

**A neurophysiological examination of voluntary
isometric contractions: Modulations in
sensorimotor oscillatory dynamics with
contraction force and physical fatigue, and
peripheral contributions to maximal force
production**

By

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Abstract

Human motor control is a complex process involving both central and peripheral components of the nervous system. Type Ia afferent input contributes to both motor unit recruitment and firing frequency, however, whether maximal force production is dependent on this input is unclear. Therefore, chapter 2 examined maximal and explosive force production of the knee extensors following prolonged infrapatellar tendon vibration; designed to attenuate the efficacy of the homonymous Ia afferent- α -motoneuron pathway. Despite a marked decrease in H-reflex amplitude, indicating an attenuated efficacy of the Ia afferent- α -motoneuron pathway, both maximal and explosive force production were unaffected after vibration. This suggested that maximal and explosive isometric quadriceps force production was not dependent upon Ia afferent input to the homonymous motor unit pool.

Voluntary movements are linked with various modulations in ongoing neural oscillations within the supraspinal sensorimotor system. Despite considerable interest in the oscillatory responses to movements per se, the influence of the motor parameters that define these movements is poorly understood. Subsequently, chapters 3 and 4 investigated how the motor parameters of voluntary contractions modulated the oscillatory amplitude. Chapter 3 recorded electroencephalography from the leg area of the primary sensorimotor cortex in order to investigate the oscillatory responses to isometric unilateral contractions of the knee-extensors at four torque levels (15, 30, 45 and 60% max.). An increase in movement-related gamma (30-50 Hz) activity was observed with increments in knee-extension torque, whereas oscillatory power within the delta (0.5-3 Hz), theta (3-7 Hz), alpha (7-13 Hz) and beta (13-30 Hz) bands were unaffected.

Chapter 4 examined the link between the motor parameters of voluntary contraction and modulations in beta (15-30 Hz) oscillations; specifically, movement-related beta decrease (MRBD) and post-movement beta rebound (PMBR). Magnetoencephalography (MEG) was recorded during isometric ramp

and constant-force wrist-flexor contractions at distinct rates of force development (10.4, 28.9 and 86.7% max./s) and force output (5, 15, 35 and 60%max.), respectively. MRBD was unaffected by RFD or force output, whereas systematic modulation of PMBR by both contraction force and RFD was identified for the first time. Specifically, increments in isometric contraction force increased PMBR amplitude, and increments in RFD increased PMBR amplitude but decreased PMBR duration.

Physical fatigue arises not only from peripheral processes within the active skeletal muscles but also from supraspinal mechanisms within the brain. However, exactly how cortical activity is modulated during fatigue has received a paucity of attention. Chapter 5 investigated whether oscillatory activity within the primary sensorimotor cortex was modulated when contractions were performed in a state of physical fatigue. MEG was recorded during submaximal isometric contractions of the wrist-flexors performed both before and after a fatiguing series of isometric wrist-flexions or a time matched control intervention. Physical fatigue offset the attenuation in MRBD observed during the control trial, whereas PMBR was increased when submaximal contractions were performed in a fatigued state.

Keywords: isometric muscle contraction; force; Ia afferent; electroencephalography; magnetoencephalography; movement-related beta decrease; post-movement beta rebound; fatigue

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List of Abbreviations

Abbreviations are defined in the text in the first instance.

ANOVA	Analysis of variance
BOLD	Blood oxygen level dependent
CCD	Cortical current density
CV	Coefficient of Variation
ECoG	Electrocorticography
EEG	Electroencephalography
EMG	Electromyography
EVC	Explosive voluntary contraction
F _{25, 50, 75, 100, 150}	Force at 25, 50, 75, 100 or 150 ms following onset
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
GABA	Gamma aminobutyric acid
HAM	Hamstrings
LOI	Location of interest
LORETA	Low-resolution brain electromagnetic tomography
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute
MRBD	Movement-related beta decrease
MRMD	Movement-related mu decrease
MVC	Maximal voluntary contraction
MVF	Maximal voluntary force
MVF _b	Baseline maximal voluntary force
MVT	Maximal voluntary torque

PET	Positron emission tomography
PMBR	Post-movement beta rebound
QUAD	Quadriceps
rCBF	Regional cerebral blood flow
RFD	Rate of force development
RMS	Root mean square
SAM	Synthetic aperture magnetometry
TFS	Time-frequency spectrum
TMS	Transcranial magnetic stimulation
VM _d	Distal vastus medialis electromyography recording site

Chapter 1

General Introduction

The work of this thesis is divided in to three sections. The first addresses the importance of Ia afferent contributions to maximal force development, and includes the study presented in chapter 2. The second examines whether movement-related changes in oscillatory activity within the sensorimotor cortex may be modulated by the motor parameters of the performed contractions (specifically the contraction force and RFD), and includes the studies presented in chapters 3 and 4. Finally, the third section investigates whether oscillatory activity within the sensorimotor cortex may be modulated when contractions are performed in a state of physical fatigue, and includes the study presented in chapter 5. These sections are introduced individually as follows:

1.1 – Peripheral contributions to maximal force generation

1.1.1 – Background

The gradation of skeletal muscle contraction force in humans is governed by the number of motor units recruited and the rate at which the activated motor units fire. In turn, both of these recruitment characteristics are principally determined by the net effect of the excitatory and inhibitory inputs to the α -motoneurons within the motor unit pool (Pierrot-Deseilligny & Burke 2005). As net excitatory input rises, larger motor units of increasing thresholds are activated in accordance with the size principle (Henneman et al. 1965), and the firing frequency of the previously recruited α -motoneurons will increase proportionally to the magnitude of depolarisation beyond motor threshold (Heckman & Binder 1991). Three types of neurons make excitatory projections to (lower) α -motoneurons of the motor unit pool: upper α -motoneurons, which are supra-spinal in origin, (excitatory) interneurons, which mediate the action of other

neurons, and type Ia afferent neurons, which emanate from muscle spindle primary endings and form part of the γ -loop. The potential for Ia afferent- α -motoneuron connections to facilitate muscle contractions has therefore come under investigation. However, while reflex activity within the γ -loop is widely accepted to offer effective contributions in locomotion (Zehr & Stein 1999), their role in maximal force production is less well understood.

1.1.2 – γ -loop contributions to motor unit recruitment

Hagbarth et al. (1986) completed a series of experiments following an anaesthetic-induced block of the right peroneal nerve that resulted in complete or partial paralysis of the pretibial muscles. During the progressive induction/recovery of the anaesthesia, decrements in maximal voluntary isometric dorsiflexion force following the peroneal nerve block were accompanied by reductions in both the number of active motor units and the firing rates of the remaining units in the tibialis anterior muscle (the magnitude of these decrements being dependent on the period of recovery following anaesthetic administration).

The cause of this impaired motor unit recruitment was explored using electrical stimulation of the peroneal nerve at a location proximal to the anaesthetic administration (Hagbarth et al. 1986). After a period of partial recovery, the paretic muscle could be driven maximally by electrical stimulation of the peroneal nerve; demonstrating that the low firing rates could not be solely dependent on deficient impulse transmission in α -motor units. M-wave amplitude was also well preserved despite significant decrements in surface EMG activity during maximal voluntary contraction (MVC) attempts. Preferential impairment of impulse transmission in the γ -motoneurons resulting in a diminished input to the α -motoneuron pool via the γ -loop was therefore proposed to contribute to the reductions in motor unit firing rates.

To test this hypothesis, vibration of the tibialis anterior tendon or passive plantarflexions were imposed during the attempted maximal contractions in the paresis recovery in order to provide an external stimulation of the primary spindle endings (Hagbarth et al. 1986). Motor unit firing rates increased from 10 to 25 Hz

and dorsiflexion force was augmented in response to both stimuli. These results led the authors to conclude that γ -loop contributions to the α -motoneuron pool may provide a “substantial tonic power supply” during maximal force production tasks. However, the “most striking” facilitation of motor unit firing rates occurred when contraction force had recovered to 25-75% of pre-anaesthetisation values, and in agreement with Humphries et al. (2004), no effect of tendon vibration or passive plantarflexion was observed prior to anaesthesia (i.e. at 100% MVC). Therefore, whilst the results provide strong evidence for a role of the γ -loop in facilitating α -motoneuron firing frequencies and contraction force at sub-maximal intensities, the efficacy of this pathway during MVCs with the fusimotor system intact was less clear.

In paradox to the facilitatory effects of a brief vibration stimulus, a continued period of vibration applied to the muscle or tendon can have inhibitory effects on the efficacy of the homonymous Ia afferent- α -motoneuron pathway (Desmedt & Godaux 1978; see also Chapter 1.1.4); a peripheral component of the γ -loop. Bongiovanni et al. (1990) applied a continuous 2-min vibration stimulus to the dorsiflexor tendons during a series of sixteen 3-4-s maximal isometric contractions (vibration commencing after the fifth and ceasing after the eleventh contraction). Both contraction force and muscle activation progressively declined across the contractions accompanied by the tendon vibration, but immediately returned to pre-vibration levels once vibration had ceased. Single motor unit recordings from the tibialis anterior demonstrated that firing frequency was attenuated, and that this was markedly greater in high threshold (initial recruitment at contraction forces >50% maximal voluntary force (MVF)) versus low threshold (initial recruitment at contraction forces <5% MVF) motor units. Approximate discharge frequencies decreased from 35 Hz to 5 Hz and 30 Hz in the high and low threshold units, respectively. In the same report, sustained one-minute maximal contractions were also performed with and without a superimposed vibration stimulus (Bongiovanni et al. 1990). The decline in both force and EMG were significantly greater during the vibration trial versus the control trial, and this was again characterised by a marked decrease in the firing frequencies of high threshold motor units. These findings, together with those of Hagbarth et al. (1986), demonstrate that peripheral input to α -motoneurons from

homonymous Ia afferents may contribute to both the recruitment of high threshold motor units and to achieving maximal firing rates of recruited motor units, however, whether maximal force development is dependent on this input is not clear.

1.1.3 – The effect of prolonged muscle/tendon vibration on maximal force production

More extended periods of muscle or tendon vibration, typically 20 to 30 minutes in duration, have been demonstrated to provoke a lasting reduction in the efficacy of the homonymous Ia afferent- α -motoneuron transmission of up to 20 minutes (Shinohara et al. 2005). Accordingly, a number of studies have utilised this technique in order to record maximum force performance in a presumed state of reduced Ia afferent- α -motoneuron efficacy.

Kouzaki et al. (2000) recorded the force and quadriceps electromyography (EMG) during isometric unilateral knee-extension MVCs performed both before and after either a 30-min tonic vibration stimulus (30 Hz) applied to the rectus femoris muscle or a 30-min period of quiescent sitting (control intervention). These authors found a ~10% decrease in maximal force and ~14% decrease in rectus femoris activity following vibration, whereas no differences were observed in the control trial. No differences in vastus medialis or vastus lateralis EMG were observed in either trial. These results were suggested to indicate that MVF capacity is impaired in a state of attenuated Ia afferent- α -motoneuron transmission. However, the muscle vibration evoked a tonic response, with action potentials recorded from the rectus femoris during the application of vibration. This low level contraction might therefore have led to a fatiguing of the muscle, which could have contributed to the reduction in MVF. Yet, despite this possibility, no attempt was made to assess the excitability of the extrafusal fibres before and after vibration; for example, by using M-wave recordings. Moreover, the efficacy of the Ia afferent- α -motoneuron pathway before and after vibration was not assessed; for example, by using H-reflex recordings. This study also recorded the peak rate of force development (RFD) during the generation of the MVCs. A ~24% decrease was reported following vibration; more than twice the relative

decrease in maximal force. However, the authors conceded that “no instruction had been given as to the speed of force development at the onset of voluntary contraction”, and as such this result should be interpreted with further caution.

In a similar study, Jackson & Turner (2003) found 6.9% and 4.2% decreases in isometric unilateral knee-extension MVF following 30 minutes of mechanical vibration applied to the rectus femoris at 30 Hz and 120 Hz, respectively. Rectus femoris EMG during the MVCs was also significantly decreased following 30 Hz vibration, but not 120 Hz vibration, whereas vastus lateralis EMG was unchanged following vibration at either frequency. No changes in either MVF or the accompanying EMG were observed following 30 minutes of quiescent sitting without vibration (control trial). In this study, participants were instructed to achieve maximal force “as rapidly as possible”. Peak RFD was recorded during this phase of the contraction, and was shown to decrease by 20.9% and 33.3% following the 30 Hz and 120 Hz vibration periods, respectively; almost five times the observed decrement in maximal force. However, the control (pre-intervention) assessments of peak RFD were highly variable between trials. Additionally, Sahaly et al. (2001) suggested that measuring RFD during the performance of maximal force contractions may not provide valid measurements of peak RFD (Sahaly et al. 2001). Moreover, no attempt to assess the efficacy of the Ia afferent- α -motoneuron pathway or the excitability of the muscle fibres was made following the 30-min vibration.

One further study by Konishi et al. (2009) investigated the effect of a 20-min vibration stimulus (50 Hz) applied to the infrapatellar tendon on maximal concentric and eccentric knee-extensor torque. Although Ia afferent firing is usually higher during eccentric than concentric contractions, due to the muscle spindles lengthening during the contraction (Burke 1978), similar decreases in both concentric (16%) and eccentric (17%) maximal voluntary torque were identified following vibration. Similar decrements in EMG were also described for both the vastus lateralis and vastus medialis, although no significant change in muscle activation of the rectus femoris was identified. These authors proposed that a reduced efficacy of Ia afferent- α -motoneuron transmission has a similar impact on different contraction types. However, the effect of the tendon vibration

on the Ia afferent- α -motoneuron pathway was not assessed, and no control trial was included.

Ushiyama et al. (2005) and Ekblom & Thorstensson (2011) both investigated the effects of a 30-min Achilles tendon vibration (100 Hz) on maximal plantar flexor strength. These investigations also included H-reflex and M-wave measurements to monitor modulations in the efficacy of the Ia afferent- α -motoneuron pathway and the excitability of the extrafusal fibres, respectively. Both of these studies reported a substantial decrease in maximum H-reflex:M-wave ratio following tendon vibration (34-39%, Ushiyama et al. 2005; 33%, Ekblom & Thorstensson 2011), indicating that their vibration stimuli were effective in attenuating the efficacy of the homonymous Ia afferent- α -motoneuron pathway. Ushiyama et al. (2005) also demonstrated significant decreases in muscle activity of both the lateral (13%) and medial (11%) heads of the gastrocnemius, but not the soleus, which resulted in a 17% decrease in isometric plantar flexor torque. Conversely, Ekblom & Thorstensson (2011) found no effect of the 30-min Achilles tendon vibration on either the maximal concentric and eccentric plantar flexion torque, or triceps surae activation during these movements. Ekblom & Thorstensson (2011) suggested that the measurement of dynamic rather than isometric contractions may have contributed to the disparity between their findings and those Ushiyama et al. (2005); however this is of course in conflict with the results of Konishi et al. (2009) (presented above). These suggestions therefore require further investigation. Overall these differing findings demonstrate that the role of Ia afferent input the motor units during maximal contractions is yet to be fully elucidated.

1.1.4 – Techniques employed in evaluations of Ia afferent- α -motoneuron efficacy and force production capacity

H-reflex

First described by Paul Hoffmann around a century ago (Hoffmann 1918), the Hoffmann (H) reflex is considered the electrical analogue of the mechanically induced stretch reflex, but bypasses the influence of the muscle spindle and

gamma motoneurons (Schieppati 1987). The H-reflex is evoked using transcutaneous electrical stimulation of a mixed nerve. Type Ia afferents have a greater diameter and lower rheobase than α -motoneurons and may therefore be recruited using stimulus currents below the motor threshold (Li & Bak 1976; Zehr 2002), particularly when using stimuli of a relatively long duration (~1-ms is typical). A H-reflex will be evoked if the electrical stimulation produces a synchronous volley in type Ia afferents that is sufficient to depolarize the homonymous α -motoneurons (with which they make direct excitatory projections) such that action potentials are produced, triggering the cascade of events that result in contraction of the muscle fibres. However, increases in the stimulus current beyond the motor threshold can lead to a reduction in the observed H-reflex due to orthodromic-antidromic cancellation of the afferent and efferent volleys, respectively. The magnitude of the evoked H-reflex is sensitive to the efficacy of Ia afferent- α -motoneuron transmission, making the H-reflex a useful tool for examining reflex modulation in response to a stimulus or intervention. The monosynaptic Ia afferent- α -motoneuron pathway and an example recording of the H-reflex are shown in Figure 1.1.

M-wave

The M-wave is evoked using the same experimental setup as the H-reflex. Increasing the stimulus current beyond the motor threshold produces a short latency compound muscle action potential (M-wave) following the direct and synchronous activation of α -motor axons. Further increases in the stimulating current results in an increase in the magnitude of the electromyographic response, until a plateau is reached, at which point the $M_{\max}$ may be measured. $M_{\max}$ is evoked by the stimulation of all motor axons and provides an estimate of the response of the entire motoneuron pool. This makes $M_{\max}$ a useful tool for the normalisation of other evoked responses, or any other form of electromyographic activity. An example of the M-wave response is shown in Figure 1.1C.

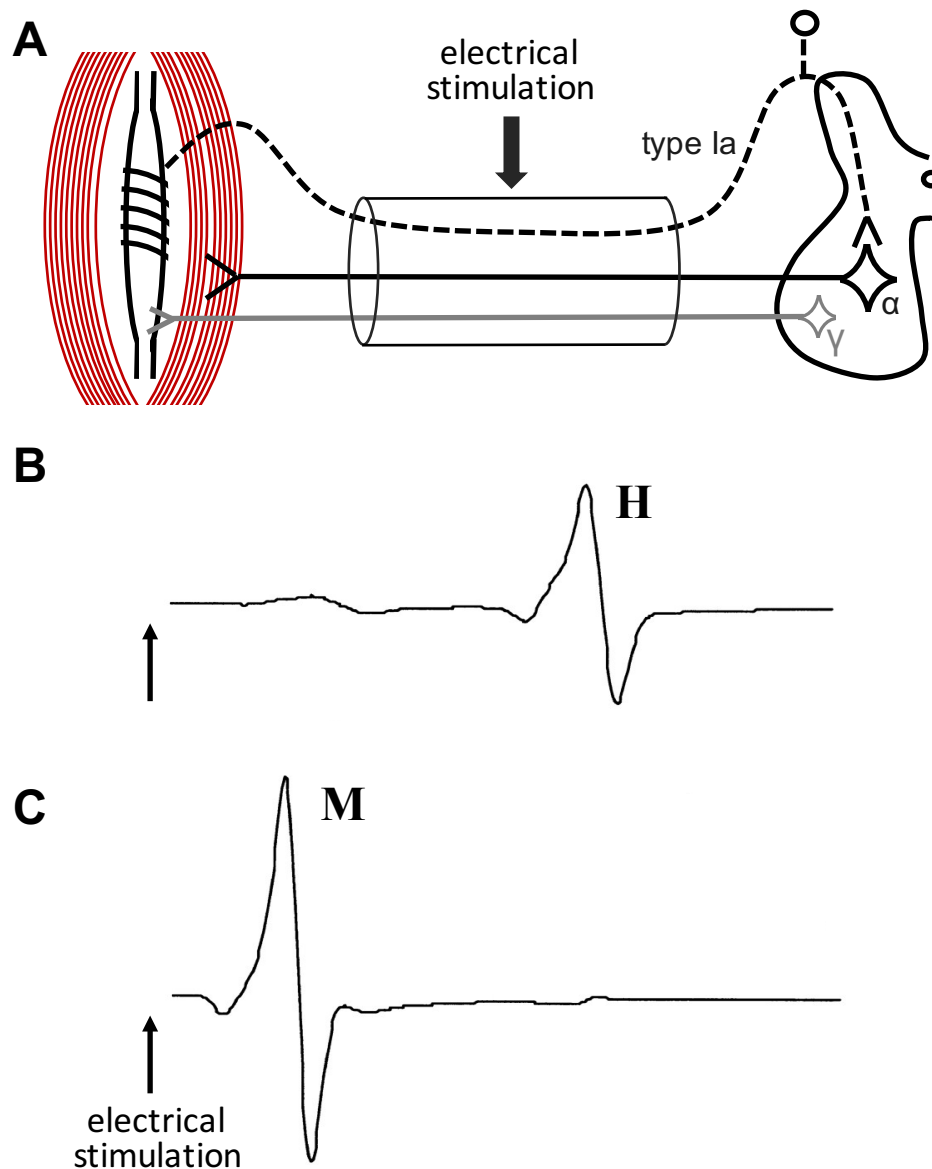


Figure 1.1 (A) The monosynaptic Ia afferent- α -motoneuron pathway (adapted from Pierrot-Deseilligny and Burke 2005, pp. 2). Ia afferents (dashed line) emanating from muscle spindle primary endings make direct excitatory projections to homonymous α -motoneurons within the spinal cord. Transcutaneous electrical stimulation of the mixed nerve can evoke the H-reflex and M-wave responses (bypassing the influence of the muscle spindle and γ -motoneurons). (B) Electromyography traces of a H-reflex and (C) M-wave are also shown. The H-reflex is evoked using a lower stimulus current than the M-wave, and arises following a greater latency as the electrophysiological pathway is longer (exact latencies and amplitudes of these responses will depend on the muscle under investigation).

The octet

Transcutaneous electrical stimulation of the mixed nerve will also produce a mechanical response from the innervated muscle. This is typically measured with the limb under investigation held in a fixed position such that the mechanical response is that of an isometric contraction. Single pulses of electrical stimulation, as per the H-reflex and M-wave, produce a twitch response, whereas entrained stimulation can be used to evoke tetanic muscle contractions. High frequency nerve stimulation can elicit contractions up to the maximal rate of force development (De Ruiter et al. 1999; Deutekom et al. 2000). For example, eight pulses at 300 Hz using a supramaximal stimulus current is sufficient to drive the muscle at its maximal RFD (de Ruiter et al. 2004). This stimulation paradigm is known as the octet, and is useful in demonstrating the maximal capacity of the muscle-tendon unit for RFD, against which voluntary efforts can be normalised.

Muscle-tendon unit vibration

Mechanical vibration applied to the muscle or tendon unit causes small changes in length in the muscle spindle that promotes type I afferent activation. While initially providing an increase in excitatory input to α -motoneurons, prolonged vibration of more than 10-20 s can attenuate the efficacy of the homonymous Ia afferent- α -motoneuron pathway (Shinohara et al. 2005); a phenomenon known as the vibration paradox (Desmedt & Godaux 1978). This depression in Ia afferent- α -motoneuron transmission may arise via one or more of a number of processes. Vibration of the muscle-tendon unit produces interneuron-mediated presynaptic inhibition of Ia terminals (Hultborn et al. 1987; Lapole et al. 2012). Additionally, with prolonged vibration over several minutes, transmitter depletion can occur at Ia synapses causing a decrease in Ia synaptic efficacy (Curtis & Eccles 1960; Hultborn et al. 1996), and the discharge threshold of Ia afferents may be increased (Hayward et al. 1986; Lin et al. 2002). Note that each of these mechanisms is presynaptic in origin, with the post-synaptic excitability of the homonymous α -motoneurons seemingly unaffected by muscle-tendon unit

vibration (Abbruzzese et al. 1997). This ability to modulate the efficacy of Ia afferent- α -motoneuron transmission makes muscle-tendon unit vibration a useful tool for studying reflex involvement in a variety of motor tasks.

1.2 – Sensorimotor cortex activity and force production

1.2.1 – Background

The primary cortical regions directly associated with motor action and somatosensory processing has long been established. For example, the somatotopic organisation of the primate primary motor cortex was first mapped over a century ago (Grünbaum & Sherrington 1901), along with the division of the primary motor and sensory cortices via the central fissure (Cushing 1909). Following these discoveries, the electrophysiological behaviour of these structures, and how this relates to their function, became a topic of considerable interest among neurophysiologists, and remains so today. One early advancement in this area followed the advent of the electroencephalogram (Berger 1929), which involves measuring differences in electric potential across the scalp. Berger described a ‘beta-type’ (16-22 Hz) rhythmic potential arising in the precentral gyrus of resting human subjects (Berger 1929), and a “blocking” of this sensorimotor rhythm during voluntary movements was later detailed by Jasper & Penfield (1949). Further advances in measurement techniques, technologies and computational capabilities have continued to elucidate the relationships between ‘cortical activity’ within the sensorimotor cortex and motor behaviours. More recent avenues of investigation have included microelectrode recordings from cells in the sensorimotor cortex of non-human primates, functional magnetic resonance imaging during motor actions, and magnetoencephalographic recordings of sensorimotor oscillations (each of which are described in more detail in the following discussions). Even so, the relationships between numerous indices of sensorimotor activity and movement

kinetics are still poorly understood. In particular, whether the motor parameters of a voluntary movement might modulate the oscillatory dynamics within the sensorimotor cortex is far from clear.

1.2.2 – Sensorimotor cortex activity and force production: single-cell recordings from non-human primates

Pioneering work by (Evarts 1968) revealed a relationship between discharge frequencies of pyramidal tract neurons in the precentral gyrus and the force characteristics of wrist flexor/extensor contractions. In this study, three adult monkeys were trained to perform alternate wrist flexion and extension movements; moving a vertical rod through a 30° range of motion in each direction within 400-700 ms. An external load of 0, 100, 200 or 400 g was applied to the rod so that it either opposed flexion or extension. In this way wrist movements involved activation of either the wrist flexors or extensors irrespective of whether the joint was moving through flexion or extension. Thus force production was dissociated from the direction of movement during task performance. Unit recordings were collected from >100 pyramidal tract neurons by inserting microelectrodes through the dura mater into the brain. Of the 31 neurons that were associated with task performance, 26 demonstrated a discharge frequency pattern that was primarily related to either the force or RFD of the contractions (or both).

This positive relationship between volitional force output and the activity of pyramidal tract neurons in the precentral gyrus was reaffirmed in a follow up study by Evarts (1969) in which two monkeys were trained to use the same apparatus (Evarts 1968) to perform isometric contractions of both the wrist flexors and extensors. The use of isometric contractions demonstrated that activity of the motor cortex pyramidal tract neurons was directly related to the active muscle force (or RFD) as opposed to the resultant joint displacement. This hypothesis was further corroborated by a separate research group (Cheney & Fetz 1980), who found that corticomotoneuronal cells within the precentral cortex demonstrated tonic firing rates that were linearly related to isometric wrist flexion/extension torque.

Although several other studies have confirmed that some precentral neurons increase their discharge frequency with active force (e.g. Thach 1978; Evarts et al. 1983; Hepp-Reymond et al. 1999); all these investigations have also found numerous cells in which an increase in activity (firing) was coincident with movement/contraction, but the level of activity was unrelated to force. In fact, only a small minority of cells within the motor cortex may moderate their activity in relation to muscular force production (Ashe 1997). For example; Taira et al. (1996) recorded impulse activity in a total of 188 cells in the arm area of the primary motor cortex in two monkeys, who were trained to accurately apply steady isometric contraction forces against a manipulandum (rigid vertical rod) in response to a visual cue (cursor and cursor target on a visual display). Each cell demonstrated a change in activity with proximal movements of the contralateral arm, but not movements of the hand/fingers (inclusion criteria). The relationship between the discharge frequency of these cells and both the magnitude and direction (in three dimensions) of the applied force was assessed using a stepwise multiple linear regression. The regression model was significant in 154 (81.9%) of the 188 cells, of which; 121 (78.6%) were related to the direction, but not the magnitude of force, 11 (7.1%) were related to the magnitude, but not the direction of force, and 22 (14.3%) were related to both the direction and magnitude of the applied force.

One further study of interest comes from Wannier et al. (1991), in which single-cell activity was recorded from both the precentral motor and postcentral sensory cortices of three adult monkeys, who were trained to finely control an isometric force (~ 0.1 - 0.9 N) applied to a transducer held between the thumb and index finger. Electrical stimulation via the inserted microelectrodes evoked a motor response at 87% of the precentral sites, but also 25% of the postcentral sites; indicating a potential role for the primary sensory cortex in force production. However, an altered firing pattern was observed prior to force onset in 56% of the task-related precentral neurons, whereas this was true in only 14% of postcentral neurons. Subsequently, these authors suggested that the primary sensory cortex might significantly contribute to the regulation of finely graded force production, but have little input to contraction initiation. Overall, these results indicate that

force production should perhaps be considered a sensorimotor (rather than simply a motor) process.

An important advantage of microelectrode recordings is that they offer a direct measurement of neuronal activity. (In healthy human subjects, cortical behaviour must usually be inferred from indirect measurements of neuronal activity). However, single-cell studies also encounter a number of inherent limitations. For example; it is difficult for single-cell recordings to determine whether the number of participating cells changes with contraction parameters, or to monitor multiple cortical regions simultaneously. The aforementioned investigations on monkeys have also only managed to study contraction force up to relatively low amplitudes; presumably to avoid physical fatigue. Therefore, non-invasive recordings from human subjects remain useful in building a more complete understanding of how the cortical activity may modulate with of the motor parameters of voluntary contractions.

1.2.3 – Sensorimotor cortex activity and force production: Functional neuroimaging using PET and fMRI

In humans, both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used to investigate the relationship between cortical activation and voluntary force production; and a number of studies have demonstrated a positive relationship between these two variables. Dettmers et al. (1995) recorded relative regional cerebral blood flow (rCBF) using PET in six healthy adult males performing 1 Hz near-isometric contractions of the right index finger (pressing a Morse-key); producing a sinusoidal-like force output with peak forces of either 5, 10, 20, 40 or 60%MVF. An increased rCBF was recorded in a number of brain locations during task performance, including the dorsal bank of the cingulate sulcus, the ventral portion of the supplementary motor area, and the ipsilateral cerebellar vermis. However, it was the contralateral sensorimotor cortex that demonstrated both the greatest relative increase in rCBF and the strongest correlation (logarithmic relationship) between rCBF and peak force during the key presses.

Thickbroom et al. (1998) examined the blood-oxygen-level dependent (BOLD) fMRI response to isometric flexion of digits 2-5. Contractions were performed at four force levels; 5, 10, 25 and 50%MVF, and were facilitated by visual feedback of a pressure gauge. This was completed within the MRI scanner, and required each force level to be maintained throughout four separate 18-s scans. The results demonstrated that greater contraction forces were accompanied by substantial increases in the number of significantly activated voxels within the central sulcus (i.e. the area of the cortex that is active during the task), in addition to small increases in the magnitude of BOLD signal change per voxel. Similarly, Cramer et al. (2002) observed activation foci to span both the precentral and postcentral gyri during repetitive hand-grip contractions at 1 Hz. Contractions were exerted against a hand-grip dynamometer at three individually defined force levels: light, medium and hard. These authors found both the activation volume and the magnitude of the BOLD signal change to increase monotonically with contraction force.

Four further investigations recorded the BOLD response during well controlled isometric contractions of the hand/fingers. Three of these studies involved ~5-s isometric hand-grip contractions performed at 20, 35, 50, 65 and 80%MVF (Dai et al. 2001), 20-s isometric index finger abductions at 5, 15, 30, 50, and 70%MVF (van Duinen et al. 2008), or during repeated (0.33 and 0.67 Hz) isometric hand-grip contractions at 10, 20, 40 and 60%MVF (Ward & Frackowiak 2003). Each of these three investigations found the magnitude of the BOLD signal to increase linearly with contraction force at a number of locations in the brain, including the contralateral sensorimotor cortex and ipsilateral cerebellum in each study. Alternatively, Keisker et al. (2009) examined the BOLD response to repeated isometric thumb and forefinger pinching ('power grip') at 10, 20 and 30%MVF and a rate of 0.5 Hz. A task-related increase in BOLD signal was also identified at several cortical locations, however, only the contralateral primary motor cortex and ipsilateral cerebellum demonstrated a significant linear relationship with contraction force.

The rate of motor task execution (specifically, the frequency of finger tapping) has also been shown to demonstrate a positive linear relationship with haemodynamic correlates of neuronal activation using both PET (Blinkenberg et

al. 1996) and fMRI (Rao et al. 1996). However, changes in movement rate inherently involve variations in numerous other motor parameters; including RFD, acceleration forces, eccentric deceleration forces, and velocity of displacement. Further investigations are therefore required to extract the relative influence of these individual parameters. For example, using isometric contractions of distinct RFDs could isolate the effect of RFD from the parameters related to displacement.

1.2.4 – Why EEG/MEG?

Without question, BOLD fMRI responses provide an invaluable measure of ‘brain activity’, with a spatial resolution at the sub-millimetre scale. However, the BOLD fMRI response reflects the metabolic demands of neuronal activity, with the haemodynamic responses underpinning the fMRI signal arising as an indirect consequence of electrical function in brain cells, and it is this electrical function that is of greater interest as this is the method of communication within the brain. Cognitive functions are mediated by electrophysiological interactions between distributed populations of neurons, and in turn these interactions produce local oscillations in neuronal activity (Donner & Siegel 2011). Electroencephalography (EEG) and magnetoencephalography (MEG) measure the electric and magnetic fields that are produced as a direct consequence of this oscillatory activity. Specifically, these fields arise from synchronous post-synaptic (dendritic) current flows in concentrated populations of neurons (Proudfoot et al. 2014). Thus, the recorded EEG/MEG is temporally synched to the underlying electrophysiological behaviour, and the temporal resolution of EEG/MEG is limited only by the maximum sampling frequency of the recording hardware; not the physiology of the response being recorded, as per the haemodynamically derived fMRI (E. Hall et al. 2014). This means that EEG and MEG are able to record the ongoing neuro-oscillatory activity within the cortex, as well as any task-driven modulations in these oscillations.

EEG and MEG (as well as fMRI) are both non-invasive techniques, which is of obvious benefit to the study of human brain function. However, this also means that the electrophysiological parameter under estimation (dendritic current flows)

must be inferred from the resultant electric (EEG) and magnetic (MEG) fields as they appear at the extracranial sites of recording. This projection (forward modelling) places an inherent limitation on the spatial resolution of EEG/MEG measurements (Proudfoot et al. 2014). In this regard, MEG offers a significant advantage compared to EEG as unlike the electric field, the magnetic field is not distorted by the biological tissues between the cortex and the recording sensors. Moreover, MEG typically offers a higher signal-to-noise ratio and a greater number of scalp-based sensors than EEG. Collectively, these factors give MEG an improved spatial resolution and sensitivity compared to EEG (E. Hall et al. 2014).

EEG does however have its own advantages. EEG sensors may be secured directly to the scalp of the participant and are therefore less susceptible to noise arising from head movement than MEG sensor arrays, which are typically housed in a helmet-shaped dewar. This is of particular advantage when investigating continuous exercise or motor-related paradigms involving forceful contractions in large muscle groups, as avoiding head movements can become challenging. There are also substantial financial benefits to EEG when compared to MEG systems, both in terms of initial outlay and maintenance costs.

1.2.5 – Oscillatory activity in the sensorimotor cortex

Electrophysiological rhythms were first recorded from the human cortex in the 1920's by Hans Berger (Berger 1929), who measured differences in electric potential across the scalp and noted the existence of a 8-13 Hz 'alpha' rhythm. Rhythmic (or oscillatory) activity arises from synchronous neuronal activity and is typically divided into frequency bands; based upon early identification of a particular topographical or biological significance. Commonly identified rhythms include the delta (~1-4 Hz), theta (~4-8 Hz), alpha (~8-13 Hz), beta (~13-30 Hz) and gamma (~30-200 Hz) bands. Once considered 'brain noise' due to their presence in states of rest, these oscillations are now regarded as being functionally significant to brain function, with subtle and focal spatiotemporal modulations in oscillatory amplitude accompanying stimulus presentation

(Stevenson et al. 2011), attentional shifts (Bauer et al. 2014) and task performance (Puts et al. 2011).

Within the sensorimotor cortices, two prominent rhythms have received particular attention; namely the mu (~7-15 Hz) and beta (~15-30 Hz) oscillations, both of which are consistently observable at rest, and demonstrate time-locked modulations in response to movement-related behaviours. Jasper & Penfield (1949) first demonstrated the decrease in amplitude of the Rolandic beta rhythm during the preparation and performance of hand and finger movements using intracortical recordings from the pre-central gyrus. A concurrent blocking of the mu rhythm was also identified in the following decade, along with a transient increase in the beta oscillations following movement termination (Chatrian et al. 1959). These phenomena have since become part of a coherent description of voluntary contraction-driven modulations in ongoing oscillatory activity. During the preparation and execution phases of unilateral movements, a decrease in mu and beta amplitude is observed, with the largest effect occurring local to contralateral primary sensorimotor cortex (Salmelin & Hari 1994; Leocani et al. 1997). Following movement cessation beta oscillations then exhibit a period of elevated amplitude (Pfurtscheller et al. 1996; Jurkiewicz et al. 2006).

These movement-related changes in sensorimotor oscillations are extremely robust across individuals. In addition, beta band amplitude changes are observed even in the absence of active muscle contraction (e.g. during passive movements (Cassim et al. 2001)), or the absence of movement altogether (e.g. during motor imagery (Schnitzler et al. 1997; Pfurtscheller et al. 2005)). This robustness has been to the advantage of neuroscientific applications; for example, brain computer interfaces involving real-time measures of movement-related changes in oscillatory amplitude (Pfurtscheller & Solis-Escalante 2009).

Recent work also suggests that task-related modulations in oscillatory rhythms, both during and after stimulation, have great potential to be used as a biomarker for pathology. For example, the beta rebound response following contraction offset is greater in healthy controls than patients with schizophrenia, and the magnitude of beta rebound in patients correlates with persistent symptoms of disease (Robson et al. *In Press*). Additionally, the extent of interhemispheric

disparity in sensorimotor beta oscillations correlates with symptom severity during early stage Parkinson's disease (S. Hall et al. 2014). Understanding sensorimotor oscillations and their modulation with motor-action might therefore be of significant value to a range of fields within human function and health. Despite this, mu and beta band changes remain relatively poorly understood. In particular, how these oscillatory phenomena might be modulated with the parameters of a motor task (e.g. contraction force) has received only a modicum of attention.

A note on Terminology:

Mu oscillations are a sensorimotor rhythm, similar in frequency to alpha oscillations reported elsewhere in the cortex. Consequently, the term 'alpha' has often been used in place of 'mu', particularly in studies utilising EEG, in which the limited spatial resolution may not have allowed for accurate distinction of mu oscillations. (In fact, where spatial resolution/precision is limited, 'alpha' might arguably be a more appropriate term as recordings may encompass both the mu rhythm and the more pervasive alpha rhythms of the cortex, which tend to be of greater amplitude (Kozelka & Pedley 1990)). However, it is important to note that these terms are not interchangeable but instead relate to separate phenomena.

The mu rhythm is spatially distinct from the most prominent alpha rhythms e.g. the occipital alpha rhythm, arising locally in the pre- and post-central areas of the sensorimotor cortex (Jasper & Andrews 1938; Chatrian et al. 1959). Moreover, several mu rhythms may be observed that are topographically mapped to specific regions of the motor/sensory homunculus (Pineda 2005). The mu rhythm also differs from alpha rhythms in its reactivity to various tasks, most notably; a decrease in mu amplitude accompanies motor activity/somatosensory processing, and mu amplitude is unaffected by closing the eyes (as opposed to an increased amplitude of the occipital alpha rhythm) (Kozelka & Pedley 1990). More importantly, this spatial separation and differing reactivity indicates a functional specificity of the mu rhythm. Decreases in synchronous rhythms are widely believed to reflect an increase in local information processing. Thus, a decrease in mu amplitude is likely to relate to an increase in motor/somatosensory processing. Specifically, it has been suggested that changes in mu amplitude

may be involved in the translation of perception to action, possibly arising locally as a down-stream effect of mirror neuron input (see Pineda 2005). Finally, the mu rhythm is often difficult to observe in the time domain, due in part to the spatially overlapping Rolandic beta rhythm that is commonly of greater amplitude, but the mu rhythm can be distinguished by its unique profile; that of a recurring mu (μ).

In the following discussions, the terminology used by the specific study under reference is adopted in each circumstance.

