demonstrate cTBS over M1 affecting activity over other brain regions connected to M1. Thus, if position and force motor planning originate in brain regions outside of M1, this plan is likely intact during planning since regions with strong cortico-cortical connections to M1 have not been shown to be affected after cTBS over M1. Therefore, we conclude that grasp planning occurring in areas other than M1 should be intact following cTBS to M1, but it may not be further incorporated within M1 and at the time of motor plan release at movement onset due to the above-described effects of cTBS on M1.

The interpretation of cTBS affecting mostly grasp execution rather than planning is further supported by our Experiment 2 data demonstrating that regardless of grasp context, subjects were unable to retrieve stored digit forces and/or position after cTBS over M1. Moreover, our S1 cTBS condition suggests that this region is important for feedback-driven modulation of digit forces based on current digit placement. This suggests that feedback processing occurs correctly when S1 is intact, but the updated force plan cannot be implemented by M1. Support for the notion of digit position and force information being encoded in other brain regions and then sent to M1 is consistent with previous literature on the roles of premotor and parietal regions in preparing and executing grasp motor-related parameters and their known inputs to M1 (see below).

cTBS effects on EEG. EEG results from Experiment 3 demonstrated that decreases in beta power and increases in theta power occur when preparing and executing a grasp and manipulation task. Given that the same tasks were used in Experiments 2 and 3, the question arises as to whether the EEG results from Experiment 3 could explain the cTBS-induced behavioral changes found in Experiment 2. Previous literature exploring cTBS-induced effects on neural oscillation frequencies has reported that cTBS results in an increase in beta power and a decrease in theta power over electrode C3 (Vernet et al., 2013), the same electrode we used to measure beta power in Experiment 3. As we found beta desynchronization during movement preparation in our task, we may speculate that the beta synchronization reported by Vernet and colleagues in response to cTBS explains, at least to some extent, the behavioral disruption we see in Experiment 2. The changes to theta modulations cannot be discussed here, as we were unable to find literature assessing changes in theta power over electrode Fcz before and after cTBS.

It is worth noting that other groups have reported somewhat different EEG-induced effects of cTBS, suggesting some variability in EEG-induced changes after cTBS. For example, McCallister and colleagues reported no significant changes within any frequency band (beta, alpha, theta, delta) following cTBS (McCallister et al., 2011), and Noh and colleagues reported a similar increase in beta power to that found by Vernet and colleagues, but no changes in theta power (Noh et al., 2012). These groups report that their differences may be due to the timing after cTBS when EEG modulations were analyzed, as well as the context with which testing was done (refer to Vernet et al. 2013 for details). One additional caveat to these comparisons is that EEG changes were being reported during rest (Vernet et al., 2013; McCallister et al., 2011; Noh et al., 2012), not during motor preparation. Thus, while these aforementioned findings (Vernet et al., 2013; McCallister et al., 2011; Noh et al., 2012) serve to provide some insight in to our results in Experiments 2 and 3, caution should be observed in using these findings to interpret our results.

Overall, the above results obtained from Experiments 1-3, utilizing EEG and TMS, together demonstrate a grasp context-dependent role of both sensorimotor (M1, S1) and frontal regions during the planning and execution of skilled object manipulation. More generally, these results highlight the value of examining the coordination of both position and force components during object grasp and manipulation, a phenomenon critical for performing dexterous manipulation tasks that share features with hand-object interactions performed in activities of daily living. This information has led to a new and more comprehensive theoretical framework of neural mechanisms underlying the control of dexterous manipulation (Figure 3.6). At the same time, our findings open new questions and lay the foundation for new research directions.

INVESTIGATING OTHER NODES OF THE GRASP NETWORK UNDERLYING REACH-TO-GRASP

While M1, S1, and frontal regions all play an important role in digit force-to-position coordination, it is likely that additional regions of brain are involved. This is supported by both monkey (Rizzolatti et al., 1988; Murata et al., 1997; Castiello, 2005; Umilta et al., 2007) and human studies (Jeannerod et al., 1995; Lemon et al., 1995; for review see Chouinard and Paus, 2010), both of which suggest that movement planning and execution are mediated by a larger fronto-parietal network (Begliomini et al., 2007b; Ehrsson et al., 2000; Ehrsson et al., 2001; Kutz-Buschbeck et al., 2001).

Ample evidence supports the role of parietal regions for encoding high-level information to form an accurate representation of a given object during goal-directed action (Taira et al., 1990; Fagg and Arbib, 1998; Anderson et al., 1997) as well as mediating sensorimotor transformations (Jeannerod, 1995). In the context of a task with a similar goal, but with unique sensorimotor requirements, the question arises as to whether parietal regions store goal-related high-level information related to a given task, e.g., required torque to prevent object rotation at the time of object lift-off. The storage of this information may be what enables the nervous system to properly modulate digit forces in response to variability in digit placement across repeated lifts, as well as to monitor and update the motor plan via the real-time comparison of observed versus expected sensorimotor events (Desmurget et al. 1999; Della-Magiorre et al. 2004; Vesia et al. 2006).

The potential role of parietal regions in the storage of high-level task goals, as well as enabling force-to-position, is also supported by the well-established role of this region for mediating activation of premotor regions (Grol et al., 2007; Rizzolatti and Luppini, 2001; Van Shie et al., 2007; Bozzachi et al., 2012; Westerholz et al., 2013) to aid in the *selection of digit placement (*Davare et al., 2010) *and corresponding force scaling* (Taubert et al., 2010). Functional imaging (Grafton et al., 1998; Ehrsson et al; 2000; Crelier et al., 2000) and transcranial magnetic stimulation studies (TMS; Davare et al., 2006, 2007, 2008) have revealed that the ventral premotor (PMv) region appears to encode information about visuomotor transformations required for proper orientation of the fingers during grasp planning (Davare et al., 2006, 2007, 2008) and the dorsal premotor region (PMd) appears to send inputs to M1 regarding proper scaling of digit forces Chouinard et al., 2005; Davare et al., 2006; Nowak et al., 2009; Taubert et al., 2010; Van Nuenen et al., 2012). A better understanding of how cortical regions beyond M1 and S1 interact to enable digit force-to-position coordination is essential to create a complete theoretical framework (top box, Fig 3.6).

In addition to cortical regions, future studies should also address interactions among subcortical structures for object manipulation. Cerebellum has been shown to be important for storing internal models shortly after learning (Shadmehr and Holcomb, 1997; Imamizu et al., 2000, 2003). The output of this forward model is sent to both parietal cortex and basal ganglia (Clower et al., 2004), to aid in processing of sensory feedback during task execution. Cerebellum may coordinate with parietal regions to retrieve stored high-level information and enable successful performance despite small changes/updates in the motor plan across repeated trials. These small changes in the motor plan, e.g., updating of digit forces in response to variability in digit placement, may be mediated by basal ganglia, which has been identified as being important for making corrective sub-movements in response to movement errors (Tunik et al., 2009). Activity related to corrective sub-movements tends to occur immediately prior to activity over M1 for initiation of a movement correction (Roy et al., 2003) during tasks utilizing novel dynamic (Tunik et al., 2009) and kinematic (Seidler and Chintalapati, 2006) perturbations, and is linked to both the timing and magnitude of movement corrections (Houk et al., 2007).