1.2.6 – Sensorimotor activity and force production: Functional neuroimaging using EEG

A handful of previous studies have investigated the relationship between sensorimotor oscillatory activity and voluntary contraction force. Some indications that contraction-driven changes in oscillatory amplitude might be modulated by the force output of the performed contractions have been reported. Mima et al. (1999) recorded surface EEG from the hand area of the contralateral sensorimotor cortex (FC3 and C3 electrodes, International 10-20 System) during isometric ‘pinching’ of a force transducer using the right thumb and little finger. The magnitude of the reductions in alpha (8-12.9 Hz) power during the constant-force contractions was linearly related to force during isometric contractions of between 10 and 60%MVF (i.e. greater reductions in alpha power during contractions of higher forces). In contrast, no significant change in either lower beta (13-20.9 Hz) or upper beta (21-30.9 Hz) power was observed between contraction forces. In a separate study, Dal Maso et al. (2012) recorded surface EEG from the vertex (Cz electrode) during both isometric knee extension and flexion. Contractions were performed at 20, 40, 60 and 80% of the “relative maximum voluntary torque” (the maximal achievable torque level without holding breath or contracting muscles not associated with knee flexion/extension). In contrast to Mima et al. (1999), these authors found the magnitude of the contraction-driven reductions in upper beta (21–31 Hz) power were linearly related to isometric knee flexion torque in their strength trained participant group. However, no torque-related modulations in beta power loss were identified during knee flexion performed by endurance trained participants, or during knee

extensions performed by either strength or endurance trained participants. In other words, the majority of their findings would indicate no change in beta power loss with contraction force. Overall, findings within the literature are inconsistent, and reports indicating that contraction-driven power loss in both the mu and beta bands are independent of contraction force are equally as prevalent within the literature.

Stančák et al. (1997) recorded surface EEG (electrode C3 or a separate electrode positioned 2.5 cm medial to C3) throughout a series of brisk (0.13 to 0.21 s duration) index finger extensions against an external load of 0, 30, 80, or 130 g. Contraction-driven reductions in both mu (8-13 Hz) and beta (14-30 Hz) power were observed, peaking during the performance of the brief movements, however the magnitude of these peaks were not modulated by the load opposing the contractions. Similarly, Cremoux et al. (2013) recorded surface EEG (electrode C3) during isometric elbow flexion contractions at 25, 50 and 75% of relative maximum torque, and found no effect of contraction torque on beta (13–31 Hz) power loss.

These latter two studies also recorded the PMBR following contraction offset, however findings were once again inconsistent. Stančák et al. (1997) observed a two-phase PMBR with peaks observed in the first and third second of the post-movement period. The magnitude of this second peak was greater following the brief finger extensions performed against the heaviest external load (130 g) compared to the unloaded extensions. Conversely, Cremoux et al. (2013) found no effect of contraction force on the amplitude of the PMBR following the isometric elbow flexor contractions at 25, 50 and 75% of relative maximum torque. The cause of these dichotomous results is not clear; however, motor parameters other than force output during the anisometric contractions (e.g. the RFD) may have contributed to the modulation of PMBR in the study of Stančák et al. (1997). Further investigations are therefore required to elucidate whether these movement-related changes in oscillatory amplitude might be modulated by the motor parameters of the performed contractions. In particular, using isometric contractions would enable the force and RFD of contractions to be isolated as independent variables.

1.3 – The effect of physical fatigue on sensorimotor cortex activity

1.3.1 – Background

Physical fatigue can be defined as a reversible decline in the force generating capacity of the neuromuscular system. During physical activity, fatigue arises not only from peripheral processes within the working muscle but also from supraspinal mechanisms within the brain (Gandevia 2001). Overall, fatigue has clear implications to physical performance, and may be experienced as a chronic activity-limiting symptom that adversely affects the quality of life in numerous patient groups. However, exactly how cortical activity is modulated during fatigue is not well understood. This is in large part due to the difficulties in accurately recording brain activity in humans, particularly during strenuous muscle contractions.

1.3.2 – Evidence for a supraspinal contribution to physical fatigue

Voluntary activation is a measure of how well a subject can drive a muscle (or muscle group) to produce maximal force (Taylor et al. 2006), and is described relative to the capacity for force production of that muscle. It is most commonly estimated using twitch interpolation (Merton 1954), which involves recording the evoked twitch response following stimulation of the motor pathway to the contracting muscle. Commonly this involves transcutaneous electrical stimulation of the motor nerve (Belanger & McComas 1981; Allen et al. 1998) or transcranial magnetic stimulation (TMS) of the motor cortex (Gandevia et al. 1996; Todd et al. 2004) during the performance of an MVC. If a superimposed twitch response is evoked by the stimulus, voluntary activation is less than 100%. (Even when unfatigued, subjects are rarely able to achieve 100% activation (Todd et al.

2003)). This means that no part of the motor pathway downstream of the point of stimulation can be operating at its capacity. Or put another way, a failure to drive the muscle maximally has occurred, and can be attributed to processes occurring upstream of the site of stimulation. When a submaximal voluntary activation is determined using TMS applied to the motor cortex; this failure to drive the muscle maximally has originated within or upstream of the motor cortex (Gandevia et al. 1996). During fatiguing exercise voluntary activation has been shown to decrease despite the efforts of the subjects to perform a maximal contraction. Again, in the example of TMS applied to the motor cortex; this decrease in voluntary activation demonstrates a progressive sub-optimal output of the motor cortex. This process is termed supraspinal fatigue (Taylor et al. 2006).

Supraspinal fatigue (as evidenced by a progressive decline in voluntary activation calculated using TMS applied to the motor cortex) has been demonstrated to occur in a variety of motor paradigms; including sustained isometric contractions at both high and low force outputs (Taylor & Gandevia 2008), intermittent MVCs (Taylor et al. 2000) and following locomotor exercise (ergometer cycling) (Sidhu et al. 2009; Goodall et al. 2012). During a sustained isometric maximal contraction, supraspinal fatigue accounts for approximately 22-30% of the decline in force occurring in the first two minutes (Taylor et al. 2006). Alternatively, supraspinal fatigue may account for 40% of the physical fatigue developed during a 43-min isometric contraction of the right elbow flexors at 15%MVF (Søgaard et al. 2006), or as much as 66% during a 70-min 5%MVF contraction of the same muscle group (Smith et al. 2007). Overall, these studies demonstrate that during physical fatigue in a variety of tasks, some of the changes that lead to a decline in force output of the muscles take place at a supraspinal level, i.e. within the brain.

1.3.3 – The effect of physical fatigue on sensorimotor activity: Investigations using fMRI

Several studies have used fMRI to observe the patterns of 'cortical activation' accompanying the performance of a fatiguing motor task. A number of these studies found increases in the fMRI signal as fatigue developed during the

prolonged performance of (at least initially) submaximal voluntary contractions. Liu et al. (2003) recorded the fMRI response (number of activated voxels) during the performance of two separate fatiguing motor tasks: a continuous 225-s unilateral handgrip contraction at 30% maximal force and a series of 320 2-s handgrips of the same intensity (67% duty cycle). An initial increase, followed by a plateau or marginal decrease in the number of activated voxels within the contralateral primary motor and sensory cortices was observed in both paradigms. In contrast, Benwell et al. (2007) found an increase in the magnitude of the BOLD response but not the number of activated voxels within the contralateral sensorimotor cortex during a comparable motor task; ~9 min of intermittent 3-s handgrip contractions at 30% maximal force (60% duty cycle).

In a similar study, van Duinen et al. (2007) recorded the BOLD fMRI response during a series of fifteen 50-s isometric abductions of the right index finger at 30% maximal force (91% duty cycle). Increases in both the intensity and area of activation were observed in a number of cortical areas including the contralateral sensorimotor cortex during the development of fatigue. However, in a separate experiment involving constant-force contractions at distinct force levels performed in an unfatigued state, increases in both the intensity and area of the BOLD response were again identified, this time with increments in contraction force (van Duinen et al. 2007). Subsequently, these authors suggested that the increases in the fMRI response within the sensorimotor cortex during the development of fatigue may represent a correlate of muscle activity, as additional motor units are recruited in order to maintain the prescribed force output.

However, augmentations in the fMRI signal have also been demonstrated to accompany fatigue onset during maximal contractions. For example, Liu et al. (2002) found a number of cortical regions, including the contralateral primary motor and sensory cortices, to demonstrate a marked increase in activated voxel volume throughout the first minute of a 2-min handgrip MVC, after which the number of activated voxels decreased back towards initial levels. This fMRI response profile was in no way a correlate of either contraction force or EMG activity, both of which decreased continuously throughout the maximal effort. Similarly, Steens et al. (2012) found the magnitude of the BOLD response within both the left precentral and postcentral gyri to increase throughout a 124-s

maximal right index finger abduction in a cohort of twenty healthy adults (a separate group of Multiple Sclerosis patients demonstrated some alternate responses). Again, this increase in cortical activation accompanied a progressive decrease in both force and EMG amplitude. Therefore, these increases in the fMRI signal cannot represent a simple correlate of increased corticospinal output to the motor unit pool.

One further study by Post et al. (2009) demonstrated a gradual increase in both the volume of activated sensorimotor cortex and the mean BOLD signal per volume during a 126-s maximal abduction of the right index finger. These authors also found an increase in EMG activity in the wrist-flexor muscles over the course of the contraction, and suggested that the increase in the volume of activated cortex may represent the activation of non-target muscles as participants endeavour to maintain a maximal torque. Conversely, the increase in the magnitude of the BOLD response during fatigue was suggested to reflect local increases in motor/sensory processing of both inhibitory and excitatory neuronal inputs. Indeed supraspinal fatigue is a complex process involving numerous inhibitory and excitatory networks, which interact to regulate corticospinal output (Tanaka & Watanabe 2012). Consequently, a comprehensive analysis of neuronal activity during physical fatigue cannot be achieved using fMRI alone.

1.3.4 – The effect of physical fatigue on sensorimotor activity: Investigations using MEG

To date, few attempts have been made to determine whether movement-related oscillatory dynamics (e.g. beta amplitude decrease) within the sensorimotor cortex are modified during physical fatigue. Tecchio et al. (2006) recorded MEG during submaximal voluntary contractions of the extensor communis digitorum, performed before and after a maximal contraction of the same muscle held until volitional exhaustion. These authors reported that the contraction-driven reductions in beta amplitude were no longer observed within the contralateral sensorimotor cortex following the fatiguing MVC; potentially suggesting a substantial effect of fatigue on the typical patterns of motor-related oscillatory behaviour. However, a number of methodological concerns should perhaps be

considered before any firm conclusions can be drawn from these results. Firstly, no control trial was performed, and attenuation in beta amplitude loss may occur as a consequence of task habituation during the early phases of task repetition (Kranczioch et al. 2008; Studer et al. 2010; Pollok et al. 2014). Additionally, no attempt to actually measure physical fatigue was made following the maximal contraction. And finally, the submaximal contractions appeared to be poorly controlled, with the force of contractions described as “about 20-35% MVC”. As such, further investigation appears warranted before the observed abolition of the contraction-driven beta amplitude loss can be wholly attributed to the assumed state of physical fatigue following the prolonged contraction. Yet, to the author’s knowledge, no investigations have made any attempt to corroborate these findings. One further study by Tanaka et al. (2011) did find a reduction in beta amplitude loss within the contralateral sensorimotor cortex during mental imagery of handgrip MVCs following a fatiguing intermittent handgrip exercise performed until task failure. However, imagined movements do not involve the same motor or sensory processing as performed movements (Schnitzler et al. 1997), and may be affected differently by physical fatigue.

1.4 – Summary and Aims

1. The recruitment of skeletal muscle involves both supraspinal and peripheral inputs to the motor unit pool. Excitatory input from Ia afferents have been demonstrated to assist in the recruitment of high threshold motor units (Bongiovanni et al. 1990), and the achievement of maximal motor unit firing rates (Hagbarth et al. 1986; Macefield et al. 1993). However, whether maximal force development is dependent on these inputs is not clear. Prolonged tendon vibration can moderate the efficacy of the homonymous Ia afferent- α -motoneuron pathway (Desmedt & Godaux 1978). Consequently, this technique has been used to assess maximal force production in conditions of impaired Ia afferent- α -

motoneuron transmission; with contrasting results being reported (Ushiyama et al. 2005; Ekblom & Thorstensson 2011). Therefore, the aim of chapter 2 was to further investigate the effect of prolonged tendon vibration on maximal and explosive force production in the knee extensors.

2. A linear relationship between voluntary contraction force and the BOLD fMRI response within the contralateral sensorimotor cortex has been demonstrated by a number of studies (Dai et al. 2001; van Duinen et al. 2008; Keisker et al. 2009). However, the BOLD fMRI response reflects the metabolic demands of neuronal activity, with the haemodynamic responses underpinning the fMRI signal arising as an indirect consequence of the electrophysiological interactions underpinning cognitive function. EEG and MEG measure the electric and magnetic fields that are produced as a direct consequence of this electrophysiological activity. Consequently, these techniques have been instrumental in constructing a coherent description of neuro-oscillatory responses to voluntary muscle contractions. This includes contralaterally preponderant decreases in sensorimotor mu and beta amplitude during contractions, followed by a post-movement rebound in beta amplitude (Pfurtscheller & Lopes da Silva 1999; Jurkiewicz et al. 2006). However, whether these phenomena are modulated with the various motor parameters of the performed contraction is still unclear. Force-related modulations in the contraction-driven mu amplitude loss (Mima et al. 1999), beta amplitude loss (Dal Maso et al. 2012), and the PMBR (Stančák et al. 1997) have all been suggested, however results are inconsistent in each case. Subsequently, chapters 3 and 4 aimed to investigate the influence of voluntary contraction force and RFD (chapter 4 only) on sensorimotor oscillatory dynamics using EEG and MEG, respectively.
3. During physical activity, fatigue arises not only from peripheral processes within the working muscle but also from supraspinal mechanisms within the brain. However, exactly how sensorimotor cortex activity is modulated

during physical fatigue is poorly understood. Increases in the BOLD fMRI signal within the sensorimotor cortex have been demonstrated during fatiguing contractions; reflecting local increases in sensorimotor processing, despite concurrent decreases in corticospinal output. Additionally, one previous study (Tecchio et al. 2006) reported that a contraction-driven beta amplitude loss was no longer observed during submaximal contractions of the extensor communis digitorum following a fatiguing maximal contraction of the same muscle. This investigation might demonstrate a potential effect of fatigue on the typical movement-related oscillatory dynamics described above; however, few investigations have attempted to corroborate these results. The aim of chapter 5 was therefore to investigate how ongoing oscillatory activity within the sensorimotor cortex might be influenced by physical fatigue.

Chapter 2:

Prolonged infrapatellar tendon vibration
does not influence quadriceps maximal
or explosive isometric force production
in man

2.1 – Abstract

The influence of muscle/tendon vibration on maximal muscle performance is unclear. Therefore, this study examined the effect of a prolonged tendon vibration stimulus on maximum voluntary contraction (MVC) and explosive voluntary contraction (EVC) performance. Eighteen young healthy males (nine strength trained and nine untrained) completed a series of isometric unilateral knee-extensions (EVCs, electrically evoked octet responses, MVCs, ramp contractions) pre and post two separate 30-min intervention trials; infrapatellar tendon vibration (80 Hz), and quiet sitting (control). $H_{\max}$ and $M_{\max}$ was measured at the start and end of each series of contractions, both pre and post intervention (i.e. at four time points). Knee extensor force and both quadriceps and hamstrings EMG were measured throughout each series of contractions. The results show vibration had no effect on either maximum force (ANOVA, trial $\times$ time interaction $P=0.92$), explosive force ($P\geq 0.36$), or the associated agonist EMG amplitude during these tasks ($P\geq 0.23$). Octet responses (8 supramaximal pulses at 300 Hz) were also unaffected by vibration ($P\geq 0.39$). Conversely, post-intervention $H_{\max}/M_{\max}$ was 60% lower in the vibration trial vs. control, and remained 38% lower at the end of the post-intervention measurements (t-test, both $P<0.01$). Individual $H_{\max}/M_{\max}$ depression did not correlate to changes in either maximum or explosive force (Spearman's Rank, $P\geq 0.54$), and training status had no influence on the effect of vibration. In conclusion, prolonged infrapatellar tendon vibration depressed H-reflex amplitude but did not affect either maximal or explosive isometric force production of the quadriceps.

2.2 – Introduction

During voluntary contractions of the skeletal muscles, the monosynaptic Ia afferent- α -motoneuron reflex pathway has been suggested to contribute to the recruitment of high threshold motor units (Bongiovanni et al. 1990), and to the achievement of high motor unit firing rates (Hagbarth et al. 1986; Macefield et al. 1993). Prolonged mechanical vibration applied to the muscle-tendon unit can attenuate the efficacy of Ia afferent- α -motoneuron transmission; which may occur via a number of mechanisms including increased presynaptic inhibition at the Ia terminals (Hultborn et al. 1987; Lapole et al. 2012), or a neurotransmitter depletion at the Ia synapses (Curtis & Eccles 1960; Hultborn et al. 1996). Accordingly, a compromised capability for maximal force production has been reported following prolonged vibration stimulus applied to either the muscle (Kouzaki et al. 2000; Jackson & Turner 2003) or tendon (Ushiyama et al. 2005; Konishi et al. 2009). However, only two previous investigations (Ushiyama et al. 2005; Ekblom & Thorstensson 2011) have made any attempt to assess the efficacy of the Ia afferent- α -motoneuron pathway (using H-reflex measurements; see Methods) alongside strength measurements following a prolonged vibration stimulus to the muscle tendon unit. Both of these studies demonstrated a decrease in triceps surae H-reflex of 31%, following 30-min of Achilles tendon vibration, but while Ushiyama et al. (2005) observed a 17% decrease in peak plantar-flexor torque, Ekblom and Thorstensson (2011) found no difference in plantar-flexor strength.

Explosive force production can be defined as the capability to increase contractile force from a low or resting level (Folland et al. 2013). It is considered integral to the performance of tasks where the time available to develop force is limited, including explosive athletic events such as jumping and sprinting (Pääsuke et al. 2001; Tillin, Pain, et al. 2013), or stabilizing the musculo-skeletal system in response to mechanical perturbation. The influence of a prolonged localised vibration on explosive force production has only been examined by two studies, both of which found marked decreases in knee extensor peak rate of force development (RFD; ~24% (Kouzaki et al. 2000); 33% (Jackson & Turner 2003)). The greater changes in explosive than maximal force production (2-5 fold greater) in these studies could indicate a greater effect of vibration on explosive

contractions compared to maximal force tasks, and potentially a greater afferent contribution to explosive actions. However, these studies did not assess the H-reflex response to vibration or the possible mechanisms for the purported reduction in explosive force (i.e. alterations in neuromuscular activation or contractile properties of the muscle). The maximum contractile capacity of the muscle-tendon unit for explosive force production can be assessed by measuring the force response to evoked octet contractions (a train of 8 supramaximal electrical impulses applied at 300 Hz over the mixed nerve innervating the muscle under investigation; de Ruiter et al. 1999; Deutekom et al. 2000). It is also interesting to note that whole-body vibration has been shown not to influence explosive force production (de Ruiter et al. 2003; Erskine et al. 2007; Hannah et al. 2013) despite minor attenuations in maximum force production in some reports (de Ruiter et al. 2003; Erskine et al. 2007).

Chronic neural adaptations have been widely documented following strength training and may include more effective use of afferent feedback during strength tasks (Folland & Williams 2007). Earles et al. (2002) found power trained athletes had lower presynaptic inhibition, and suggested these individuals may benefit from a greater utilisation of the fusimotor pathway, particularly during explosive force production. Furthermore, improvements in peak RFD after resistance training have been found to correlate with increases in H-reflex amplitude (Holtermann et al. 2007), and this could indicate that alterations in the efficacy of the Ia afferent- α -motoneuron pathway influences explosive force production. The relative importance of the Ia afferent- α -motoneuron pathway to maximal motor performance might therefore be further explored by comparing the effect of a prolonged tendon vibration stimulus on explosive force production between strength trained and untrained individuals.

The primary aim of this study was to investigate the influence of a prolonged infrapatellar tendon vibration intervention, on maximal and explosive knee extensor force production. Secondary aims were to examine whether any post-vibration changes in volitional force production resulted from neural or contractile mechanisms, determine if individual changes in H-reflex following vibration were related to the alterations in maximal or explosive force production, and whether the effects of vibration differed between strength trained and untrained

participants. A decrease in maximal and explosive force production, neuromuscular activation and H-reflex amplitude after prolonged tendon vibration were hypothesised.

2.3 – Methods

Participants

Participants were eighteen healthy, injury-free males, with no known history of neuromuscular or skeletal disorders. The cohort comprised nine strength trained and nine recreationally active, but not systematically trained participants. The strength trained individuals (age 20 ± 2 years, stature 1.83 ± 0.08 m, body mass 85.2 ± 13.5 kg, (mean $\pm$ SD)) included five track and field athletes and four intermittent sports athletes who were accustomed to performing regular strength training and explosive power activities (4 to 10 strength/power sessions per week for at least 3 years) in their habitual training. The untrained individuals were recreationally active but not involved in competitive sports, or strength/power training (age 22 ± 2 years, stature 1.81 ± 0.08 m, body mass 76.7 ± 10.0 kg). The experimental procedures were approved by the Loughborough University Ethical Advisory Committee, and each participant provided written informed consent prior to their involvement.

Experimental design

Participants visited the laboratory on four occasions, ~7 days apart, and at a consistent time in the afternoon. The first two visits served as familiarisation with participants performing all of the experimental measurements during both sessions. Participants did not experience tendon vibration during familiarisation. The third and fourth visits comprised a randomised cross-over design, with a series of voluntary and electrically evoked unilateral isometric contractions of the knee extensors of the dominant leg performed pre and post either; a 30-min period of vibration to the ipsilateral infrapatellar tendon (vibration trial), or 30 min

of quiescent sitting (control trial). The knee extension contractions were designed to assess volitional function as well as neural (via EMG) and contractile (via evoked responses) mechanisms for any change in function and included; explosive voluntary contractions (EVC), evoked octet contractions (to determine the muscle's maximum capacity for explosive force production), maximal voluntary contractions (MVC), and ramp contractions to evaluate the EMG-force relationship. To assess the influence of the measured contractions, as well as the interventions, on the amplitude of the maximal H-reflex, all H-reflex and M-wave responses were recorded at both the start and end of each volitional and evoked contractions series, with the whole procedure repeated pre- and post-intervention. The timing of experimental measurements was strictly controlled as detailed in Table 2.1. Participants were advised to abstain from strenuous or atypical exercise for 36 h prior to the experimental trials, and to avoid the intake of nutritional stimulants (e.g. caffeine) on the day of the trial. Participants were also blinded from the hypothesised effects of the tendon vibration until after the final trial was completed.

The knee-extensors were investigated as this is an important locomotory muscle group with a mixed muscle fibre composition that provides an effective model for measurements of explosive force production. Furthermore previous studies of explosive force production following vibration have used this muscle group (Jackson & Turner 2003; Kouzaki et al. 2000); and H-reflex recordings from the VM demonstrate good within-session reliability ($H_{\max}/M_{\max}$ ICC, 0.92; Folland et al. (2008)).

Table 2.1 Order and timing of the volitional and evoked contractions conducted pre- and post-intervention

Time (min:s)	Measurement	Repetitions	Rest (s)
0:00	H-Reflex	4 stimuli × 5 currents	10
3:20	M-wave	3	10
4:00	Explosive voluntary contractions	6	15
5:30	Evoked octet contractions	3	15
6:20	Maximal voluntary contractions	2	30
7:30	Ramp voluntary contractions	2	30
9:20	H-Reflex	4 stimuli × 5 currents	10
12:40	M-wave	3	10

Intervention

Throughout both interventions (vibration and control) participants remained seated in the isometric strength testing chair and avoided contractions of the leg muscles. In the vibration trial, mechanical vibration was applied perpendicular to the mid-portion of the infrapatellar tendon for 30 min using an electromagnetic shaker (V201, Ling Dynamic Systems, Royston, UK) mounted on a tripod and fitted with a custom built concave steel head (10 × 20 mm surface). A control unit (TPO-20, Ling Dynamic Systems, Royston, UK) powered the vibration. In order to accurately characterise the vibration stimulus, seven additional volunteers were submitted to 5 min of infrapatellar vibration with the tripod hosting the electromagnetic shaker positioned on a portable 3-axis force plate (9286AA, Kistler, London, UK) and the vibrating unit filmed using a high-speed video camera (1000 Hz sampling rate; Phantom 4, Vision Research, Wayne, NJ). Analysis of ground reaction forces and the high-speed video confirmed the mean force applied to the tendon during vibration was ~20 N, and the peak-to-peak amplitude of the vibrating head was ~1.5 mm. Both procedures measured the frequency of vibration as 80 Hz, which has been demonstrated to preferentially activate Ia-afferents (Roll et al. 1989).

Vibration began 30 s after the completion of the pre-intervention measurements, and post-intervention measurements commenced 30 s following the cessation of vibration. The same separation between pre- and post-intervention measurements was maintained in the control trial during which participants simply remained seated.

Force measurements

All testing took place with participants seated in a custom built isometric knee-extension strength testing chair (Figure 2.1), which was individually adjusted to produce hip and knee angles of 110° and 120°, respectively. Adjustable waist and shoulder straps were applied firmly to restrain the participant and prevent extraneous movements. Force data were collected using a calibrated S-beam strain gauge (0-1500 N linear range; Force Logic, Swallowfield, UK) attached in series with an ankle brace fastened 2 cm proximal to the lateral malleolus, and positioned perpendicular to the tibia. Force data were sampled and recorded at 5000 Hz using an external A/D converter (Micro 1401, CED, Cambridge, UK) and a PC utilising Spike 2 software (CED, Cambridge, UK). The force signal was low pass-filtered at 500 Hz with a 4th order Butterworth digital filter, and notch filtered at 50 Hz with an infinite impulse response digital filter (q-factor of 50) to remove mains frequency noise. Real-time biofeedback of contraction force was provided on a computer monitor positioned in front of the participant.



Figure 2.1 The isometric knee extension strength testing chair used for all measurements and both interventions (main), and the position of the vibrator on the infrapatellar tendon (inset).

Electromyography measurements

Surface EMG was recorded using two Delsys Bagnoli-4 acquisition systems (Delsys, Boston, MA). Following shaving, gentle abrasion and cleansing with ethanol, two double differential bar electrodes (10 mm inter-electrode distance; Bagnoli DE-2.1, Delsys, Boston, MA) were positioned over each of the superficial muscles of the quadriceps at specific percentages of thigh length (greater trochanter to lateral knee joint centre distance) from the superior border of the patella as follows: vastus medialis, 35% and 25%; vastus lateralis, 55% and 45%; and rectus femoris, 65% and 55%. The proximal and distal electrodes on each muscle were offset laterally and medially, respectively, from the longitudinal mid-

line of the muscle belly by ~10 mm, and aligned parallel to the presumed orientation of the muscle fibres. One electrode was placed over the midline of the muscle belly of both the semitendinosis and biceps femoris long head of the hamstrings (HAM), 45% of thigh length from the popliteal fossa. A reference electrode was situated over the patella of the same leg.

The EMG signals were amplified ($\times 1000$; differential amplifier, 20–450 Hz), sampled at 5000 Hz and synchronised with the force data using the same data acquisition equipment. EMG signals were later band-pass filtered at 6–500 Hz with a 4th order Butterworth digital filter, and a 100 Hz infinite impulse response digital notch filter was applied to selected recordings where appropriate, prior to further analyses. Note: this notch filter was required due to noise generated by the steel frame of the knee extension rig as opposed to a poor impedance matching of differential electrodes. It was later found that grounding the frame of the rig was effective in removing (or greatly reducing) the presence of the 100 Hz noise.

The distal vastus medialis (VM_d, 25% of thigh length from the patella) EMG was used to assess H-reflex and these responses were normalised to $M_{\max}$ (see Electrical stimulation) from the same recording site. Volitional EMG from each of the 6 agonist muscle recording sites were normalised to $M_{\max}$ (of the same site) recorded at the start of the contractions series, before an average was calculated for the six sites (QUAD).

Electrical stimulation

Transcutaneous electrical stimulation was applied to the femoral nerve in the femoral triangle. The anode (70 × 100 mm carbon rubber electrode; Electro-Medical Supplies, Greenham, UK) was coated in electrode gel and positioned over the greater trochanter. A custom adapted cathode (10 mm diameter, protruding 20 mm from a 35 × 55 mm plastic base; Electro-Medical Supplies, Greenham, UK) was positioned according to the optimal twitch-response from a small stimulus current and secured in place using tape. Electrical stimuli were 1-ms square wave pulses, delivered by a constant current variable voltage

stimulator (DS7AH, Digitimer Ltd, Welwyn Garden City, UK), triggered via Spike2. Stimuli were separated by 10 s to minimise post activation depression (Crone & Nielsen 1989). Participants were also instructed to fix their gaze directly ahead, and avoid movements of the body, head and jaw so as to minimise Jendrassik facilitation (Kameyama et al. 1989). All stimulation was applied with the leg muscles relaxed.

H-reflex

The H-reflex is considered the electrical analogue of the mechanically induced stretch reflex, although it bypasses the influence of the muscle spindle and gamma motoneurons (Schiepatti et al. 1987). H-reflex measurements therefore provide an assessment of the efficacy of the monosynaptic Ia afferent- α -motoneuron pathway, which the vibration intervention was designed to perturb. The H-reflex is a well established technique with studies reporting high intra-session and inter-session reliability in a number of muscles including the vastus medialis (Hopkins & Wagie 2003).

Once seated in the strength rig, with EMG and stimulating electrodes in place, a stimulus-response calibration curve was conducted to establish the stimulus currents for eliciting H-reflex and $M_{\max}$ responses in the proceeding trial. Current increments varied widely depending on individual responses; ranging from 0.3 to 2.0 mA during H-reflex responses (~15 currents, 3 stimuli per current), before increasing in larger increments once M-wave amplitude had superseded that of the H-reflex response. Stimulus current increased until a plateau in both M-wave and twitch force responses were observed. Five separate currents for eliciting H-reflex responses were selected; ranging from the shoulder of the ascending limb on the response-curve (judged by visual inspection) to the emergence of an M-wave, with three intermediate stimulus currents evenly spaced in between. $M_{\max}$ were evoked using supramaximal stimuli, 25% above that required to achieve a plateau in M-wave responses.

The duration of reflex depression following vibration could be influenced by the volitional activity involved in performing maximal strength tasks. Therefore, H-

reflex measurements were repeated following functional performance measures in order to establish whether reflex depression persisted throughout these tasks. Measurements of H-reflex amplitude are often made at a current intensity that generates a specific motor response (e.g. 10-20% $M_{\max}$) to ensure stability of the input stimulus. However, a disproportionate change in the excitability of the afferent axons (relative to efferent axons) following repetitive spindle activation during vibration could invalidate this method. H-reflex responses were therefore elicited at five current intensities to safeguard against possible lateral shifts in the response curve, and to capture $H_{\max}$. H-reflex responses were also measured at rest. The primary objective of the present investigation was to determine the effects of vibration on maximal volitional performance (i.e. MVC & EVC) and therefore sustained volitional contractions for extended periods during H-reflex recordings were avoided in order to prevent fatigue that might compromise the primary functional measurements. The current authors presume that similar considerations led to previous studies in this field (Ushiyama et al. 2005; Ekblom & Thorstensson 2011) also electing to measure $H_{\max}/M_{\max}$ at rest.

Experimental protocol

Following the calibration curve, a 5-min rest was enforced before experimental measurements commenced (time 0:00, Table 2.1). Four H-reflex (per stimulus current) and three M-wave responses were elicited in ascending order of stimulus current. The peak-to-peak amplitude of the H-reflex responses were averaged for each stimulus current, and the current eliciting the highest H-reflex, defined as $H_{\max}$, was normalised to $M_{\max}$ (mean peak-to-peak amplitude of the maximal M-wave responses).

The EVC were performed in response to a verbal cue. Participants were instructed to contract the knee-extensors as “fast and hard” as possible. Of the six attempts only those efforts exceeding 70% of maximal voluntary force, and with a stable baseline force (i.e. counter-movement or pre-tension of <0.5 N deviation from baseline) were considered for further analysis. Of these, the two EVC displaying the highest peak RFD (numerical differential [5 ms epoch] of the force-time plot) were selected for further analysis, and the results averaged

across these two contractions. Force was measured at 50, 100 and 150 ms following force onset (F_{50} , F_{100} and F_{150} , respectively), and the amplitude of the EMG signal was assessed as the root mean square (EMG_{RMS}) from 0-50, 50-100 and 100-150 ms following EMG onset (earliest onset from any of the agonist muscle recordings). Force and EMG onsets for all contractions were manually identified by the same trained investigator using a systematic standard method (Tillin et al. 2010). Briefly, onset was defined as the last peak or trough before force/EMG exceeded the limits of the noise during the preceding 500 ms. Systematic manual identification by a trained observer is considered to provide highly accurate event detection (Tillin, Folland, et al. 2013; Allison 2003; Soda et al. 2010; Staude 2001; Kuriki et al. 2011). The reliability of this methodology has also been confirmed previously (between-trial, within-subject coefficients of variations for explosive force; $\leq 14.6\%$ (Tillin, Pain, et al. 2013); $\leq 16.6\%$ (Buckthorpe et al. 2012)).

Three octet contractions (eight pulses at 300 Hz) were evoked at 15 s intervals using the same current as for M_{max} . The evoked force response was assessed at 25, 50 and 75 ms following force onset and averaged across the three contractions. The force response to the octet provides an assessment of the maximal capacity of the muscle-tendon unit for explosive force production (de Ruiter et al. 2004).

Participants then performed two knee extension MVCs, exerting maximum effort for 3-5 s. The maximum voluntary force (MVF) was the highest force over a 500 ms epoch during the two repetitions, and EMG_{RMS} was calculated for the corresponding time window. Verbal encouragement was given during contractions and a horizontal line denoting maximal force achieved in the familiarisation sessions was presented on the screen.

Finally, in order to provide a more complete description of neuromuscular activation throughout a range of sub-maximum forces, participants performed ramp contractions by linearly increasing knee-extension force from rest to maximum force in 4 s. A line showing the target rate of force development was displayed on screen to facilitate an appropriate time-course. The amplitude and median frequency of the QUAD EMG were recorded for 250 ms epochs (± 125 ms)

at specific relative forces; 20, 40, 60 and 80% MVF, and averaged across the two contractions. The time taken to reach 80% of MVF was also recorded.

Participant dropout

The vastus medialis is a challenging location from which to record the H-reflex, not least because the quadriceps femoris is a proximal muscle and thus lies closer to the spinal cord than distal muscles such as the soleus, from which the H-reflex is more commonly investigated. The effect of this proximal location is that the difference in latencies between the M-wave and H-reflex is lower (such that the M-wave and H-reflex responses were often found to overlap) making accurate quantification of H-reflex magnitude difficult. As a result, potential participants in which the the stimulus threshold for evoking a H-reflex was close to the motor threshold were excluded from the study due to difficulties in obtaining a range of stimulus frequencies over which an H-reflex was both clearly distinguishable and free from interference with the direct motor response. The prevalence of drop out for this reason alone was almost one third.

Further dropout was encountered due to discomfort experienced from the octet procedure. The electrical stimulus was generally well tolerated, however, within the highly trained participant group in which high forces were rapidly generated in responses to the electrical stimulus, the mechanical action of the quadriceps forcing the posterior surface of the knee against the leg support of the rig produced discomfort. Two highly trained participants withdrew their participation for this reason, prior to a subtle redesign of the profile of the leg support, which seemed to attenuate this problem. One further participant was asked to withdraw following a mild psychosomatic response to the general electrical stimulation procedure.

Statistical analyses

Repeated measures general linear models were used to determine the effects of trial (vibration vs. control) and time (either pre- vs. post-intervention (two time

points); or at the start and end of the contractions series conducted pre- and post-intervention (four time points)). Post-hoc comparisons involved paired samples t-tests to evaluate differences between the two trials at specific time points. To examine the influence of training status on the effects of vibration, these general linear models were repeated with group (trained/untrained participants) added as an independent variable.

Following normalisation to their respective pre-intervention values, the differences between post-vibration and post-control $H_{\max}/M_{\max}$, EVC force and MVF were calculated as a percentage of their post-control values ($H_{\max}/M_{\max}$ from the start of the contractions series were used). These individual changes in $H_{\max}/M_{\max}$ following vibration were not normally distributed (Shapiro-Wilk; $P=0.02$) and so Spearman's rank correlations were used to examine how post-vibration changes in $H_{\max}/M_{\max}$ related to changes in the functional performance measures (EVC force and MVF). Data are expressed as mean $\pm$ standard deviation, and are presented for all 18 participants together (except where between groups comparisons were specifically sought). A P-value below 0.05 was considered statistically significant.

2.4 – Results

Volitional & evoked explosive contractions

EVC force production remained consistent throughout both trials (ANOVA, trial $\times$ time interaction for F_{50} , F_{100} & F_{150} , all $P \geq 0.35$; main effect of time, all $P \geq 0.44$; Figure 2.2A&C), as did both QUAD $EMG_{RMS}/M_{\max}$ (ANOVA, trial $\times$ time interaction for 0-50, 50-100 & 100-150 ms, all $P \geq 0.10$; Figure 2.2B&D) and HAM EMG_{RMS} (0-50, 50-100 & 100-150, all $P \geq 0.55$). The intrinsic contractile capacity of the muscle-tendon unit for explosive force production, in response to an evoked octet, was also unaffected by the vibration stimulus (ANOVA, trial $\times$ time interaction for F_{25} , F_{50} & F_{75} , all $P \geq 0.36$; main effect of time, all $P \geq 0.10$; Figure 2.3).

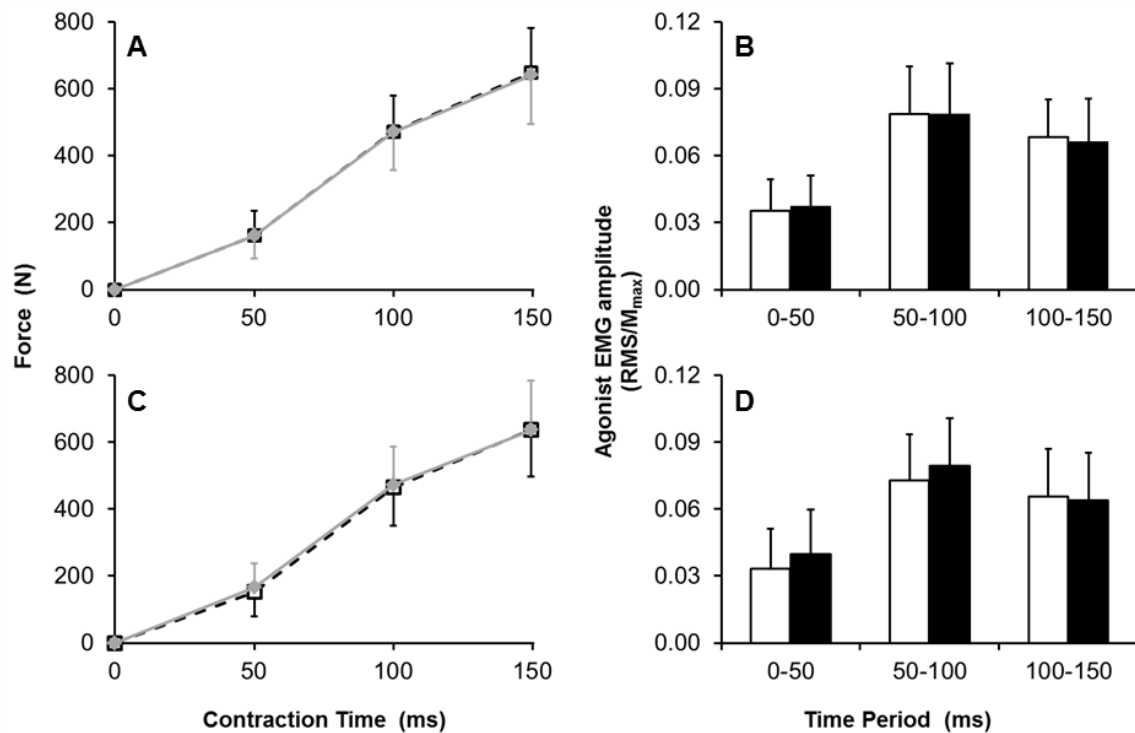


Figure 2.2 Explosive force production and agonist EMG amplitude during the first 150 ms of explosive voluntary contractions; measured pre- (open squares/bars) and post-intervention (filled diamonds/bars) in both the vibration (A&B) and control (C&D) trials. Data are mean $\pm$ SD (n=18).