These basal gangia-M1 interactions may aid in the required updating of the force motor plan after contact and prior to lift onset in response to across-trial variability in digit placement. While it is important to note that updating the force motor plan is not triggered by an ‘error’ *per se*, the same neural structures could be involved in updating the motor plan due in response to trial-to-trial variability in digit position. This is supported by previous work demonstrating that anticipatory scaling of digit forces is aided by non-invasive stimulation over M1 in older adults (Parikh and Cole, 2015), a mechanism that perhaps serves to enhance processing between basal ganglia and M1 for updating the force motor plan.

Basal ganglia may also be involved in maintaining sensorimotor memories for digit placement, as patients who have damage to this region appear less able to recall previously used digit placement when performing an object grasp and manipulation task similar to that used in Experiments #2-3 (Lukos et al., 2010). These findings suggest a role for both basal ganglia and cerebellum in the retrieval of sensorimotor memories and the subsequent integration of sensory feedback during task execution.

CLINICAL APPLICATIONS

While Experiments 1-3 each provided new knowledge concerning the role of cortical regions for sensorimotor control during skilled manipulation, the results of these experiments also point to clinically-oriented applications.

Rehabilitation Robotics. Recent evidence in patients who have suffered a stroke and spinal cord injury suggests that rehabilitation robots may overly constrain joint motions, and may not be more effective than traditional types of movement therapies (Hidler et al., 2009). Our contribution in providing novel insight to the neural components of position-force coordination will help design novel therapies to focus on the specific needs of the patient. For example, it has been suggested that humans learn more when errors (Thoroughman and Shadmehr, 2000) or performance in general is more variable (Ziegler et al., 2010). New rehabilitation devices could model the trial-to-trial variability seen during natural object grasp and manipulation, inducing larger variability in kinematic task properties to train the patient's ability to adjust grasp forces. A robotic device could facilitate trial-and-error learning using different combinations of digits and corresponding digit placement to modulate this kinematic variability in a controlled way to best improve functional ability (Fu and Santello, in press).

Neuro-rehabilitation. Stroke is one of the leading causes of motor impairment in the United States and Europe (Oxford Journal of Neurology: Stroke, 2012; Nowak et al., 2009). Stroke affects functional connectivity within and between cortical regions. This can lead to a range of sensorimotor deficits that vary as a function of lesion onset, lesion size, and time post-stroke. Many patients, over time, experience a range of motor recovery, but currently the neurological mechanisms underlying this functional recovery are not well understood. To date, a leading hypothesis explaining sustained impairment is due to transcallosal inhibition, whereby greater inhibition on the ipsilesional hemisphere from the contralesional hemisphere prevents recovery in damaged regions of M1 (Lioumis et al., 2012). As changes in M1 excitability have been previously reported as a good prognostic sign (Delvaux et al., 2003; Trompetto et al., 2000), currently neuromodulation-based therapies target M1. This strategy promotes plasticity and functional recovery (Nudo et al., 1996). However, targeting other regions in the motor network, including bilateral premotor (O'Shea et al., 2007; Johansen-Berg et al., 2002) and parietal areas (Ward et al., 2003), may also serve as effective strategies to aid in functional recovery after neural injury by activating and strengthening connections critical for reaching and grasping. Greater understanding of the role of different regions of the grasping network, as addressed in the present work, may serve to improve the efficacy of these neuro-stimulation approaches.

Neural Prosthetics. Human case studies have shown that cortical cells can regain and maintain activation levels for prosthetic control, even after periods of immobility (e.g. locked-in syndrome; quadriplegia) (Kennedy et al., 2000; (Shoham et al., 2001). Thus, recording of cortical neurons has been considered for various prosthetic technology ever since the activation of cortical neurons prior to movement was demonstrated (Umilta et al., 2007). In general, brain machine interface (BMI) research has mainly focused on M1 recordings (Schwartz, 2004), likely due to extensive knowledge over M1's role in movement (e.g. velocity, direction and force) (Reina et al., 2001). More recently Aflafo et al., (2015) examined the role of posterior parietal cortex as a candidate for BMI application in a human patient with full paralysis. Findings demonstrated that the subject could exert control of single neurons by imagining simple movements. This is the first time that high-level motor intentions have been decoded from a region other than M1, and demonstrates the potential for other regions as reliable sources for BMI application. Signals may work independently of M1, but could also serve to complement M1 recording to optimize BMI control.

A better understanding of brain areas communicating with M1 for the control of digit position and force coordination - as outlined in this dissertation - could lead to advances in BMI control. Our new model outlining neural control of object grasp in a more natural context may assist in improving our understanding of when and where to extract neural signals from for BMI application. This has the potential for both speed of control and the ability to control more complex movements of a robotic limb. In addition, understanding the neural mechanisms of sensorimotor integration and control may serve to enable novel algorithms to enable similar ability in a BMI device. Feedback for prosthetic technology is an active area of research, and understanding how feedback is used to update the motor plan could help advance the use of feedback in prosthetic technology, affording better user control.

FINAL THOUGHTS

Previous research on the neural bases of hand control has focused on experimental designs that require subjects to grasp objects at predetermined locations, i.e., constrained grasp. Our more natural grasp model provides a more comprehensive understanding of the neural mechanisms mediating planning and control of object grasping and dexterous manipulation, and thus provides insight about the cortical circuitry involved in activities of daily living, such as self-feeding, buttoning-unbuttoning a shirt, and tool use. This new knowledge can potentially be used for clinical applications including brain-machine interfaces and rehabilitation robotics.

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APPENDIX A

IRB APPROVALS AND HUMAN SUBJECTS CONSENT FORMS

SUBJECT CONSENT FORM

Noninvasive brain-machine interfaces for upper extremities

SCHOOL OF BIOLOGICAL AND HEALTH SYSTEMS ENGINEERING: ARIZONA STATE UNIVERSITY

INTRODUCTION

The purposes of this form are to provide you (as a prospective research participant) information that may affect your decision as to whether or not to participate in this research and to record the consent of those who agree to be involved in the study.

RESEARCHERS

Marco Santello, Ph.D., (Professor, School of Biological and Health Systems Engineering), Justin M. Fine, Ph.D., (postdoctoral scholar, School of Biological and Health Systems Engineering)

STUDY PURPOSE

This study will investigate changes in brain activity patterns as you operate, see and feel a virtual hand being controlled by your brain waves. We will measure your brain waves and upper arm muscular activities using non-invasive (non-penetrating) methods during simple object grasping and lifting tasks with your own hand or a virtual/robotic hand. The robotic hand will be controlled (e.g., the opening and closing of its fingers) by your brain activity.

DESCRIPTION OF RESEARCH STUDY

You will be one of approximately 40 able-bodied healthy individuals to be asked to participate in this project. You will be asked to perform the following procedures at the Neural Control of Movement Laboratory, room 171 Physical Education Building East.

(As you read please check the boxes).
☐Procedure 1: Preparation stage (up to 60 minutes):

1. You will have your head fitted with an electroencephalogram (EEG) cap (similar to a swim cap) that will measure non-invasively the activity of your brain. The EEG cap may be filled with gel to ensure good contact.
2. Stickers will be placed above and below your eyes in order to record eye blinks, behind your ears to secure EEG electrodes, and also on your head to hold the headband.

3. Small vibrators (similar to those used in cell phones) may be fitted on your skin to provide a sense of the force applied to the object.

4. You will be shown grasping movements on the prosthetic/virtual hand, and will be asked to imagine yourself controlling these.
☐Procedure 2: Testing (up to 60 minutes):

1. You will be asked to sit in a chair.

2. Household objects (e.g., credit card, baseball, bottle, etc.) or instrumented objects equipped with force sensors (ATI) will be placed, one at the time, in front of you.

3. After presentation of each object, you will be allowed to freely reach for and grasp the object using the prosthetic/virtual hand.

4. During the session, brain (EEG) signals, the movement of your arm and the robotic hand, and the muscular (EMG) activity of your finger flexors and extensors will be continuously recorded. You will have the opportunity to see the robotic hand and the EEG and EMG sensors before signing this consent form. The experiments will require one to three sessions per week, for at least a period of four weeks. Your total time commitment may vary from 12 to 50 hours (a maximum of 25 sessions) depending on the number of sessions you participate.

RISKS

The procedures described above are widely used in research and are not known to be physically harmful to you. There are no known long-term effects associated with the tasks or events experienced during this study. You may experience a mild degree of physical discomfort due to the wearing of the EEG cap, fatigue, and the risk of allergy to the adhesive used in attaching the sensors.

BENEFITS

While you will not directly benefit from participation, your participation may help investigators better understand how the brain learns to control an assistive prosthetic hand and adapt to sensory feedback.

NEW INFORMATION

If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

CONFIDENTIALITY

Every effort will be made to maintain the confidentiality of your participation in this project. Each subject’s name will be paired with a code number by the principal investigator. This code number will appear on all written materials. The list pairing the subject’s name to the assigned code number will be kept separate from all research materials and will be available only to the principal investigator. Confidentiality will be maintained within legal limits.

WITHDRAWAL

You may choose to withdraw from the study at any time. If you do withdraw, then any data collected from you prior to your withdrawal will only be used under your verbal consent.

COMPENSATION

For this study, you may be monetarily compensated for your time in the study. If being provided monetary compensation, you will be given $10 for the full 2 Hr. session.

COMPENSATION FOR ILLNESS AND INJURY

If you consent to participate in the study, then your consent does not waive any of your legal rights. However, no funds have been set aside to compensate you in the event of an injury.

VOLUNTARY CONSENT

1. I understand that informed consent is required of all persons participating in this project.

2. All procedures have been explained to me and all my questions have been answered to my satisfaction.

3. Any risks and/or discomforts have been explained to me.

4. Any benefits have been explained to me.

5. I understand that any questions that I have concerning the research study or my participation in the research study, before or after my consent, will be answered by Marco Santello, Ph.D., Neural Control of Movement Laboratory, School of Biological and Health Systems Engineering, ECG334, at 480-965-8279.

I also understand that if I have questions about my rights as a subject/participant in this research, or if I feel I have been placed at risk, I can contact the Chair of the Human subjects Institutional Review Board, through the ASU Research Compliance Office, at 480-965-6788

6. I have been told that I may refuse to participate or to stop my participation in this project at any time before or during the project. I may also refuse to answer any question.

7. All information that is obtained in connection with this project and that can be identified with me will remain confidential as far as possible within legal limits. Information gained from this study that can be identified with me may be released to no one other than the principal investigator. The results may be published in scientific journals, professional publications, or educational presentations without identifying me by name.

8. This form explains the nature, demands, benefits and any risk of the project. By signing this form I agree knowingly to assume any risks involved. My participation is voluntary. I may choose not to participate or to withdraw my consent and discontinue participation at any time without penalty or loss of benefit. In signing this form, I am not waiving any legal claims, rights or remedies. A copy of this consent form will be offered to me.

Agreement for the Use of Video Recordings

If you consent to participate in this study, please indicate whether you agree to be recorded on video during the study by checking the appropriate box below. If you agree, please also indicate whether the video clips can be used for publication/presentations. If you do not agree to be recorded in video, or for the video to be used in publications/presentations, you will still be eligible for participation in this study.
☐I agree to be recorded in video during the experiment.
☐I agree that the video recordings can be used in publication/presentations.

My signature means that I agree to participate in the study.

___________________________	______________________	____________
Subject's Signature	Printed Name	Date

INVESTIGATOR'S STATEMENT

"I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for

Research Integrity and Assurance to protect the rights of human subjects. I have provided (offered) the subject/participant a copy of this signed consent document”

Signature of Investigator_____________________________ Date__________

CONSENT FORM

BDNF Genotype, Cortical Plasticity and Recovery from Stroke

INTRODUCTION

The purposes of this form are to provide you (as a prospective research study participant) information that may affect your decision as to whether or not to participate in this research and to record the consent of those who agree to be involved in the study.

RESEARCHERS

Principle Investigator:
Marco Santello, Ph.D., School of Biological and Health Systems Engineering, Fulton College of Engineering

STUDY PURPOSE

The purpose of the research is to examine how genetics might influence the brain's capacity to change during learning. Specifically, we are examining how one part of the brain the motor cortex, changes when people are learning a new motor skill. This is important because this information can help us guide further studies in people with neurological disorders such as stroke, Parkinson's or traumatic brain injury.

DESCRIPTION OF RESEARCH STUDY

If you decide to participate, then as a study participant you will join a study funded by the National Institute of Neurological Disorders and Stroke. The study involves three possible phases. In the first phase we will first take a cheek swab that will be used to determine the presence or absence of certain genes. These genes are very common in the population and are why we are interested in them. You will be tested on a series of tasks to examine your basic motor abilities. If you are selected for the second phase of the study, we will then use a technique called transcranial magnetic stimulation (TMS) that allows us to measure the organization of your motor cortex. This involves passing a brief magnetic pulse over your skull to excite the neurons in your brain and cause the muscles in your hand to make very small contractions that we can measure. In this case you will need to also obtain an MRI of your brain. This will be done off campus and will require one of the researchers to bring you to the MRI facility. You may then be invited back to participate in the third phase of the study that will examine how learning a motor task changes the organization of your motor cortex. This phase involves four sessions over two weeks. At each session we will test your motor learning ability and measure your cortical responses using TMS.

In some instances, you will be asked to lift objects up from the table, hold them, and replace them. The task and objects may include those encountered in activities of daily living (coffee mug, water bottle, etc), or instrumented object equipped with force sensors (ATI). We may also change object properties such as mass (usually less than 1000 g and up to 2000 g if two hands are used), center of mass, or texture of the graspable surfaces. Reflective markers will be attached to the object and/or hand using a tape to track the motion of the object and/or the hand while subjects perform various tasks. You willyou’re your right hand and/or left hand and grasp the object with 2, 3, or 5 digits. During lifting, you may be required to control the orientation of the objects, hold it for less than 5 seconds, and replace it on the table. Each experimental session consists of several blocks of trials. The total number of trials during one session would not exceed 100 (usually less than 40). You may be asked to come back for multiple sessions to be tested on the same or similar tasks. The time between two successive sessions can vary from several minutes to hours or days. TMS will be delivered during or between tasks to understand the role of brain areas in object manipulation.