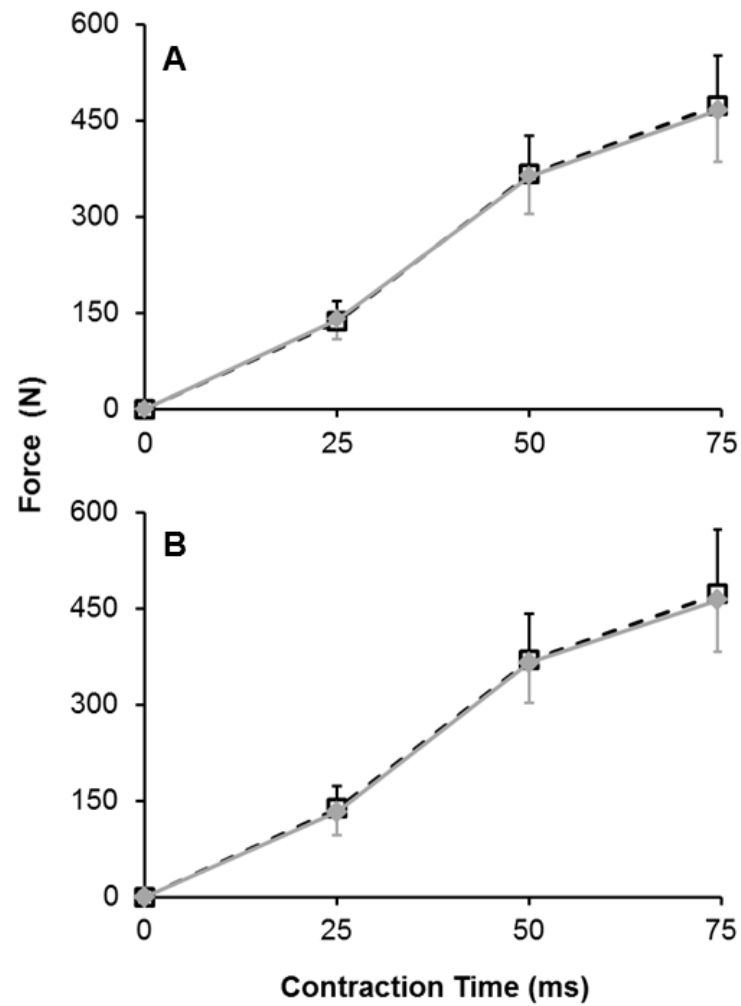


Figure 2.3 Force production during the first 75 ms of the evoked octet contractions; measured pre- (open squares) and post-intervention (filled diamonds) in both the vibration (A) and control trials (B). Data are mean $\pm$ SD (n=18).

Maximal voluntary contractions

Maximal force production was not influenced by the vibration intervention (ANOVA, MVF trial $\times$ time interaction, $P=0.92$; main effect of time, $P=0.80$; Figure 2.4A). Correspondingly, no change in EMG amplitude was observed in either the agonist (QUAD EMG_{RMS}/M_{max} trial $\times$ time interaction, $P=0.78$; Figure 2.4B) or antagonist (HAM EMG_{RMS} trial $\times$ time interaction, $P=0.49$) at MVF.

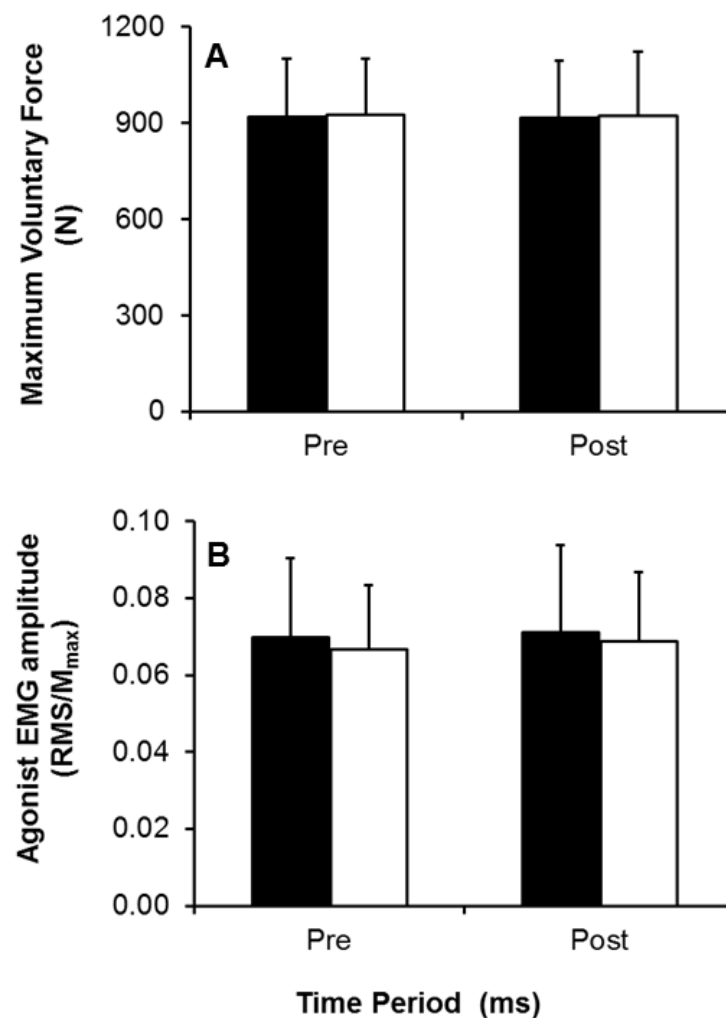


Figure 2.4 Maximal voluntary force (A) and agonist EMG amplitude at MVF (B) measured pre- and post-intervention in the vibration (filled bars) and control (open bars) trials. Data are mean $\pm$ SD ($n=18$).

Ramp contractions

The EMG-force relationship during the ramped contractions was unaffected by the vibration stimulus. Neither the amplitude (trial $\times$ time interaction, $P \geq 0.52$; main effect of time, $P \geq 0.11$; Figure 2.5A&C) nor the median frequency (trial $\times$ time interaction, $P \geq 0.77$; main effect of time, $P \geq 0.24$; Figure 2.5B&D) of the QUAD EMG showed any modification following either intervention throughout the range of submaximal forces (20, 40, 60 or 80% MVF). Time taken to reach 80% MVF also displayed no trial $\times$ time interaction ($P=0.15$), or difference pre- to post-intervention ($P=0.98$).

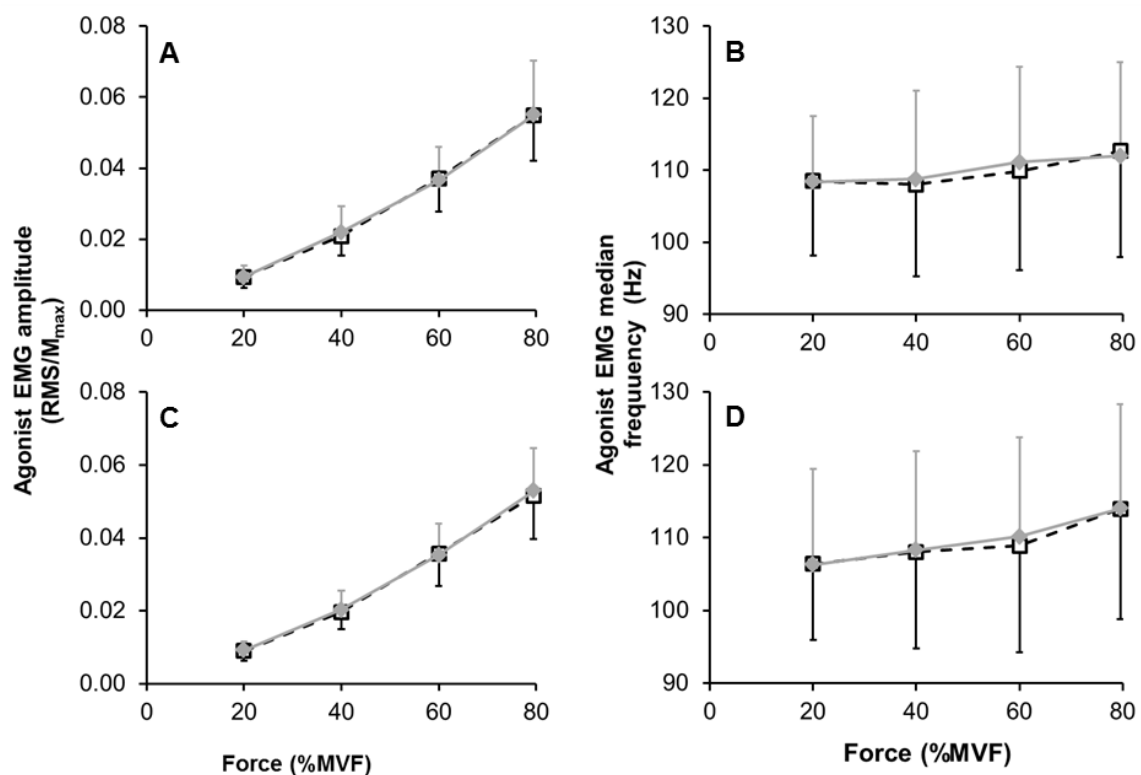


Figure 2.5 The force-EMG amplitude relationship during the ramp contractions; measured pre- (open squares) and post-intervention (filled diamonds) in both the vibration (A&B) and control (C&D) trials. Data are mean $\pm$ SD ($n=18$).

H-reflex & M_{max}

Example VM_d H_{max} recordings from the start of the contraction series both pre- and post-vibration for one participant are shown in Figure 2.6A. There was a different H-reflex response for the two interventions (ANOVA, H_{max}/M_{max} trial × time interaction $P < 0.001$; Figure 2.6B). Pre-intervention VM_d H_{max}/M_{max} was similar for both trials ($P \geq 0.36$), whereas post-intervention values were 60.2% ($P < 0.001$) and 38.1% ($P = 0.004$) lower in the vibration trial compared to the control trial at the start and end of the volitional and evoked contractions series, respectively. The current at which the highest H-reflex was elicited did not change throughout the trials (ANOVA, trial × time interaction $P = 0.46$; main effect of time $P = 0.06$). M_{max} was stable over time (VM_d $P = 0.61$; QUAD $P = 0.34$), deviating from initial values by $< 2.1\%$ (VM_d and QUAD) during both trials.

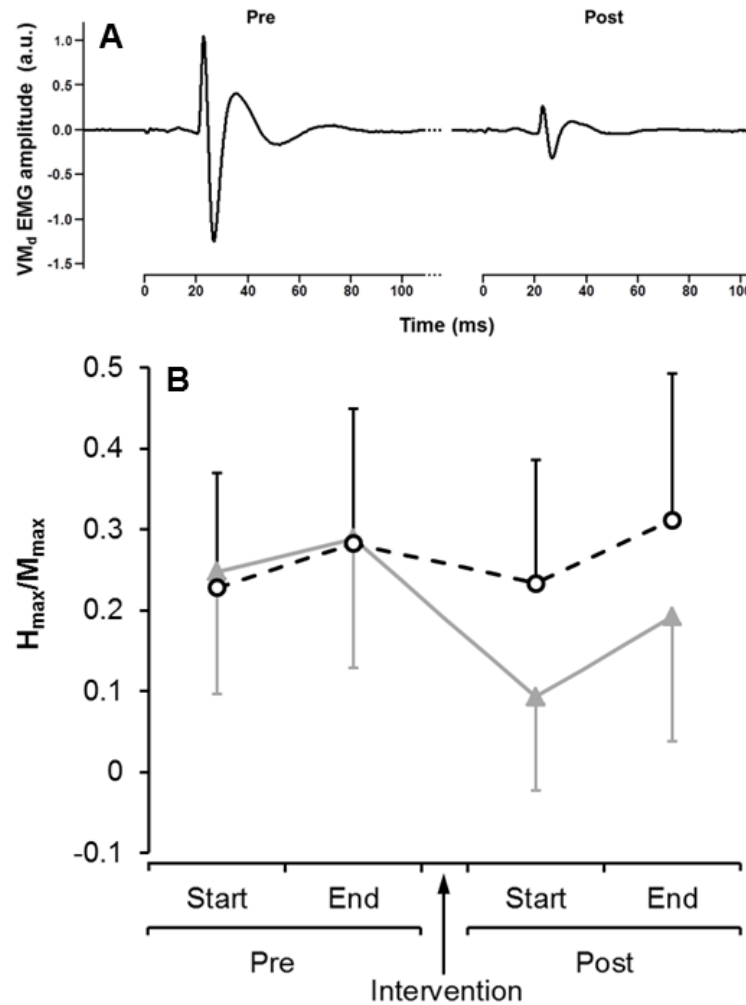


Figure 2.6 (A) Example of maximal H-reflex recordings from the distal vastus medialis (VM_d) recording site of one participant, recorded at the start of the volitional and evoked contraction series both pre- and post-vibration. Abscissas are time aligned with the input of the electrical stimulus. (B) H_{max}/M_{max} at all four measurement time-points in both the vibration (filled triangles) and control (open circles) trials. Data are mean $\pm$ SD (n=18). * Significant difference between vibration and control trials (P<0.01).

Individual variability & training status

The attenuation of VM_d H_{max}/M_{max} following vibration (percentage difference from control) was highly variable between individuals (range -100 to +24.3%). However, the effectiveness of the vibration at reducing H_{max}/M_{max} was not

correlated with the equivalent changes in EVC force production (F_{50} , F_{100} and F_{150} ; all $P \geq 0.54$) or MVF ($P = 0.71$).

The attenuation of $VM_d H_{max}/M_{max}$ was not influenced by training status (trial $\times$ time $\times$ group interaction $P = 0.93$). Whilst the trained participants produced higher explosive (voluntary and evoked) and maximal forces (all $P < 0.001$), the groups had similar responses to the two interventions (no trial $\times$ time $\times$ group interaction for F_{50} , F_{100} or F_{150} , all $P \geq 0.45$; octet F_{25} , F_{50} or F_{75} , all $P \geq 0.12$; MVF, $P = 0.14$).

2.5 – Discussion

The main finding of the present investigation was that application of a continuous 30-min vibration stimulus to the infrapatellar tendon did not affect maximal or explosive knee-extensor force production, whereas vastus medialis H-reflex amplitude was substantially reduced throughout these post-vibration contractions. There was no association between the individual changes in H-reflex and volitional performance (EVC or maximal force), and no effect of strength training status on the responses to the vibration intervention was identified.

Contrary to the hypothesis, the 30-min tendon vibration had no effect on force production during the initial 150 ms of the EVCs. This is in contrast to two studies that reported substantial decreases in peak RFD of the knee-extensors following 30 min of rectus femoris vibration (~24%, Kouzaki et al. (2000); 70%, Jackson & Turner (2003)). However, the validity of these previously reported decrements may be questionable given that Kouzaki et al. (2000) provided no instructions to generate force at a maximal rate, and the control (pre-intervention) assessments of peak RFD were highly variable between trials in the study by Jackson & Turner (2003). These studies also measured peak RFD during maximal strength contractions, which would likely have led to significant underestimates of maximal RFD (Sahaly et al. 2001). Moreover, more rigorous assessments of explosive force production were unaffected by whole-body vibration (de Ruiter et al. 2003; Erskine et al. 2007; Hannah et al., 2013). The present results also indicated that EMG amplitude during the EVCs remained unchanged, as did the amplitude and frequency of EMG during submaximal ramp contractions.

MVF and the associated EMG amplitude were also unaffected by the 30-min vibration. This is in agreement with one study (Ekblom & Thorstensson 2011), but in contrast to a number of other studies that have observed decrements in maximal force production of between 7 and 17% following prolonged vibration (Kouzaki et al. 2000; Jackson & Turner 2003; Ushiyama et al. 2005; Konishi et al. 2009). The cause of the dichotomy among these results is not clear. However, one study did not have a control trial (Konishi et al. 2009), three did not measure extrafusal fibre excitability (via $M_{\max}$ recordings) (Kouzaki et al. 2000; Jackson & Turner 2003; Konishi et al. 2009), and the present study was the first to monitor the intrinsic contractile properties of the muscle-tendon unit (via evoked octet contractions). The present study showed a 60% decrease in quadriceps (VM_d) $H_{\max}/M_{\max}$ following the vibration period. This is in agreement with previous studies that have demonstrated decrements in triceps surae H-reflex responses following a similar tendon vibration stimulus ($\geq 55\%$ (Heckman et al. 1984); 36% (Ushiyama et al. 2005); 33% (Ekblom & Thorstensson 2011)). Although a 60% reduction in resting $H_{\max}/M_{\max}$ should not be thought to reflect a 60% decrease in homonymous spinal reflex function during voluntary contractions, these results may indicate that the vibration intervention was effective in compromising the efficacy of the homonymous Ia afferent- α -motoneuron pathway. The present investigation was the first to have measured H-reflex both pre and post functional performance measures following a prolonged vibration stimulus, and demonstrated that H-reflex was still attenuated (38%) following the completion of the functional performance measures. This may infer that all of the functional measures were performed under conditions of a compromised Ia afferent- α -motoneuron pathway. The present results also showed that the excitability of the extrafusal fibres was unaffected by the vibration intervention, as demonstrated by the consistent $M_{\max}$ responses during both trials. Additionally, no change in evoked octet forces was evident following either intervention, illustrating that the intrinsic contractile properties of the muscle-tendon unit were unaffected by the prolonged tendon vibration.

Overall, despite a substantial reduction in $H_{\max}/M_{\max}$ observed both at the start and end of the post-vibration measurements, none of the volitional measurements were affected following either intervention. Furthermore, at an

individual level the magnitude of H-reflex depression did not demonstrate any correlation with the changes in either maximal or EVC force production. These results could suggest that performance of maximal and explosive voluntary contractions of the quadriceps are not dependent on contributions to neural drive via homonymous Ia afferents. In addition, these results were similar for both strength trained and untrained individuals.

Repetitive activation of Ia afferents during vibration may attenuate the efficacy of the Ia afferent- α -motoneuron pathway via one or more of a number of processes, including; transmitter depletion at the Ia afferent terminals (Curtis & Eccles 1960; Hultborn et al. 1996), interneuron-mediated presynaptic inhibition (Lapole et al. 2012), and reduced excitability of the Ia afferents (Lin et al. 2002). In the present investigation, vibration had no effect on the current at which VM_d H_{max} was elicited, suggesting that this latter mechanism was not the determining factor underlying H-reflex depression. Bongiovanni et al. (1990) proposed that MVF suppression was primarily due to transmitter depletion, whereas the depression in H-reflex may be due to a presynaptic inhibition of transmitter release at the monosynaptic Ia terminals. If these processes were to show different time-courses following prolonged vibration there could be a disparity in the recovery of MVF and H-reflex, allowing MVF to recover while H-reflex depression remained. This possibility remains highly speculative as the recovery of these processes has been poorly defined.

Alternatively, H-reflex measurements, particularly resting measurements, may not provide an accurate reflection of the efficacy of the (more functionally relevant) entire γ -loop following prolonged vibration. Stretch reflexes have been reported to increase after vibration (Heckman et al. 1984; van Boxtel 1986; Shinohara et al. 2005) despite concurrent depressions in H-reflex also being observed (Heckman et al. 1984; van Boxtel 1986). Additionally, any effect of the tendon vibration on the Golgi tendon organs, and the efficacy of their inhibitory input to the α -motoneurons via inhibitory Ib interneurons remains unknown. In summary, the cause of the dichotomy between the present results, along with those of Ekblom and Thorstensson (2011), and the more prevalent finding within the literature of a reduction in maximal motor output following prolonged muscle/tendon vibration is not clear.

In conclusion; quadriceps maximal and explosive force production tasks were unaffected by a 30-min tendon vibration, whereas H-reflex amplitude decreased markedly. Individual depressions in H-reflex did not correlate with changes in either EVC or maximal force production, and training status appeared to have no effect on the influence of vibration on reflex or functional performance measures. These results may indicate that for isometric contractions of the quadriceps muscle group maximal and explosive force production is not dependent upon input to the α -motoneurons via homonymous Ia afferents.

Chapter 3

Does sensorimotor cortex activity
change with quadriceps femoris torque
output? A human
electroencephalography study

3.1 – Abstract

Encoding muscular force output during voluntary contractions is widely perceived to result, at least in part, from modulations in neuronal activity within the sensorimotor cortex. However, the underlying electrophysiological phenomena associated with increased force output remains unclear. This study directly assessed sensorimotor cortex activity using electroencephalography (EEG) in humans performing isometric knee-extensions at a range of discrete torque levels. Fifteen healthy males (age 24 ($s=5$) years) completed one familiarisation and one experimental trial. Participants performed a cyclic series of 60 isometric knee-extension contractions with the right leg, including 15 contractions of 5-s duration at each of four discrete torque levels: 15, 30, 45 and 60% of maximal voluntary torque (MVT). Isometric knee-extension torque, quadriceps electromyography and EEG were recorded at rest and throughout all the contractions. EEG (0.5-50 Hz) was collected using a 32-channel active-electrode cap. A voxel-based LORETA analysis calculated cortical activation within the sensorimotor cortex (one of 27 MNI coordinates) for the entire 0.5-50 Hz range (cortical current density (CCD)), as well as for each constituent frequency band in this range (delta, theta, alpha, beta and gamma). Gamma band (30-50 Hz) cortical activity increased with contraction torque (ANOVA, $P=0.03$). Conversely, activity within the other frequency bands was not modulated by torque ($P\geq 0.09$), nor was overall CCD ($P=0.11$). Peripheral neuromuscular activation (quadriceps EMG amplitude) demonstrated distinct increases between each torque level ($P<0.01$). In conclusion, sensorimotor cortical activity within the gamma band demonstrated an overall increase with contraction torque, whereas both CCD and each of the other constituent frequency bands were not modulated by increments in torque magnitude during isometric knee-extension contractions up to 60%MVT.

3.2 – Introduction

Understanding the cortical encoding of skeletal muscle contractions, including the force of contractions, is of wide relevance to human function and health; including neurological disorders, brain computer interfacing, healthy ageing and the responses to physical training/rehabilitation. Several studies on non-human primates have suggested that a number of cells within the motor cortex modulate their activity in relation to the isometric contraction force of an active muscle (Evarts 1968; Cheney & Fetz 1980; Evarts et al. 1983; Hepp-Reymond et al. 1999). However, animal investigations have typically been limited to studying relatively low force amplitudes, and it is difficult to detect changes in the number of participating cells or modifications in whole populations of cells.

In humans, studies utilising positron emission tomography (PET; Dettmers et al., 1995) and functional magnetic resonance imaging (fMRI; Thickbroom et al. 1998; Dai et al. 2001; Cramer et al. 2002; Ward & Frackowiak 2003; van Duinen et al. 2008; Keisker et al. 2009) have found cortical activation in sensorimotor regions of the brain to increase with increments in force during isometric or near-isometric contractions of the fingers/hand. However, findings are not unequivocal; Ludman et al. (1996) found no difference in fMRI BOLD signal during cyclic finger flexion of a light and heavy load, and Christensen et al. (2000) found no correlation between bipedal recumbent cycling load and cerebral blood flow related activation within the motor cortex. Moreover, both PET and fMRI techniques measure haemodynamic responses within localised regions of the brain as an indirect surrogate of neuronal activity. In contrast, measuring cortical electrical activity provides a direct index of neuronal activation as this is the method of communication within the central nervous system.

Decreases in surface electroencephalography (EEG) amplitude have been observed within the alpha frequency band with increments in force during isometric 'pinching' using the thumb and little finger (Mima et al. 1999). Similarly, Dal Maso et al. (2012) found beta band activity to decrease with increments in isometric knee flexion force in strength trained individuals. However, findings to date have been inconsistent; both isometric elbow flexion force (Cremoux et al. 2013) and the magnitude of a resistive load applied against index finger

extensions (Stančák et al. 1997) were found to have no effect on the amplitude of EEG recorded during contractions. All of these studies have related contraction force to changes in EEG recordings as they appear at the scalp. In contrast, source localisation of EEG signals represents an increasingly viable technique for the measurement of neuronal activity within sensorimotor cortex regions of interest during motor tasks.

Recent investigations (Brümmer et al., 2011; Schneider et al., 2013) have evaluated the source localised EEG signal originating within the motor cortex during the performance of incremental ergometer cycling, and have reported an increased cortical activation to accompany greater cycling loads. However, cycling is a complex movement, with multiple joints involved and numerous muscles each producing a constantly changing amount of force at different times throughout the movement. Analysis of constant torque isometric contractions of a single large muscle (e.g. the quadriceps), over a range of discrete force levels may provide a more experimentally controlled situation in order to observe the cortical encoding of skeletal muscle force production. Moreover, these studies (Brümmer et al., 2011; Schneider et al., 2013) only reported the power of the EEG signal for the entire 0.5-50 Hz recording (known as cortical current density (CCD)), which does not enable examination of activity patterns in the narrower constituent frequency bands.

The aim of this study was to examine cortical activity within the sensorimotor cortex as determined by source localised EEG measurements during constant torque isometric contractions of the quadriceps muscle group at a range of discrete torque levels. Sensorimotor activity within the delta, theta, alpha, beta and gamma bands was determined, in addition to overall CCD.

3.3 – Methods

Participants

The data for one participant included a high amplitude noise component in the recorded EEG signals during almost all of the submaximal contractions performed and was therefore excluded from further analysis. Subsequently,

participants were fifteen healthy, injury-free, recreationally active males with no known history of neuromuscular or skeletal disorders (mean $\pm$ s: age 24 ± 5 years, stature 1.80 ± 0.06 m, body mass 76.7 ± 9.9 kg). The experimental procedures were approved by the Loughborough University Ethical Advisory Committee, and each participant provided written informed consent prior to their involvement.

Experimental protocol

A familiarisation session was completed 5-14 days prior to the experimental trial, during which participants rehearsed performing maximal and submaximal isometric knee-extension contractions. The experimental trial involved the determination of maximal voluntary torque, and a cyclic series of 60 submaximal isometric knee extension contractions; 15 contractions at each of four distinct torque levels (15, 30, 45 and 60% of maximal torque) (Figure 3.1). Electromyography (EMG), EEG and torque were measured simultaneously during submaximal contractions, and real-time graphical feedback of contraction torque was displayed on a computer monitor positioned in front of the participant. All contractions were performed with the right leg. Participants were advised to abstain from strenuous or atypical exercise for 36 hours prior to the experimental trial, and to avoid the intake of nutritional stimulants (e.g. caffeine) on the day of the trial.

Maximal voluntary contractions (MVCs): Following a prescribed warm-up of submaximal isometric knee extensor contractions, participants performed four MVCs, with 40 s rest between contractions. Participants were instructed to exert a maximum effort of knee-extension torque continuously for 3-5 s, with visual biofeedback and verbal encouragement provided. Maximal voluntary torque (MVT) was determined as the highest torque over a 500 ms epoch during the four repetitions, and amplitude of the quadriceps signal (EMG_{MVT}) was also calculated for this time window. Participants rested for 10-min following the MVCs, allowing for the EEG cap to be fitted and the EEG signals to be visually inspected.

Submaximal contractions: For each contraction, in response to a verbal cue, participants increased knee-extensor torque to the required level and maintained

this torque until instructed to relax (after ~5 s). Horizontal lines representing 15, 30, 45 and 60%MVT were displayed on the monitor to facilitate accurate maintenance of these target torques. Each contraction torque was performed three times, before proceeding to the next torque level in ascending order, with this sequence of 12 contractions cycled through five times (Figure 3.1A). The time interval between successive contractions increased with torque level to minimise fatigue (20, 30, 40 and 50 s, respectively; Figure 3.1B). Two minutes after the completion of the submaximal contractions, two further MVCs were performed to assess whether any fatigue-related decrement in MVT had occurred.

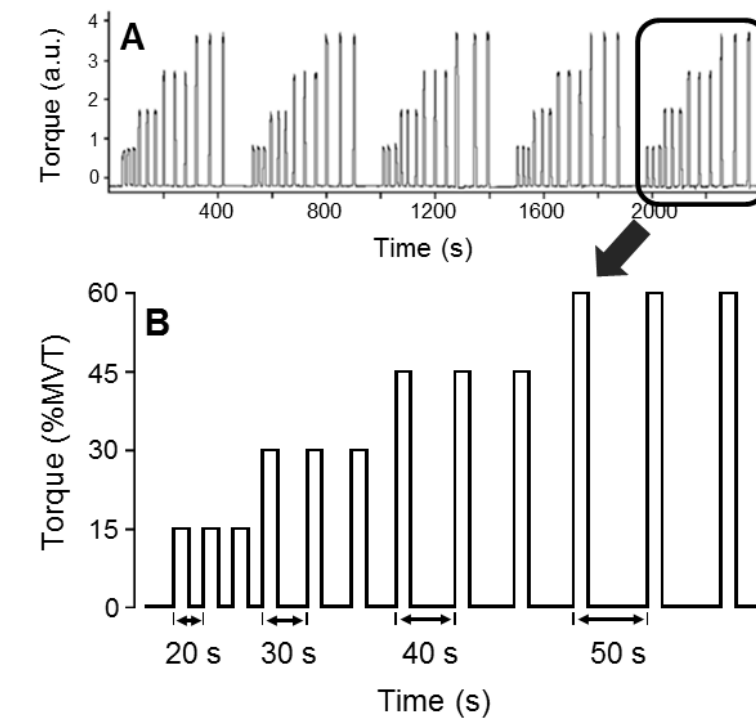


Figure 3.1 An example recording of knee-extensor torque during the series of submaximal isometric contractions (A), and a schematic illustration of one of the five sets of twelve 5-s contractions (B).

Six 60-s segments of resting EEG data were also collected; one prior to the submaximal contractions, and after every set of 12 contractions. During resting collections, participants were instructed to keep their eyes closed, refrain from moving/talking and focus on themselves in order to minimize shifts in cognitive activity Brümmer et al. (2011).

Torque measurements

Isometric knee-extensor torque of the right leg was measured with participants seated in a dynamometer (Con-Trex; CMV AG, Dübendorf, Switzerland) with hip and knee angles of 95° and 110°, respectively. The rotational axes of the crank arm and right knee joint were aligned, and the ankle brace was fastened 20 mm proximal to the lateral malleolus of the ankle. Adjustable waist and shoulder straps were used to prevent extraneous body movements, and the participants were instructed to keep their arms relaxed with their hands resting in their lap throughout all contractions. Torque data were sampled and recorded at 2000 Hz using an external A/D converter (Micro 1401, CED, Cambridge, UK) and a PC utilising Spike 2 software (CED, Cambridge, UK).

Electroencephalography measurements

BrainVision Recorder 1.2 (Brain Products, Munich, Germany) recorded EEG at a sampling frequency of 500 Hz (0.016 Hz high pass filter, time constant 10 s, 6 dB/oct; 1000 Hz low pass filter, 30 dB/oct) using a portable actiCAP system (Brain Products, Munich, Germany) that was equipped with 32 Ag/AgCl electrodes. A flexible EEG cap with chinstrap was used to maintain electrode positions against the scalp. One of three caps (notionally: small, medium or large) was selected depending on participant head size. This cap adapted to individual head shape and was permeable to air to avoid heating during contractions. According to the international 10:20 system, EEG data was recorded at (approximate) electrode positions Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, TP9, P7, P3, Pz, P4, P8, TP10, PO9, O1, Oz, O2, and PO10. To ensure electrode positions were as accurate as

possible the locations for electrodes Fp1 and Fp2 were first measured and marked on the forehead prior to placing the cap. In fitting the cap, further care was taken to ensure that electrode Cz was positioned over the vertex, and that C3 and C4 were symmetrically situated. Reference (FCz) and ground (AFz) electrodes were mounted additionally. Distances between electrodes were ~50 mm to avoid possible cross-talk due to salt bridges (perspiration rate was not measured; however, subjectively perspiration rate increased but was not profuse (i.e. substantially less than during whole-body exercise e.g. cycling)). Each electrode was filled with SuperViscTM electrode gel (Easycap GmbH, Herrsching, Germany) to optimize conductivity. Analogue EEG signals were amplified and converted to digital signals using the BrainVision 1.2 software.

Electromyography measurements

Surface EMG was recorded using pre-amplified ($\times 100$) single differential wireless electrodes (20-450 Hz bandwidth; Trigno, Delsys, Boston, USA). Following shaving, gentle abrasion and cleansing with ethanol, two electrodes were positioned over each of the superficial muscles of the quadriceps at specific percentages of thigh length (greater trochanter to lateral knee joint centre distance) from the superior border of the patella as follows: vastus medialis, 35% and 25%; vastus lateralis, 55% and 45%; and rectus femoris, 65% and 55%. The proximal and distal electrodes on each muscle were offset laterally and medially, respectively, from the longitudinal mid-line of the muscle belly by ~10 mm, and aligned parallel to the presumed orientation of the muscle fibres. The EMG signals were sampled at 2000 Hz and synchronised with the torque data using the same data acquisition equipment.

Data analyses

A synchronised marker within the torque, EEG and EMG signals was manually triggered using the Spike2 software when contraction torque was subjectively determined to have stabilised at the required level. Data were segmented into 4.5-s periods immediately following these markers. Data segments were

excluded from further analysis if the torque was not maintained throughout the corresponding 4.5 s (the downward deflection initiating the return of torque to baseline commenced <4.5 s after the marker).

BrainVision Analyzer 2.0.4 (Brain Products, Munich, Germany) was used for offline EEG data processing, including careful visual inspection and systematic exclusion procedures. EEG signals were high- and low-pass filtered at 0.5 and 50.0 Hz, respectively, using infinite impulse response digital filters (time constant 0.3183099 s, 48 dB/oct). Segments of EEG data that were determined to contain a high noise component were excluded from subsequent analysis (semi-automatic artefact rejection filter; gradient < 50.0 μV , max/min amplitude -100 to 100 μV). Eye blink artefacts were generally confined to Fp1, Fp2 and the frontal electrodes and not typically present in the electrode channels located over the motor regions (i.e. C3, Cz and C4), nevertheless, data segments seen to contain eye blinks following the semi-automatic artefact rejection filter (offline visual inspection) were discarded prior to subsequent analyses. A voxel-based, integrated low-resolution brain electromagnetic tomography (LORETA) (Bai et al. 2007; Grech et al. 2008; Pascual-marqui et al. 2002) calculated cortical activity ($\mu\text{V}^2/\text{mm}^4$) at 27 Montreal Neurophysiological Institute (MNI) coordinates in a $3 \times 3 \times 3$ cube; (x:y:z) -10, 0, 10: -20, -30 -40: 50, 60, 70 (i.e. 10 mm separation in medial-lateral, anterior-posterior and superior-inferior directions). This configuration led to substantial overlap between voxels (spheres of 20 mm diameter on MNI-Average-305-T1 head model) such that a comprehensive covering of the leg area of the sensorimotor cortex was achieved, which also allowed for variations in individual brain anatomy (see Appendix 3.1). Data from individual contractions (segments) that were >2 standard deviations from the mean (of the ≤ 15 contractions at that torque level for each individual participant) were excluded from the remaining analyses. Subsequently, for each participant, the voxel that displayed the greatest change in cortical activity between rest and during the contractions (average cortical activity of the four torque levels; fold change from rest) was selected as the region of interest within the sensorimotor cortex. For each torque level data were then averaged within individuals before group means were calculated. Each of these analyses were performed for the whole 0.5-50 Hz frequency band (cortical current density (CCD)), and within each

of the constituent frequency bands individually; 0.5-3 (delta), 3-7 (theta), 7-13 (alpha) 13-30 (beta) and 30-50 Hz (gamma). The number of contractions excluded during the course of the analyses, and the voxel demonstrating the peak change in cortical activity from rest (and thus selected as the sensorimotor region of interest) may therefore have differed between frequency bands.

EMG signals were band-pass filtered at 6-500 Hz with a 4th order bidirectional Butterworth digital filter, prior to further analyses. The amplitude of the EMG signal was calculated as the root mean square (EMG_{RMS}). EMG_{RMS} for each recording site during submaximal contractions was normalised to EMG_{MVT} before an overall average for the six quadriceps recording sites was determined.

To assess the steadiness and thus the distinctiveness of the different torque levels intraindividual coefficients of variation in contraction torque were calculated using the mean and standard deviation of 9000 data points (4.5 s × 2000 Hz) of each submaximal contraction, and averaged within individuals for each torque level before group means were determined (intraindividual within-contraction coefficients of variation). Coefficients of variation in cortical activity were calculated using the mean and standard deviation of the 15 contractions at each torque level (minus any excluded contractions), with group means subsequently determined for each frequency band (intraindividual between-contractions coefficients of variation).

Statistical analyses

A mixed measures ANOVA was used to compare absolute cortical activity between frequency bands (independent measure = frequency, repeated measure = torque level). One-way repeated measures ANOVAs were used to test for significant effects of knee extensor torque on EMG_{RMS}, and cortical activity within each separate frequency band. Prior to these one-way ANOVAs, EEG data were log transformed as follows: $\ln(((\text{'cortical activity during contraction'} - \text{'cortical activity at rest'}) / \text{'cortical activity at rest'}) + 1)$. Comparisons of cortical activity between frequency bands were made at the location of peak change in CCD (fold change from resting values). Comparisons of cortical activity between torque

levels were made at the individual locations of peak change for each frequency band. Post hoc Sidak corrections were applied where main effects were identified. Where no main effect of torque was identified paired t-tests assessed whether any change between rest and contraction were evident (average of all four torque levels; absolute cortical activity data).

The presented EMG and torque data include data segments that were subsequently excluded following the EEG-related exclusion criteria. A paired t-test was used to assess if any changes in MVT had occurred following the submaximal contractions. A P-value below 0.05 was considered statistically significant. Data are expressed as group means $\pm$ standard error of the mean.

3.4 – Results

Participants were able to accurately maintain the prescribed torque output with mean torque values of 15.3 ± 0.1 , 30.0 ± 0.2 , 45.1 ± 0.4 and $59.8 \pm 0.3\%$ MVT, and the steadiness of these contractions was reflected by the low intraindividual within-contraction coefficients of variation (2.9 ± 0.2 , 2.1 ± 0.2 , 2.1 ± 0.2 and $2.3 \pm 0.2\%$ MVT, respectively). EMG_{RMS} at each torque level was significantly different from all other levels ($P < 0.01$; Figure 3.2), demonstrating that peripheral neuromuscular activation increased with each successive torque level. MVT was unchanged following the series of 60 submaximal contractions (pre 284.3 ± 11.1 Nm vs. post 278.6 ± 10.3 Nm, paired t-test $P = 0.11$) suggesting that the protocol was not fatiguing.

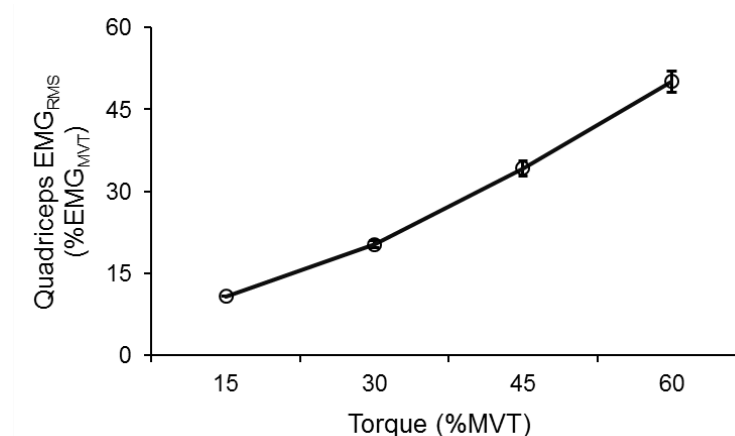


Figure 3.2 The EMG-torque relationship of the knee extensors. EMG amplitude at each torque level was significantly different from all other torque levels ($P < 0.01$ following Sidak post hoc corrections). Data are mean $\pm$ SEM ($n=15$).

Following application of the exclusion criteria, the number of data segments included in the final EEG analyses varied slightly between frequency bands. Subsequently, the mean amount of contraction time included in the analyses ranged between 55.2-57.0 (15%MVT), 52.5-56.4 (30%MVT), 52.8-57.6 (45%MVT) and 45.9-50.7 (60%MVT) s of data per participant (of a maximum possible 67.5 s).

No significant effect of knee-extensor contraction torque on CCD was identified (whole 0.5-50 Hz frequency band; one-way ANOVA, $P=0.11$; Figure 3.3). However, absolute cortical activity within the constituent frequency bands differed considerably (ANOVA, main effect of frequency, $P < 0.01$; Figure 3.4). Cortical activity within the gamma band (30-50 Hz) was less than the other frequency bands ($P \leq 0.03$), whereas activity in the delta band (0.5-3 Hz) was approximately double that of any other frequency band ($P < 0.01$); thereby imposing a disproportionate influence on CCD than patterns of activation within other frequency bands.

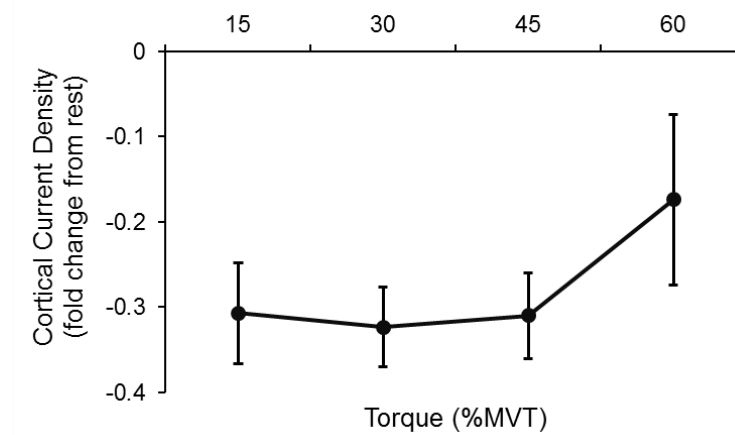


Figure 3.3 Cortical activity within the sensorimotor cortex for the whole 0.5-50 Hz frequency band (cortical current density) expressed as fold changes from resting values. Data are mean $\pm$ SEM (n=15).

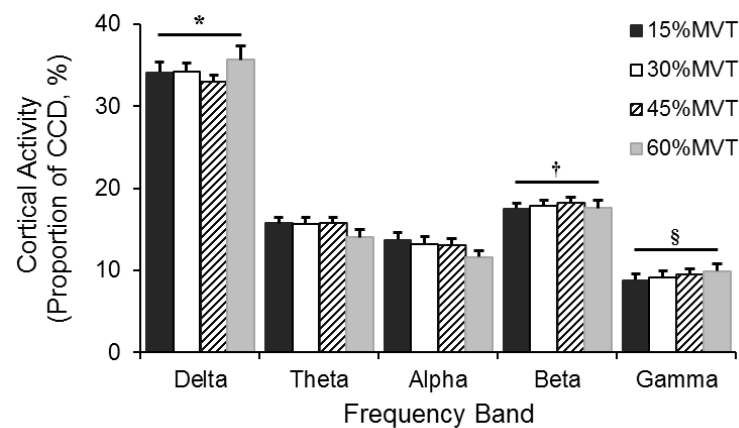


Figure 3.4 Absolute cortical activity within each of the constituent frequency bands (delta, 0.5-3; theta, 3-7; alpha, 7-13; beta, 13-30; gamma, 30-50 Hz) expressed in proportion to the whole 0.5-50 Hz band (cortical current density (CCD)). Cortical activity within all frequency bands was measured at the same sensorimotor location as CCD. Annotations denote significant main effects of frequency: * higher than all other frequency bands; § lower than all other bands; † higher than the alpha and gamma band only ($P < 0.05$ following Sidak post hoc corrections). Data are mean $\pm$ SEM (n=15).

Cortical activity within the gamma band increased with contraction torque (one-way ANOVA, $P=0.03$; Figure 3.5), although no significant differences between individual torque levels were identified following post hoc analysis. Activity within the other frequency bands was not modulated by torque (delta, $P=0.09$; theta, $P=0.68$; alpha, $P=0.95$; beta, $P=0.11$). Paired t-tests showed that delta, theta and alpha activity was significantly lower during contractions compared with rest (paired t-test, $P\leq 0.02$), whereas no change was observed within the beta band ($P=0.34$).

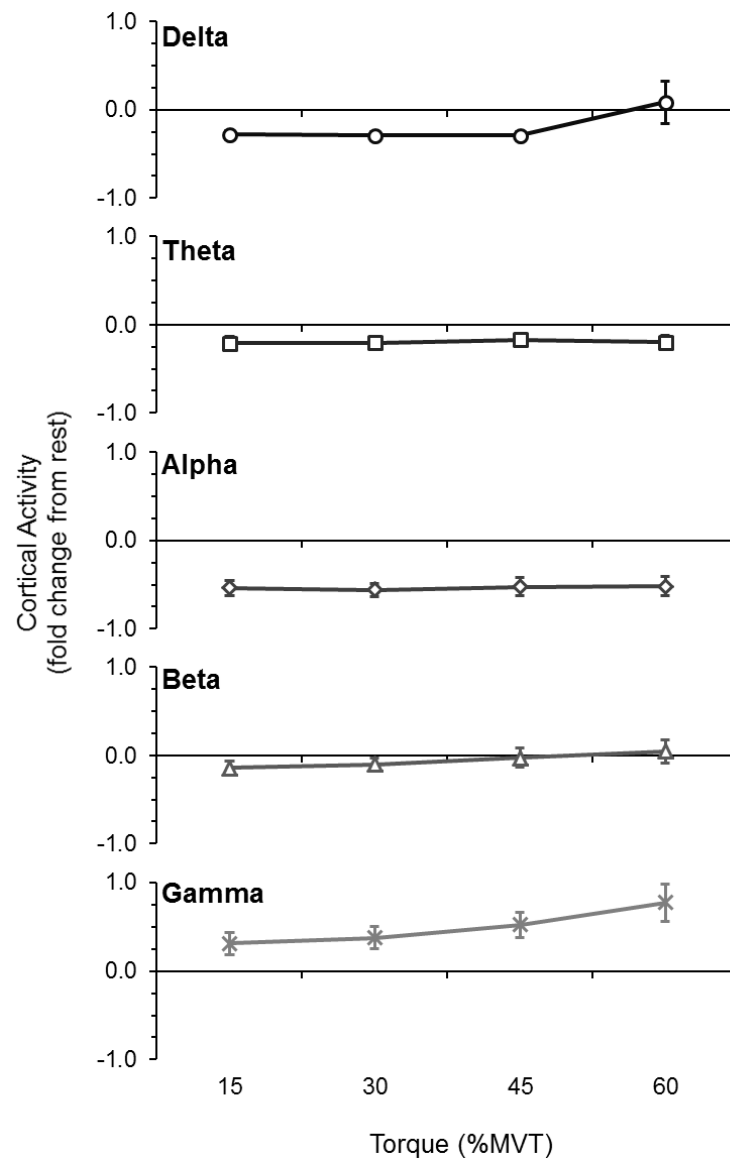


Figure 3.5 Cortical activity within each of the constituent frequency bands, expressed as a fold change from resting values (delta, 0.5-3; theta, 3-7; alpha, 7-13; beta, 13-30; gamma, 30-50 Hz). Cortical activity was measured at the sensorimotor locations of peak change for each individual frequency band. Data are mean $\pm$ SEM ($n=15$). Note: ANOVA revealed a significant effect of torque on gamma activity, but no differences between individual torque levels were identified following Sidak post-hoc corrections.

The variability in cortical activity at each torque level is displayed in Table 3.1. No effect of torque level on the intraindividual between-contractions (n=15 minus any exclusions) coefficients of variation in absolute cortical activity was identified for any of the frequency bands (one-way ANOVA, $P \geq 0.23$).

Table 3.1 Intraindividual between-contractions coefficients of variation for absolute cortical activity at each torque level within each of the constituent frequency bands (delta, 0.5-3; theta, 3-7; alpha, 7-13; beta, 13-30; gamma, 30-50 Hz). Data are mean $\pm$ SEM (n=15).

Torque (%MVT)	Coefficients of variation: Cortical activity					
	CCD	Delta	Theta	Alpha	Beta	Gamma
15	25.2 $\pm$ 3.8	32.2 $\pm$ 2.9	25.2 $\pm$ 3.2	21.1 $\pm$ 3.2	19.5 $\pm$ 2.7	28.4 $\pm$ 5.5
30	21.6 $\pm$ 3.7	27.7 $\pm$ 2.7	24.7 $\pm$ 2.0	22.6 $\pm$ 3.2	19.6 $\pm$ 2.9	26.3 $\pm$ 5.4
45	21.5 $\pm$ 2.7	30.2 $\pm$ 2.7	25.1 $\pm$ 3.0	22.1 $\pm$ 3.4	19.0 $\pm$ 2.9	25.9 $\pm$ 4.7
60	24.5 $\pm$ 3.6	34.1 $\pm$ 5.3	23.8 $\pm$ 2.3	22.3 $\pm$ 2.0	20.1 $\pm$ 2.3	24.1 $\pm$ 5.8

3.5 – Discussion

This study aimed to examine cortical activity within the sensorimotor cortex during constant torque isometric contractions of the quadriceps femoris at a range of discrete torque levels. Participants were able to accurately perform contractions at the four distinct levels of torque, which exhibited clear differences in peripheral neuromuscular activation as shown by the EMG amplitude. The main finding was that whilst source localised EEG measures of gamma band cortical activity demonstrated a subtle overall increase with contraction torque, both total CCD and activity within the other specific frequency bands were unaffected by torque magnitude during contractions.

The increase in sensorimotor gamma band activity that was observed is in contrast to one comparable study that found no changes in motor cortex gamma activity during isometric knee flexion/extension contractions over a similar range of torque levels (~15-59%MVT; Dal Maso et al. (2012)). However, a number of studies have suggested that gamma range oscillations, spread over a large cortical area, may have a functional role in attention during the anticipation and performance of sensorimotor tasks (Murthy & Fetz 1996a; Murthy & Fetz 1996b; Rougeul-Buser 1994). Bonnet and Arand (2001) also suggested that 26-49 Hz activity may relate to the level of physiological arousal in the central nervous system. The present results may therefore reflect an increase in attention or arousal when performing contractions of a greater strength. In addition, that the variability in gamma activity between contractions was similar across torque levels (and in fact lowest at the 60%MVT torque level; Table 3.1) might substantiate that a neurological phenomenon was responsible for the overall increase in gamma activity rather than the incursion of a noise source e.g. muscle artefacts.

Cortical activity within both the alpha and beta bands was unaffected by contraction torque. This is in accordance with two previous studies involving isometric elbow flexion (Cremoux et al. 2013) and loaded finger extensions (Stančák et al. 1997). Conversely, an increased suppression of cortical activity with increments in contraction strength has been identified in the alpha band during a pinching task (Mima et al. 1999) and in an upper beta band (21-31 Hz) during isometric knee flexion contractions performed by strength trained participants (Dal Maso et al. 2012). However, Dal Maso and colleagues (2012) did not identify any torque-related modulations in beta activity during knee flexion performed by endurance trained participants, or during knee extensions performed by either strength or endurance trained participants. Stančák et al. (1997) found that peak changes in alpha/beta activity corresponded to the duration rather than amplitude of agonist EMG activation during brief finger movements. This could indicate that cortical activity within alpha and/or beta frequency bands may be modulated by motor parameters other than the force of contraction. That beta activity did not differ from rest in the current study ($P=0.34$) was perhaps surprising. Attenuations in beta band activity accompanying motor

task performances have been consistently demonstrated by previous studies (Jasper & Penfield 1949; Pfurtscheller & Lopes da Silva 1999; Jurkiewicz et al. 2006). However, beta oscillations may be re-established, at least partially, during the held phase of steady contractions (Penfield 1954; Kilavik et al. 2013). Moreover, the rest condition within the current study involved participants assuming an extremely relaxed state. Contrasting rest with contraction periods may therefore have involved marked differences in arousal and attention as well as alterations in the motor state (Vogt et al. 2014). A more analogous state of arousal/alertness between contraction periods and the baseline comparison may therefore be beneficial to future studies comparing rest to periods of motor activity.

Total CCD did not differ between contraction strengths. This was in accordance with four of the five component frequency bands (delta to beta), the exception being gamma band activity which increased. Gamma exhibited the lowest absolute cortical activity of the five frequency bands, and therefore would have had the smallest influence on the total CCD. The finding that CCD was not modulated with contraction torque may appear to be in contrast with observations of increased CCD with increments in power output during ergometer cycling (Brümmer et al. 2011; Schneider et al. 2013), however, as cycling involves the coordination of a number of muscles performing anisometric contractions, it is plausible that cortical activity concerning motor variables other than force may have contributed to these increases in sensorimotor activity. Indeed Ashe (1997) suggested that static and dynamic force outputs may be controlled by fundamentally different cortical processes. Moreover, the cortical responses to whole body exercise (i.e. a dynamic, bilateral multiple joint motor task with more comprehensive physiological (e.g. cardiovascular) responses) could be very different to isolated single-joint motor tasks. In either case, these possibilities were beyond the scope of the current investigation.

The present results are in contrast to a number of studies using fMRI measures of cortical activation (Dai et al. 2001; Cramer et al. 2002; Ward & Frackowiak 2003; van Duinen et al. 2008; Keisker et al. 2009), which have observed linear relationships between activation within a highly localised region of the sensorimotor cortex and isometric contraction force. Current EEG technologies

have a lower spatial resolution compared with fMRI techniques, which may limit their sensitivity to changes in the activity of what may be only a small percentage of sensorimotor cells that regulate isometric torque production (Ashe 1997). Direct measures of neuronal activity offering a greater spatial resolution may be required before any firm conclusions can be made. Future research should therefore aim to measure the site-specific modulations in cortical activity with a greater spatial resolution than is currently available with EEG, for example with the use of magnetoencephalography (MEG).

In addition to the limited spatial precision provided by EEG, the location of the brain from which the analysed signal was recorded was estimated based on a standard (Montreal Neurological Institute) model. Differences in anatomy as well as minor misplacements of the EEG cap would have resulted in the modelled brain coordinates referring to different regions of the cortex within each participants' brain. In an attempt to accommodate for this inaccuracy, a large area of the modelled brain was selected as potentially representing the leg area of the sensorimotor cortex (see Appendix 3.1). The disadvantage of this approach was that the selected region of interest for each participant may have related to different regions of their cortex, and the calculation of group averages across different regions of the participants' cortex could have affected the results. Obtaining anatomical MRIs of each participant's brain would enable coregistration of the recorded EEG signal with the topography of each participants' cortex. This would provide a level of control that the sampled EEG were arising from the same region of the cortex in each individual.

Finally, a lack of overall samples at each torque level should be acknowledged. This would have affected the signal-to-noise ratio of the results, and compromised the ability of the analyses to discern changes in beta oscillatory power from rest.

In conclusion; gamma band activity within the sensorimotor cortex, recorded during muscular contraction, was shown to exhibit a subtle overall increase with increments in isometric knee-extension torque, however, whether this phenomenon reflects an explicit relationship with muscular force or a more general increase in other task-related processes (e.g. attention) is not clear. Total

CCD and sensorimotor cortical activity at lower frequencies (delta, theta, alpha and beta) were not modulated by torque output over the range 15 to 60%MVT.

Chapter 4

Modulation of post-movement beta
rebound by contraction force and rate of
force development

4.1 – Abstract

Movement induced modulation of neural oscillations in the beta band are one of the most robust neural oscillatory phenomena in the brain. In the preparation and execution phases of movement, a loss in beta oscillatory amplitude is observed (the movement related beta decrease (MRBD)). This is followed by a rebound above baseline on movement cessation (the post movement beta rebound (PMBR)). These effects have been measured widely, and recent work suggests that they may have significant importance: They have potential to form the basis of biomarkers for disease, and have been used in neuroscience applications ranging from brain computer interfaces to markers of neural plasticity. However, despite the robust nature of both MRBD and PMBR, the effects themselves are poorly understood. In this study, a carefully controlled isometric wrist flexion paradigm was employed to isolate two fundamental movement parameters; force output, and the rate of force development (RFD). The results show that neither altered force output nor RFD has any effect on the MRBD. In contrast, PMBR was altered by both parameters: specifically, the force output of a muscle contraction significantly modulates PMBR, with higher force resulting in greater amplitude. RFD also modulates PMBR, with a greater RFD resulting in a PMBR which is significantly higher in amplitude and shorter in duration. These findings demonstrate that careful control of movement parameters can systematically change PMBR; further for temporally protracted movements (low RFD) the PMBR can be over 7s in duration. This means accurate control of movement and judicious selection of paradigm parameters are critical in future clinical and basic neuroscientific studies of sensorimotor cortex beta oscillations.

4.2 – Introduction

Neural oscillations are a ubiquitous phenomenon generated in multiple brain regions and observable using either invasive (microelectrode) or scalp based (electroencephalography (EEG) or magnetoencephalography (MEG)) measurements. These oscillations comprise periodic signals typically measured in the 1-200 Hz frequency range, and are generated by rhythmic electrical activity synchronised across neuronal assemblies. They were first reported by Hans Berger (Berger 1929), who measured differences in electric potential across the scalp and noted the existence of an 8-13 Hz ‘alpha’ rhythm. Further prominent frequency ranges have subsequently been identified including the delta (1-4 Hz), theta (4-8 Hz), beta (13-30 Hz) and gamma (30-200 Hz) bands. Measurable oscillations are present even when the brain is at “rest” (i.e. when a subject is asked to “do nothing”) and for many years such effects were considered “brain noise”. However more recently it has been shown that oscillations play an important role in co-ordinating brain activity, with subtle and focal spatiotemporal changes in oscillatory signatures being linked to stimulus presentation (Stevenson et al. 2011), attentional shifts (Bauer et al. 2014) and task performance (Puts et al. 2011).

In the sensorimotor system, motor action has been linked with robust changes in neural oscillations in the beta band. Prior to and during unilateral movements a decrease in beta amplitude is observed, beginning shortly before movement onset and sustained throughout movement, with the largest effect occurring local to contralateral primary sensorimotor cortex (Jasper & Penfield 1949; Salmelin & Hari 1994; Pfurtscheller et al. 2003; Jurkiewicz et al. 2006). This is known as the movement related beta decrease (MRBD). Following movement cessation, beta oscillations exhibit a period of elevated (above baseline) amplitude, known as the post-movement beta rebound (PMBR), which can last up to several seconds in duration (Pfurtscheller et al. 1996; Jurkiewicz et al. 2006). These beta band amplitude changes are extremely robust across individuals, they occur during both internally (self-paced) and externally cued movements (Pfurtscheller & Lopes da Silva 1999) as well as during cognitive tasks that require a motor component (Brookes et al. 2012). In addition, similar effects are observed even in

the absence of movement if, for example, a subject is asked to 'think about moving' (Schnitzler et al. 1997; Pfurtscheller et al. 2005).

Despite their robustness, beta band changes remain relatively poorly understood. High amplitude beta oscillations are thought to reflect inhibition (Cassim et al. 2001; Gaetz et al. 2011), a hypothesis supported by quantifiable relationships between beta amplitude and local concentrations of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) (higher GABA concentrations predict higher beta amplitude (Jensen et al. 2005; Gaetz et al. 2011; Hall et al. 2011; Muthukumaraswamy et al. 2013)). This means that the observed MRBD likely reflects an increase in processing (reduced inhibition) during movement planning and execution; whereas the PMBR is thought to reflect the active inhibition of neuronal networks recruited during the preparation and execution phases of the motor activity (Alegre et al. 2008; Solis-Escalante et al. 2012). What is clear from recent work is that beta modulation, both during and after stimulation, has great potential to be used as a biomarker for pathology, with examples including Parkinson's disease (S. Hall et al. 2014) and schizophrenia [Robson et al., 2015]. Further, the PMBR has been used in neuroscientific applications ranging from characterization of neural plasticity (Gaetz et al. 2010; Mary et al. 2015) to use in brain computer interfaces (Pfurtscheller & Solis-Escalante 2009). However, despite a vast number of emerging applications, precise characterization of the neural generators of MRBD and PMBR, including their modulation by task, remains incomplete.

Previous studies have shown little modulation of MRBD with task parameters. For example, the reduction in beta amplitude during volitional contractions of the fingers/arm has been shown to be unrelated to both movement speed (Stancák & Pfurtscheller 1996; Stancák & Pfurtscheller 1995) and the weight of a manipulated load (Pistohl et al. 2012; Stančák et al. 1997). In agreement, Stevenson et al. [2011] showed that event related decreases in beta amplitude within the visual cortices was not modulated by changing visual stimulus intensity (Michelson contrast) or timing (drift frequency). Such findings have led some authors to describe event related beta amplitude decrease as a cortical 'gate' with a 'switching off' of beta oscillations necessary to facilitate local 'activity'. (Indeed in the sensorimotor domain this might be consistent with the observation

that Parkinson's disease patients (with bradykinesia) exhibit abnormally high resting amplitude of beta oscillations.) In contrast, PMBR is more variable in its relationship with task parameters. Stevenson et al. [2012] found the beta rebound to correlate negatively with inter-stimulus interval during median nerve electrical stimulation. A greater PMBR has also been observed following finger extension movements performed against a heavy resistive load compared to unloaded extensions (Stančák et al. 1997), whereas no systematic difference in PMBR was identified following slow and brisk finger movements (Stancák & Pfurtscheller 1996; Stancák & Pfurtscheller 1995; Stančák et al. 1997). At face value this may suggest that PMBR is related to the magnitude of force output, but not to the speed of muscular contraction. However, even during apparently simple movement tasks numerous movement parameters are changing simultaneously such as contraction force and rate of force development, but also joint position, velocity and direction of movement (which determines the type of contraction i.e. concentric, isometric or eccentric). To date, precise experiments investigating neuro-oscillatory behaviour in response to single movement parameters are lacking.

The present paper employs an isometric (static) task to remove the influence of movement (joint position, velocity and direction of movement etc.) and thus enables two fundamental parameters of motor output, force and rate of force development (RFD), to be examined individually. MEG is used to measure MRBD and PMBR in two experiments designed to isolate force and RFD as systematically controlled independent variables, and hence elucidate their influence on beta band oscillatory dynamics. In this way, it is shown that although MRBD is unchanged by force or RFD, PMBR can be modulated systematically, both in amplitude and duration.

4.3 – Methods

Subjects

Fifteen healthy adults (11 males, 2 left handed, age 28 ± 5 (mean $\pm$ std) years) with no known history of neurological conditions or neuromuscular / skeletal

disorders, volunteered their participation. The experimental procedures were approved by the Loughborough University Ethical Advisory Committee, and each subject provided written informed consent prior to their involvement. All experimental measurements were carried out in the MEG facility at the Sir Peter Mansfield Imaging Centre, University of Nottingham, UK.

Experimental protocol

Subjects were seated upright in the MEG system with their right forearm and hand positioned in a custom built isometric wrist-flexion dynamometer that was secured rigidly to the armrest of the MEG system. The dynamometer held the subject's forearm in a neutral position of pronation/supination, radial/ulnar deviation and wrist flexion/extension. In all experiments, subjects were asked to exert wrist-flexion force against a cylindrical handle that was attached in series to a strain gauge (see Figure 1A). During the experiment, subjects viewed a visual display that showed (in real-time) force output as a function of time. Subjects were shown a temporal profile of target force output prior to the initiation of contraction and attempted to match their force output to the target profiles. During the contraction real-time measured force output was overlaid on the target profile and thus provided feedback (see Figures 1B and 1C). Two separate experiments were undertaken in a pseudo-randomised order across subjects:

- *Experiment 1 – Constant-force contractions:* Subjects performed contractions at four different force levels which were set at 5%, 15%, 35% and 60% of the individual subject's maximum voluntary force output (MVF). Each contraction involved holding the target force as steadily as possible for 3 s. The target profile (see Figure 1B) appeared on the visual display 3 s prior to the start of the prescribed constant-force contraction and remained on screen for a total of 9.25 s (leaving a blank screen). A new target profile appeared every 25 s. Three contractions were performed at each force level, before proceeding to the next force level in ascending order. This sequence of 12 contractions was repeated 5 times for a total of 60 contractions, providing 15 contractions at each force level (see also Figure 1D).

- *Experiment 2 – Ramp contractions:* Subjects performed ramp contractions (i.e. a linear increase in force output over time) at three different rates of force development (RFDs). Each contraction involved following a target profile that increased linearly from rest to 65% MVF, in a time of 0.75, 2.25 or 6.75 s (see Figure 1C). Thus the prescribed RFDs were 86.7%, 28.9% and 10.4% of the subject's maximum voluntary force per second ($\text{MVF} \cdot \text{s}^{-1}$), respectively. The target profiles appeared 2 s prior to the start of the prescribed ramp contraction and remained on screen for 9.25 s. A new target profile appeared every 25 s. Four contractions were completed at each RFD before proceeding to the next RFD in descending order, with this sequence of 12 contractions repeated five times for a total of 60 contractions; 20 at each RFD (see Figure 1E).

In all subjects, the experimental session comprised determination of MVF, followed by completion of the two MEG experiments described above. To determine a subject's MVF, subjects performed three maximal voluntary contractions (no MEG acquisition), with 30 s rest between each. Subjects were instructed to exert a maximum effort of wrist-flexion force continuously for 3 s, with visual biofeedback and verbal encouragement provided. MVF was determined as the overall peak force (averaged over a 200 ms epoch) during these three contractions. In all subjects, a familiarisation session was completed 3-14 days prior to the experimental session. This involved subjects undertaking the constant-force, ramp and MVF contractions until they were able to perform each task with a high degree of accuracy. During MEG acquisition subjects were instructed to refrain from any movements other than the prescribed wrist-flexion. No verbal feedback was provided during performance of the experiments. Subjects were asked to abstain from strenuous or atypical exercise for 36 hours prior to the study, and to avoid the intake of nutritional stimulants (e.g. caffeine) within two hours of the study.

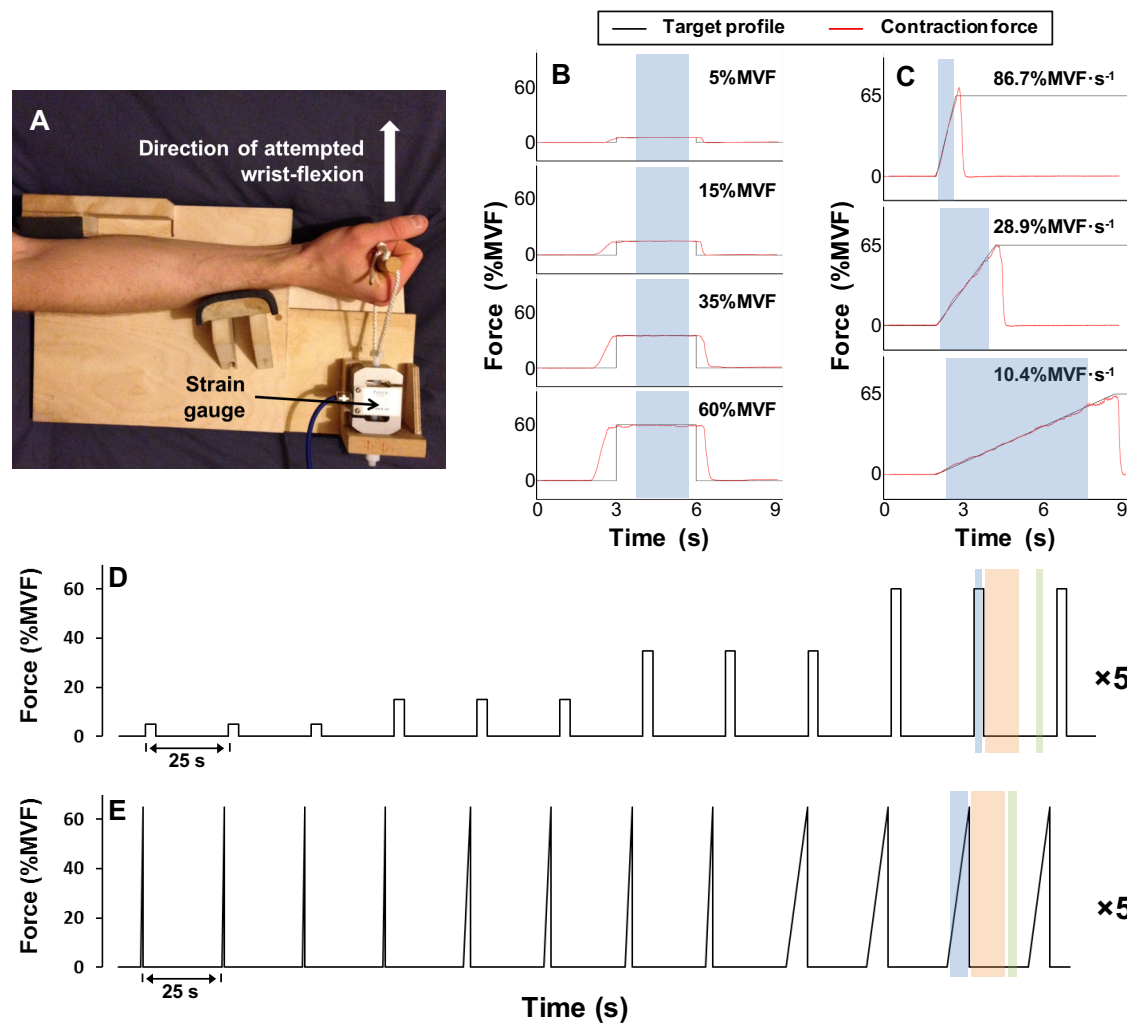


Figure 4.1 (A) A photograph of the isometric wrist-flexion dynamometer. (B/C) Each target force profile (black) with single examples of real-time visual feedback showing contraction force overlaid (red). B) Target profiles for the constant-force contractions at 5% (top), 15% (upper centre), 35% (lower centre) and 60% (bottom) maximal voluntary force. C) Target profiles for the ramp contractions, with rates of force development of 86.7% (top), 28.9% (centre) and 10.4% (bottom) maximum voluntary force output per second. (D) A schematic diagram of the constant-force contractions experiment. (E) A schematic diagram of the ramp contractions experiment. Blue, orange and green zones show time-periods during which MRBD, PMBR (10-s window) and baseline oscillatory amplitude were measured, respectively (one example shown; D&E).

Data Collection

MEG data were acquired at a sampling frequency of 600 Hz using a 275 channel CTF MEG system (MISL, Coquitlam, Canada) operating in third order synthetic gradiometer configuration. Three localisation coils were attached to the head as fiducial markers (nasion, left preauricular and right preauricular) prior to the recording. Energising these coils at the start and end of data acquisition enabled localisation of the fiducial markers relative to the MEG sensor geometry. In order to co-register brain anatomy to the MEG sensor array, each subject's head shape was digitised, using a 3D digitiser (Polhemus IsoTrack, Colchester, VT, USA), relative to the fiducial markers prior to the MEG recording. Volumetric anatomical MR images were acquired using a 3 T MR system (Phillips Achieva, Best, Netherlands) running an MPRAGE sequence (1 mm³ resolution). Following data acquisition, the head surface was extracted from the anatomical MR image and coregistered (via surface matching) to the digitised head shape for each subject. This allowed complete coregistration of the MEG sensor array geometry to the brain anatomy, thus facilitating subsequent forward and inverse calculations.

Force data were measured using a calibrated S-beam strain gauge (0-500 N linear range; Force Logic, Swallowfield, UK) housed in the isometric wrist-flexion rig. Force data were sampled at 2000 Hz by a PC running Spike 2 software (CED, Cambridge, UK), via an external A/D converter (Micro 1401, CED, Cambridge, UK). A marker was inserted within the MEG and force recordings of each individual contraction to time-synchronise the two data sets.

Data Analyses

An overview of the MEG data analysis pipeline is shown schematically in Figure 2. Initially, MEG data were inspected visually. Common sources of interference, for example the magnetomyogram, magnetooculogram and magnetocardiogram, have well characterised neuromagnetic signatures which are easily identified. Here, any trials deemed to contain excessive interference generated via such sources were excluded. Further, to facilitate consistent analyses across experiments; markers were inserted into the MEG dataset in order to delineate

the start and end of a contraction. Contraction onset was defined as the time at which force reached 2%MVF (ramp contractions) or the start of the plateau phase on the target profile (constant-force contractions); contraction offset was determined as the time at which the contraction force fell below 2%MVF when returning to rest (both experiments).

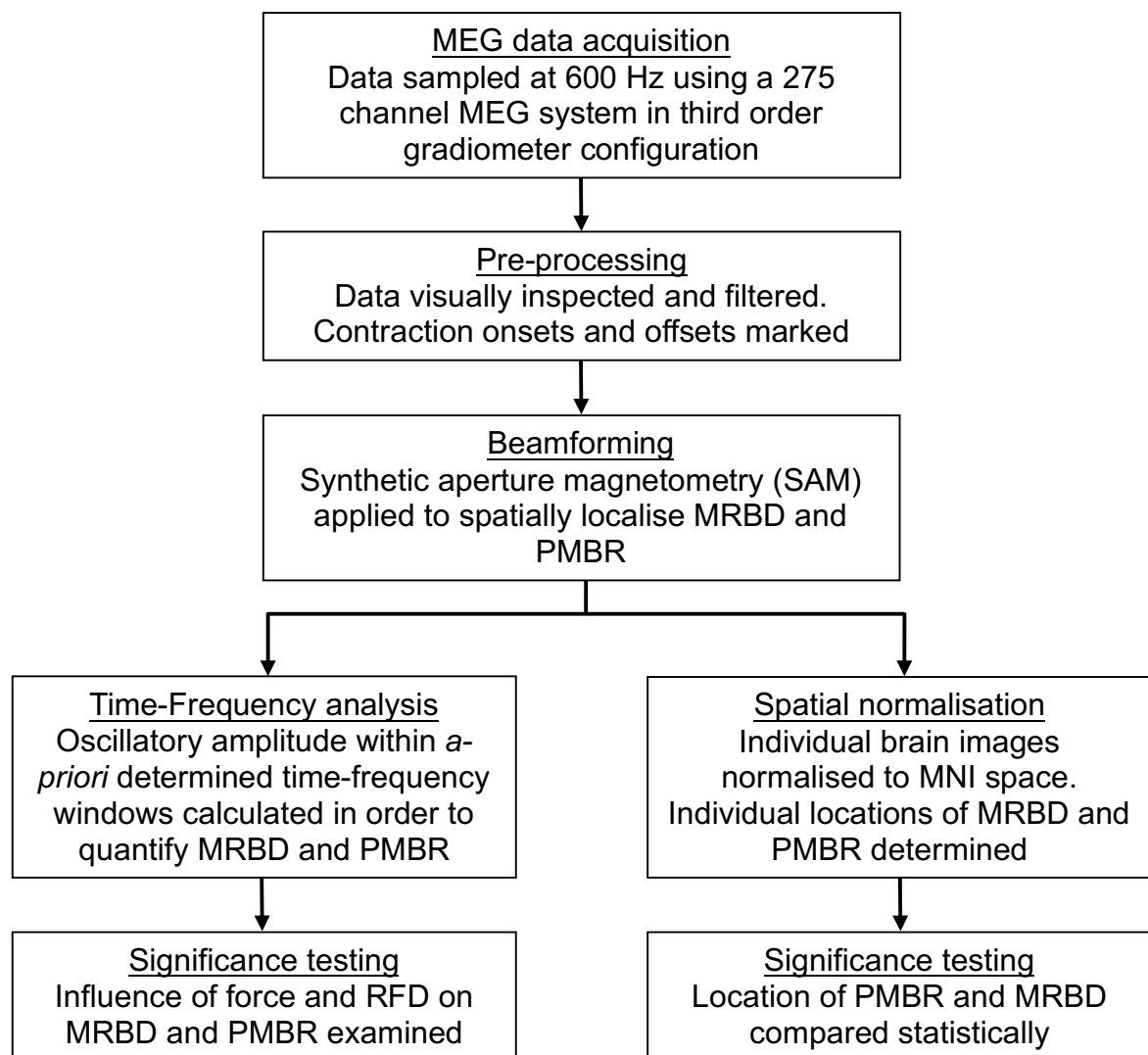


Figure 4.2 Schematic diagram showing the MEG data analysis pipeline.

Spatial signature of beta changes

Following pre-processing, MEG data were analysed using synthetic aperture magnetometry (SAM) (Vrba & Robinson 2001), a beamforming variant that has been applied successfully to localise neural oscillatory amplitude changes in many studies (van Drongelen et al. 1996; Van Veen et al. 1997; Robinson & Vrba 1998; Gross et al. 2001; Hillebrand et al. 2005). Data were first filtered to the beta (15-30 Hz) band. This exact frequency band was iteratively determined by generating time-frequency spectra (see below) and evaluating the banded power responses. Importantly, the selection of a 15 Hz lower boundary avoided overlap between beta and mu responses. Following this, oscillatory amplitude was contrasted in active and control time windows in order to delineate the spatial signatures of beta amplitude change. To localise MRBD:

- For the constant-force contractions, the active window was defined as $[0.75 < t < 2.75 \text{ s}]$ relative to contraction onset.
- For the ramp contractions, the active window spanned $[0.05 < t < 0.65 \text{ s}]$, $[0.15 < t < 1.95 \text{ s}]$ and $[0.45 < t < 5.85 \text{ s}]$ relative to contraction onset for the 86.7, 28.9 and 10.4% MVF·s⁻¹ contractions respectively.

In order to localise PMBR:

- An active window commencing 0.75 s after contraction offset and lasting for 4 s was used for both the constant-force and ramp experiments.

In all cases control windows were defined within a $[20.8 < t < 24.8 \text{ s}]$ time window relative to the initial presentation of the target profile. Note that the concatenated duration of active and control windows were equal in each analysis (Brookes et al. 2008). The forward model was based upon a multiple local sphere head model and the forward calculation by Sarvas (Sarvas 1987; Huang et al. 1999). Pseudo-t-statistical images (5 mm³ isotropic resolution) were generated showing regions of beta band oscillatory amplitude change between the active and control time windows. Spatial clusters, occurring within sensorimotor regions were identified and used as locations of interest (LOIs) for subsequent analysis.

Time-frequency spectra

Following identification of LOIs using SAM, time-frequency spectrograms were generated for each individual subject in order to measure oscillatory dynamics throughout the experiment. A SAM beamformer was employed with weighting parameters determined for each LOI using a covariance window spanning the 1Hz-150Hz frequency range, and a time window encompassing the entire experimental recording (excluding trials rejected for excessive interference). The derived beamformer weights for each location were multiplied by the MEG data (filtered 1Hz-150Hz) in order to get a 'virtual sensor' time-series showing the evolution of electrical activity at that location. Virtual sensor time-series were frequency filtered into 31 overlapping frequency bands, and a Hilbert transform was used to generate the amplitude envelope of oscillations within each band. Specifically, the beta envelope of interest within the current investigation was generated by combining two of these overlapping frequency bands (15-25 and 20-30 Hz). These envelope time-courses were then averaged across trials within each condition type (i.e. 4 target forces for the constant-force contractions and 3 target RFDs for the ramp experiment). Averaged envelopes were then concatenated in the frequency dimension to generate a single time-frequency spectrum (TFS) per subject, for each LOI identified. TFSs were subsequently averaged over all subjects leaving a single TFS for LOIs at the spatial maxima of the MRBD and PMBR. Note that TFSs were temporally aligned to contraction onset to examine MRBD, and contraction offset to analyse PMBR.

The effect of force/RFD on MRBD/PMBR

In order to assess the effect of force and RFD on MRBD and PMBR, first the force measures were analysed. For the constant-force contractions, force output was determined in the $[0.75 < t < 2.75 \text{ s}]$ window relative to contraction onset. Average force values were calculated first within each individual (for each force level), and subsequently across individuals to determine an overall group mean. For each ramp contraction, RFD was calculated for each successive 10%MVF increment in force between 2 and 62%MVF (i.e. 10%MVF/time taken). Overall RFD for each individual contraction was then determined as the average RFD of

these six increments. Mean averages of these values were again calculated within each individual, and subsequently across subjects.

To assess the effect of force or RFD on neural oscillations, summary values of MRBD and PMBR were extracted from the TFS data in each subject individually. MRBD was calculated as the integral of beta amplitude within the same active time windows as those used for SAM analyses (see above), and was divided by the duration (in seconds) of the window. Thus MRBD represents the average beta amplitude decrease during contraction. For the PMBR, the integral of the beta envelope was calculated in the $[0 < t < 10 \text{ s}]$ window relative to contraction offset in order to allow for this protracted response to reach baseline. (PMBR was not normalised by duration.) For both the MRBD and PMBR responses, results were generated based on LOIs for each response and each individual separately. This analysis yielded a single value of both PMBR and MRBD, for each condition, for each subject. These values were then averaged across subjects and plotted against either force (constant-force experiment) or RFD (ramp experiment). In addition, for the beta rebound, whether any observable changes in the measured integral were driven by changes in PMBR amplitude or duration was investigated. For this reason, post-hoc tests were also undertaken. Using data averaged across trials and subjects, the PMBR duration was measured as the total continuous time window during which the beta envelope was greater than 20% of its overall maximum value. The PMBR amplitude was estimated as the mean value of the envelope within this window.