In some instances, you will interact with a virtual reality (VR) environment by applying forces with their thumb and index finger to levers attached to robotic devices. The robotic devices are motorized mechanical linkages that generate forces in response to forces exerted by the fingertips, thus generating the feeling of grasping a real object. To strengthen this feeling, the perceived object is displayed on a computer monitor placed in front of the subject. The maximum output of the device is limited to very small forces (up to a maximum of 6 Newtons). The VR environment contains virtual objects that participants need to grasp and manipulate through the robotic device. When not performing the task, participants can rest their hand and forearm on a foam pad. Each experimental session consists of several blocks of trials. The total number of trials during one session would not exceed 300 (usually less than 150). Participant may need to come back for subsequent sessions with the same or similar task requirements. The inter-session time varies between hours and days. TMS will be delivered during or between tasks to understand the role of brain areas in object manipulation.

In some instance, you will receive low electrical current to your skull for about 20 min to alter the neurons in your brain using a technique called transcranial direct current stimulation (tDCS). However, this low current will not cause any contractions in your hand muscles. For this purpose, we will place two electrodes on your skull that will be secured using elastic straps. The current will be delivered using a battery-driven device connected to the electrodes. You will perform motor tasks before and after the delivery of low current. In some instances, the task will be performed with one hand or both hands. In other instances, two subjects will perform the same motor task together. You may be asked to perform the VR task (described above) while you receive tDCS. At each session we will test your motor learning ability and measure your cortical responses using TMS.

If you say YES, then your participation in the first phase of the study will last two hours at PEBE 174. Approximately {1,200) subjects will be participating in the first phase and 180 in all three phases of the study.

RISKS

The current methods carry minimal safety risks. Some people report that their scalp muscles have discomfort, and/or a headache comes and goes after TMS, though both of these issues are less of a problem in the particular scalp areas we will be stimulating. Headaches can last an hour or more. Possible ·effects on hearing have been described and so subjects and investigators will be asked to wear earplugs during any TMS to avoid this possibility. While no current evidence is available which suggests TMS may be damaging to fetus, pregnant females will not be included in the study. As with any electronic device or appliance, using it the wrong way could result in electric shock. While this is very, very unlikely, it cannot be completely excluded as a possibility. The risks of injury or discomfort in this research are minimal. There is a possibility that the linkage system will move you at an uncomfortable speed, however, several safety precautions have been implemented to reduce this risk. Specifically, the maximal speed of the movement imposed by the linkage system is set below human physiological limits. If these speeds are exceeded the linkage system is designed to immediately shutdown. Although your fingers you will be attached to the device via Velcro-like straps, you will be able to remove your fingers from the device if you feel any discomfort to let go of the object to protect yourself from potential discomfort, pain, or injury. The metal cylindrical object is powered and connected to the USB port of a pc with proper shielding and grounding. The risk of getting static shock is no different than using metal objects in daily life. However, as with any research, there is some possibility that you may be subject to risks that have not yet been identified. You may feel tingling sensation or itching during tDCS application. However, as tDCS will be delivered using a battery-driven portable device, there is absolutely no risk of electrical shock with tDCS. tDCS has been used on a large number of subjects including young, older, and patients with stroke, Parkinson’s disease or traumatic brain injury. No side effects of tDCS have been observed/reported.

BENEFITS

Although you will not benefit individually from participation in the research, this study will help us to understand the relationship between the brain's capacity to change and specific genotypes. This information will be used to guide further studies in brain injured populations.

NEW INFORMATION

If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

CONFIDENTIALITY

All information obtained in this study is strictly confidential unless disclosure is required by law. The results of this research study may be used in reports, presentations, and publications, but the researchers will not identify you. In order to maintain confidentiality of your records, Marco Santello will code all of your information so your identity cannot be determined from any of the data. The key to the code is kept in a separate location from the data and the data are locked in a cabinet. Only Dr. Marco Santello and the research assistant that enrolled you in the study will have access to both the codes and the code key.

WITHDRAWAL PRIVILEGE

It is ok for you to say no. Even if you say yes now, you are free to say no later, and withdraw from the study at any time. Your decision will not affect your relationship with Arizona State University or otherwise cause a loss of benefits to which you might otherwise be entitled.

COSTS AND PAYMENTS

The researchers want your decision about participating in the study to be absolutely voluntary. Yet they recognize that your participation may pose some inconvenience. You will be paid $20 for the first session. If you are chosen to participate in the second phase of the study you will be paid a total of $40 and an additional $80 for participating in phase three. All payments are made at the end of each phase.

COMPENSATION FOR ILLNESS AND INJURY

If you agree to participate in the study, then your consent does not waive any of your legal rights. However, no funds have been set aside to compensate you in the event of injury.

VOLUNTARY CONSENT

Any questions you have concerning the research study or your participation in the study, before or after your consent, will be answered by one of the following people: Dr. Marco Santello (480-965-8279), Qiushi Fu (480-965-8279), Justin Fine (480-965-8279), or Patrick McGurrin (480-965-8279)

If you have questions about your rights as a subject/participant in this research, or if you feel you have been placed at risk; you can contact the Chair of the Human Subjects Institutional Review Board, through the ASU Office of Research Integrity and Assurance, at 480-965 6788.

This form explains the nature, demands, benefits and any risk of the project. By signing this form you agree knowingly to assume any risks involved. Remember, your participation is voluntary. You may choose not to participate or to withdraw your consent and discontinue participation at any time without penalty or loss of benefit. In signing this consent form, you are not waiving any legal claims, rights, or remedies. A copy of this consent form will be given (offered) to you.

Your signature below indicates that you consent to participate in the above study.

Subject's Signature	Printed Name	Date
Legal Authorized Representative (if applicable)	Printed Name	Date

INVESTIGATOR'S STATEMENT

"I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Human Research Protections to protect the rights of human subjects. I have provided (offered) the subject/participant a copy of this signed consent document."

Signature of Investigator______________________ Date ____________

APPENDIX B

SUPPLEMENTARY MATERIAL FOR CHAPTER 3

S1. TMS AND EEG GENERAL PROCEDURES

The transcranial magnetic stimulation (TMS) coil was held tangential to the scalp, perpendicular to the direction of the central sulcus, 45° from the mid-sagittal line, with the handle pointing backward to induce current in the postero-anterior direction. For analysis of motor evoked potentials (MEPs), we removed trials in which electromyography (EMG) activity during the 150-ms window prior to the spTMS was larger than 2 standard deviations of the mean baseline activity (calculated as the mean of the rectified EMG signal during a short period of rest). This was done to ensure that recorded MEP values were not affected by baseline EMG activity at the time of spTMS stimulation.

Scalp electroencephalography (EEG) was recorded with a standard 10-20 layout. Sixty channels were recorded from the scalp with an AFz ground and left mastoid reference. Scalp electrodes FT9, FT10, PO9, and PO10 were used to record electrooculogram (EOG) signals, selected based on their distance from our regions of interest. EOG electrodes for horizontal eye movements were placed at the canthus of each eye, while vertical EOG electrodes were placed above and below the left eye. Any electrode showing abnormally noisy activity were interpolated using a spherical algorithm. Trial epochs were then created using a time window (−1500 ms to 3000 ms) around the object contact event (time 0). Any epochs containing large scalp EMG activity or where subjects did not comply with task instructions were excluded (< 10% of all trials).