In order to assess statistically the effect of force and RFD on MRBD and PMBR, permutation testing was employed. A simple linear regression was applied to the graphs of mean MRBD/PMBR versus force/RFD and the gradient of the regression slope was determined. It was reasoned that if force/RFD was affecting MRBD/PMBR then a non-zero gradient would be observed, whereas under a null hypothesis where force/RFD had no effect, then the gradient would be close to zero. It was further reasoned that under this null hypothesis, the order of conditions (i.e. the order of the four force outputs in the constant-force experiment, or equivalently the order of the three rates of force development in

the ramp experiment) could be switched around with no effect on the result. This latter consideration was used to form empirical null distributions testing for the effect of 1) force on MRBD, 2) force on PMBR, 3) RFD on MRBD and 4) RFD on PMBR. In each case, within each subject the order of conditions was switched randomly (different random switch for each subject). The data were then averaged across subjects to generate a 'sham' plot of mean MRBD/PMBR versus force/RFD and the 'sham' linear regression slope determined. The gradient of the regression slope in the 'real' data was then compared to the null distribution and a p-value measured as the integral of the distribution between the real gradient value and infinity divided by the total integral of the distribution.

For measurements of MRBD and PMBR integral a result was considered significant at a level of 0.05; however, this was halved to account for a two tailed test (i.e. either a significantly positive or negative gradient). It was further divided by 4 to account for multiple comparisons across the 4 tests that were undertaken. This meant that a p-value less than 0.00625 in any one single test would indicate statistical significance. Measurements of PMBR duration and amplitude are obviously related directly to integral metrics. These were therefore treated separately to the integral measurements above. Four separate two tailed tests were performed to investigate amplitude and duration in the constant-force and ramp experiments. In order to account for these multiple comparisons a false discovery rate (FRD) correction was applied (Benjamini–Hochberg procedure).

Location of the MRBD/PMBR response

Finally, significant difference in the spatial location of MRBD and PMBR were identified. First, individual brain images were normalised to an anatomical standard (Montreal Neurological Institute (MNI) brain) using FLIRT in FSL, which allowed for the formation of group means, and comparisons to be made between the spatial locations of the MRBD and PMBR responses. Following this, the MNI coordinates for each peak (MRBD and PMBR) in each subject were recorded. Having obtained x (left-right) y (anterior-posterior) and z (inferior-superior) MNI coordinates, the difference in location between MRBD and PMBR was measured as a simple three element vector. It was reasoned that any systematic spatial

shift between MRBD and PMBR would manifest as a vector with a consistent direction (e.g. it might be hypothesised that in all subjects, PMBR would be shifted in the positive y direction with respect to MRBD). For this reason, significance of the spatial shift was determined using a two-sided signed rank test of the null hypothesis that any difference in x, y or x coordinates originated from a distribution whose median is zero. The threshold for significance ($p < 0.05$) was Bonferroni corrected (by dividing by 6 to give 0.0083) to account for multiple comparisons across the 3 elements of the vector, and the two separate experiments (constant-force and RFD).

4.4 – Results

All subjects were able to accurately perform the prescribed motor tasks. The force outputs (group mean $\pm$ standard deviation) during the constant-force contractions were 5.4 ± 0.3 , 15.3 ± 0.5 , 34.9 ± 0.5 and $59.4 \pm 0.5\%$ MVF. The mean RFDs during the ramp contractions were 86.4 ± 9.9 , 29.7 ± 1.5 and $9.9 \pm 0.3\%$ MVF $\cdot s^{-1}$.

Figure 3 shows the primary results of the constant-force experiment. The spatial signatures of MRBD and PMBR, in an individual representative subject, are shown in Figures 3A and 3E respectively. A clear MRBD, local to sensorimotor cortex was observed in all subjects, and a clear PMBR, again local to sensorimotor cortex was observed in 13 of the 15 subjects (see also the spatial analysis below). Time-frequency spectrograms, averaged across subjects, are shown in Figures 3B and 3F; Figure 3B shows the case for LOI at the peak MRBD and Figure 3F shows the case for LOI at the peak PMBR. In both cases, the upper panel shows 5%MVF, the upper middle 15%MVF, the lower middle 35%MVF and the bottom panel 60%MVF. In all of the TFS plots, blue represents a decrease in oscillatory amplitude with respect to baseline whereas yellow reflects an increase. Note that for MRBD, time zero indicates contraction onset; for PMBR, time zero indicates contraction offset. A clear decrease in beta oscillations (the MRBD) is observed both preceding and throughout the motor task. This is followed by an increase above baseline following task cessation (the PMBR). Given the close spatial proximity of the peaks in MRBD and PMBR it is

unsurprising that Figures 3B and 3F are similar, with the main features observable at both spatial locations. Note also that, in addition to beta band effects, a decrease in mu rhythm (8-13Hz) is also apparent both preceding and throughout movement, however this was inconsistent across subjects and therefore was not analysed further. Interestingly, the TFSs suggest that whilst force output appears to have little effect on MRBD, a clear increase in PMBR amplitude with force output is evident. Figure 3C shows average MRBD amplitude remains approximately equivalent for each force output, suggesting that there is no consistent effect of force output on MRBD. Figure 3D illustrates the null distribution (in blue) with the measured gradient from the real data overlaid in red, and shows that that no significant effect of force on MRBD was observed. In contrast, Figure 3G shows average PMBR (total integral) plotted against force, with a clear linear change in PMBR with force output. Figure 3H illustrates the null distribution with the measured gradient overlaid, and shows that the linear modulation is significant even after correction for multiple comparisons ($p = 0.0013$).

Figure 4 shows the primary results of the ramp contractions experiment. The layout is equivalent to that of Figure 3. The spatial signatures of MRBD and PMBR, in an individual representative subject, are shown in Figures 4A and 4E respectively. Average time-frequency spectrograms extracted from LOI at the peaks of MRBD and PMBR are shown in Figures 4B and 4F respectively. A clear decrease in beta oscillations preceding and throughout movement, and a beta rebound occurring on movement cessation is again illustrated. No statistically significant modulation of either MRBD or PMBR was observed with changing RFD; as illustrated in Figures 4C, 4D, 4G and 4H.

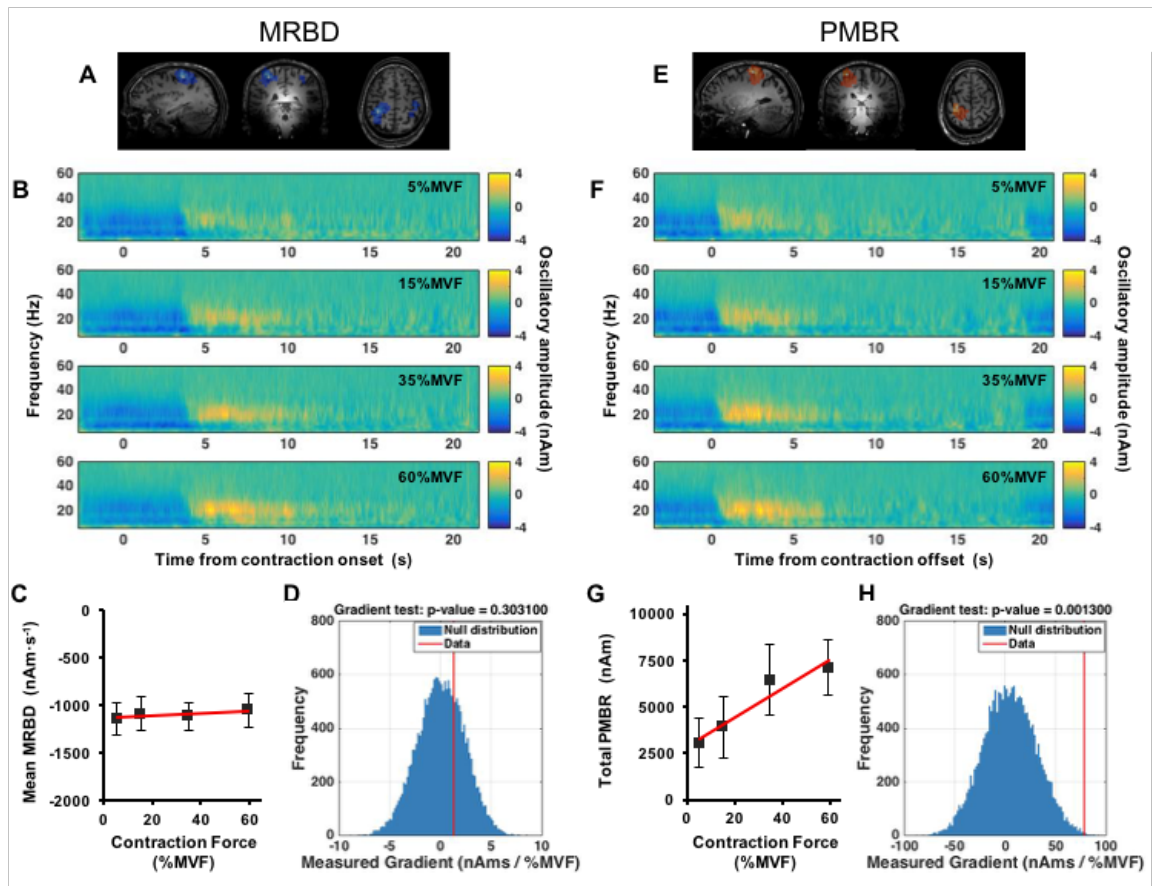


Figure 4.3 Results of the constant-force experiment. A/E) Spatial signatures of MRBD (A) and PMBR (E) in a single subject. B/F) Time-frequency spectrograms extracted from locations of interest at the peak MRBD (B) and PMBR (F); upper to lower panels represent (prescribed) 5%MVF, 15%MVF, 35%MVF and 60%MVF contractions. Note that for MRBD, time zero indicates contraction onset; for PMBR, time zero indicates contraction offset. C/G) Average MRBD during the contraction (C) and total PMBR integral over the 10 s post contraction period (G) plotted against force. D/H) The null distribution (blue) with the measured MRBD (D) and PMBR (H) gradient from real data overlaid in red. Note significant ($p_{\text{corrected}} < 0.05$) modulation of PMBR with force output was observed.

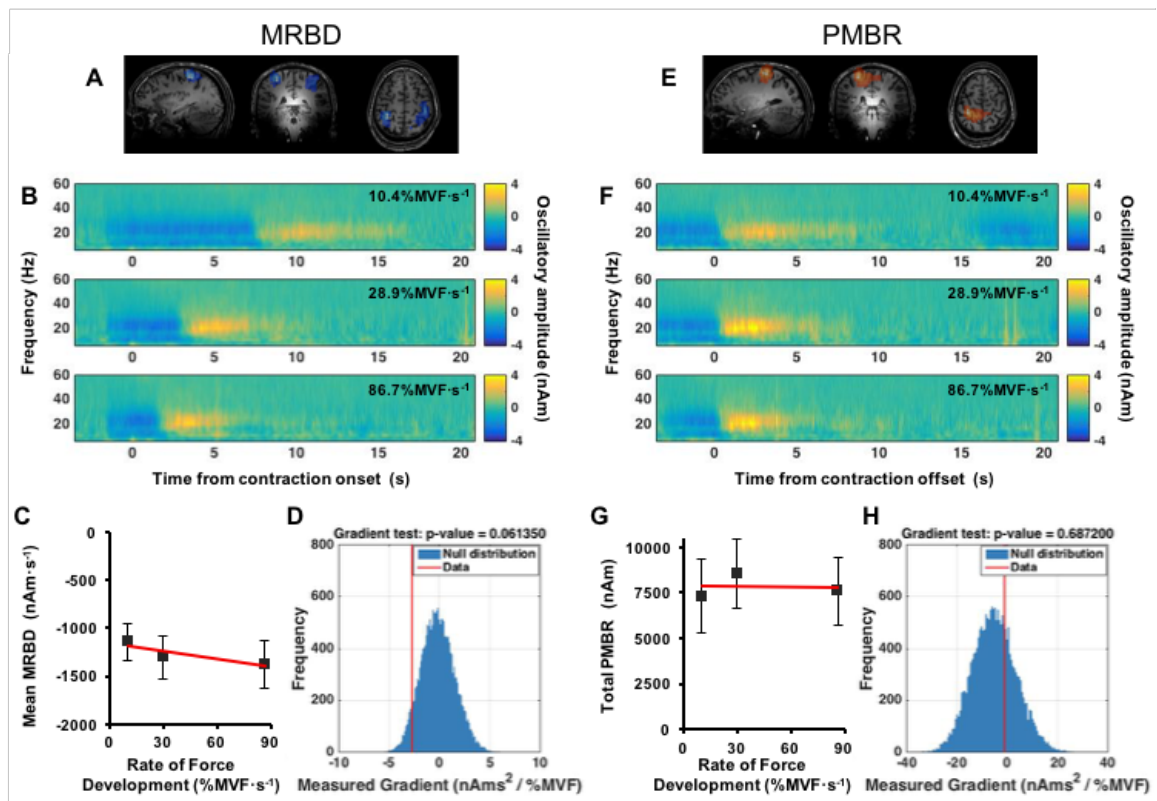


Figure 4.4 Results of the ramp experiment. A/E) Spatial signatures of MRBD (A) and PMBR (E) in a single subject. B/F) Time-frequency spectrograms extracted from locations of interest at the peak MRBD (B) and PMBR (F); upper to lower panels represent (prescribed) 10.4% MVF·s⁻¹, 28.9% MVF·s⁻¹, and 86.7% MVF·s⁻¹ contractions. Note that for MRBD, time zero indicates contraction onset; for PMBR, time zero indicates contraction offset. C/G) Average MRBD during the contraction (C) and total PMBR integral over the 10 s post contraction period (G) plotted against RFD. D/H) The null distribution (blue) with the measured MRBD (D) and PMBR (H) gradient from real data overlaid in red. Note no significant modulation of either MRBD or PMBR with RFD.

The results above show only MRBD and PMBR integral. However, for the PMBR, an increased integral, which was measured in the $[0 < t < 10 \text{ s}]$ window post contraction offset, could be driven either by an increase in amplitude of the response, an increased duration of the response, or a combination of the two. For this reason, both PMBR amplitude and duration were tested further. Figure 5 shows PMBR amplitude and duration measured during the constant-force experiment. Figure 5A shows the time-courses of the beta envelopes in blue, with estimated duration and mean amplitude overlaid in black. Figure 5B shows the duration of the PMBR plotted against force output (upper panel), and Figure 5C shows amplitude of the PMBR plotted against force output (upper panel). These relationships are tested statistically in the lower panels of Figures 5B and 5C. Note that the increase in PMBR amplitude with force is significant ($p = 0.008$). However, the apparent increase in PMBR duration with force did not reach significance following FDR correction.

Figure 6 shows the PMBR amplitude and duration measured during the ramp experiment. Figure 6A shows the time-courses of the beta envelopes in blue, with the estimated duration and mean amplitude overlaid in black. Figure 6B shows the duration of PMBR plotted against RFD whilst Figure 6C shows amplitude of the PMBR plotted against RFD. The lower panels of Figures 6B and 6C show associated statistical testing. Interestingly, PMBR duration reduces significantly ($p = 0.008$) with RFD, PMBR amplitude increases significantly ($p = 0.004$). It is noteworthy that these two significant results combine to generate the negative result (shown in Figure 4G) that PMBR integral is unaffected by RFD. This finding is discussed further below.

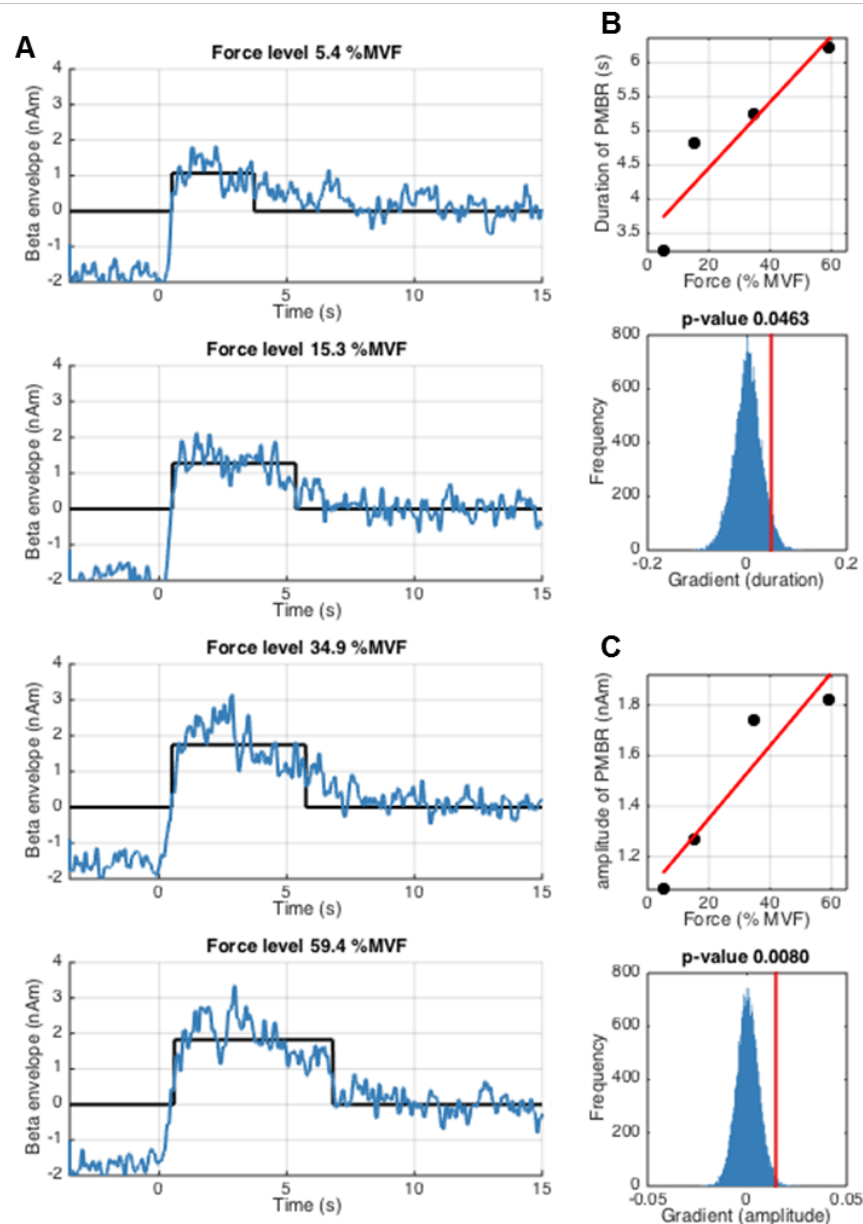


Figure 4.5 Measurement of PMBR amplitude and duration during the constant-force experiment. A) Shows the average beta band envelope time-courses (blue) for each of the four force outputs; time $t = 0$ denotes contraction offset. The black lines show the estimated duration and mean amplitude of the PMBR. B) Duration of PMBR plotted against force output (upper panel) and the measured gradient (PMBR duration against force) (red line) alongside the null distribution in blue (lower panel). C) Mean amplitude of PMBR plotted against force output (upper panel) and the measured gradient (PMBR amplitude against force) (red line) alongside the null distribution in blue (lower panel). Note that whilst amplitude of PMBR increases significantly with force output, duration fails to reach significance following FDR correction.

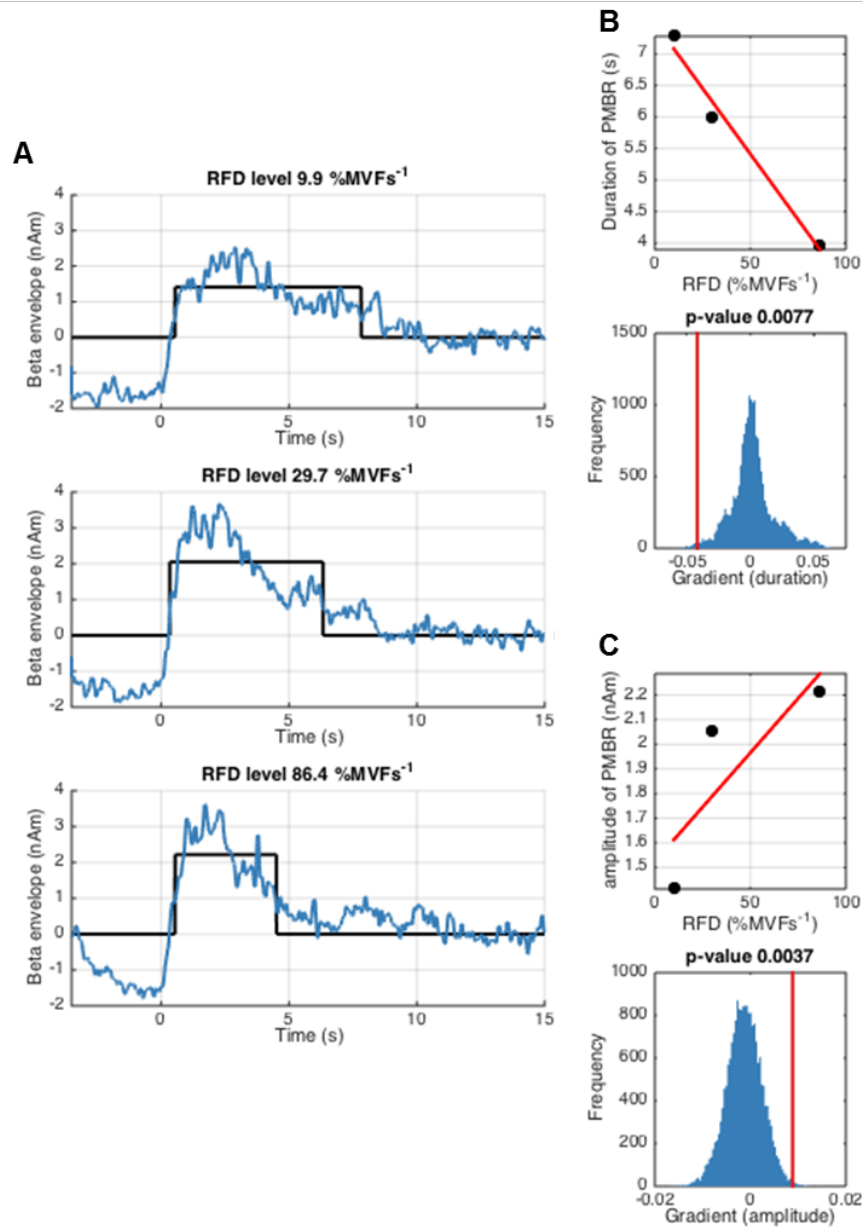


Figure 4.6 Measurement of PMBR amplitude and duration during the ramp experiment. A) Shows the average beta band envelope time-courses (blue) for each of the three RFDs; time $t = 0$ denotes contraction offset. The black lines show the estimated duration and mean amplitude of the PMBR. B) Duration of PMBR plotted against RFD (upper panel) and the measured gradient (PMBR duration against RFD) (red line) alongside the null distribution in blue (lower panel). C) Mean amplitude of PMBR plotted against RFD (upper panel) and the measured gradient (PMBR amplitude against force) (red line) alongside the null distribution in blue (lower panel). Note that as rate of force development is increased (and the duration of the ramp contraction decreased) the duration of PMBR is significantly reduced, and PMBR amplitude is significantly increased.

Finally, Figure 7 and Table 1 show the results of the spatial analyses, testing a hypothesis that the MRBD and PMBR are generated in different cortical regions. Figures 7A and 7B show the localisation for the constant-force and ramp contractions respectively. The top row of Figures 7A and 7B show the spatial locations of the derived peaks in all subjects, plotted in MNI space. The bottom rows show group average locations. The mean and standard deviation of the x, y and z coordinates across all subjects are shown in Table 1, alongside the most likely cortical locations of these mean MNI coordinates according to the Oxford-Harvard brain atlas. The statistical analysis showed that for the constant-force contractions there is a significant ($p_{\text{corrected}} < 0.05$) shift in the anterior (positive y) direction for the PMBR compared to the MRBD. Although the same trend was observed in the ramp contractions this failed to reach statistical significance.

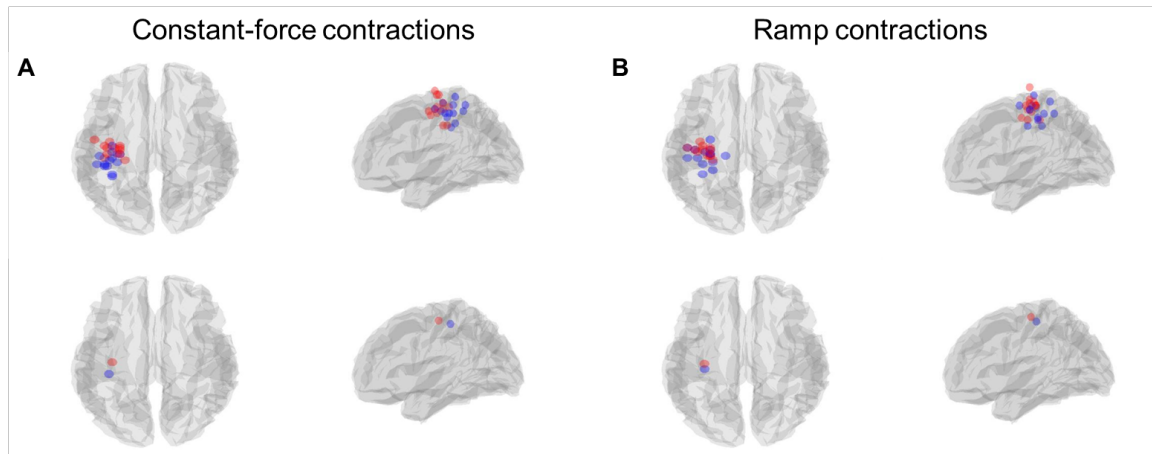


Figure 4.7 Peak locations of the MRBD (blue) and PMBR (red) for each individual subject (top row) and the group average (bottom row), in both the constant-force (A) and ramp (B) experiments.

Table 4.1 MNI coordinates and associated most likely cortical locations (according to the Oxford-Harvard atlas) of the MRBD and PMBR. (The * indicates a significant difference from the corresponding MRBD coordinate following Bonferroni correction for the 6 comparisons made ($p_{\text{corrected}} < 0.05$)).

	MNI coordinates			Cortical Location
	x	y	z	
Constant-force contractions				
MRBD	-36.4 ± 1.3	-31.5 ± 2.1	50.7 ± 2.1	postcentral gyrus
PMBR	-33.7 ± 1.9	-19.9 ± 1.6*	54.9 ± 2.9	precentral gyrus
Ramp contractions				
MRBD	-32.9 ± 2.1	-27.2 ± 2.4	52.7 ± 2.3	postcentral gyrus
PMBR	-32.6 ± 1.7	-21.4 ± 1.4	58.5 ± 2.5	Precentral gyrus

4.5 – Discussion

Movement induced modulation of neural oscillations in the beta band is one of the most robust neural oscillatory phenomena in the brain. Specifically, in the preparation and execution phases of a motor task, a loss in beta oscillatory amplitude is observed (MRBD) and this is followed by a rebound above baseline (PMBR) on task cessation. These effects have been measured widely, and recent work suggests that they may have great potential to inform important biomarkers for disease. For example, the PMBR is greater in healthy controls than patients with schizophrenia, and the magnitude of the PMBR in patients correlates with persistent symptoms of disease (Robson et al. *In Press*). In individuals with Parkinson's disease, where movements are limited and poorly controlled, both MRBD and PMBR are reduced in amplitude (Heinrichs-Graham et al. 2014; Pollok et al. 2012). However, despite the robust nature and high potential value of beta measurements, the effects themselves are poorly understood. In this study, a carefully controlled isometric wrist flexion paradigm

was employed to isolate two important movement parameters; namely force output and the rate of force development (RFD). The results show that neither altered force output nor RFD has any effect on the MRBD. In contrast, PMBR was systematically altered by both parameters; specifically, higher force output results in significantly greater PMBR amplitude. Further, a greater RFD results in a PMBR which is shorter in duration, and higher in amplitude.

The finding that MRBD is related to neither force output nor RFD supports a number of previous studies suggesting that the event related beta decrease acts as a cortical 'gate', the magnitude of which is unrelated to stimulus parameters. The results are also in accordance with previous investigations suggesting that neither contraction force (Cremoux et al. 2013; Stančák et al. 1997) nor movement velocity (Stancák & Pfurtscheller 1996; Stancák & Pfurtscheller 1995) influence MRBD observed during contractions. In addition, previous work has shown a distinct 'on/off' property to stimulus evoked beta amplitude reductions, not only in sensorimotor cortex but also in the visual and somatosensory systems (Stevenson et al. 2011; Stevenson et al. 2012). In contrast, previous investigation into the PMBR has found it to be more variable across stimulus conditions (Stevenson et al. 2012). Nevertheless, to the author's knowledge this paper represents the first demonstration of monotonic increase in PMBR amplitude with force output, and the first demonstration of increased PMBR amplitude and decreased duration with RFD. The results are in some agreement with those of Stančák et al. [1997] who demonstrated a greater PMBR following loaded finger extensions against their heaviest external load (130 g) compared to their unloaded extensions; although other movement parameters, including RFD, would also have varied between different external loads. Contrary to the current findings, no difference in PMBR was reported following isometric elbow flexion between 25 and 75% maximal force (Cremoux et al. 2013). The reason for this discrepancy is not clear, and further investigation of this phenomenon, including whether it may differ across muscle groups, may therefore be warranted.

Prior to more focussed discussion of the results, it is helpful to understand the purported role of beta oscillations. In general, beta oscillations are thought to exert an inhibitory influence within the sensorimotor system, with a decrease in beta amplitude potentially reflecting a switch to a state in which a greater range of

movements can be made. It has been shown that voluntary movements are slowed during periods of high beta oscillations (Gilbertson et al. 2005), and when beta rhythms are entrained using transcranial alternating-current stimulation (Pogosyan et al. 2009). In addition, it is known that attending to a particular location in the body causes shifts in beta amplitude (Bauer et al. 2012; van Ede et al. 2014), consistent with the notion that such events inhibit ipsilateral cortex and promote encoding in contralateral cortex. The increase (above baseline levels) in beta amplitude following a movement (the PMBR) has been suggested to reflect inhibition of motor activity (Alegre et al. 2008; Solis-Escalante et al. 2012), which may facilitate motor control by preventing the generation of further unwanted movements.

The precise relationship between oscillatory amplitude (which reflects high synchrony across many neurons) and inhibition is not clear, however it has been argued that reduced synchrony allows greater flexibility to encode information in cellular assemblies (Brookes et al. 2015). Further evidence for the inhibitory influence of beta synchrony comes from neurochemistry. Beta oscillations likely depend upon a delicate balance between excitation and inhibition. This in turn is primarily driven by glutamate (the major excitatory neurotransmitter in the cortex) and GABA (the major inhibitory neurotransmitter in the cortex). There is good evidence to suggest that beta modulation is strongly related to GABAergic inhibition. For example, using magnetic resonance spectroscopy, Gaetz et al. [2011] have shown that the magnitude of PMBR across subjects correlates positively with individual subject GABA levels, pointing towards a positive influence of GABA on PMBR. Muthukumaraswamy and colleagues [2013] have provided evidence that blocking GABA uptake via administration of Tiagabine alters baseline and task induced modulation of beta oscillations. A separate pharmaco-MEG study by Hall et al. [2011] used administration of the GABA-A receptor modulator diazepam to show that MRBD is a GABA-A mediated process whereas PMBR appeared to be generated by a non-GABA-A mediated process. Collectively, this evidence points towards the beta band response being a potential marker of GABAergic inhibition. If this is indeed the case, then the beta band response offers a direct and non-invasive way to probe neurochemical

imbalance in diseases such as schizophrenia where there is good evidence that GABA levels may be disturbed.

In the present study, the findings provide new information with regards to the PMBR which may help to disentangle its functional role and generate new hypotheses to be tested in future work. It was shown that, with greater force output an increase in PMBR amplitude is observed (Figure 5) but there is no significant change in the duration of the response. This potentially suggests that a greater degree of inhibitory control is required following high force contraction in order to return to a pre-contraction state. When peak force output is kept constant but the duration over which this force is attained is decreased, (i.e. increasing RFD) PMBR duration decreases while amplitude increases (Figure 6). These two components of the rebound (amplitude and duration) might be affected by independent aspects of the task, for example; it is possible that the variation in duration of the rebound might be related to the duration of the stimulus; i.e. longer stimulus durations will result in longer rebounds. Previous work (Stevenson et al. 2011) investigated the effect of increasing the duration of the motor stimulus (1 to 6 s) on beta responses and found increases in the integrated PMBR with increased stimulus duration up to 4 s. However, the paradigm design meant that as stimulus duration increased, the “rest period” decreased (minimum 4 s) (in order to maintain a constant trial length). Therefore, any prolongation of PMBR may not have been fully captured, and more importantly, measures of baseline beta amplitude may have been collected during the latter stages of the PMBR, resulting in underestimation of the PMBR and overestimation of MRBD during the longer duration stimuli. Indeed, short inter-stimulus intervals are a consistent problem in studies of this type. The current findings show that the duration of the PMBR can be in excess of 7 s. Therefore, when interpreting the changes in oscillatory power, both during and following stimulation, it is important to ensure that the electrophysiological response has fully returned to baseline before baseline itself is quantified.

The variation in amplitude of the rebound with RFD is less intuitive. Recall that in the RFD experiment, the peak force output is maintained for all RFDs, and only the rate at which that force is attained is varied. The constant force experiment showed a clear increase in PMBR with force output and, if one believes the

simplest hypothesis that PMBR amplitude is affected by force alone, then the finding of significantly modulated PMBR amplitude in the RFD experiment is counter intuitive. Although highly speculative, it is possible that this difference in amplitude may be driven by competing excitatory and inhibitory effects. When contractions are sustained over a longer time period, the sensation of the handle in the subjects' hand may be retained following stimulus cessation, thereby causing a sensory aftereffect which might dampen the post-stimulus rebound by evoking a concurrent stimulus for beta decrease. For example, it may be the case that, under a hypothesis that MRBD and PMBR have different neural generators, the sensory aftereffect would generate MRBD in sensory cortex, but the cessation of contraction would generate PMBR in motor cortex. The inherent spatial smoothness of the beamformer estimated time series would necessarily mix these two effects, so increased aftereffect induced MRBD could artifactually decrease the apparent PMBR. This dampening of post-stimulus effects due to aftereffects has previously been reported for visual stimuli (static versus flashing checkerboards) in EEG alpha rebounds (Mullinger et al. 2015) and functional Magnetic Resonance Imaging (fMRI) post-stimulus responses (Sadaghiani et al. 2009; Mullinger et al. 2015).

This study has provided some evidence that the MRBD and PMBR originate via different neural generators. The idea that the MRBD and PMBR are fundamentally different processes is well established; for example, Donner and Siegel [2011] proposed that decreased beta amplitude is associated with local encoding processes, whereas increased post stimulus beta amplitude is associated with integrative processes over large networks. Firstly, the observation that MRBD was not related to either force or RFD, whereas PMBR was, adds support to suggestions that these may be independent phenomena (Feige et al. 1996; Cassim et al. 2001; Jurkiewicz et al. 2006). Additionally, it was shown that in one of the two experiments, a significant anterior shift in the spatial location of the PMBR compared to the MRBD is measurable. These results are in good agreement with several previous studies that have observed an anterior shift in the PMBR compared to the MRBD (Stancák & Pfurtscheller 1995; Salmelin et al. 1995; Jurkiewicz et al. 2006).

Finally, the data presented here have important implications for the interpretation of post-stimulus undershoots measured in fMRI data (Buxton 2012; van Zijl et al. 2012). This part of the response was historically believed to be vascular in origin (Buxton et al. 1998) however there is a growing body of evidence that this response reflects neuronal activity (Shmuel et al. 2006; Sadaghiani et al. 2009; Mullinger et al. 2013). Recent work has shown that the post-stimulus fMRI response to a 10 s median nerve stimulus is correlated with the EEG alpha activity measured in a 10s window post-stimulation (Mullinger et al. 2013). The work in this current study shows that, for long duration stimuli, the rebound will occur on this time scale, rather than 1-3 s as is often previously reported. This therefore provides potential new evidence for the link between electrophysiology and fMRI measures of post-stimulus activity. Furthermore, previous studies have noted some changes in fMRI undershoot amplitude and/or duration with varying stimulus duration (Chen et al. 1998; Hu et al. 1997; Jin & Kim 2008). Conversely a separate study showed no significant effects of stimulus amplitude or duration on post-stimulus undershoot responses (Chen & Pike 2009) but in this study data had been grouped over visual and motor cortices which may have hidden the effects of interest in one sensory area. Further investigation is required to determine whether task-specific modulations in the PMBR measured using MEG might translate to the post-stimulus responses measured using fMRI.

Finally, the sole intention of the present study was to investigate the dependence of beta band oscillatory phenomena on force output and RFD. Nevertheless, it is important to note that a number of other electrophysiological effects are observable in sensorimotor cortex, including the phase locked movement induced evoked response. Previous work has suggested that the magnitude of these movement-related cortical potentials might modulate with both force and RFD (do Nascimento et al. 2005; Siemionow et al. 2000). No attempt to confirm these findings was made as contraction kinematics surrounding force onset was not carefully controlled, which would have undermined the validity of such analyses. Future work should therefore aim to integrate these phase locked effects with measurements of oscillatory power.

In conclusion, a carefully controlled isometric wrist flexion paradigm was employed to isolate two fundamental movement parameters; force output, and

the rate of force development (RFD). The results show that the amplitude of movement related beta band decrease is the same regardless of changes in either force or RFD. In contrast, systematically changing the force output of a muscle contraction results in a linear modulation of PMBR, with a higher force outputs resulting in greater amplitudes of post-stimulus response. Further, it was found that increasing RFD generates significant increases in amplitude and decreases in duration of PMBR. These findings demonstrate that careful control of movement parameters can systematically change PMBR; further for temporally protracted movements (low RFD) the PMBR can be over 7s in duration. This means accurate control of movement and judicious selection of paradigm parameters are critical in future clinical and basic neuroscientific studies of sensorimotor cortex beta oscillations.

Chapter 5

The effect of physical fatigue on
oscillatory dynamics of the sensorimotor
cortex

5.1 – Abstract

While physical fatigue is known to arise in part from supraspinal mechanisms within the brain exactly how brain activity is modulated during fatigue is not well understood. Therefore, this study examined how typical neuro-oscillatory responses to voluntary muscle contractions were affected by fatigue. Eleven healthy adults (age 27 ($s = 4$) years) completed two experimental trials in a randomised crossover design. Both trials first assessed baseline maximal voluntary isometric wrist-flexion force (MVFb). Participants then performed an identical series of fourteen prescribed isometric wrist-flexor contractions ($2 \times 100\%MVFb$, $10 \times 40\%MVFb$, $2 \times 100\%MVFb$) both before and after one of two interventions: forty 12-s contractions at $55\%MVFb$ (fatigue trial) or $5\%MVFb$ (control trial). Magnetoencephalography (MEG) was used to characterise both the movement-related mu and beta decrease (MRMD and MRBD) and the post-movement beta rebound (PMBR) within the contralateral sensorimotor cortex during the submaximal ($40\%MVFb$) contractions, while the maximal voluntary contractions ($100\%MVFb$) were used to monitor physical fatigue. The fatigue intervention induced a substantial physical fatigue that endured throughout the post-intervention measurements ($28.9\text{--}29.5\%$ decrease in MVF, $P < 0.001$). Fatigue had a significant effect on both PMBR (ANOVA, trial $\times$ time interaction: $P = 0.018$) and MRBD ($P = 0.021$): the magnitude of PMBR increased following the fatigue but not the control interventions, whereas MRBD was decreased post-control but not post-fatigue. Mu oscillations were unchanged throughout both trials. In conclusion, physical fatigue resulted in an increased PMBR, and offset attenuations in MRBD.

5.2 – Introduction

Physical fatigue can be defined as a reversible decline in the force generating capacity of the neuromuscular system. During physical activity, fatigue arises not only from peripheral processes within the active skeletal muscle(s) but also from supraspinal mechanisms within the brain. Supraspinal fatigue is a component of central fatigue, relating to a progressively suboptimal output from the motor cortex. Supraspinal fatigue can account for as much as 66% of the exhibited physical fatigue during a prolonged low-intensity muscle contraction (Smith et al. 2007), and as much as 30% during a 2-min maximal contraction (Taylor et al. 2006). Overall, fatigue has clear implications to physical performance, and may be experienced as a chronic activity-limiting symptom that adversely affects the quality of life in numerous patient groups. However, exactly how brain activity is modulated during physical fatigue is not well understood. This is in large part due to the difficulties in accurately recording brain activity in humans, particularly during strenuous muscle contractions.