S2. LEARNING OF SKILLED MANIPULATION OCCURS THROUGH TRIAL-TO-TRIAL DIGIT FORCE MODULATION TO VARIABLE POSITION BUT ONLY FOR UNCONSTRAINED GRASPING.

As done in our previous work (Fu et al. 2010), digit load force and position distributions (d_{LF} and d_y, respectively) for each trial were normalized to generate z-scores and used for linear regression analysis to assess the relation between these two variables in the *con* and *uncon* groups of the EEG study and four experimental groups from the TMS study (M1 *con*, M1 *uncon*, S1 *uncon*, and Vertex groups). Z-scores were computed by normalizing d_{LF} and d_y for each subject by removing the mean from the value of each trial and dividing the result by the standard deviation of the mean.

As T_{com} is learned within the first three trials (Fu et al. 2010, 2011), we used all *con* and *uncon* trials after learning had occurred for the EEG experiment (30 trials per subject), and trials 4-10 of the *Learn* block and all trials in the *Pre* block (22 trials per subject) for the TMS experiment (Fig. 3.2). We found higher d_y variability in all *uncon* than *con* grasping conditions from the EEG and TMS experiments (all $p < 0.05$). As expected from our previous work, the larger d_y variability in *uncon* was compensated by trial-to-trial modulation of d_{LF}. Specifically, we found significant negative correlations between d_{LF} and d_y only for the *uncon* grasping condition. For the EEG experiment, the *r*-value was –0.513 ($p < 0.05$) for *uncon* and –0.096 ($p > 0.05$). For the TMS experiment, we found significant negative correlations between d_{LF} and d_y in M1 *uncon,* S1 *uncon,* and *Vertex* conditions (r = –0.445, –0.541, and –0.462, respectively; all $p < 0.05$), but not in the M1 *con* group (r = 0.080, $p > 0.05$).

S3. cTBS TO M1 AND S1 FAILS TO SIGNIFICANTLY REDUCE CORTICOSPINAL EXCITABILITY FOLLOWING EXPOSURE TO OBJECT MANIPULATION

We found no change in corticospinal excitability (CSE) when cTBS was delivered over M1 in the experimental groups (M1 *con*: $t_{(9)} = -2.052$, M1 *uncon*: $t_{(9)} = -2.314$, and S1 *uncon*: $t_{(9)} = -0.991$, respectively; all $p > 0.05$) nor M1 in the control groups (*Sham*, *no-cTBS*, and *Vertex*: all p-values > 0.05; Fig. B.1).

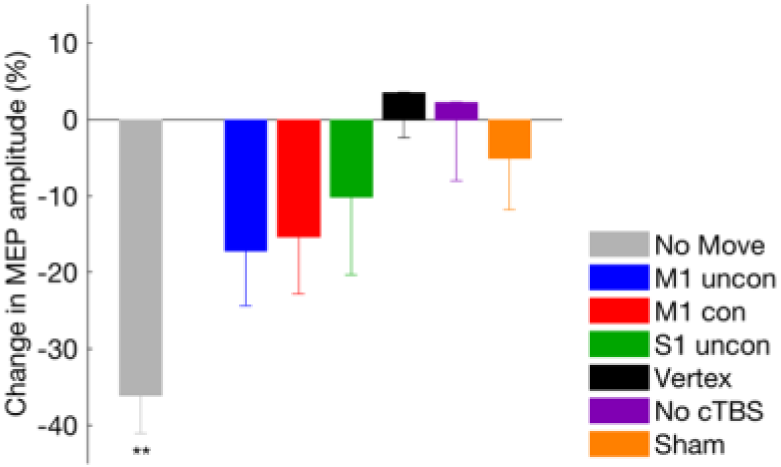

*Figure B.1. Corticospinal excitability. Change in CSE was assessed as percent change in the amplitude of motor evoked potentials (MEP) when comparing pre- versus post-cTBS, or following rest (No Move group). All groups except the No cTBS group received cTBS over M1, S1, or Vertex. ** denotes P < 0.0125. Data are averages (± SE) of all subjects.*

While these findings may seem surprising, our protocol is different from previous work that reported a reduction in CSE following cTBS over M1 in the absence of a motor task (Huang et al., 2005). Whether an active motor behavior is absent or present following cTBS is an important consideration as this affects the mechanisms trough which cTBS affects CSE (Wickliffe and Bear, 1996; Gentner et al., 2008; Silvanto et al., 2007; Huang et al., 2007). Therefore, to further validate our cTBS protocol and account for our CSE findings in the M1 groups, we performed an additional test on a *No move* group (*n* = 6) where we assessed the effects of cTBS over M1 on MEP size without having subjects perform our manipulation task (Fig. 3.2). In this group and consistent with previous work, we found a significant decrease in MEP amplitude ($t_{(9)} = –7.172$, $p < 0.05$; Fig. B.1).

S4. cTBS CONTROLS DID NOT AFFECT CONTROL OF COMPENSATORY TORQUE

In addition to the *Vertex* group, we ran three additional control experiments. In each of the control groups described below, participants were given the same task instructions given to subjects in the three experimental groups (Fig. 3.2).

Sham (*n* = 10): Corticospinal excitability (CSE) was assessed using single-pulse TMS (spTMS) over contralateral (left) M1 region immediately after the *Pre* block and before the start of the *Post* block, corresponding to the time immediately before and 5 minutes after cTBS. cTBS was delivered to a second coil placed immediately behind subject's head with current directed away from the scalp while the coil over contralateral (left) M1 remained in place. This setup meant that subjects heard the sound elicited by stimulation, but did not experience any somatosensory effect of stimulation on the scalp. This control group was used to control for any somatosensory effects (Duecker et al., 2009) caused by the auditory cue of cTBS on the control of object manipulation.

No cTBS (*n* = 6): This group did not receive cTBS. CSE was assessed using single-pulse TMS (spTMS) over contralateral (left) M1 region immediately after the *Pre* block and before the start of the *Post* block. This was done to assess the influence of MEP-induced movements on object manipulation control. Muscle twitches caused by spTMS over M1 have been shown to affect grasping behavior in subsequent lifts (Flanagan and Johansson, 2002). Therefore, the results of this control condition were used to ensure that any change in behavior found in the experimental groups was specifically due to a ‘virtual lesion’ over the cortical area targeted by cTBS.

No Stim (*n* = 6): Neither spTMS nor cTBS were delivered during the experiment.

To assess learning-related changes in the control of object manipulation (T_{com}), we performed a 4 x 2 between-within rmANOVA with *Group* (4 levels: *Sham, no cTBS, No Stim, Vertex*) as the between-subject factor, and *Block* (2 levels: *learn1*, *learn5*) as the within-subject factor. We opted to include the *Vertex* group in this analysis to ensure that there were no differences across any of the control groups. This inclusion also served to validate that having included any control groups in the main analysis with the M1 c*on*, M2 *uncon*, and S1 *uncon* groups would have produced similar results. We report a significant main effect of *Block* ($F_{(1,28)}$ = 320.46, $p < 0.05$), but no significant *Block* × *Group* interaction ($F_{(1,28)}$ = 2.50, $p > 0.05$). Individual rmANOVAs for each group confirmed that the magnitude of T_{com} significantly increased by the end of the *Learn* block (learn1 vs. learn5, Fig. B.2) for all control groups (significant main effect of *Block,* all p-values < 0.05).