Previous attempts at neuroimaging the brain during physical fatigue have largely relied upon functional magnetic resonance imaging (fMRI). Here, an increase in sensorimotor ‘cortical activation’ is inferred from increases in the blood-oxygen-level dependent (BOLD) fMRI signal, which have been found to accompany fatigue onset during the performance of both maximal (J. Z. Liu et al. 2002; Steens et al. 2012) and submaximal isometric contractions (Liu et al. 2003; van Duinen et al. 2007; Benwell et al. 2007). However, the haemodynamically derived fMRI signal is physiologically and temporally remote from the electrical activity that is of primary interest as the method of communication within the brain. Specifically, the electrophysiological interactions between neurons produce local oscillations in electric and magnetic fields that can be measured non-invasively using electroencephalography (EEG) and magnetoencephalography (MEG), respectively. Moreover, MEG offers an improved spatial resolution and sensitivity compared to electroencephalography (EEG), due in part to the fact that magnetic fields are not distorted by the biological tissues between the cortex and recording sensors (Cheyne 2013). Consequently, MEG can be used to record neuro-oscillatory dynamics within highly localised regions of the cortex.

In the sensorimotor system, motor action has been linked with robust changes in neural oscillations in the mu (~7-15 Hz) and beta (~15-30 Hz) bands. During the preparation and performance of unilateral movements, decreases in both mu and beta amplitude are observed, with the largest effect occurring local to the contralateral primary sensorimotor cortex (Jasper & Penfield 1949; Salmelin & Hari 1994; Pfurtscheller et al. 2003). These phenomena are known as the movement-related mu/beta decrease (MRMD/MRBD). Following movement cessation beta oscillations then exhibit a period of elevated amplitude, known as the post-movement beta rebound (PMBR) (Pfurtscheller et al. 1996; Jurkiewicz et al. 2006). These phenomena have been measured widely, and recent work suggests that they may have great potential to inform important biomarkers for disease. For example, PMBR is greater in healthy controls than patients with schizophrenia, and the magnitude of PMBR in patients correlates with persistent symptoms of disease (Robson et al. *In Press*). In individuals with Parkinson's disease, where movements are limited and poorly controlled, both MRBD and PMBR are reduced in amplitude (Heinrichs-Graham et al. 2014; Pollok et al. 2012). Additionally, these phenomena may have further clinical utility by informing brain computer interfaces (Pfurtscheller & Solis-Escalante 2009).

Despite their robust nature and high potential value these movement-related oscillatory phenomena are poorly understood. Specifically, whether these phenomena are modulated by physical fatigue is largely unknown, even though this may have important implications for the measurement and interpretation of these phenomena and how it may also inform our understanding of the nature of fatigue. One preliminary study measured sensorimotor oscillations during submaximal contractions performed in a state of physical fatigue and reported an elimination of MRBD (Tecchio et al. 2006). This might indicate a strong influence of fatigue on the typically robust movement-related oscillatory dynamics described above, crucially however, no control trial was conducted within this study making it impossible to isolate fatigue and time/habituation effects. Therefore, the purpose of this study was to conduct a rigorous investigation of how movement-related oscillatory dynamics within the sensorimotor cortex are influenced by physical fatigue.

5.3 – Methods

Participants

Fourteen healthy adults with no known history of neurological or musculoskeletal disorders volunteered their participation. Three participants found the fatigue protocol (described below) particularly challenging, such that they were unable to maintain the post-intervention contractions for the prescribed time, and were omitted from subsequent analyses. This left a total of eleven participants (7 males, 2 left handed, age 27 ± 4 years [mean $\pm$ standard deviation]). The experimental procedures were approved by the Loughborough University Ethical Advisory Committee, and each participant provided written informed consent prior to their involvement. All experimental measurements were carried out in the MEG facility at the Sir Peter Mansfield Imaging Centre, University of Nottingham, UK.

Overview

Participants were well familiarised with the isometric wrist-flexion tasks and the MEG environment prior to their participation in two experimental trials; conducted in a randomised crossover design, ~ 7 days apart, and at a consistent time of day. For both experimental trials, maximum voluntary force was first established at baseline (MVF_b), in order to prescribe the force of all subsequent contractions. Each trial involved one of two interventions: a series of forty contractions of 12 s duration at either 5% MVF_b (control trial) or 55% MVF_b (fatigue trial). Participants also completed an identical series of fourteen contractions both pre- and post-intervention; including ten contractions at 40% MVF_b to measure movement-related oscillatory dynamics with MEG, and a total of four maximal voluntary contractions to monitor fatigue. Participants were advised to abstain from strenuous or atypical exercise for 36 hours prior to each trial, and to avoid the intake of nutritional stimulants (e.g. caffeine) within two hours of the trial. A summary of the experimental protocols is illustrated in Figure 5.1.

Experimental set-up and force data collection

Participants were seated upright in the MEG system with their right forearm and hand positioned in a custom built isometric wrist-flexion dynamometer that was secured to the armrest of the MEG system (Figure 5.1A&B). The dynamometer held the participant's arm in a neutral position of pronation/supination, radial/ulnar deviation and wrist flexion/extension. Waist and right forearm straps were lightly applied to maintain a consistent posture, but without risk of restricting blood flow. Participants were instructed to exert wrist-flexion force against a cylindrical handle that was attached in series to a strain gauge. Force data were measured using a calibrated S-beam strain gauge (0-500 N linear range; Force Logic, Swallowfield, UK) housed in the isometric wrist-flexion dynamometer. Force data were sampled at 2000 Hz by a PC running Spike 2 software (CED, Cambridge, UK), via an external A/D converter (Micro 1401, CED, Cambridge, UK). The handle was sewn onto a mitt that participants wore throughout the trials to ensure a consistent position of the handle relative to the hand (and therefore a constant lever length). Participants were also instructed to refrain from any movements other than the prescribed wrist-flexion (e.g. gripping).

Force prescription and feedback was facilitated by participants viewing a visual display throughout the experimental procedures. They were presented with a temporal profile of target force output prior to each of the prescribed contractions and attempted to match their contraction force to the target profiles as closely as possible. Real-time (measured) contraction force was overlaid on the target profile and this provided feedback (see Figure 5.1C). The target force profile for each contraction included a 2 or 3 s rest period ($0\%MV F_b$), a linear ramp of 1-s duration, and a constant-force (plateau) phase at the prescribed force output. Each profile was displayed on the screen for a total of either 10 s (40 and $100\%MV F_b$ contractions) or 15 s (5 and $55\%MV F_b$ contractions), and disappeared to leave a blank screen immediately following each contraction. Participants received prior instructions to cease the contraction as soon as the target force profile had disappeared from the screen. A new target force profile appeared on the display screen every 30 s. An additional 90 s of rest was provided both before and after the 40-contraction interventions.

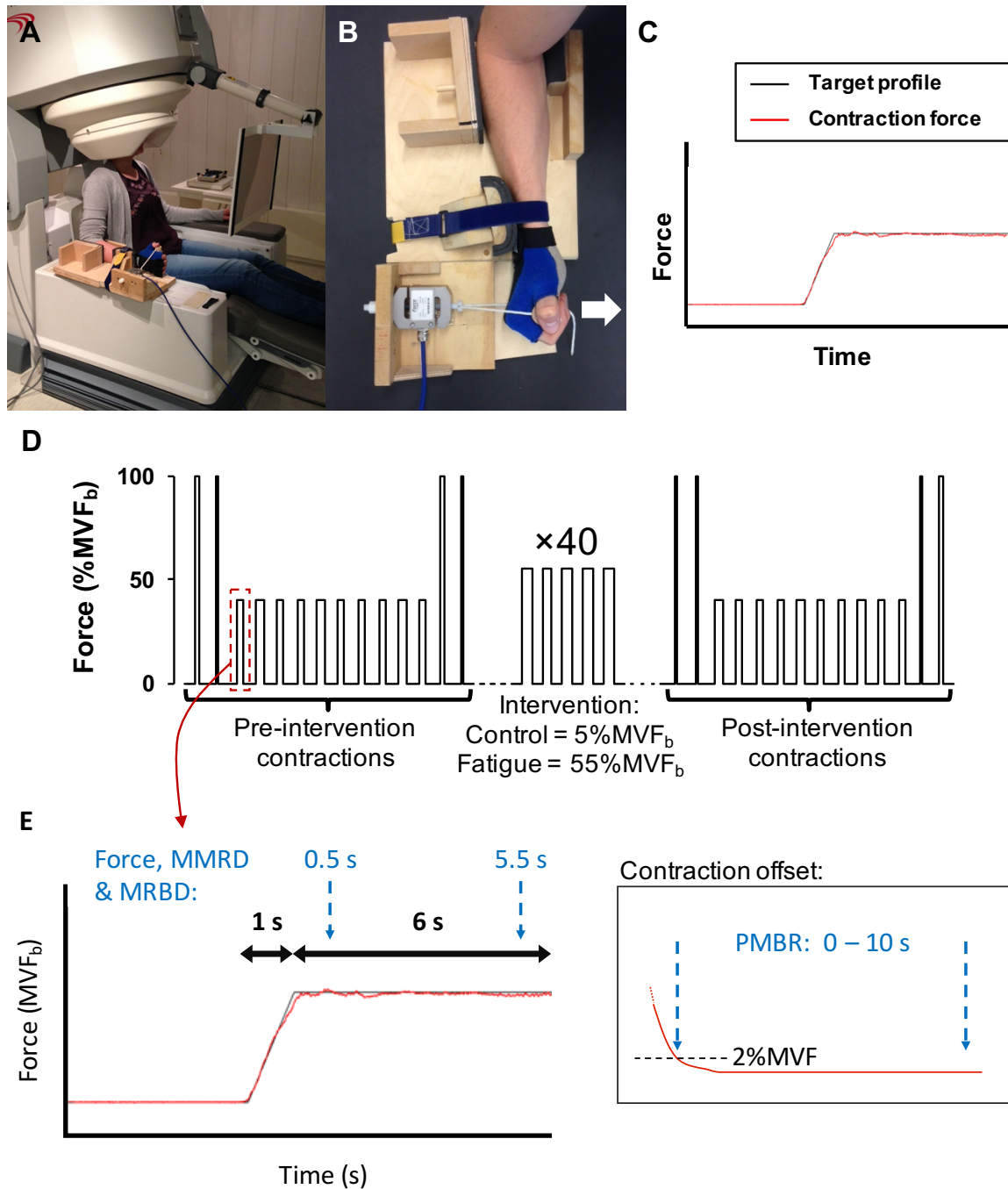


Figure 5.1 A) A participant seated within the MEG scanner. B) A forearm positioned within the isometric wrist-flexion dynamometer (white arrow denotes direction of isometric force application). C) An example of a target force profile with the real-time visual feedback of the performed contraction force overlaid. D) A schematic of the experimental protocol. E) A schematic of the data measurement periods (blue annotations) during the 40% MVF contractions.

Preliminary measurements

Each trial started with a short warm up of submaximal isometric wrist-flexions. Participants then completed four maximal voluntary contractions, with 30 s rest between contractions, from which a baseline value of maximal voluntary force (MVF_b) was established. Participants were instructed to exert a maximum effort of wrist-flexion force continuously for 3 s, with visual biofeedback and verbal encouragement provided. The peak force (200 ms epoch) during these contractions was used as the measure of MVF_b from which all subsequent force outputs were prescribed. A 5-min rest was then provided before commencing the pre-intervention contractions.

Pre- and post-intervention contractions and MEG data collection

Pre- and post-intervention contractions involved identical series of fourteen prescribed wrist-flexion contractions: two maximal voluntary contractions (MVF_{start}), ten contractions at 40% MVF_b , and a further two maximal contractions (MVF_{end}) (Figure 5.1D). The 40% MVF_b contractions were of 6-s duration, and performed every 30-s, in order to measure neuro-oscillatory behaviour during (MRMD & MRBD) and post-contraction (PMBR) with MEG. These MEG recordings provided the primary outcome measures before and after fatigue/control. Submaximal contractions were used so that they could be performed in enough volume to collect a sufficient quantity of MEG data, and that the same motor task (with respect to force output) could be replicated even during a state of physical fatigue. The maximal voluntary contractions were used to determine MVF at four time-points (not including MVF_b), and monitor each participants' fatigue throughout each trial. For these maximal contractions, the target force profile displayed a 3-s constant-force phase at 100% MVF_b , and participants had received prior instructions to perform a maximal effort of wrist-flexion for this duration.

MEG data were collected during the series of 40% MVF_b contractions. MEG data were acquired at a sampling frequency of 600 Hz using a 275 channel CTF MEG

system (MISL, Coquitlam, Canada) operating in third order synthetic gradiometer configuration. Three localisation coils were attached to the head as fiducial markers (nasion, left preauricular and right preauricular) prior to the recording. Energising these coils at the start and end of data acquisition enabled localisation of the fiducial markers relative to the MEG sensor geometry. In order to coregister brain anatomy to the MEG sensor array, each participant's head shape was digitised (Polhemus IsoTrack, Colchester, VT, USA) relative to the fiducial markers prior to the MEG recording. Volumetric anatomical MR images were acquired using a 3 T MR system (Phillips Achieva, Best, Netherlands) running an MPRAGE sequence (1-mm³ resolution). Following data acquisition, the head surface was extracted from the anatomical MR image and coregistered (via surface matching) to the digitised head shape for each participant. This allowed complete coregistration of the MEG sensor array to the brain anatomy, thus facilitating subsequent forward and inverse calculations. A marker was inserted within the MEG and force recordings of each individual contraction to time-synchronise the two data sets. A marker was inserted within the MEG and force recordings of each individual contraction to time-synchronise the two data sets.

Fatigue and control interventions

Both interventions comprised a series of 40 contractions; each of 12-s duration, performed every 30 s, and at a constant-force of either 5%MVF_b (control trial) or 55%MVF_b (fatigue trial). The fatigue intervention was designed to induce physical fatigue, whereas the control intervention was designed to involve the same number and duration of contractions as the fatigue intervention, but without posing a physical challenge. As fatigue developed during the fatigue trial, participants attempted to maintain the 55%MVF_b force output for as much of the 12 s as they could, and maintained a maximal effort of force output thereafter. The specific force level for the fatigue intervention (55%MVF_b) was selected following lengthy pilot testing, which found this protocol to be realisable by most participants, while also being fatiguing to all those who attempted it.

Data Analyses

Mean force output and steadiness (within participant standard deviation; 40%MVF_b contractions only) were determined for each individual contraction. Averages of these mean and steadiness values were calculated first within each individual, and subsequently across participants to determine group means. The first and last 0.5 s of each contraction (constant-force phase) were excluded from all analyses to ensure force output was at the prescribed level throughout the analysed time-window.

MEG data were analysed using synthetic aperture magnetometry (SAM) (Vrba & Robinson 2001), a beamforming variant used to localise neural oscillatory amplitude changes. Data were first filtered to the mu (7-15 Hz) and beta (15-30 Hz) bands. Oscillatory amplitude was then contrasted in active and control time windows in order to delineate the spatial signatures of mu and beta amplitude change. To localise MRMD and MRBD an active window between 0.5 and 5.5 s of the 40%MVF_b contractions was used. To localise PMBR an active window commencing 0.25 s after contraction offset and lasting 5 s was used. (Contraction offset was defined as the time at which contraction force fell below 2%MVF_b when returning to rest and used to define the timing of PMBR measurements). In all cases, the control window commenced 20 s after the prescribed contraction onset (start of the ramp on the target force profile) and lasted for 5 s. The forward model was based upon a multiple local sphere head model and the forward calculation by Sarvas (Sarvas 1987; Huang et al. 1999). Pseudo-t-statistical images (5 mm³ isotropic resolution) were generated showing regions of oscillatory amplitude change in the mu and beta bands. Spatial clusters, occurring within sensorimotor regions were identified and used as locations of interest (LOIs) for subsequent analysis.

Following identification of LOIs using SAM, time frequency spectrograms were generated for each individual participant in order to measure oscillatory dynamics throughout the trials. A SAM beamformer was employed with weighting parameters determined for each LOI using a covariance window spanning the 1-150 Hz frequency range, and a time window encompassing the twenty 40%MVF_b contractions and inter-contraction rest periods (pre- and post-intervention

measurements were concatenated). The derived beamformer weights for each location were multiplied by the MEG data (filtered 1-150 Hz) in order to get a 'virtual sensor' time-series showing the evolution of electrical activity at that location. Virtual sensor time-series were frequency filtered into 31 overlapping frequency bands, and a Hilbert transform was used to generate the amplitude envelope of oscillations within each band. These envelope time-courses were then averaged across the ten contractions; both pre- and post-intervention, in both the fatigue and control trials. Averaged envelopes were then concatenated in the frequency dimension to generate a single time frequency spectrum (TFS) per participant, for each LOI identified. TFSs were subsequently averaged over all participants leaving a single TFS for the spatial maxima of MRMD, MRBD and PMBR.

To assess the effect of fatigue on neural oscillations, mean values of MRMD, MRBD and PMBR were extracted from the TFS data for each participant individually. MRMD and MRBD were calculated as the integral of 7-15/15-30 Hz amplitude across the same active time windows as those used for SAM analyses (see above), and were divided by the duration (in seconds) of the windows. Thus, MRMD and MRBD represent an average mu/beta amplitude decrease during the 40%MVF_b contractions (where 'mu/beta amplitude' = the integral across the 7-15/15-30 Hz frequency band). For PMBR, the total integral of the beta envelope was calculated between 0-10 s following contraction offset, which allowed for this protracted response to reach baseline. Results were generated based on LOIs for each response and each individual separately. This analysis yielded a single value of MRMD, MRBD and PMBR for each participant, both pre- and post-intervention in both the fatigue and control trials (i.e. four values per participant). These values were then averaged across participants to determine group means. MRMD, MRBD and PMBR were also calculated as percentage changes from baseline (resting) amplitude during the control windows used for SAM analyses.

Individual responses were confirmed as local to the contralateral sensorimotor cortex in individual brain space following SAM beamforming, however, to characterise the group mean spatial location of MRMD, MRBD and PMBR, individual brain images were normalised to an anatomical standard (Montreal Neurological Institute (MNI) brain) using FLIRT in FSL. The MNI coordinates for

each peak (MRMD, MRBD and PMBR) in each participant were then measured, before averaging across participants to create group means for each of the x (left-right) y (anterior-posterior) and z (inferior-superior) coordinates. The most likely cortical locations of the mean coordinates were then determined using the Oxford-Harvard brain atlas.

Two-way repeated measures ANOVAs were used to compare both force output and oscillatory amplitude changes between trials (control vs. fatigue trial) and over time (pre- vs. post-intervention, or 4 time-points for MVF). Following a significant trial $\times$ time interaction effect in MRBD and PMBR, post-hoc paired t-tests were performed to elucidate the cause of these effects. Following a significant interaction effect in MVF; two post-hoc one-way repeated measures ANOVAs with Bonferroni corrections were conducted to compare MVF across the four time-points for each trial. Paired t-tests were also used to compare MVF between trials, and the average contraction force between the first and last five repetitions of the fatigue intervention. A P-value below 0.05 was considered statistically significant. Data are expressed as group means $\pm$ standard error of the mean (SEM) unless otherwise stated.

5.4 – Results

Force measurements

Eleven participants were able to accurately perform the prescribed 40%MVFb contractions throughout both trials (Table 5.1). Neither intervention had any influence on either the mean force output (ANOVA; trial, time and trial $\times$ time interaction effects: all $P \geq 0.269$) or the steadiness of force output (all $P \geq 0.096$) during the 40%MVFb contractions. Thus, the motor task during which MEG activity was assessed was kinetically equal before and after both interventions.

Table 5.1 Wrist flexion force during the contractions at a target force of 40%MVFb. 'Pre'/'Post': pre-/post-intervention. Steadiness: within participant standard deviation

Performed Force (%MVF _b)	Control Trial		Fatigue Trial	
	Pre	Post	Pre	Post
Mean	40.00 $\pm$ 0.17	40.05 $\pm$ 0.15	39.87 $\pm$ 0.15	39.80 $\pm$ 0.18
Steadiness	0.95 $\pm$ 0.06	0.99 $\pm$ 0.08	1.01 $\pm$ 0.08	1.12 $\pm$ 0.10

Wrist-flexion MVFb was similar for the fatigue and control trials (mean $\pm$ standard deviation: 282.8 $\pm$ 82.6 N and 278.1 $\pm$ 74.4 N, respectively; t-test, $P=0.531$). During the fatigue intervention, maintaining 55%MVFb for 12 s became supra-maximal for all participants. Overall, the mean force was 23.0% lower in the last five contractions compared to the first five (of forty) (53.7 $\pm$ 0.5 vs. 41.3 $\pm$ 2.2%MVFb; t-test, $P<0.001$), demonstrating the occurrence of fatigue during this intervention. Conversely, the 5%MVFb contractions in the control intervention were performed without any difficulty or sensations of fatigue.

The fatiguing effect of the fatigue intervention was clearly demonstrated by the MVF measurements (ANOVA; trial $\times$ time interaction effect: $P<0.001$; Figure 5.2).

Both MVF_{post-start} and MVF_{post-end} were attenuated from their respective pre-intervention values in the fatigue trial ($-29.5 \pm 3.0\%$ and $-28.9 \pm 2.4\%$, ANOVA: $P < 0.001$ following Bonferroni adjustments), but not the control trial ($P \geq 0.511$); thus demonstrating the intervention ($40 \times 55\%$ MVFb contractions) induced a substantial fatigue that lasted throughout the post-intervention measurements. Additionally, paired t-tests confirmed that MVF differed between the two experimental trials in both post-intervention measurements ($P < 0.001$), but not pre-intervention ($P \geq 0.531$). No differences were observed between MVF_{start} and MVF_{end} either pre- or post-intervention in either trial ($P \geq 0.063$), indicating that the 40% MVFb contractions did not have a significant fatiguing effect in themselves.

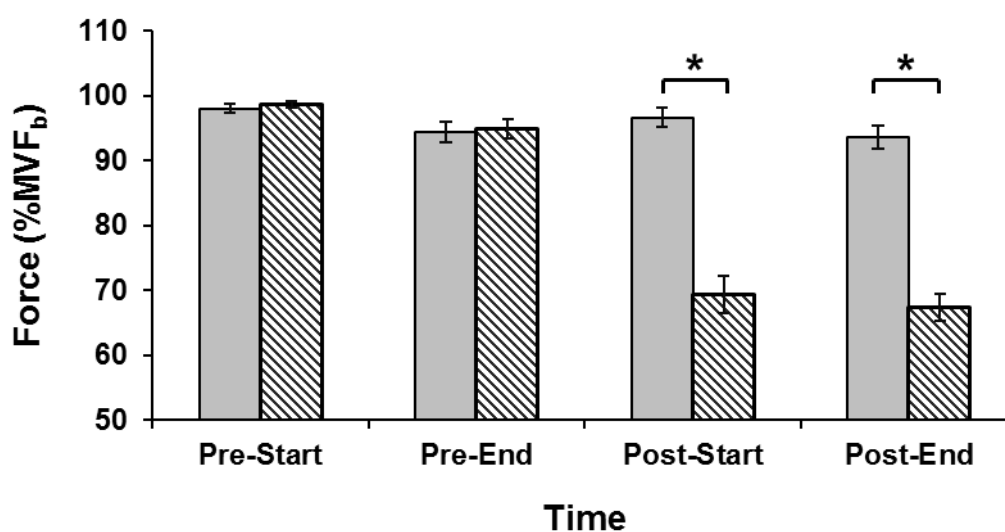


Figure 5.2 Maximum voluntary force (as an index of fatigue) measured at four time points throughout the control (solid) and fatigue (striped) trials. ‘Pre’/‘Post’ = pre-/post-intervention. ‘Start’/‘End’ = immediately before/after 40% MVFb contractions. * = significant difference between trials ($P < 0.05$ following Bonferroni corrections). Data are group means $\pm$ SEM ($n=11$).

MEG measurements

A clear MRMD, local to the contralateral sensorimotor cortex, was observed in 9 of the 11 participants. Figure 5.3A illustrates the locations of peak MRMD for all participants, plotted in MNI space. Figure 5.3B shows the time-frequency spectrograms extracted from the locations of MRMD (shown in Figure 5.3A), and averaged across participants. In each TFS, blue represents a decrease in oscillatory amplitude with respect to baseline whereas yellow reflects an increase. Figure 5.3B illustrates a clear decrease in mu oscillations (the MRMD) occurring prior to and throughout the 40%MVFb contractions in each TFS. Figure 5.3C shows the magnitude of the baseline (resting) mu amplitude at the location of MRMD, averaged across participants, both pre- and post-intervention in both trials. Similarly, figure 5.3D shows the average magnitude of MRMD. Statistical analysis revealed that resting mu amplitude was similar both pre- and post-intervention in both trials (ANOVA; trial, time and trial $\times$ time interaction effects: all $P \geq 0.092$; Figure 5.3C). MRMD was also similar throughout both trials (ANOVA; trial, time and trial $\times$ time interaction effects: all $P \geq 0.325$; Figure 5.3D), suggesting that there was no consistent effect of physical fatigue on mu band oscillatory dynamics.

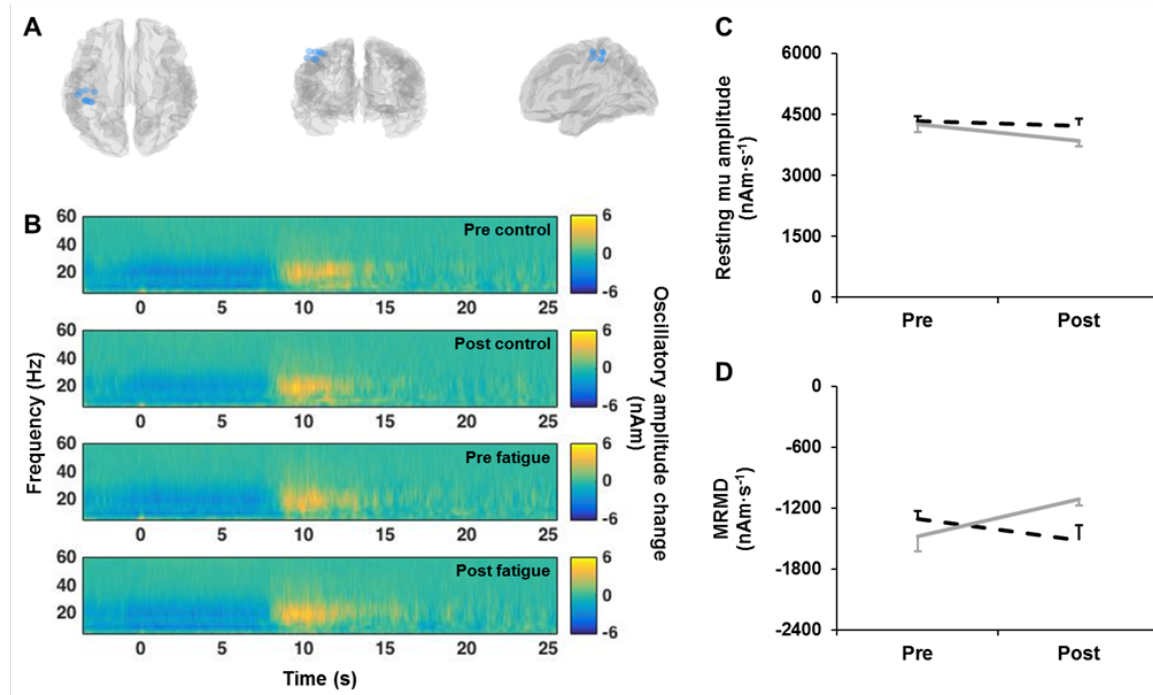


Figure 5.3 Locations of peak MRMD during the 40%MVF_b contractions for each individual participant (blue dots) (A), time-frequency spectrograms extracted from locations of peak MRMD (B; time 0 = prescribed contraction onset), average mu amplitude at rest (20-25 s) (C), and average MRMD amplitude (1.5-6.5 s) (D) in both the control (grey lines) and fatigue (dashed lines) trials. Data are group means $\pm$ SEM (n=9).

The primary results for the beta band analyses are shown in Figures 5.4 and 5.5. The layouts are equivalent to that of Figure 5.3 (described above). A clear MRBD within the contralateral sensorimotor cortex was observed in 10 of the 11 participants (Figure 5.4A). This involved a decrease in beta amplitude immediately prior to and throughout the 40%MVF_b contractions, which was evident both pre-and post-intervention in both trials (Figure 5.4B). Resting beta activity at the location of MRBD decreased from pre- to post-intervention (ANOVA, time effect: $P=0.014$; Figure 5.4C), however these changes were similar in both trials (trial and trial $\times$ time interaction effects: both $P \geq 0.278$). However, MRBD demonstrated a differing response to the two interventions (ANOVA, trial $\times$ time

interaction: $P=0.021$; Figure 5.4D); decreasing from pre- to post-intervention in the control trial (t-test: $P=0.006$), but not the fatigue trial ($P=0.470$).

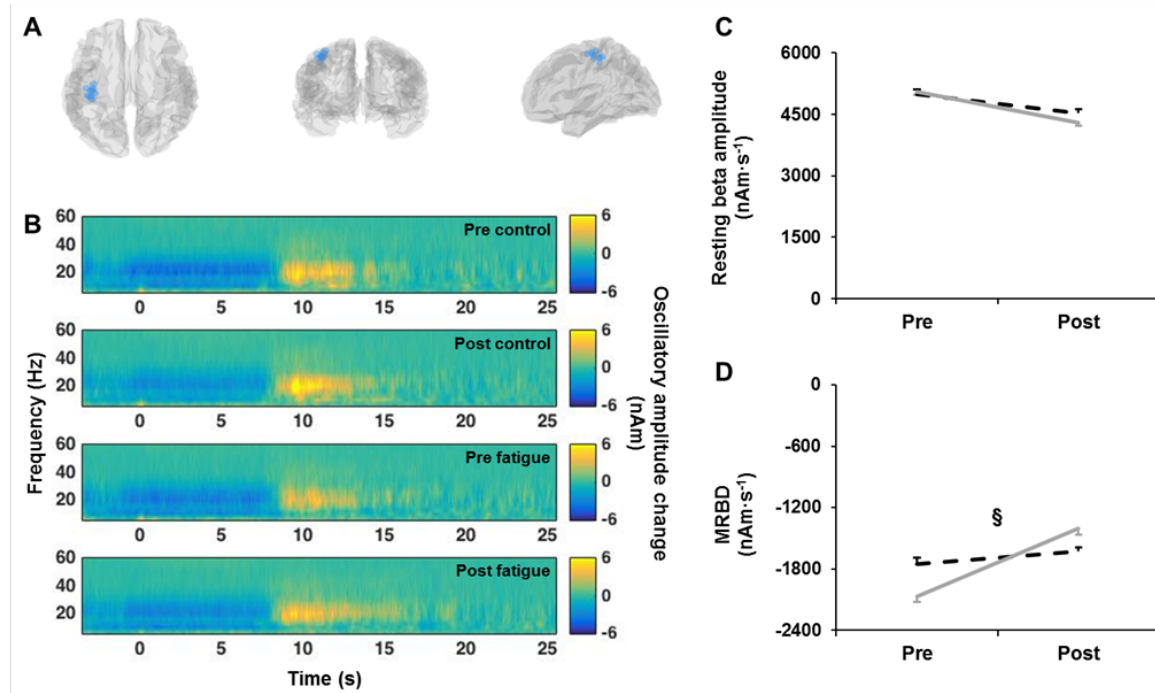


Figure 5.4 Locations of peak MRBD during the 40%MVF_b contractions for each individual participant (blue dots) (A), time-frequency spectrograms extracted from locations of peak MRBD (B; time 0 = prescribed contraction onset), average beta amplitude at rest (20-25 s) (C), and average MRBD amplitude (1.5-6.5 s) (D) in both the control (grey lines) and fatigue (dashed lines) trials. § = Significant trial × time interaction ($P<0.05$). Data are group means $\pm$ SEM ($n=10$).

A clear PMBR, again local to the contralateral sensorimotor cortex, was observed in 9 of the 11 participants (Figure 5.5A). PMBR commenced shortly after contraction offset and lasted for several seconds (Figure 5.5B). Resting beta amplitude at the location of PMBR also decreased following both interventions, and with no difference between trials (ANOVA, time effect: $P=0.031$; trial and trial

× time interaction effects: both $P \geq 0.138$; Figure 5.5C). Conversely, the magnitude of PMBR was affected by physical fatigue (ANOVA; trial × time interaction: $P=0.018$; Figure 5.5D); demonstrating an increase following the fatigue intervention (t-test: $P<0.001$), but not the control intervention ($P=0.623$).

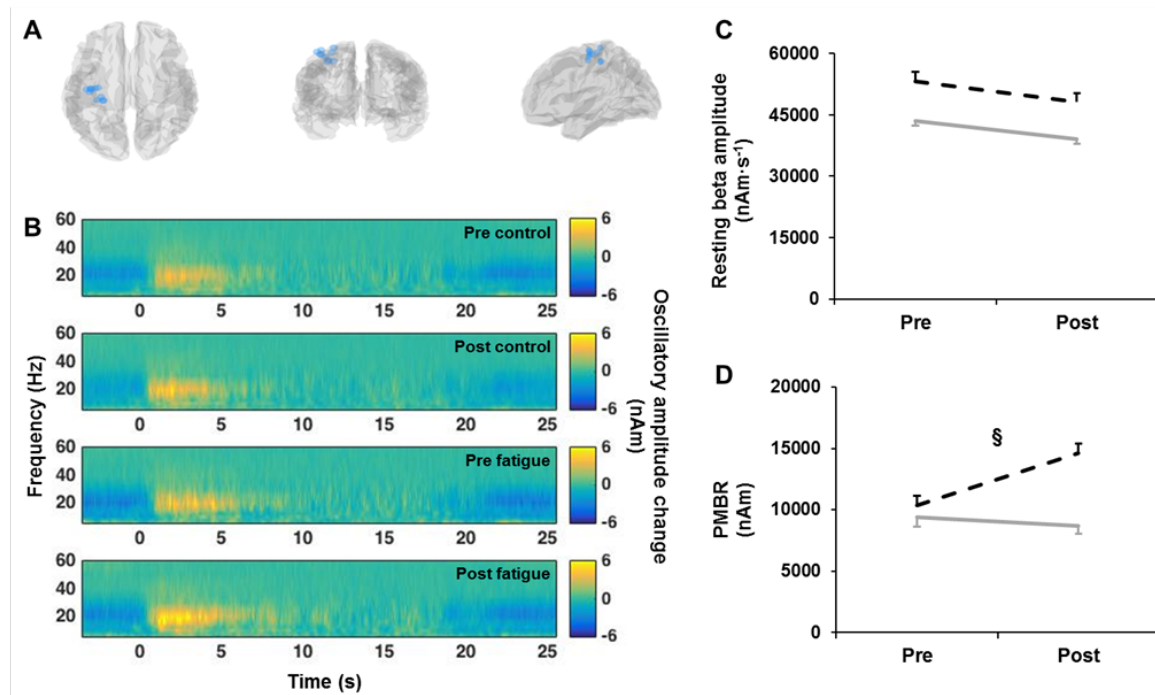


Figure 5.5 Locations of peak PMBR following the 40%MVFb contractions for each individual participant (blue dots) (A), time-frequency spectrograms extracted from locations of peak PMBR (B; time 0 = contraction offset), average beta amplitude at rest (C), and PMBR amplitude (0-10 s) (D) in both the control (grey lines) and fatigue (dashed lines) trials. § = Significant trial × time interaction ($P<0.05$). Data are group means $\pm$ SEM ($n=9$).

The mean MNI coordinates of MRMD, MRBD and PMBR are displayed in Table 5.2, alongside the most likely cortical locations of these coordinates according to

the Oxford-Harvard brain atlas. These results show the spatial peaks of MRMD and MRBD were located postcentrally, whereas PMBR arose precentrally.

Table 5.2 Average MNI coordinates and the most likely cortical locations (according to the Oxford-Harvard brain atlas) of the MRMD, MRBD and PMBR

	MNI coordinates			Cortical Location
	x	y	z	
MRMD	-41.9±1.7	-30.6±2.0	54.0±1.4	postcentral gyrus
MRBD	-37.7±0.8	-24.2±1.8	53.7±1.3	postcentral gyrus
PMBR	-33.4±1.8	-21.8±2.1	58.1±1.8	precentral gyrus

Overall, whether MRMD, MRBD and PMBR were expressed in absolute terms (presented above), or relative to resting oscillatory amplitude (percentage change), the effects of physical fatigue on these oscillatory phenomena were extremely similar. Relative MRBD showed a trial × time interaction, with a substantial decrease after the control intervention and no change following the fatigue intervention (Table 5.3). This was despite the decrease in resting beta amplitude observed in both trials. In addition, relative PMBR also demonstrated a tendency for a trial × time interaction for relative PMBR, with a greater rebound observed post-fatigue but not post-control.

Table 5.3 MRMD, MRBD and PMBR expressed relative to resting amplitude. 'Pre'/'Post': pre-/post-intervention. Data are group means $\pm$ SEM (beta, n=10; mu and PMBR, n=9)

Relative Amplitude Loss/Increase (% resting amplitude)	Control Trial		Fatigue Trial		Trial $\times$ time interaction (P value)
	Pre	Post	Pre	Post	
MRMD	-32.2 $\pm$ 1.4	-28.7 $\pm$ 1.2	-30.4 $\pm$ 1.7	-33.2 $\pm$ 1.7	0.215
MRBD	-41.1 $\pm$ 1.0	-31.9 $\pm$ 1.1	-34.9 $\pm$ 0.9	-36.4 $\pm$ 0.9	0.005
PMBR	21.8 $\pm$ 2.0	23.4 $\pm$ 2.1	24.1 $\pm$ 2.4	36.3 $\pm$ 3.0	0.095

5.1 – Discussion

This study examined the effect of physical fatigue on MRMD, MRBD and PMBR in healthy individuals. The main findings were: (1) MRBD was maintained following the fatigue inducing intervention, whereas a reduction in MRBD was observed following the control intervention, and (2) the magnitude of PMBR increased following the fatigue but not the control intervention. Additionally, MRMD was unchanged following either intervention.

From the force recordings it was clear that the fatigue intervention induced substantial physical fatigue (~30% reduction in MVF), and that this fatigue endured throughout the post-intervention measurements. Moreover, despite the observed fatigue, eleven of the fourteen initial participants were able to accurately perform the prescribed 40%MVF_b contractions, which were used to assess neuro-oscillatory dynamics, before and after both interventions.

A reduction in MRBD was observed following the control intervention but not the fatiguing intervention. This attenuation in beta amplitude loss during the control trial was most likely a consequence of task habituation found to occur during the early phases of task repetition (Kranczioch et al. 2008; Studer et al. 2010; Pollok et al. 2014). It has been suggested that with increasing task familiarity there is a reduced involvement of various sensorimotor-related networks (Mancini et al.

2009), and that reduced MRBD with task habituation is a neurophysiological marker of early cortical reorganisation (Pollok et al. 2014). The results of the present investigation indicate that this habituation response was counteracted by the fatiguing intervention. Although the mechanism by which this was achieved is beyond the scope of this investigation, it might be speculated that the task dynamics, at least from a cortical perspective, might change with the induction of fatigue. For example, physical fatigue requires an increased corticospinal output to maintain the prescribed force output and also induces extensive group III and IV afferent feedback in response to metabolite accumulation (Taylor & Gandevia 2008).

That MRBD was maintained following the fatigue intervention is in contrast to one preliminary study that reported a complete elimination of MRBD during submaximal contractions of the extensor communis digitorum performed after a prolonged MVC of the same muscle (Tecchio et al. 2006). However, this study lacked both a control trial and an objective measure of physical fatigue. (In the current investigation, the presence of fatigue throughout the post-intervention measurements was clearly demonstrated by the ~30% decrease in MVF versus pre-fatigue values.) Furthermore, these authors found agonist electromyography amplitude during the submaximal contractions to be unaffected by the intervention, in contrast to the widely documented increase in electromyography amplitude that would be expected to accompany fatigue (Bigland-Ritchie et al. 1986; Dorfman et al. 1990). It is therefore possible that the abolished MRBD reported as a consequence of fatigue may instead reflect a habituation effect, analogous to the attenuation in MRBD observed in the control trial of the current investigation.