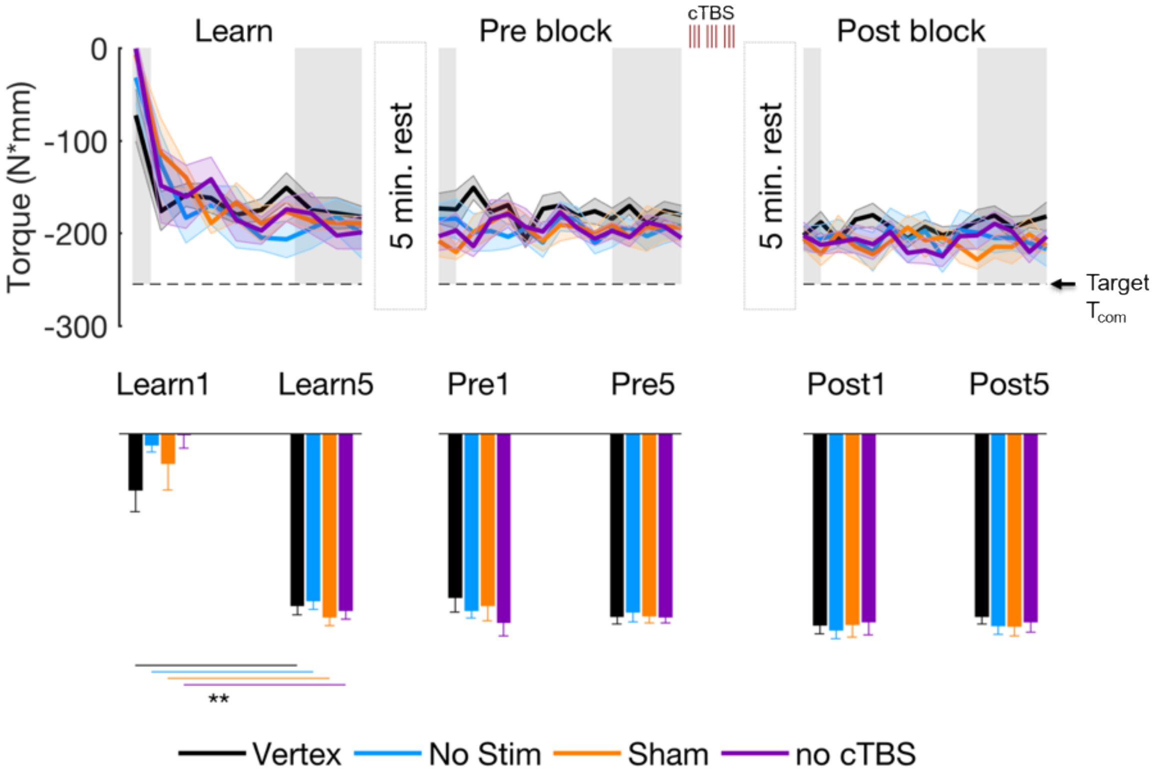

*Figure B.2. Compensatory torque: Control groups. Top plots show compensatory torque (T_{com}) during Learn, Pre, and Post blocks in the Vertex, No Stim, Sham, and No cTBS groups. Data are plotted in the same format as Figure 4. ** denotes $P < 0.0125$.*

In addition, we confirmed that object manipulation performance remained stable during trials after learning and prior to cTBS using a 4 × 3 between-within rmANOVA with *Group* (4 levels: *Sham, no-cTBS, No Stim, Vertex*) as the between-subject factor, and *Block* (3 levels: *learn5*, *pre1*, *pre5*) as the within-subject factor. After learning, T_{com} and peak object roll remained invariant at the beginning of the *Pre* block (no main effect of *Block*: $F_{(2,56)} = 0.267$, $p > 0.05$; no significant *Block* × *Group* interaction: $F_{(2,56)} = 0.572$, $p > 0.05$; Supplementary Fig. 1b). This comparison confirmed both that the rest period between the *Learn* and *Pre* blocks (Fig. 4) had no significant effect on performance (learn5 vs. pre1) and that object manipulation performance was stable throughout the *Pre* block (pre1 vs. pre5).

To assess whether offline cTBS stimulation caused changes in T_{com} during the *Pre* and *Post* blocks, we used a 4 × 3 between-within rmANOVA with *Group* (4 levels: *Sham, no-cTBS, No Stim, Vertex*) as a between-subject factor and *Block* (3 levels: pre5, post1, post5) as the within-subject factor. We found no main effect of *Block* ($F_{(2,56)} = 2.73$, $p > 0.05$) nor significant *Block* × *Group* interaction ($F_{(2,56)} = 0.42$, $p > 0.05$). This confirmed that subjects maintained similar object manipulation performance throughout the remainder of the *Pre* and *Post* blocks (Fig. B.2) for all control groups.

Lastly, between-group comparisons for all control groups revealed no between-group differences during the *Learn, Pre, or Post* block trials (all p-values > 0.05, Fig. B.2). This confirms that cTBS to sites other than M1 and S1, and/or the presence of spTMS between blocks, did not affect skilled object manipulation performance. Similar findings were found for peak object roll (see below).

S5. THE EFFECTS OF CTBS ON COMPENSATORY TORQUE AFFECTED PERFORMANCE OF SKILLED MANIPULATION BUT ONLY IN EXPERIMENTAL GROUPS

While we designated T_{com} as our primary variable of interest to assess subject's task performance, we also performed full analyses on object roll data. Overall, we report a significant linear correlation between T_{com} and peak object roll for all groups, all p-values < 0.05), and note that the findings from analyses of both variables were identical. For completeness, here we report the results of peak object roll analyses, and preface that the findings align with those of T_{com}.

We used predefined subsets of trials within each experimental block to quantify subject's performance. We performed a 4 x 2 between-within repeated measure ANOVA (rmANOVA) with *Group* (4 levels: M1 *uncon*, M1 *con*, *S1,* Vertex) as the between-subject factor, and *Block* (2 levels: learn1, learn5) as the within-subject factor to assess learning. We report a significant main effect of *Block* ($F_{(1,36)} = 67.05$, $p < 0.05$), but a non-significant *Block* × *Group* interaction ($F_{(1,36)} = 0.706$, $p > 0.05$). Individual rmANOVAs for each group confirmed that peak object roll significantly decreased by the end of the *Learn* block (learn1 vs. learn5, top plot in Fig. B.3) for the M1 *uncon*, M1 *con*, *S1 uncon,* and *Vertex* groups (main effect of *Block,* all p-values < *0.05*).

In an additional 4 × 3 rmANOVA with *Group* (4 levels: M1 *uncon*, M1 *con*, *S1 uncon,* Vertex) as the between-subject factor, and *Block* (3 levels: learn5, pre1, pre5) as the within-subject factor we confirmed that after learning, peak object roll values remained invariant (no main effect of *Block* ($F_{(2,72)} = 0.624$, $p > 0.05$) or significant *Block* × *Group* interaction ($F_{(2,72)} =$

0.691 , $p > 0.05$). This comparison confirmed both that the rest period between the *Learn* and *Pre* blocks (Fig. 4) had no significant effect on performance (learn5 vs. pre1) and that performance was stable throughout the *Pre* block (pre1 vs. pre5).