To the authors' knowledge this was the first study to investigate the effect of physical fatigue on PMBR. The results demonstrated that PMBR was augmented following the fatiguing intervention but not the control intervention. The PMBR is believed to reflect an active inhibition of neuronal networks recruited during the preparation and execution phases of motor actions (Alegre et al. 2008; Solis-Escalante et al. 2012). Therefore, higher PMBR after fatigue may reflect a greater inhibitory response of neural networks that were more highly activated/excited during contraction; potentially due to increases in corticospinal output or

somatosensory processing (either directly or indirectly). For example, the magnitude of the PMBR may be positively related to the volume of muscle recruited during voluntary contractions (Pfurtscheller et al. 1998; chapter 4), which increases with the development of fatigue. Alternatively, Cassim et al. (2001) proposed that movement-related somatosensory processing may be fundamental to the engenderment of the PMBR, having observed a PMBR to be present following passive finger movements but not active movements performed under ischaemic deafferentation. Therefore, increased activity of fatigue sensitive afferents may also have contributed to the larger PMBR observed following the development of physical fatigue.

That PMBR may be modulated by fatigue has wide implications for the measurement and interpretation of this phenomenon. Recent work has demonstrated that PMBR has the potential to be used as a biomarker for pathology, with examples including Parkinson's disease (Pollok et al. 2012; Heinrichs-Graham et al. 2014; S. Hall et al. 2014) and schizophrenia (Robson et al. *In Press*). Judicious design of study protocols is therefore essential to ensure the PMBR is not affected by the experimental procedures, particularly when investigating disorders in which susceptibility to fatigue represents a common symptom.

Resting beta amplitude at the locations of both MRBD and PMBR demonstrated similar decreases following both interventions. De Pauw et al. (2013) noted a decreased resting beta activity across the whole brain after a prolonged intensive cycling performance in the heat; designed to induce supraspinal fatigue. Additionally, Jagannath & Balasubramanian (2014) found widespread decreases in beta amplitude following a monotonous 60-min simulated driving task, which was suggested to encompass elements of both mental fatigue and physical fatigue (due to the extended period of posture maintenance). In the present study, the decrease in beta amplitude following the interventions was not specific to the fatigue trial; however, other fatigue modalities, such as mental fatigue arising from the prolonged periods of concentration and task repetition, might have contributed to this beta decrease. Although this possibility may be difficult to confirm as different modalities of mental fatigue may influence spontaneous oscillatory activity in different ways (Shigihara et al. 2013).

Fatigue had no effect on either resting mu amplitude or MRMD, which were both unchanged following both interventions. This indicated that mu activity within the sensorimotor cortex was not affected by either the induction of physical fatigue, or the prolonged period of task adherence involved in both trials.

Finally, it should be acknowledged that any potential effect of handedness on the observed results is not known. Volunteers were not screened for handedness upon selection for the study, and with a final sample of only 2 left hand dominant participants (out of the eleven to complete the study) it was not realistic to investigate any potential influence handedness may have had. In conclusion, this study revealed two novel findings regarding the effects of physical fatigue on movement-related sensorimotor oscillatory dynamics. Firstly, physical fatigue offset the attenuation in MRBD observed with repetition of a motor task in a non-fatiguing control trial. Secondly, PMBR was increased when submaximal contractions were performed in a state of physical fatigue; which supports an emerging theory that PMBR is sensitive to increases in corticospinal output and changes in sensory input, both of which would be expected to occur with physical fatigue.

Chapter 6

General Discussion

6.1 – Introduction

1. In addition to the supraspinal motor drive, the recruitment of skeletal muscle involves peripheral inputs to the motor unit pool. Excitatory input from Ia afferents has been shown to contribute to the recruitment of high threshold motor units (Bongiovanni et al. 1990), and the achievement of maximal motor unit firing rates (Hagbarth et al. 1986; Macefield et al. 1993). However, whether maximal force development is dependent on this input is not certain. Subsequently, the aim of chapter 2 was to examine both maximal and explosive force production in the knee extensors following a prolonged vibration of the infrapatellar tendon, which was designed to attenuate the efficacy of the homonymous Ia afferent- α -motoneuron pathway.
2. Neural oscillations are a ubiquitous phenomenon generated in multiple cortical regions, and are observable using non-invasive measurement techniques including EEG and MEG. In the sensorimotor system, particular attention has been paid to the link between motor action and modulations in mu (~7-15 Hz) and beta (~15-30 Hz) oscillations. Numerous studies have reported somatotopically organised decreases in mu and beta amplitude during the preparation and execution of voluntary movement, followed by a period of elevated beta amplitude on movement cessation (e.g. Jurkiewicz et al. 2006). However, despite the considerable level of interest in the oscillatory responses to movements *per se*, the potential influence of the motor parameters of the movements under investigation is poorly understood. Therefore, the aim of chapters 3 and 4 was to examine the influence of voluntary contraction force/torque and RFD on sensorimotor oscillatory dynamics.
3. During continued performance of a motor task, physical fatigue develops through both supraspinal and peripheral processes (Gandevia et al. 1996). However, whether the initial oscillatory responses to the motor task are

modified when the efficacy of the neuromuscular pathway facilitating the movement is challenged (i.e. as physical fatigue develops) has received a paucity of attention. The aim of chapter 5 was therefore to investigate how ongoing oscillatory activity within the sensorimotor cortex might be affected by physical fatigue.

6.2 – Is maximal voluntary force development dependent upon Ia afferent input to the motor unit pool?

The results of chapter 2 indicated that both MVF and maximal RFD of the knee-extensors were unaffected by a 30-min vibration of the infrapatellar tendon despite concurrent decreases in H-reflex indicating a reduced efficacy of the homonymous Ia afferent- α -motoneuron pathway. These findings are in accordance with one previous investigation (Ekblom & Thorstensson 2011), but in direct contrast to a number of other studies that have observed both 7-17% decrements in maximal force production (Kouzaki et al. 2000; Jackson & Turner 2003; Ushiyama et al. 2005; Konishi et al. 2009) and ~24-70% reductions in peak RFD (Kouzaki et al. 2000; Jackson & Turner 2003) following prolonged muscle/tendon vibration. However, numerous concerns regarding the methodologies employed in a number of these previous studies have been described (chapters 1 & 2). While these shall not be listed again here in any detail, it is perhaps worth repeating that in two of these previous studies (Kouzaki et al. 2000; Jackson & Turner 2003) vibration was applied directly to the rectus femoris muscle, evoking a tonic response that could have led to an accumulated muscle fatigue over the 30-min vibration period. Despite this, potential changes in extrafusal fibre excitability were not assessed in either of these studies. Additionally, these same studies measured RFD during the performance of maximal force contractions, which are unlikely to provide valid measurements of peak RFD (Bemben et al. 1990; Sahaly et al. 2001)

Nevertheless, the cause of these dichotomous results is not certain. This may be due in part to the fact that the mechanisms underlying the attenuated H-reflex response was not known. Repetitive activation of Ia afferents during prolonged tendon vibration might attenuate the efficacy of the Ia afferent- α -motoneuron

pathway via a number of processes; including transmitter depletion at the Ia afferent terminals (Curtis & Eccles 1960; Hultborn et al. 1996) and interneuron mediated presynaptic inhibition (Lapole et al. 2012). However, presynaptic inhibition of Ia afferents is decreased during voluntary contractions (Hultborn et al. 1987). Therefore, although highly speculative, it is plausible that both a recovery from neurotransmitter depletion and a return to pre-vibration levels of presynaptic inhibition during contractions was complete before performing the explosive (4 min 30 s following vibration termination) and maximal force contractions (6 min 50 s following vibration termination), while levels of presynaptic inhibition of Ia afferents at rest remained elevated. This could explain why the results of chapter 2 differed from those of previous investigations (Kouzaki et al. 2000; Jackson & Turner 2003; Ushiyama et al. 2005; Konishi et al. 2009); each of which completed all assessments of maximal force production within 5 min following the cessation of vibration. Of course further investigation on the time-courses of these mechanisms (which have been poorly defined to date) is required to explore this proposition.

In general, it is recommended that H-reflexes should be evoked upon a background level of muscle activation (primarily to ensure a consistent level of motoneuron excitability). However, in the presented work (chapter 2), H-reflex responses were recorded at rest as the primary objective of this study concerned the effect of vibration on the functional performance measures (i.e. maximal force and peak RFD), and sustaining volitional contractions during the collection of the H-reflex recordings could have led to physical fatigue, which would have compromised the functional performance measurements. The consistent $M_{\max}$ responses also indicated that the excitability of the extrafusal fibres was not affected by the tendon vibration. Additional recommendations also suggest that H-reflexes might be evoked with a current intensity that generates a specific motor response (e.g., 10–20 % $M_{\max}$) to help ensure stimulus constancy (Zehr 2002). However, a disproportionate change in the excitability of afferent axons (compared to efferent axons) following repetitive spindle activation during the tendon vibration would have invalidated this method (Lin et al. 2002). Moreover, for H-reflexes to accurately represent transmission efficacy in Ia afferent- α -motoneuron synapses during maximal contractions, they themselves would have

to be recorded during maximal contractions (Stein & Thompson 2006). This would be almost impossible during assessments of peak RFD, and would likely compromise the validity of MVF assessments; although future studies specifically investigating the effect of prolonged vibration on H-reflex amplitude during maximal contractions would provide a valuable contribution to the current literature. Importantly, the reader should be reminded that the 60% reductions in resting $H_{\max}/M_{\max}$ reported in chapter 2 were not considered to reflect a 60% decrease in homonymous spinal reflex function during the voluntary contractions. Instead these results were simply intended to indicate that the vibration intervention appeared to be effective in compromising the efficacy of the homonymous Ia afferent- α -motoneuron pathway.

Overall, whether maximal voluntary force development is dependent upon Ia afferent input to the motor unit pool remains unclear. The results suggest that maximal force development may still be achieved under conditions of impaired Ia afferent- α -motoneuron transmission, however, further investigation may be warranted to validate these assertions, and help to explain why comparable investigations have indicated otherwise. One appropriate future study would involve a repeated measures design, including measurements of functional performance (i.e. MVF) in isolation in one trial, and assessments of the efficacy of the homonymous Ia afferent- α -motoneuron pathway (via H-reflexes) during the performance of these same functional measures in another trial. Both trials might involve a 30-min tendon vibration stimulus, with experimental measurements taken before, and at several time-points after vibration (matched in both trials). This approach would enable any vibration-induced decrements in the efficacy of the Ia afferent- α -motoneuron pathway during the performance of the maximal force measures to be quantified (as opposed to inferring some unknown level of attenuation from decrements observed at rest). These separate trials would also ensure that the functional performance measures were not compromised by the superimposition of the H-reflex measurements. In addition, attention should be paid to whether the vibration evokes a tonic response with regular action potentials evident in the EMG of the homonymous muscle; a simple measure that was absent from chapter 2.

6.3 – Contraction-driven changes in sensorimotor oscillations: Any modulation with the motor parameters of voluntary contractions?

Chapter 3 included EEG measures of cortical activity from the leg area of the motor cortex (i.e. from 27 separate MNI coordinates that formed a $3 \times 3 \times 3$ cube: (x;y;z coordinates) -10, 0, 10; -20, -30, -40; 50, 60, 70) during isometric knee-extensions of the right leg at four prescribed torque levels: 15, 30, 45 and 60%MVT. Oscillatory power was analysed within five frequency bands: 0.5-3 (delta), 3-7 (theta), 7-13 (alpha), 13-30 (beta) and 30-50 Hz (gamma) using LORETA analyses. In chapter 4, MEG was collected during the performance of both constant-force and ramp isometric wrist-flexion at distinct levels of force (5, 15, 35 and 60%MVF) and RFD (10.4, 28.9 and 86.7%MVF·s⁻¹), respectively. Contraction-driven reductions in beta (15-30 Hz) amplitude were spatially localised using beamforming (SAM), and time-frequency analyses were conducted at the locations of peak change within the sensorimotor regions of each individual participant. Contraction-driven reductions in mu (7-15 Hz) amplitude were also identified in some participants, however these responses were inconsistent (8 out of 15 participants demonstrated a significant mu amplitude loss during both experiments) and as such were not included within chapter 4. Additionally, contraction-driven changes in oscillatory amplitude were sought at frequencies <7 Hz and >30 Hz, however, no significant contrasts between rest and during contraction were identified (data not shown).

Chapter 3 reported the magnitude of the contraction-driven reductions in alpha amplitude to be unaffected by the torque of the performed knee-extensions. Similarly, for the participants of chapter 4 that did demonstrate a significant contraction-driven mu amplitude loss, the magnitude of the mu decrease was unaffected by either the force or RFD of wrist-flexion (data not shown). These results are consistent with a number of investigations, which have suggested contraction-driven alpha amplitude loss to be unrelated to voluntary contraction force of the index finger extensors (Stančák et al. 1997), knee flexors/extensors (Dal Maso et al. 2012) and elbow flexors (Cremoux et al. 2013). In contrast, one study (Mima et al. 1999) found the magnitude of the alpha (8-12.9 Hz) amplitude loss during contractions to be positively related to the force of isometric pinching between the first and fifth digit. The cause of this inconsistency is not clear. Alpha

activity has been proposed to reflect an inhibitory control of cortical processing (Klimesch et al. 2007), with a decrease in alpha amplitude representing a release of inhibition. Although the motor parameters (at least force/torque and RFD) of a voluntary contraction appear unrelated to task-driven decreases in alpha amplitude, other parameters such as task difficulty might influence the magnitude of alpha amplitude loss (Dujardin et al. 1995). Therefore, although speculative, task dynamics other than the force of finger pinching may have led to the variable alpha decreases reported by Mima et al. (1999). Overall, the current results further indicate that contraction-driven reductions in sensorimotor alpha/mu amplitude are unrelated to the motor parameters of force/torque and RFD during voluntary isometric contractions.

Both chapters 3 & 4 found the changes in beta amplitude between contraction and rest to be unaffected by either contraction force/torque or RFD. These results are perhaps contrary to one study (Dal Maso et al. 2012), which reported a greater beta (21-31 Hz) amplitude loss during isometric knee-flexion contractions of higher forces in strength-trained individuals. However, these authors found no differences in beta amplitude loss were observed when the same motor task was completed by endurance trained participants, or during knee extensions performed by either cohort. In other words, the majority of their findings were in agreement with the presented results. Several other investigations have also found the magnitude of the contraction-driven reductions in beta amplitude to be independent of both contraction force (Stančák et al. 1997; Mima et al. 1999; Cremoux et al. 2013) and movement speed (Stancák & Pfurtscheller 1995; Stancák & Pfurtscheller 1996); although chapter 4 was the first study to compare oscillatory responses between isometric contractions of distinct RFDs. These findings are also in agreement with investigations that found information contained within the beta signal may be used to differentiate between periods of movement and rest, but does not enable the decoding of movement characteristics such as grasp type/posture (Pistohl et al. 2012; Chestek et al. 2013). Moreover, a similar trend has also been observed away from the motor system; with beta amplitude decreases within the visual cortex showing no relation to either the intensity (Michelson contrast) or timing (drift frequency) of a visual stimulus (Stevenson et al. 2011).

Collectively, these results support the hypothesis that the sensorimotor beta rhythm may provide a localised gating of cortical activity (Perez-Orive et al. 2002) with a distinct 'on/off' property (Stevenson et al. 2011). High amplitude beta oscillations are widely believed to reflect inhibition. This premise is supported by pharmacological interventions, for example, administration of GABAergic agonists elicits increased amplitude of the beta rhythm in healthy individuals (Jensen et al. 2005; Hall et al. 2011). (Note: gamma aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian cortex). A reduction in sensorimotor beta amplitude during voluntary contractions might therefore reflect a release of GABAergic inhibition, enabling task-related processing to occur. Overall, beta amplitude loss in the sensorimotor cortex appears to be functionally relevant to the induction of voluntary contractions, while being independent of the parameters of the performed contractions.

Finally, chapter 3 observed a significant overall increase in 30-50 Hz gamma activity with increments in knee extension torque. This was an unexpected finding. Low frequency (<50 Hz) gamma rhythms having received far less attention within the literature than the more prominent mu and beta rhythms, which demonstrate robust contraction-driven decreases in amplitude. Also, Dal Maso et al. (2012) observed similar decreases in 35-45 Hz power during isometric knee extension/flexion of between 20 and 80% maximal torque. However, a greater amplitude of gamma (31-50 Hz) has previously been reported during near-maximal (>80%MVF) vs. submaximal (10-60%MVF) contractions of the first and fifth digits (Mima et al. 1999), although no difference was identified between submaximal contraction forces, and the augmented gamma activity was ubiquitous across fronto-central regions of the cortex. Additionally, augmentations in ~30-50 Hz gamma activity have previously been attributed to increases in attention (Rougeul-Buser 1994) and physiological arousal (Bonnet & Arand 2001). Therefore, the observed increases in gamma activity in chapter 3 may have related to the cognitive demands of increasing contraction strength (and possibly task difficulty), rather than the motor parameters of the voluntary contractions.

Although the results of chapters 3 and 4 were largely in agreement, a couple of discrepancies were present. The movement-related reduction in sensorimotor

beta amplitude is a robust phenomenon consistently demonstrated by numerous studies (Jasper & Penfield 1949; Salmelin & Hari 1994; Pfurtscheller & Lopes da Silva 1999; Pfurtscheller et al. 2003; Jurkiewicz et al. 2006); which, once again, was clearly identified in chapter 4, but not chapter 3. The reason for this discrepancy was unclear. While beta oscillations may be partially re-established during the held phase of constant-force contractions (Penfield 1954; Kilavik et al. 2013), a significant decrease would have perhaps still been expected to endure the length of the contraction, as observed in Figure 4.3A.

Additionally, in chapter 3, 30-50 Hz gamma amplitude was significantly elevated during contractions compared to rest, and increased further with increments in contraction torque, whereas in chapter 4, no significant change in the 30-50 Hz band was observed between contractions and rest. These increases in gamma amplitude (chapter 3) were attributed to changes in physiological arousal and/or the attentional demands of the higher torque contractions. The disparity in results between the two chapters may therefore have resulted from minor differences in the study designs, which could have led to a difference in the arousal/attentional levels during the assessment of baseline 30-50 Hz amplitude. In chapter 3, baseline amplitude was collected during one minute blocks of EEG recording, during which participants were instructed to close their eyes and relax ("focusing on themselves") as much as possible. This may have led to a reduction in both arousal and attentional focus compared to a more typical waking state. In comparison, chapter 4 measured baseline amplitude during shorter periods of rest between each contraction. This latter approach is more common within the literature; benefiting from a more comparable state of attention/arousal between task and rest periods, as well as minimising the influence of drifts in baseline oscillations on the quantification of task-driven changes in oscillatory amplitude. This approach was re-adopted for chapter 5, and is recommended for future EEG studies. Additionally, different experimental models were adopted: chapter 3 involved contractions of proximal lower limb muscles (quadriceps femoris), whereas chapter 4 involved distal muscles in the upper limb. These muscle groups have contrasting functional purposes; with the quadriceps involved in locomotion and the wrist-flexors used primarily in object manipulation. To the author's knowledge, chapter 3 is unique in its adoption of a unilateral knee-

extension paradigm for the measurement of movement-related oscillatory dynamics. Future research contrasting the oscillatory responses to contractions of functionally distinct muscle groups may therefore be warranted.

Oscillations of higher frequencies

In concluding that low frequency (<50 Hz) rhythms may not be directly related to the motor parameters of voluntary contractions, a logical next step might be to explore the higher frequency oscillations. In addition to the mu and beta amplitude loss, an increase in the higher frequency gamma (>70 Hz) activity has also been identified within the contralateral sensorimotor cortex during voluntary muscle contractions (Crone et al. 1998; Pfurtscheller et al. 2003; Miller et al. 2007). Although no significant contraction-driven increase in gamma amplitude was identified in chapter 4, this is most likely due to the specific study design employed. Muthukumaraswamy (2010) found a strong gamma-band activity to be present around the onset of force production, but not during the held phase of a near-isometric constant-force contraction, whereas, in order that force and RFD were distinct between comparisons, chapter 4 included only the constant-force and constant-RFD phases of the isometric contractions in its analysis (i.e. the analysis windows did not span contraction onset).

In one recent investigation, Flint et al. (2014) attempted to decode the force of brief voluntary contractions from electrocorticography (ECoG) recordings collected from 10 patients undergoing intracranial monitoring prior to surgical treatment for epilepsy. Each patient had an electrode array covering the hand area of the primary motor cortex. Recordings were collected while patients pinched a force transducer between the thumb and index finger of the hand contralateral to the recording array. This behaviour was performed for between 5-10 min, with the peak force of the isometric pinches ranging from 2 to 69 N (across all subjects). The authors were able to decode the performed isometric force from the ECoG recorded from the primary motor cortex with a high accuracy ($60 \pm 6\%$ [mean $\pm$ SE] explained variance), with the high gamma band (70-115 Hz in particular) and the local motor potential (a time domain feature) providing the greatest fraction of the explained variance. Conversely, in

accordance with the results of chapters 3 and 4, features extracted from the mu and beta frequencies provided poor decoding of the continuous force output. This study (Flint et al. 2014) might indicate that the recorded gamma responses may contain some content regarding the force of voluntary muscle contractions. However, other investigations (Szurhaj et al. 2005; Cheyne et al. 2008; Muthukumaraswamy 2010) have shown that increases in sensorimotor cortex gamma activity occur after the onset of EMG; prompting suggestions that this gamma activity might not be pertinent to the control of muscular force output, but may instead reflect the activation of localised oscillatory networks by either afferent (Muthukumaraswamy 2010) or reafferent (Cheyne et al. 2008) feedback to the sensorimotor cortex during movement. Moreover, these latter suggestions are consistent with the existing hypothesis that high frequency oscillations might represent an integration of somatosensory and motor-related information streams (Mackay 1997).

Oscillations in other regions of the brain

It appears that oscillatory rhythms of the sensorimotor cortex do not reflect the parameters of voluntary movements. However, oscillatory activity within other regions of the brain, particularly the sub-cortical structures, has not been considered in the prior discussion, as this was beyond the scope of the presented studies (the non-invasive EEG and MEG techniques involved in chapters 3 and 4 are insensitive to these deeper lying neural assemblies). Oscillatory activity of subcortical structures can be recorded intracranially using ECoG. Using this approach, Joundi et al. (2012) found a positive correlation between 70-90 Hz gamma activity within the subthalamic nucleus and movement speed during reaching movements. Similarly, Brucke et al. (2012) observed a correlation between 60-80 Hz activity in the globus pallidus internus and the displacement and velocity of pronation/supination movements. However, Jenkinson et al. (2013) suggested that for both these studies (Brucke et al. 2012; Joundi et al. 2012), the increase in gamma activity may be representative of the conscious effort being applied, rather than coding for any specific motor parameter.

Non-rhythmical features of EEG/MEG

Overall, the functional role of neural oscillations does not appear to include the encoding of task parameters such as voluntary contraction force or RFD. However, other features of the EEG/MEG signal may contain information related to task characteristics. For example, the magnitude of the movement-related potential (a transient feature of the electrophysiological signal occurring in the supplementary motor area and sensorimotor cortex during movement preparation) has been found to correlate with both the force and RFD of isometric contractions of the elbow flexors (Siemionow et al. 2000) and plantarflexors (do Nascimento et al. 2005). However, the study of movement-related cortical potentials is restricted to events surrounding the onset of discrete movements, and thus do not give information regarding the control of force production during ongoing movements. Decrypting the cortical encoding of ongoing movements would be of particular benefit to various areas of research; including brain computer interfacing, and diagnostics of neurological diseases.

Other measures of neuronal activity

Microelectrode recordings from individual cells of the primary motor cortex have shown the activity (spiking frequency) of these cells may be closely related to muscular force during volitional contractions (Evarts 1968; Cheney & Fetz 1980). This would indicate that the motor cortex might be highly relevant in the control of muscular force production. However, these microelectrode recordings examine the rate of axonal spiking in these cells, whereas the EEG and MEG (as well as the ECoG) signals are derived from dendritic current flows (Hall et al. 2014). Moreover, only a small minority of motor cortex cells may modulate their activity in relation to muscular force production (Ashe, 1997), and this activity may not be measureable on the macroscopic scale of non-invasive measures such as EEG and MEG, which instead reflect the synchronous activity of tens of thousands of cells (Proudfoot et al. 2014).

6.4 – The effect of physical fatigue on oscillatory dynamics

Chapter 5 recorded the movement-related oscillatory responses to submaximal isometric contractions performed both before and after either a physically fatiguing intervention (40 contractions of 12 s duration at 55%MVF) or a control intervention of the same duration (40 contractions of 12 s duration at 5%MVF). The results showed that the contraction-driven beta amplitude loss was unchanged following the fatiguing intervention, whereas a reduction in the beta amplitude loss was observed after the control intervention. Conversely, the magnitude of the PMBR was increased following the fatiguing but not the control intervention.

These results are in contrast to one previous MEG study (Tecchio et al. 2006), which reported a total abolition of the contraction-driven beta amplitude loss during submaximal contractions of the extensor communis digitorum performed after a prolonged MVC of the same muscle. However, this study did not include a control trial, and the extent of physical fatigue induced by the MVC was not examined. In fact, these authors found no difference in the agonist EMG amplitude between the submaximal contractions performed before and after the prolonged MVC, whereas an increase would have been expected to accompany physical fatigue (Bigland-Ritchie et al. 1986; Dorfman et al. 1990). Therefore, it is possible that the abolition of the contraction-driven beta amplitude loss may not have been a consequence of physical fatigue, but some other mechanism such as a time/habituation effect. This hypothesis may be supported by the observation that a reduction in the magnitude of the beta amplitude loss was also present in the control trial of chapter 5.

Attenuation of the contraction-driven beta amplitude loss has been shown to accompany task habituation occurring during the early phases of task repetition (Kranczioch et al. 2008; Studer et al. 2010; Pollok et al. 2014). This reduced amplitude loss has been suggested to represent a neurophysiological marker of early cortical reorganisation (Pollok et al. 2014), which might occur as the task becomes more familiar and requires lower involvement of various sensorimotor-related networks (Mancini et al. 2009). In chapter 5, no attenuation in the contraction-driven beta amplitude loss was observed during the fatigue trial, which might indicate that this habituation response was counteracted by the development of fatigue. During physical fatigue, a gradual increase in the motor

drive is required to maintain a consistent force output, and the sensory feedback to the cortex may be augmented by peripheral factors such as the accumulation of metabolites (Taylor & Gandevia 2008). Although speculative, it is possible that continuous amendments in cortical processing in response to these progressive fatigue-related processes may prevent the task from becoming familiar; thereby impeding the cortical reorganisation involved in the habituation of the task.

The main focus of chapter 5 was on the movement-related oscillatory dynamics identified in chapter 4. The aim was to investigate whether these phenomena are modified when the homeostasis of the neuromuscular pathway facilitating a particular movement is challenged (in this instance, by using physical fatigue). The contraction-driven reductions in mu and beta amplitude loss were located in the contralateral sensorimotor cortex, and so this was the region of cortex examined by chapter 5. However, physical fatigue may have a greater influence on other regions of the brain, upstream of the motor cortex. As physical fatigue develops, transcranial magnetic stimulation of the motor cortex evokes a gradually increasing amplitude of superimposed twitch response during maximal voluntary force output (Gandevia et al. 1996). This demonstrates a progressively sub-optimal output from the motor cortex (i.e. a progression of supraspinal fatigue), and that no part of the motor pathway “from the motor cortex to the myofibril” can be operating at capacity (Gandevia et al. 1996). Thus, some component of the physical fatigue must be occurring upstream of the motor cortex.

Future research should investigate how other regions of the cortex are affected by fatigue. During the analysis of Chapter 5, contrasting oscillatory amplitude between the constant-force phases of contractions performed before and after the fatiguing intervention did not identify any significant changes in oscillatory amplitude anywhere across the cortex (at least none that were consistent across participants; data not shown). A subtle shift in focus to examine how different regions of the cortex are affected by physical fatigue (rather than how physical fatigue affects the contraction-driven changes in oscillatory amplitude) may therefore require a substantial shift in the analytical approach. An appropriate next step might be to perform a connectivity analysis on the recorded MEG to

examine how the interaction between different cortical locations is modulated during fatigue.

6.5 – Modulations of PMBR

To the author's knowledge chapter 4 was the first study to show PMBR to be systematically modulated by the motor parameters of the preceding voluntary contraction. Specifically, a higher force output resulted in a significantly greater PMBR amplitude, and a greater RFD resulted in a PMBR which was shorter in duration, and higher in amplitude. Additionally, chapter 5 was the first study to investigate the effect of physical fatigue on PMBR; demonstrating a greater PMBR following contractions performed by a fatigued muscle group.

The results of chapter 4 are in some agreement with those of Stančák et al. (1997) who observed a higher PMBR amplitude following finger extensions performed against a heavy external load (130 g) compared to unloaded extensions. However, contrary to chapter 4, no difference in PMBR was reported following isometric elbow flexion between 25 and 75%MVT (Cremoux et al. 2013). The reason for this inconsistency is unclear, and further investigation of the PMBR response, including whether it may differ across muscle groups, may therefore be warranted.

The PMBR is widely believed to reflect a GABAergic inhibition of the sensorimotor networks established during motor actions. For example, Gaetz et al. (2011) demonstrated a positive correlation between the magnitude of PMBR and local GABA concentrations (measured using magnetic resonance spectroscopy). Chapters 4 and 5 might therefore indicate that stronger GABAergic action may be evoked following contractions of higher forces and following contractions performed in a state of physical fatigue, respectively. The exact cause of the augmented PMBR is not immediately clear; however, both studies (chapters 4 and 5) proposed that elevations in PMBR might represent inhibition of sensorimotor networks that are in states of higher activity/excitation. In support of this hypothesis; greater sensorimotor BOLD responses are observed during contractions of higher force outputs (Dai et al. 2001; Cramer et

al. 2002; Ward & Frackowiak 2003; van Duinen et al. 2008; Keisker et al. 2009) and during contractions performed in a state of physical fatigue (Benwell et al. 2007; van Duinen et al. 2007; Post et al. 2009; Steens et al. 2012), with these increases in the fMRI signal expected to arise from a combination of increases in both efferent and afferent processing. Moreover, the PMBR may be positively related to the BOLD signal change during voluntary contractions (Parkes et al. 2006). Increases in both efferent and afferent processing might therefore necessitate more extensive GABAergic activity following contraction termination in order to actively inhibit the sensorimotor networks recruited during the contraction, and to re-establish the inhibitory circuits underpinning the 'idling' cortical rhythms (Pfurtscheller et al. 2005; Stevenson et al. 2011). This hypothesis could be further examined by future studies investigating whether other (perhaps external) stimuli that evoke a graded BOLD response also result in an incremental beta rebound.

In the ramp contractions paradigm of chapter 4, an increase in PMBR duration and a decrease in PMBR amplitude were found to accompany increases in RFD. However, by keeping the peak force of the ramp contractions constant, the duration of the contractions was shortened with increases in RFD, and it was speculated that this change in the length of contraction may have influenced PMBR duration, rather than the RFD itself. Specifically, it was suggested that longer contractions may result in longer PMBRs. One previous investigation (Stevenson et al. 2011) has investigated the effect of increasing the duration of a motor stimulus (1, 2, 4 and 6 s of index finger tapping) on beta responses and found increases in the integrated PMBR with increases in stimulus duration up to 4 s, after which a slight decrease was noted. However, the study design involved a fixed trial length of 12 s, meaning that as stimulus duration increased, the rest period between bouts of finger tapping decreased (minimum 4 s). Therefore, any further prolongation of PMBR following 6 s of finger tapping may not have been fully captured. Moreover, measures of baseline beta amplitude may have been collected during the latter stages of the PMBR, resulting in an underestimation of the PMBR during the longer duration stimuli.

An explanation as to why the amplitude of PMBR may have increased with RFD is less intuitive. However, this effect appeared to be less linear than the

previously described results, with a lower amplitude PMBR observed following the $9.9\% \text{ MVF} \cdot \text{s}^{-1}$ contractions than both the 29.7 and $86.4\% \text{ MVF} \cdot \text{s}^{-1}$ contractions, which were of a similar amplitude (see Figure 5.6A&C). Subsequently, it was speculated that when the ramp contractions were sustained over a longer time period, the sensation of the handle in the participant's hand may have been retained following contraction cessation, contributing to a sensory aftereffect that might have dampened the recorded PMBR by evoking a concurrent stimulus for beta decrease. The hypothesis here is that a sensory aftereffect may produce a stimulus-driven beta decrease in the sensory cortex that overlaps (temporally and spatially) with the PMBR in the adjacent motor cortex, leading to an underestimation of the extra-cranially recorded PMBR. In accordance with this hypothesis, previous studies using both EEG (Mullinger et al. 2015) and fMRI (Mullinger et al. 2015; Sadaghiani et al. 2009) have attributed dampening of (the recorded) post-stimulus responses in the visual cortex to aftereffects following different visual stimuli (static vs. flashing checkerboards).

The results of chapter 4 were useful not only in extending our understanding of the PMBR, but also provided two important recommendations for future studies of post-stimulus beta rebound responses. Firstly, use of motor tasks in investigations of beta oscillations must ensure that the parameters of the performed contractions are carefully controlled so as to remove the influence of movement parameters on the magnitude and duration of the PMBR. Secondly, a sufficient inter-stimulus interval must be incorporated in to the study design so that the full rebound response can be characterised, and more importantly, an accurate assessment of baseline oscillatory amplitude can be made that is not biased by a lengthy rebound response. Furthermore, longer inter-stimulus breaks may help prevent the development of physical fatigue, which may also influence the magnitude of PMBR as shown in chapter 5.

6.6 – MRBD and PMBR: independent phenomena?

Chapters 4 and 5 have provided some evidence that MRBD and PMBR originate via separate neural generators. Firstly, a significant anterior shift in the spatial location of the PMBR compared to the MRBD was shown in the constant-force

contractions experiment in chapter 4. This was supported by a similar (albeit non-significant) trend in the ramp contractions paradigm, and although no statistical analysis was conducted, chapter 5 also reported PMBR to arise anteriorly to MRBD. These results are in agreement with several previous investigations that have also reported PMBR to arise anteriorly to MRBD (Stancák & Pfurtscheller 1995; Salmelin et al. 1995; Jurkiewicz et al. 2006). In addition, the results of Chapter 4 showed PMBR was systematically modulated by both the force and RFD of the performed contractions, whereas MRBD was unaffected by either parameter. Similarly, chapter 5 demonstrated PMBR to be increased following the development of physical fatigue, whereas MRBD was unchanged. These results are again in agreement with the previous investigations, which have suggested the MRBD to exhibit a distinct 'on/off' property, while the PMBR might be more variable in its relationship with task parameters (Stevenson et al. 2011; Stevenson et al. 2012).

Further dissimilarities between MRBD and PMBR have also been reported previously. For example, the beta power loss during contractions may be more widespread (spatially) than the ensuing PMBR (Pfurtscheller et al. 1996), and the frequency of the PMBR has been reported as slightly higher (Feige et al. 1996), or lower (Müller-Putz et al. 2007) than the preceding MRBD.

One argument for MRBD and PMBR not being wholly independent is that one phenomenon is seldom observed without the other. The only exception (to the author's knowledge) comes from an investigation by Cassim et al. (2001), which reported an abolition of PMBR following ischaemic deafferentation. These authors suggested that afferent feedback may therefore be fundamental to the engenderment of the PMBR, however, a rebound in beta power has been observed following imagined contractions; both in healthy controls (Pfurtscheller et al. 2005; Schnitzler et al. 1997), and in a paraplegic patient (Müller-Putz et al. 2007).

Overall, the hypothesis that the MRBD and PMBR are fundamentally different processes is not new. Donner and Siegel (2011) proposed that decreases in beta amplitude may be associated with local encoding processes, whereas increases in beta amplitude might reflect integrative processes over large networks.

Moreover, Muthukumaraswamy et al. (2013) suggested that PMBR may be a GABA_A receptor mediated process while PMBR may be GABA_B receptor mediated. Nevertheless, the results of the present findings add support to the hypothesis that these two oscillatory phenomena may reflect the actions of separate neuronal substrates (Feige et al. 1996; Pfurtscheller et al. 1996b), and may have functionally distinct roles (Jurkiewicz et al. 2006).

6.7 – Summary of the Key Findings

1. Chapter 2 addressed the importance of Ia afferent contributions to maximal force development. It found both maximal and explosive force production were unaffected following a 30-min tendon vibration. This was despite a marked decrease in H-reflex amplitude, which indicated that the vibration stimulus was effective in attenuating the efficacy of the Ia afferent- α -motoneuron pathway. These results indicated that for isometric contractions of the quadriceps muscle group, maximal and explosive force production may not be dependent upon input to the α -motoneurons via homonymous Ia afferents.
2. Chapters 3 and 4 examined whether movement-related changes in oscillatory amplitude might be modulated by the motor parameters of the performed contractions (specifically contraction force/torque and RFD). The main findings were:
 - a. Chapters 3 and 4 found the changes in alpha/mu and beta amplitude between contraction and rest to be unaffected by either contraction force/torque or RFD.
 - b. Chapter 3 observed the 30-50 Hz gamma band activity during contractions to be augmented with increments in knee-extension torque, although this was attributed increases in physiological arousal and/or the attentional demands of the higher torque contractions, rather than the motor parameters directly.
 - c. Chapter 4 showed monotonic modulation of PMBR with both wrist-flexor contraction force and RFD. Specifically, increases in PMBR amplitude accompanied increases in isometric contraction force; and both an increase in PMBR amplitude and a decrease in PMBR duration accompanied the increments in RFD.

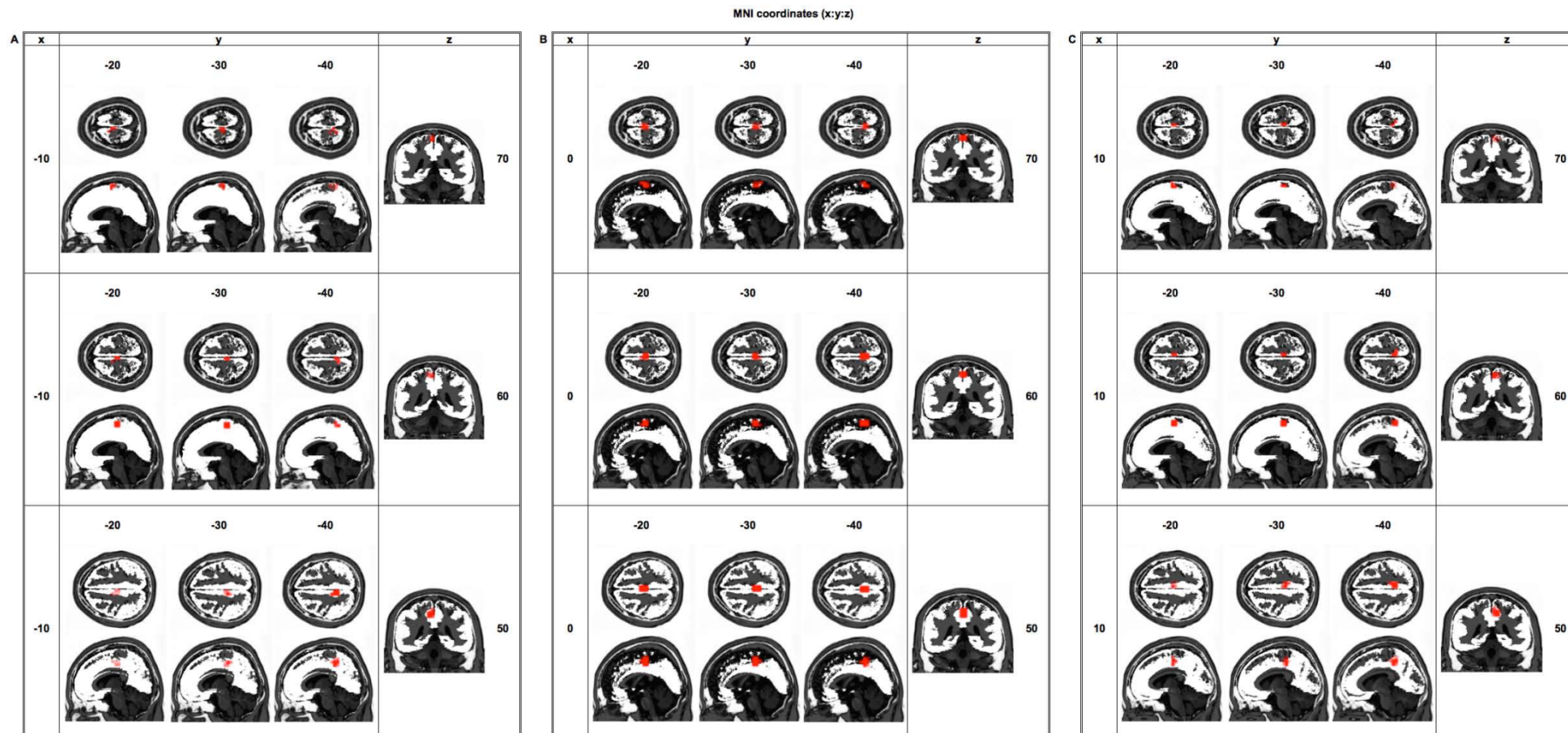
- d. Chapter 4 also found PMBR could be >7 s duration. This result highlighted the necessity for future study designs to incorporate an inter-stimulus interval sufficient enough for assessments of baseline oscillatory amplitude to be made following the completion of the PMBR.
3. Chapter 5 investigated whether oscillatory activity within the sensorimotor cortex may be modulated when contractions were performed in a state of physical fatigue. The results demonstrated:
 - a. MRBD was attenuated during the control trial, whereas the magnitude of MRBD was maintained during the fatigue trial. This finding indicated that physical fatigue might counteract a habituation response, whereby the MRBD is reduced as a motor task becomes familiar (as observed in the control trial).
 - b. PMBR was increased following the fatiguing intervention, but remained unchanged following during the control trial. This increase in PMBR was thought to represent an increase in GABAergic action. Specifically, it was suggested that contractions performed in a state of physical fatigue may involve an increase in both efferent and afferent processing, and that a greater GABAergic action might then be necessary to actively inhibit the sensorimotor networks recruited during these contractions.