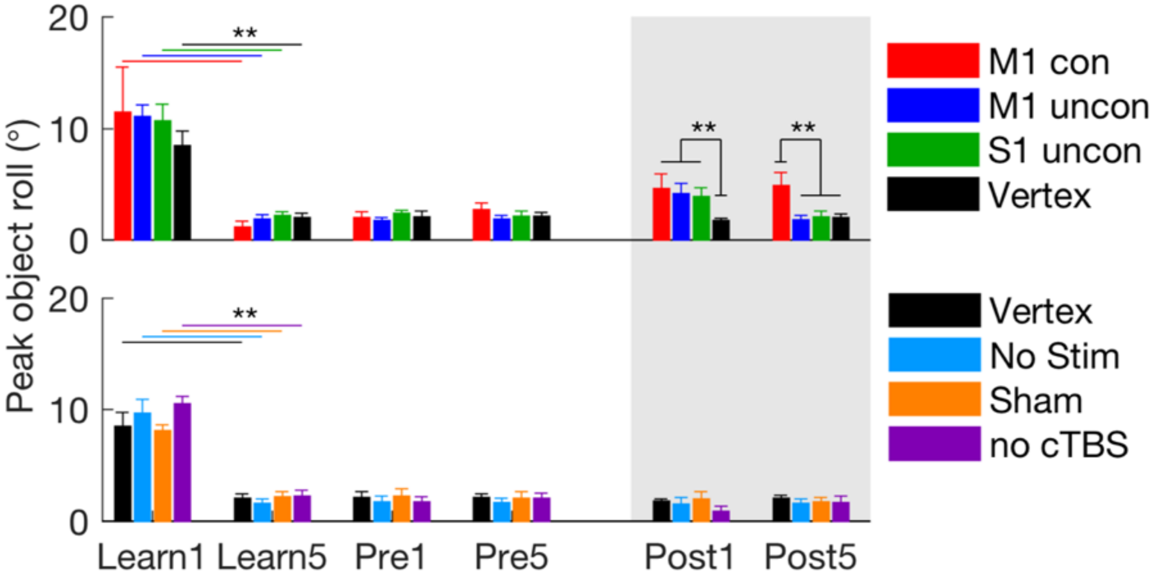

*Figure B.3. Object roll: Experimental and control groups. Peak object roll for each block of trials from all experimental (top) and control (bottom) groups. Note that Vertex data is from a control group and is plotted with data from experimental groups in the top plot and together with all other control conditions in the bottom plot. Data are plotted in the same format as Figure 4. ** denotes $P < 0.0125$.*

The primary aim of our experiment was to determine whether offline cTBS stimulation over M1 and S1 would impair subject’s ability to generate the learned T_{com} necessary to minimize object roll. We found cTBS effects on T_{com} that varied according to the experimental group (Fig. 4). To quantify the extent to which cTBS-induced effects on T_{com} had behavioral consequences on skilled manipulation performance, we explored the effect of cTBS over M1, S1, and Vertex on peak object roll by performing a 4 × 3 between-within rmANOVA with *Group* (4 levels: M1 *uncon*, M1 *con*, S1 *uncon*, Vertex) as the between-subject factor, and *Block* (3 levels: pre5, post1, post5) as the within-subject factor.

We report a significant main effect of *Block* ($F_{(2,72)} = 15.94$, $p < 0.05$) as well as a significant *Block* × *Group* interaction ($F_{(2,72)} = 6.38$, $p < 0.05$) for all groups. We found that performance by subjects in all groups was characterized by similar peak object roll at the end of the *Pre* block (pre5; all comparisons, $p > 0.05$). At the beginning of the *Post* block, however, peak object roll in the M1 *uncon*, M1 *con, and S1 uncon* groups were significantly greater relative to that of the *Vertex* group (post1, all p-values < 0.05). The larger peak object roll for the M1 and S1 groups was similar (post1; all p-values > 0.05), suggesting that a virtual lesion over M1 and S1 had a similar effect on the ability to minimize object roll in the first trial immediately after cTBS over M1.

Additionally, we explored within-group differences in object roll using separate one-way rmANOVAs for each group. In the *Vertex* group, we found no significant changes in peak object roll (no main effect of *Block* ($F_{(2,18)} = 0.132$, $p > 0.05$), confirming that cTBS over Vertex did not impair performance. In contrast, we report a significant main effect of *Block* for M1 *con*, M1 *uncon*, and S1 *uncon* groups ($F_{(2,18)} = 14.17$, 6.98, and 7.43, respectively; all $p < 0.05$). During *uncon* grasping, T_{com} was significantly reduced after a virtual lesion over M1 and S1 (pre5 vs. post1), which led to a significantly larger peak object roll in the M1 *uncon* and S1 *uncon* groups ($t_{(9)} = –4.05$ and –2.80, respectively; both $p < 0.05$) groups. Furthermore, this cTBS effect on skilled manipulation performance was short-lived, as by the end of the *Post* block (pre5 vs. post5) peak object roll became statistically similar to that of the *Pre* block in both the M1 *uncon* and S1 *uncon* groups ($t_{(9)} = 0.254$ and 0.230, respectively; both $p > 0.05$; Fig. B.3). In contrast, the change in peak object roll was still found at the end of the *Post* block for the M1 *con* group (pre5 vs. post5: $t_{(9)} = –4.383$, $p < 0.05$). Consistent with the lack of effect of cTBS on T_{com}, manipulation performance in the control groups (Fig. B.2), peak object roll was not significantly different when comparing post1 or post5 with pre5 trials (bottom plot in Fig. B.3; all $p > 0.05$).

APPENDIX C

SUPPLEMENTARY MATERIAL FOR CHAPTER 4

TIME FREQUENCY DATA FOR ELECTRODE C3

One goal of our experiment was to explore power modulations in the beta (16-28 Hz) range. In the main text, we report differences maps (Fig 4.6) across grasp type (*uncon* minus *con*). Here we report individual data plots for each grasp context across all time epochs used for analysis. Namely, data points for analysis were obtained from 300-ms windows from five different epochs. We included three epochs that we considered to occur during movement preparation, including time of ready cue, time of go cue, and reaction time. In addition, we included two additional epochs during the movement execution phase, including object contact, and object lift-off.

Time-frequency power values were normalized to the average baseline power at that frequency. Baseline power was calculated from all trials in the experimental session, with a window spanning from −500 to −250 ms before the ‘ready’ cue (see Fig 4.1). This converts EEG power into event-related desynchronization or synchronization (ERD/ERS; Pfurtscheller & Da silva, 1999), and normalizing to one baseline (pre-ready) allowed a uniform visual and quantitative analysis of ERD/ERS across epochs.