6.8 – Future research

The key findings reported above include a number of novel results which might open up further avenues for exploration. In particular, future studies should seek to:

1. Examine the effect of prolonged tendon vibration on the efficacy of the homonymous Ia afferent- α -motoneuron pathway during the performance of maximal force production.
2. Investigate the movement-related oscillatory responses to different contraction types (i.e. isometric/concentric/eccentric contractions).
3. Examine the PMBR response to constant-force isometric contractions of different durations.
4. Corroborate the reported effects of physical fatigue on MRBD and PMBR using other fatiguing paradigms.
5. Examine how the interaction between different cortical locations is modulated during physical fatigue using connectivity analyses of MEG recordings.

Appendix 3.1: The areas of the cortex (shown in red over the MNI-Average-305-T1 head model) comprising each of the 27 voxels at which the LORETA analyses were performed. Voxel locations are described by the shown Montreal Neurophysiological Institute (MNI) coordinates. For each frequency band within each participant; the voxel exhibiting the greatest change in cortical activity from rest was selected as the region of interest within the sensorimotor cortex (see Data analyses).



References

- Abbruzzese, M. et al., 1997. Testing for pre-synaptic and post-synaptic changes in the soleus H reflex pathway following selective muscle vibration in humans. *Neuroscience Letters*, 231, pp.99–102.
- Alegre, M. et al., 2008. Oscillatory changes related to the forced termination of a movement. *Clinical Neurophysiology*, 119(2), pp.290–300.
- Allen, G., McKenzie, D. & Gandevia, S., 1998. Twitch interpolation of the elbow flexor muscles at high forces. *Muscle & Nerve*, 21(3), pp.318–328.
- Allison, G.T., 2003. Trunk muscle onset detection technique for EMG signals with ECG artefact. *Journal of Electromyography and Kinesiology*, 13(3), pp.209–216.
- Ashe, J., 1997. Force and the motor cortex. *Behavioural Brain Research*, 87, pp.255–269.
- Bai, X. et al., 2007. Evaluation of cortical current density imaging methods using intracranial electrocorticograms and functional MRI. *NeuroImage*, 35(2), pp.598–608.
- Bailey, S.P. et al., 2008. Changes in EEG during graded exercise on a recumbent cycle ergometer. *Journal of Sports Science and Medicine*, 7, pp.505–511.
- Bauer, M. et al., 2014. Attentional modulation of alpha/beta and gamma oscillations reflect functionally distinct processes. *Journal of Neuroscience*, 34(48), pp.16117–16125.
- Bauer, M., Kennett, S. & Driver, J., 2012. Attentional selection of location and modality in vision and touch modulates low-frequency activity in associated sensory cortices. *Journal of Neurophysiology*, 107(9), pp.2342–2351.
- Belanger, A. & McComas, A., 1981. Extent of motor unit activation during effort. *Journal of Applied Physiology*, 51(5), pp.1131–1135.
- Bemben, M., Clasey, J. & Massey, B., 1990. The effect of the rate of muscle

- contraction on the force-time curve parameters of male and female subjects. *Research Quarterly for Exercise and Sport*, 61(1), pp.96–99.
- Benwell, N., Mastaglia, F. & Thickbroom, G., 2007. Changes in the functional MR signal in motor and non-motor areas during intermittent fatiguing hand exercise. *Experimental Brain Research*, 182(1), pp.93–97.
- Berger, H., 1929. Über das elektrenkephalogramm des menschen. *Arch Psychiat Nervenkr*, 87, pp.527–570.
- Bigland-Ritchie, B., Cafarelli, E. & Vøllestad, N., 1986. Fatigue of submaximal static contractions. *Acta Physiologica Scandinavica. Supplementum*, 556, pp.137–148.
- Blinkenberg, M. et al., 1996. Rate dependence of regional cerebral activation during performance of a repetitive motor task: a PET study. *Journal of Cerebral Blood Flow and Metabolism*, 16(5), pp.794–803.
- Bongiovanni, L., Hagbarth, K.-E. & Stjernberg, L., 1990. Prolonged muscle vibration reducing motor output in maximal voluntary contractions in man. *Journal of Physiology*, 423, pp.15–26.
- Bonnet, M.H. & Arand, D.L., 2001. Impact of activity and arousal upon spectral EEG parameters. *Physiology & Behavior*, 74(3), pp.291–298.
- van Boxtel, A., 1986. Differential effects of low-frequency depression, vibration-induced inhibition, and posttetanic potentiation on H-reflexes and tendon jerks in the human soleus muscle. *Journal of Neurophysiology*, 55, pp.551–568.
- Brookes, M. et al., 2015. Complexity measures in magnetoencephalography: Measuring “disorder” in schizophrenia. *Plos One*, 10(4), p.e0120991.
- Brookes, M. et al., 2008. Optimising experimental design for MEG beamformer imaging. *NeuroImage*, 39(4), pp.1788–1802.
- Brookes, M. et al., 2012. Task induced modulation of neural oscillations in electrophysiological brain networks. *NeuroImage*, 63(4), pp.1918–1930.

- Brucke, C. et al., 2012. Scaling of movement is related to pallidal γ oscillations in patients with dystonia. *Journal of Neuroscience*, 32(3), pp.1008–1019.
- Brümmer, V. et al., 2011. Primary motor cortex activity is elevated with incremental exercise intensity. *Neuroscience*, 181, pp.150–162.
- Buckthorpe, M. et al., 2012. Reliability of neuromuscular measurements during explosive isometric contractions, with special reference to electromyography normalization techniques. *Muscle & Nerve*, 46, pp.566–76.
- Buxton, R., 2012. Dynamic models of BOLD contrast. *NeuroImage*, 62(2), pp.953–961.
- Buxton, R., Wong, E. & Frank, L., 1998. Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magnetic Resonance in Medicine*, 39(17), pp.855–864.
- Cassim, F. et al., 2001. Does post-movement beta synchronization reflect an idling motor cortex? *NeuroReport*, 12(17), pp.3859–3863.
- Chatrian, G., Petersen, M. & Lazarte, J., 1959. The blocking of the rolandic wicket rhythm and some central changes related to movement. *Electroencephalography and Clinical Neurophysiology*, 11(3), pp.497–510.
- Chen, J. & Pike, G., 2009. Origins of the BOLD post-stimulus undershoot. *NeuroImage*, 46(3), pp.559–568.
- Chen, W. et al., 1998. Spatial and temporal differentiation of fMRI BOLD response in primary visual cortex of human brain during sustained visual simulation. *Magnetic Resonance in Medicine*, 39(4), pp.520–527.
- Cheney, P. & Fetz, E., 1980. Functional classes of primate corticomotoneuronal cells and their relation to active force. *Journal of Neurophysiology*, 44(4), pp.773–791.
- Chestek, C. et al., 2013. Hand posture classification using electrocorticography signals in the gamma band over human sensorimotor brain areas. *Journal of Neural Engineering*, 10(2), p.026002.

- Cheyne, D., 2013. MEG studies of sensorimotor rhythms: a review. *Experimental Neurology*, 245, pp.27–39.
- Cheyne, D. et al., 2008. Self-paced movements induce high-frequency gamma oscillations in primary motor cortex. *NeuroImage*, 42(1), pp.332–342.
- Christensen, L. et al., 2000. Cerebral activation during bicycle movements in man. *Experimental Brain Research*, 135, pp.66–72.
- Cramer, S. et al., 2002. Motor cortex activation is related to force of squeezing. *Human Brain Mapping*, 16(4), pp.197–205.
- Cremoux, S. et al., 2013. Motor-related cortical activity after cervical spinal cord injury: Multifaceted EEG analysis of isometric elbow flexion contractions. *Brain Research*, 1533, pp.44–51.
- Crone, C. & Nielsen, J., 1989. Methodological implications of the post activation depression of the soleus H-reflex in man. *Experimental Brain Research*, 78, pp.28–32.
- Crone, N. et al., 1998. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain*, 121, pp.2301–2315.
- Curtis, D. & Eccles, J., 1960. Synaptic action during and after repetitive stimulation. *Journal of Physiology*, 150, pp.374–398.
- Cushing, H., 1909. A note upon the faradic stimulation of the postcentral gyrus in conscious patients. *Brain*, 32, pp.44–53.
- Dai, T. et al., 2001. Relationship between muscle output and functional MRI-measured brain activation. *Experimental Brain Research*, 140, pp.290–300.
- Dal Maso, F., Longcamp, M. & Amarantini, D., 2012. Training-related decrease in antagonist muscles activation is associated with increased motor cortex activation: evidence of central mechanisms for control of antagonist muscles. *Experimental Brain Research*, 220, pp.287–295.
- Desmedt, J. & Godaux, E., 1978. Mechanism of the vibration paradox: excitatory

- and inhibitory effects of tendon vibration on single soleus muscle motor units in man. *Journal of Physiology*, 285, pp.197–207.
- Dettmers, C. et al., 1995. Relation between cerebral activity and force in the motor areas of the human brain. *Journal of Neurophysiology*, 74(2), pp.802–815.
- Deutekom, M. et al., 2000. No acute effects of short-term creatine supplementation on muscle properties and sprint performance. *European Journal of Applied Physiology*, 82(3), pp.223–229.
- Donner, T. & Siegel, M., 2011. A framework for local cortical oscillation patterns. *Trends in Cognitive Science*, 15(5), pp.191–199.
- Dorfman, L., Howard, J. & McGill, K., 1990. Triphasic behavioral response of motor units to submaximal fatiguing exercise. *Muscle and Nerve*, 13(7), pp.621–628.
- van Drongelen, W. et al., 1996. A spatial filtering technique to detect and localize multiple sources in the brain. *Brain Topography*, 9(1), pp.39–49.
- van Duinen, H. et al., 2007. Effects of motor fatigue on human brain activity, an fMRI study. *NeuroImage*, 35(4), pp.1438–1449.
- van Duinen, H. et al., 2008. Relation between muscle and brain activity during isometric contractions of the first dorsal interosseus muscle. *Human Brain Mapping*, 29(3), pp.281–99.
- Dujardin, K., Bourriez, J. & Guieu, J., 1995. Event-related desynchronization (ERD) patterns during memory processes: effects of aging and task difficulty. *Electroencephalography and Clinical Neurophysiology*, 96(2), pp.169–182.
- Earles, D. et al., 2002. Pre-and post-synaptic control of motoneuron excitability in athletes. *Medicine & Science in Sports & Exercise*, 34(11), pp.1766–1772.
- van Ede, F., Szebényi, S. & Maris, E., 2014. Attentional modulations of somatosensory alpha, beta and gamma oscillations dissociate between anticipation and stimulus processing. *NeuroImage*, 97, pp.134–141.

- Ekblom, M. & Thorstensson, A., 2011. Effects of prolonged vibration on H-reflexes, muscle activation, and dynamic strength. *Medicine & Science in Sports & Exercise*, 43, pp.1933–1939.
- Erskine, J. et al., 2007. Neuromuscular and hormonal responses to a single session of whole body vibration exercise in healthy young men. *Clinical Physiology and Functional Imaging*, 27, pp.242–248.
- Evarts, E., 1969. Activity of pyramidal tract neurons during postural fixation. *Journal of Neurophysiology*, 32(3), pp.375–385.
- Evarts, E. et al., 1983. Motor cortex control of finely graded forces. *Journal of Neurophysiology*, 49(5), pp.1199–1215.
- Evarts, E., 1968. Relation of pyramidal tract activity to force exerted during voluntary movement. *J Neurophysiology*, 31, pp.14–27.
- Feige, B. et al., 1996. Neuromagnetic study of movement-related changes in rhythmic brain activity. *Brain Research*, 734(1), pp.252–260.
- Flint, R. et al., 2014. Extracting kinetic information from human motor cortical signals. *NeuroImage*, 101, pp.695–703.
- Folland, J., Buckthorpe, M. & Hannah, R., 2013. Human capacity for explosive force production: Neural and contractile determinants. *Scandinavian Journal of Medicine & Science in Sports*, 24(6), pp.894-906.
- Folland, J., Wakamatsu, T. & Fimland, M., 2008. The influence of maximal isometric activity on twitch and H-reflex potentiation , and quadriceps femoris performance. *European Journal of Applied Physiology*, 104, pp.739–748.
- Folland, J.P. & Williams, A.G., 2007. The Adaptations to Strength Training Increased Strength. *Sports Medicine*, 37(2), pp.145–168.
- Gaetz, W. et al., 2010. Neuromagnetic imaging of movement-related cortical oscillations in children and adults: Age predicts post-movement beta rebound. *NeuroImage*, 51(2), pp.792–807.
- Gaetz, W. et al., 2011. Relating MEG measured motor cortical oscillations to

- resting γ -aminobutyric acid (GABA) concentration. *NeuroImage*, 55(2), pp.616–621.
- Gandevia, S., 2001. Spinal and supraspinal factors in human muscle fatigue. *Physiological reviews*, 81(4), pp.1725–89.
- Gandevia, S. et al., 1996. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. *Journal of Physiology*, 490(2), pp.529–536.
- Gilbertson, T. et al., 2005. Existing motor state is favored at the expense of new movement during 13-35 Hz oscillatory synchrony in the human corticospinal system. *The Journal of Neuroscience*, 25(34), pp.7771–7779.
- Goodall, S. et al., 2012. Transcranial magnetic stimulation in sport science: A commentary. *European Journal of Sport Science*, (14), pp.S332–S340.
- Grech, R. et al., 2008. Review on solving the inverse problem in EEG source analysis. *Journal of NeuroEngineering and Rehabilitation*, 5, p.25.
- Gross, J. et al., 2001. Dynamic imaging of coherent sources: Studying neural interactions in the human brain. *PNAS*, 98(2), pp.694–699.
- Grünbaum, A. & Sherrington, C., 1901. Observations on the Physiology of the Cerebral Cortex of the Anthropoid Apes. *Proceedings of the Royal Society of London*, 69, pp.206–209.
- Hagbarth, K.-E. et al., 1986. Gamma loop contributing to maximal voluntary contractions in man. *Journal of Physiology*, 380, pp.575–591.
- Hall, E. et al., 2014. The relationship between MEG and fMRI. *NeuroImage*, 102(1), pp.80–91.
- Hall, S. et al., 2014. GABA-mediated changes in inter-hemispheric beta frequency activity in early-stage Parkinson's disease. *Neuroscience*, 281, pp.68–76.
- Hall, S. et al., 2011. The role of GABAergic modulation in motor function related neuronal network activity. *NeuroImage*, 56(3), pp.1506–1510.

- Hannah, R., Minshull, C. & Folland, J., 2013. Whole-body vibration does not influence knee joint neuromuscular function or proprioception. *Scandinavian Journal of Medicine & Science in Sports*, 23, pp.96–104.
- Hayward, L. et al., 1986. Tendon vibration-induced inhibition of human and cat triceps surae group I reflexes: evidence of selective Ib afferent fiber activation. *Experimental Neurology*, 94, pp.333–347.
- Heckman, C. et al., 1984. Can Ib axons be selectively activated by electrical stimuli in human subjects? *Experimental Neurology*, 86, pp.576–582.
- Heckman, C. & Binder, M., 1991. Computer simulation of the steady-state input-output function of the cat medial gastrocnemius motoneuron pool. *Journal of Neurophysiology*, 65(4), pp.952–967.
- Heinrichs-Graham, E. et al., 2014. Neuromagnetic evidence of abnormal movement-related beta desynchronization in Parkinson's disease. *Cerebral Cortex*, 24(10), pp.1–10.
- Henneman, E., Somjen, G. & Carpenter, D., 1965. Excitability and inhibability of motoneurons of different sizes. *Journal of Neurophysiology*, 28(3), pp.599–620.
- Hepp-Reymond, M. et al., 1999. Context-dependent force coding in motor and premotor cortical areas. *Experimental Brain Research*, 128, pp.123–133.
- Hillebrand, A. et al., 2005. A new approach to neuroimaging with magnetoencephalography. *Human Brain Mapping*, 25(2), pp.199–211.
- Hoffmann, P., 1918. Über die beziehung der sehnenreflexe zur willkürlichen bewegung und zum tonus. *Z Biol*, 68, pp.351–370.
- Holtermann, A. et al., 2007. Enhanced H-reflex with resistance training is related to increased rate of force development. *European Journal of Applied Physiology*, 101, pp.301–312.
- Hopkins, J. & Wagie, N., 2003. Intrasession and intersession reliability of the quadriceps Hoffmann reflex. *Electromyography and Nlinical neurophysiology*, 43(2), pp.85–89.

- Hu, X., Le, T. & Uğurbil, K., 1997. Evaluation of the early response in fMRI in individual subjects using short stimulus duration. *Magnetic Resonance in Medicine*, 37(6), pp.877–884.
- Huang, M., Mosher, J. & Leahy, R., 1999. A sensor-weighted overlapping-sphere head model and exhaustive head model comparison for MEG. *Physics in Medicine and Biology*, 44(2), pp.423–440.
- Hultborn, H. et al., 1987. Assessing changes in presynaptic inhibition of Ia fibres: a study in man and the cat. *The Journal of Physiology*, 389(1), pp.729–756.
- Hultborn, H. et al., 1996. On the mechanism of the post-activation depression of the H-reflex in human subjects. *Experimental Brain Research*, 108, pp.450–462.
- Humphries, B. et al., 2004. The influence of vibration on muscle activation and rate of force development during maximal isometric contractions. *Journal of Sports Science and Medicine*, 3(1), pp.16–22.
- Jackson, S. & Turner, D., 2003. Prolonged muscle vibration reduces maximal voluntary knee extension performance in both the ipsilateral and the contralateral limb in man. *European Journal of Applied Physiology*, 88, pp.380–386.
- Jagannath, M. & Balasubramanian, V., 2014. Assessment of early onset of driver fatigue using multimodal fatigue measures in a static simulator. *Applied Ergonomics*, 45(4), pp.1140–1147.
- Jasper, H. & Andrews, H., 1938. Electro-encephalography III. Normal differentiation of occipital and precentral regions in man. *Archives of Neurology and Psychiatry*, 39, pp.96–115.
- Jasper, H. & Penfield, W., 1949. Electrocorticograms in man: Effect of voluntary movement upon the electrical activity of the precentral gyrus. *Archiv für Psychiatrie und Zeitschrift Neurologie*, 183, pp.163–174.
- Jenkinson, N., Kühn, A. & Brown, P., 2013. γ oscillations in the human basal ganglia. *Experimental Neurology*, 245, pp.72–76.

- Jensen, O. et al., 2005. On the human sensorimotor-cortex beta rhythm: sources and modeling. *NeuroImage*, 26(2), pp.347–355.
- Jin, T. & Kim, S.-G., 2008. Cortical layer-dependent dynamic blood oxygenation, cerebral blood flow and cerebral blood volume responses during visual stimulation. *NeuroImage*, 43(1), pp.1–9.
- Joundi, R. et al., 2012. Oscillatory activity in the subthalamic nucleus during arm reaching in Parkinson's disease. *Experimental Neurology*, 236(2), pp.319–326.
- Jurkiewicz, M. et al., 2006. Post-movement beta rebound is generated in motor cortex: Evidence from neuromagnetic recordings. *NeuroImage*, 32, pp.1281–1289.
- Kameyama, O., Hayes, K. & Wolfe, D., 1989. Methodological considerations contributing to variability of the quadriceps H-reflex. *American Journal of Physical Medicine & Rehabilitation*, 68(6), pp.277–282.
- Keisker, B. et al., 2009. Differential force scaling of fine-graded power grip force in the sensorimotor network. *Human Brain Mapping*, 30, pp.2453–65.
- Kilavik, B. et al., 2013. The ups and downs of beta oscillations in sensorimotor cortex. *Experimental Neurology*, 245, pp.15–26.
- Klimesch, W., Sauseng, P. & Hanslmayr, S., 2007. EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Research Reviews*, 53(1), pp.63–88.
- Konishi, Y., Kubo, J. & Fukudome, A., 2009. Effects of prolonged tendon vibration stimulation on eccentric and concentric maximal torque and EMGs of the knee extensors. *Journal of Sports Science and Medicine*, 8, pp.548–552.
- Kouzaki, M. et al., 2000. Decrease in maximal voluntary contraction by tonic vibration applied to a single synergist muscle in humans. *Journal of Applied Physiology*, 89, pp.1420–1424.
- Kozelka, J. & Pedley, T., 1990. Beta and mu rhythms. *Journal of Clinical Neurophysiology*, 7(2), pp.191–207.

- Kranczioch, C. et al., 2008. Short-term learning of a visually guided power-grip task is associated with dynamic changes in EEG oscillatory activity. *Clinical Neurophysiology*, 119(6), pp.1419–1430.
- Kuriki, H. et al., 2011. Comparison of different analysis techniques for the determination of muscle onset in individuals with patellofemoral pain syndrome. *Journal of Electromyography and Kinesiology*, 21, pp.982–987.
- Lapole, T., Canon, F. & Pérot, C., 2012. Acute postural modulation of the soleus H-reflex after Achilles tendon vibration. *Neuroscience Letters*, 523(2), pp.154–157.
- Leocani, L. et al., 1997. Event-related coherence and event-related desynchronization/synchronization in the 10 Hz and 20 Hz EEG during self-paced movements. *Electroencephalography and Clinical Neurophysiology*, 104(3), pp.199–206.
- Li, C. & Bak, A., 1976. Excitability characteristics of the A- and C-fibers in a peripheral nerve. *Experimental Neurology*, 50, pp.67–79.
- Lin, C.-Y. et al., 2002. Excitability of human muscle afferents studied using threshold tracking of the H reflex. *Journal of Physiology*, 545(2), pp.661–669.
- Liu, J. et al., 2003. Human brain activation during sustained and intermittent submaximal fatigue muscle contractions: an FMRI study. *Journal of Neurophysiology*, 90(1), pp.300–312.
- Liu, J. et al., 2002. Nonlinear cortical modulation of muscle fatigue: a functional MRI study. *Brain Research*, 957(2), pp.320–329.
- Ludman, C. et al., 1996. Force of voluntary exercise does not affect sensorimotor cortex activation as detected by functional MRI at 1.5 T. *NMR in Biomedicine*, 9(5), pp.228–32.
- Macefield, V. et al., 1993. The firing rates of human motoneurons voluntarily activated in the absence of muscle afferent feedback. *Journal of Physiology*, 471, pp.429–443.
- Mackay, W., 1997. Synchronized neuronal oscillations and their role in motor

- processes. *Trends in Cognitive Sciences*, 1(5), pp.176–183.
- Mancini, L. et al., 2009. Short-term adaptation to a simple motor task: A physiological process preserved in multiple sclerosis. *NeuroImage*, 45(2), pp.500–511.
- Mary, A. et al., 2015. Aging reduces experience-induced sensorimotor plasticity. A magnetoencephalographic study. *NeuroImage*, 104, pp.59–68.
- Merton, P., 1954. Voluntary strength and fatigue. *Journal of Physiology*, 123, pp.553–564.
- Miller, K. et al., 2007. Spectral changes in cortical surface potentials during motor movement. *The Journal of Neuroscience*, 27(9), pp.2424–2432.
- Mima, T. et al., 1999. Force level modulates human cortical oscillatory activities. *Neuroscience Letters*, 275, pp.77–80.
- Müller-Putz, G. et al., 2007. Event-related beta EEG-changes during passive and attempted foot movements in paraplegic patients. *Brain Research*, 1137(1), pp.84–91.
- Mullinger, K. et al., 2015. fMRI post-stimulus undershoots in visual cortex are neuronal in origin. In *ISMRM Proc.* p. 2415.
- Mullinger, K. et al., 2013. Poststimulus undershoots in cerebral blood flow and BOLD fMRI responses are modulated by poststimulus neuronal activity. *PNAS*, 110(33), pp.13636–13641.
- Murthy, V.N. & Fetz, E.E., 1996a. Oscillatory activity in sensorimotor cortex of awake monkeys: Synchronization of local field potentials and relation to behavior. *Journal of Neurophysiology*, 76, pp.3949–3967.
- Murthy, V.N. & Fetz, E.E., 1996b. Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. *Journal of Neurophysiology*, 76, pp.3968–3982.
- Muthukumaraswamy, S., 2010. Functional properties of human primary motor cortex gamma oscillations. *Journal of Neurophysiology*, 104(5), pp.2873–

- Muthukumaraswamy, S. et al., 2013. The effects of elevated endogenous GABA levels on movement-related network oscillations. *NeuroImage*, 66, pp.36–41.
- do Nascimento, O., Nielsen, K. & Voigt, M., 2005. Relationship between plantar-flexor torque generation and the magnitude of the movement-related potentials. *Experimental Brain Research*, 160(2), pp.154–165.
- Pääsuke, M., Ereline, J. & Gapeyeva, H., 2001. Knee extension strength and vertical jumping performance in nordic combined athletes. *The Journal of Sports Medicine and Physical Fitness*, 41, pp.354–361.
- Parkes, L., Bastiaansen, M. & Norris, D., 2006. Combining EEG and fMRI to investigate the post-movement beta rebound. *NeuroImage*, 29(3), pp.685–696.
- Pascual-marqui, R.D. et al., 2002. Functional imaging with low resolution electromagnetic tomography (LORETA): review , comparisons , and new validation. *Japanese Journal of Clinical Neurophysiology*, 30, pp.81–94.
- De Pauw, K. et al., 2013. Brain mapping after prolonged cycling and during recovery in the heat. *Journal of applied physiology (Bethesda, Md. : 1985)*, 115(9), pp.1324–31.
- Penfield, W., 1954. Mechanisms of voluntary movement. *Brain*, 77(1), pp.1–17.
- Perez-Orive, J. et al., 2002. Oscillations and sparsening of odor representations in the mushroom body. *Science*, 297(5580), pp.359–365.
- Pfurtscheller, G. et al., 2005. Beta rebound after different types of motor imagery in man. *Neuroscience Letters*, 378(3), pp.156–159.
- Pfurtscheller, G. et al., 2003. Spatiotemporal patterns of beta desynchronization and gamma synchronization in corticographic data during self-paced movement. *Clinical Neurophysiology*, 114(7), pp.1226–1236.
- Pfurtscheller, G. & Lopes da Silva, F., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clinical*

- Neurophysiology*, 110(11), pp.1842–1857.
- Pfurtscheller, G. & Solis-Escalante, T., 2009. Could the beta rebound in the EEG be suitable to realize a “brain switch”? *Clinical Neurophysiology*, 120(1), pp.24–29.
- Pfurtscheller, G., Stancák, A. & Neuper, C., 1996. Post-movement beta synchronization. A correlate of an idling motor area? *Electroencephalography and Clinical Neurophysiology*, 98(4), pp.281–293.
- Pfurtscheller, G., Zalaudek, K. & Neuper, C., 1998. Event-related beta synchronization after wrist, finger and thumb movement. *Electroencephalography and clinical neurophysiology*, 109(2), pp.154–60.
- Pierrot-Deseilligny, E. & Burke, D., 2005. *The circuitry of the human spinal cord: its role in motor control and movement disorders*, Cambridge University Press.
- Pineda, J. a., 2005. The functional significance of mu rhythms: Translating “seeing” and “hearing” into “doing.” *Brain Research Reviews*, 50(1), pp.57–68.
- Pistohl, T. et al., 2012. Decoding natural grasp types from human ECoG. *NeuroImage*, 59(1), pp.248–260.
- Pogosyan, A. et al., 2009. Boosting cortical activity at Beta-band frequencies slows movement in humans. *Current Biology*, 19(19), pp.1637–1641.
- Pollok, B. et al., 2014. Changes of motor-cortical oscillations associated with motor learning. *Neuroscience*, 275, pp.47–53.
- Pollok, B. et al., 2012. Motor-cortical oscillations in early stages of Parkinson’s disease. *The Journal of Physiology*, 590(13), pp.3203–3012.
- Post, M. et al., 2009. Voluntary activation and cortical activity during a sustained maximal contraction: An fMRI study. *Human Brain Mapping*, 30(3), pp.1014–1027.
- Proudfoot, M. et al., 2014. Magnetoencephalography. *Practical Neurology*, 14(5),

pp.336–343.

- Puts, N. et al., 2011. Regionally specific human GABA concentration correlates with tactile discrimination thresholds. *The Journal of Neuroscience*, 31(46), pp.16556–16560.
- Rao, S. et al., 1996. Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex. *Journal of Cerebral Blood Flow and Metabolism*, 16(6), pp.1250–1254.
- Robinson, S. & Vrba, J., 1998. Functional neuroimaging by synthetic aperture magnetometry. In T. Yoshimoto et al., eds. *Recent Advances in Biomagnetism*. Sendai, Japan: Tohoku University Press, pp. 302–305.
- Robson, S. et al., Abnormal visuomotor processing in schizophrenia. *NeuroImage Clinical*.
- Roll, J., Vedel, J. & Ribot, E., 1989. Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study. *Experimental Brain Research*, 76, pp.213–222.
- Rougeul-Buser, A., 1994. Electrocortical rhythms in the 40 Hz band in cat: in search of their behavioural correlates. In G. Buzsáki et al., eds. *Temporal Coding in the Brain*. Berlin: Springer-Verlag, pp. 103–114.
- de Ruiter, C. et al., 2004. Initial phase of maximal voluntary and electrically stimulated knee extension torque development at different knee angles. *Journal of Applied Physiology*, 97(5), pp.1693–1701.
- de Ruiter, C. et al., 2003. Short-term effects of whole-body vibration on maximal voluntary isometric knee extensor force and rate of force rise. *European Journal of Applied Physiology*, 88, pp.472–475.
- De Ruiter, C. et al., 1999. Temperature effect on the rates of isometric force development and relaxation in the fresh and fatigued human adductor pollicis muscle. *Experimental Physiology*, 84(6), pp.1137–1150.
- Sadaghiani, S., Uğurbil, K. & Uludağ, K., 2009. Neural activity-induced modulation of BOLD poststimulus undershoot independent of the positive

- signal. *Magnetic Resonance Imaging*, 27(8), pp.1030–1038.
- Sahaly, R. et al., 2001. Maximal voluntary force and rate of force development in humans - importance of instruction. *European Journal of Applied Physiology*, 85, pp.345–350.
- Salmelin, R. et al., 1995. Functional segregation of movement-related rhythmic activity in the human brain. *NeuroImage*, 2(4), pp.237–243.
- Salmelin, R. & Hari, R., 1994. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience*, 60(2), pp.537–550.
- Sarvas, J., 1987. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Physics in Medicine and Biology*, 32(1), pp.11–22.
- Schieppati, M., 1987. Excitability of human soleus motoneurons. , pp.271–284.
- Schneider, S. et al., 2013. Cortical current density oscillations in the motor cortex are correlated with muscular activity during pedaling exercise. *Neuroscience*, 228, pp.309–314.
- Schnitzler, A. et al., 1997. Involvement of primary motor cortex in motor imagery: a neuromagnetic study. *NeuroImage*, 6(3), pp.201–208.
- Shigihara, Y. et al., 2013. Two types of mental fatigue affect spontaneous oscillatory brain activities in different ways. *Behavioral and brain functions: BBF*, 9(1), p.1.
- Shinohara, M. et al., 2005. Prolonged muscle vibration increases stretch reflex amplitude, motor unit discharge rate, and force fluctuations in a hand muscle. *Journal of Applied Physiology*, 99, pp.1825–1842.
- Shmuel, A. et al., 2006. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nature Neuroscience*, 9(4), pp.569–577.
- Sidhu, S., Bentley, D. & Carroll, T., 2009. Locomotor exercise induces long-

- lasting impairments in the capacity of the human motor cortex to voluntarily activate knee extensor muscles. *Journal of Applied Physiology*, 106(2), pp.556–565.
- Siemionow, V. et al., 2000. Relationship between motor activity-related cortical potential and voluntary muscle activation. *Experimental Brain Research*, 133, pp.303–311.
- Smith, J. et al., 2007. Sustained contraction at very low forces produces prominent supraspinal fatigue in human elbow flexor muscles. *Journal of Applied Physiology*, 103, pp.560–568.
- Soda, P. et al., 2010. Human movement onset detection from isometric force and torque measurements: a supervised pattern recognition approach. *Artificial Intelligence in Medicine*, 50(1), pp.55–61.
- Søgaard, K. et al., 2006. The effect of sustained low-intensity contractions on supraspinal fatigue in human elbow flexor muscles. *Journal of Physiology*, 573(2), pp.511–523.
- Solis-Escalante, T. et al., 2012. Cue-induced beta rebound during withholding of overt and covert foot movement. *Clinical Neurophysiology*, 123(6), pp.1182–1190.
- Stancák, A. & Pfurtscheller, G., 1995. Desynchronization and recovery of beta rhythms during brisk and slow self-paced finger movements in man. *Neuroscience Letters*, 196(1-2), pp.21–24.
- Stancák, A. & Pfurtscheller, G., 1996. Event-related desynchronisation of central beta-rhythms during brisk and slow self-paced finger movements of dominant and nondominant hand. *Cognitive Brain Research*, 4(3), pp.171–183.
- Stančák, A., Riml, A. & Pfurtscheller, G., 1997. The effects of external load on movement-related changes of the sensorimotor EEG rhythms. *Electroencephalography and Clinical Neurophysiology*, 102, pp.495–504.
- Staude, G., 2001. Precise onset detection of human motor responses using a

- whitening filter and the log-likelihood-ratio test. *IEEE Transactions on Biomedical Engineering*, 48(11), pp.1292–305.
- Steens, a. et al., 2012. Mechanisms underlying muscle fatigue differ between multiple sclerosis patients and controls: A combined electrophysiological and neuroimaging study. *NeuroImage*, 59(4), pp.3110–3118.
- Stein, R. & Thompson, A., 2006. Muscle reflexes in motion: How, what, and why? *Exercise and Sport Sciences Reviews*, 34(4), pp.145–153.
- Stevenson, C. et al., 2012. Paired pulse depression in the somatosensory cortex: Associations between MEG and BOLD fMRI. *NeuroImage*, 59(3), pp.2722–2732.
- Stevenson, C., Brookes, M. & Morris, P., 2011. β -Band correlates of the fMRI BOLD response. *Human Brain Mapping*, 32(2), pp.182–97.
- Studer, B. et al., 2010. The effects of practice distribution upon the regional oscillatory activity in visuomotor learning. *Behavioral and Brain Functions*, 6(1), p.8.
- Szurhaj, W. et al., 2005. Intracerebral study of gamma rhythm reactivity in the sensorimotor cortex. *European Journal of Neuroscience*, 21(5), pp.1223–1235.
- Tanaka, M., Shigihara, Y. & Watanabe, Y., 2011. Central inhibition regulates motor output during physical fatigue. *Brain Research*, 1412, pp.37–43.
- Tanaka, M. & Watanabe, Y., 2012. Supraspinal regulation of physical fatigue. *Neuroscience and Biobehavioral Reviews*, 36(1), pp.727–734.
- Taylor, J. & Gandevia, S., 2008. A comparison of central aspects of fatigue in submaximal and maximal voluntary contractions. *Journal of Applied Physiology*, 104(2), pp.542–550.
- Taylor, J., Todd, G. & Gandevia, S., 2006. Evidence for a supraspinal contribution to human muscle fatigue. *Clinical and Experimental Pharmacology and Physiology*, 33, pp.400–405.

- Taylor, J.L. et al., 2000. Supraspinal fatigue during intermittent maximal voluntary contractions of the human elbow flexors. *Journal of Applied Physiology*, 89, pp.305–313.
- Tecchio, F. et al., 2006. Cortical short-term fatigue effects assessed via rhythmic brain-muscle coherence. *Experimental Brain Research*, 174(1), pp.144–151.
- Thach, W., 1978. Correlation of neural discharge with pattern and force of muscular activity, joint position, and direction of intended next movement in motor cortex and cerebellum. *Journal of Neurophysiology*, 41(3), pp.654-676.
- Thickbroom, G. et al., 1998. Isometric force-related activity in sensorimotor cortex measured with functional MRI. *Experimental Brain Research*, 121, pp.59–64.
- Tillin, N. et al., 2010. Neuromuscular performance of explosive power athletes versus untrained individuals. *Medicine & Science in Sports & Exercise*, 42(4), pp.781–790.
- Tillin, N., Folland, J. & Pain, M., 2013. Identification of contraction onset during explosive contractions. Response to Thompson et al. “Consistency of rapid muscle force characteristics: influence of muscle contraction onset detection methodology” [J Electromyogr Kinesiol 2012;22(6):893-900]. *Journal of Electromyography and Kinesiology*, 23(4), pp.991–994.
- Tillin, N., Pain, M. & Folland, J., 2013. Explosive force production during isometric squats correlates with athletic performance in rugby union players. *Journal of Sports Sciences*, 31, pp.66–76.
- Todd, G., Gorman, R. & Gandevia, S., 2004. Measurement and reproducibility of strength and voluntary activation of lower-limb muscles. *Muscle & Nerve*, 29(6), pp.834–842.
- Todd, G., Taylor, J. & Gandevia, S., 2003. Measurement of voluntary activation of fresh and fatigued human muscles using transcranial magnetic stimulation. *Journal of Physiology*, 551(2), pp.661–671.
- Ushiyama, J. et al., 2005. Difference in aftereffects following prolonged Achilles tendon vibration on muscle activity during maximal voluntary contraction

- among plantar flexor synergists. *Journal of Applied Physiology*, 98, pp.1427–1433.
- Van Veen, B. et al., 1997. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical engineering*, 44(9), pp.867–880.
- Vogt, T. et al., 2014. Artificial gravity exposure impairs exercise-related neurophysiological benefits. *Physiology & Behavior*, 123, pp.156–161.
- Vrba, J. & Robinson, S., 2001. Signal processing in magnetoencephalography. *Methods*, 25(2), pp.249–271.
- Wannier, T., Maier, M. & Hepp-Reymond, M., 1991. Contrasting properties of monkey somatosensory and motor cortex neurons activated during the control of force in precision grip. *Journal of neurology*, 65(3), pp.572–589.
- Ward, N. & Frackowiak, R., 2003. Age-related changes in the neural correlates of motor performance. *Brain*, 126(4), pp.873–888.
- Zehr, E., 2002. Considerations for use of the Hoffmann reflex in exercise studies. *European Journal of Applied Physiology*, 86(6), pp.455–468.
- Zehr, E. & Stein, R., 1999. What functions do reflexes serve during human locomotion? *Progress in Neurobiology*, 58(2), pp.185–205.
- van Zijl, P., Hua, J. & Lu, H., 2012. The BOLD post-stimulus undershoot, one of the most debated issues in fMRI. *NeuroImage*, 62(2), pp.1092–1102.