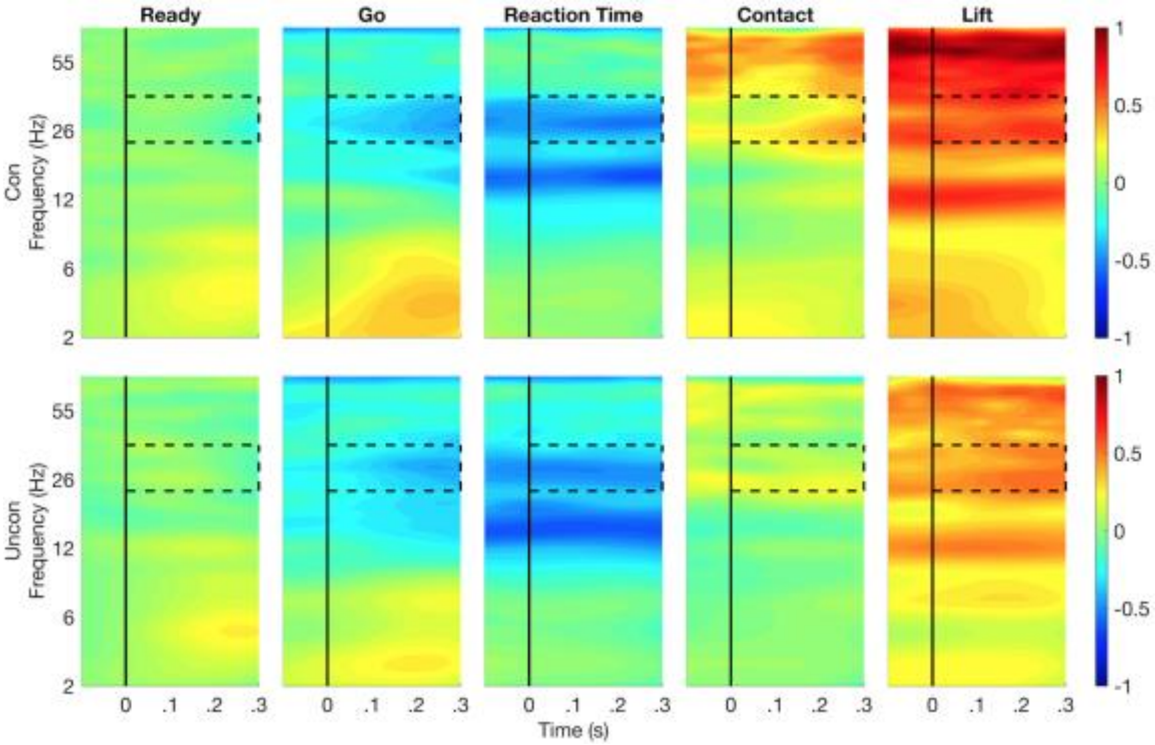

Figure C.1. Mean EEG time frequency data from electrode C3 across all time epochs for both con and uncon trials. All data is normalized to a baseline period prior to the ready cue. The black dotted box represents the window used for analysis of beta band activity (17-28 Hz). The vertical black line represents the zero point of the epoch, which either represents the timing of a cue (ready, go) or the onset of a behavioral event (reaction time, contact, lift).

THE EFFECT OF BLOCK ORDER ON BEHAVIORAL VARIABLES

One consideration for only including the randomized trial sets in the EEG analysis was due to the presence of block order effects. Our initial behavioral analysis (see Chapter 4 methods) assessed the mean data for blocked and randomized trial data irrespective of order, suggesting that overall trial performance was similar irrespective of block type (blocked or randomized). However, a subsequent analysis that accounted for block order identified subtle, yet distinct, differences in performance.

To account for this in our main analyses (see Chapter 4 results), we included block order as a factor in the linear mixed model for our primary analyses. This would inform us whether the relationship between our neural and behavioral data were influenced by this block order. While the results of the EEG analysis can be found in the main text, here we report the effects of block order (see Fig 4.1) on our behavioral data.

COMPENSATORY TORQUE GENERATION

Results of the blocked condition demonstrated that while behavioral differences were not present when performing the task in the *con* and *uncon* blocks (T_{com}: no main effect of *Grasp:* $F_{(1,20)} = 0.845$, $p > 0.05$), there was some influence of block order (significant *Grasp* × *Order* interaction: $F_{(1,20)} = 4.374$, $p < 0.05$). Post-hoc analyses revealed significantly different T_{com} when the *uncon* block came prior to the con block ($t_{(10)} = -2.602$, $p < .05$), but not the other way around ($t_{(10)} = 0.097$, $p > .05$).

DIGIT POSITION AND FORCES

In response to an order interaction for the T_{com} data, we also assessed the magnitudes of the underlying position and force variables (d_y, F_{GF}, d_{LF}) that together generate T_{com}. Overall we found no significant differences for d_y (no main effect of *Grasp:* $F_{(1,20)} = 0.105$, $p > 0.05$) nor d_{LF} (no main effect of *Grasp:* $F_{(1,20)} = 0.249$, $p > 0.05$), In addition, there was no significant change in these values due to the order of block presentation, as similar magnitudes of these variables were reported regardless of whether the *con* or *uncon* block were delivered first (d_y, d_{LF}; no significant *Grasp* × *Order* interaction: both p-values > .05). Alternatively, we did find that while in general subjects tended to apply similar grip force (F_{GF}) in the *con* and *uncon* grasp contexts (no main effect of *Grasp:* $F_{(1,20)} = 0.772$, $p > 0.05$), we did find an effect of block order for this variable (significant *Grasp* × *Order* interaction: $F_{(1,20)} = 6.897$, $p < 0.05$). However, post-hoc analyses did not reveal any significant differences (after Bonferroni correction) across grasp type or block order.

VARIABILITY IN DIGIT PLACEMENT

We found that d_y variability values were higher in *uncon* versus *con* grasping (main effect of *Grasp:* $F_{(1,20)} = 8.467$, $p < 0.05$), with no effect of block order. (no *Grasp* × *Order* interaction: $F_{(1,20)} = 0.483$, $p > 0.05$), suggesting that block order had no effect on variability in digit placement.

GRIP FORCE RATE

Overall there was a tendency for grip force RMSE values (see Chapter 4 methods) to be higher in *uncon* versus *con* grasping (main effect of *Grasp:* $F_{(3,60)} = 8.460$, $p < 0.05$). Additionally, we found that block order also affected RMSE values (significant *Grasp* × *Order* interaction: $F_{(1,20)} = 4.635$, $p < 0.05$). Post-hoc analysis revealed a significant difference in RMSE only when the *uncon* block came first ($t_{(10)} = 3.258$, $p < .05$). Interestingly, this suggests that when the *con* block came first, RMSE values were not significantly difference between the *con* and *uncon* grasp types.

REACTION TIME

Reaction time (RT) was larger for *uncon* relative to *con* group (main effect of *Grasp:* $F_{(1,20)} = 5.297$, $p < 0.05$). Interestingly, we also report a tendency for block order to affect reaction times (significant *Grasp* × *Order* interaction: $F_{(1,20)} = 10.43$, $p < 0.05$). Post-hoc analysis revealed a significant difference in RT only when the *uncon* block came first ($t_{(10)} = 3.300$, $p < .05$). These results demonstrate that when the *uncon* block context was delivered first, RT was larger for *uncon* relative to *con*. However, when the *con* context was delivered first the RT for the subsequent *uncon* block was not significantly different.

While we note the interesting nature of these findings, we opted to focus the scope of the main text on differences in EEG dynamics when planning during constrained and unconstrained grasping. We accounted for these block order effects in our statistical analysis to ensure that any potential effects of block order did not confound our comparison of *con* versus *uncon* during randomized trials *(*see Chapter 4 methods), and highlight that future work will aim to better explore these order differences, from both a behavioral and neural perspective.