UNIVERSITÉ DE SHERBROOKE

Faculté des sciences de l'activité physique

Département de kinanthropologie

L'étude de la contribution des mécanismes dépendants de la répétition aux processus de consolidation des mémoires motrices dans le cortex moteur primaire et de la manifestation électrophysiologique du traitement des récompenses monétaires au-dessus des aires cérébrales motrices

Par

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The study of the contribution of repetition-dependent mechanisms to consolidation processes in the primary motor cortex and the electrophysiological manifestations of monetary reward processing over cortical motor areas

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A été évalué par un jury composé des personnes suivantes :

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Résumé

Le présent mémoire cherche à fournir un aperçu des mécanismes neurophysiologiques qui sous-tendent les deux mécanismes principaux d'apprentissage impliqués dans la consolidation des mémoires motrices dans le cortex moteur primaire (M1). Bien que le modèle cellulaire le plus accepté pour la formation des mémoires motrices soit la potentialisation à long-terme (long-term potentiation, en anglais), la littérature suggère que les mécanismes d'apprentissage qui initient le stockage synaptique des mémoires motrices dépendent de la plasticité Hebienne (i.e., répétitions dans les mouvements) et des récompenses vécues pendant l'acquisition d'une nouvelle habileté motrice.

La première contribution scientifique du présent mémoire aborde la contribution des mécanismes Hebbiens d'apprentissage à la consolidation des mémoires motrices dans le M1. Dans ce premier projet, la stimulation magnétique transcrânienne (SMT) a été utilisée pour interférer avec l'activité neuronale du M1 lorsque les participants acquéraient et exécutaient de nouveaux comportements moteurs pendant l'atteinte d'un plateau de performance (i.e., répétitions dans les mouvements). Les résultats démontrent que la formation des mémoires motrices dans le M1 est initiée lorsque les comportements moteurs sont de plus en plus répétés, ce qui suggère que le stockage synaptique des mémoires motrices dans M1 est dépendant de la répétition des comportements pendant l'acquisition. Le deuxième projet scientifique a cherché à mettre en lumière la contribution des régions motrices au traitement des récompenses dans un contexte moteur en utilisant l'enregistrement d'activités électroencéphalographiques. Entre autres, suite à l'octroi d'une récompense, les résultats démontrent une augmentation de la puissance spectrale dans la bande de fréquences bêta (20-30 Hz) des électrodes motrices contralatérales à la main utilisée pendant la tâche motrice. Dans l'ensemble, bien que ce deuxième projet ne puisse statuer sur la contribution spécifique du M1 dans la consolidation des mémoires motrices sur la base des récompenses vécues pendant l'acquisition, les résultats qui en

émergent pourraient être un reflet des substrats neuronaux impliqués dans ce mécanisme d'apprentissage.

Dans un premier temps, la discussion intègre ces deux contributions et, dans un deuxième temps, donne un aperçu des perspectives futures de recherche qui émanent de ces deux contributions scientifiques. Globalement, les hypothèses de recherche suggérées se concentrent principalement autour de la démonstration d'une association ou d'un lien causal entre la formation des mémoires motrices dans le M1, le traitement de récompenses, les réponses spectrales en bêta ainsi que l'activité dopaminergique. Au travers de la discussion, les hypothèses spécifiques ainsi que les moyens méthodologiques pour les tester – qui vont des techniques de stimulation cérébrale non invasives à l'enregistrement d'activité électroencéphalographique et même jusqu'à l'étude des variations génétiques interindividuelles dans l'expression des gènes régulant l'activité dopaminergique – sont décrits.

Abstract

The present thesis seeks to provide insights into the contribution of the two major learning mechanisms driving motor memory consolidation in the primary motor cortex (M1): repetition-dependent and reward-based learning mechanisms. However, because evidence remains scarce on this last learning mechanism, the study of the neural manifestation of reward processing in motor areas was investigated.

More specifically, the first scientific contribution presented in this thesis sought to address the contribution of repetition-dependent mechanisms to motor memory consolidation in M1. As such, the first project used single-pulse transcranial magnetic stimulation (TMS) to interfere with M1 activity as participants executed newly learned motor behaviors during a performance asymptote. Results revealed that motor memory formation in M1 was initiated when behaviors were repeating, suggesting that repetition-dependent mechanisms contributed to retention in M1. The second scientific contribution sought to use scalp electroencephalography (EEG) recordings to investigate the electrophysiological manifestations of reward processing over cortical motor areas. Overall, results revealed that increases in beta-band power (20-30 Hz) over contralateral motor electrodes are modulated by reward processing. Although these results did not allow specifically addressing the contribution of reward-based learning mechanisms to consolidation in M1, they nonetheless provide the plausible neural substrates involved in this learning mechanism.

The discussion first sought to integrate these two projects and second to provide an overview of the future perspectives that the two projects have led to. Overall, the proposed research projects mainly revolve around the demonstration of the associations– even maybe causality – between motor memory consolidation in M1, reward processing, beta-band power and dopaminergic activity. Throughout the discussion, working hypotheses as well as the methodological means to test them – ranging from non-invasive brain stimulation to electroencephalography recordings and even to the study of interindividual variations in the expression of dopamine-related genes – are outlined.

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1. Introduction: the importance of motor learning

1.1. The intimate relationship between the brain and motor behaviors

The brain is the generator of all voluntary behaviors. In fact, some experts in neuroscience believe that the core reason biological organisms possess a brain is to interact with the environment via movements (Wolpert, 2013). Although some exceptions can be found – for instance, unicellular organisms (i.e., the bacteria *E. coli* [Sterling and Laughlin, 2015]) or multicellular organisms (i.e., the glass sponge *Rhabdocalyptus dawsoni* [Miller, 2009]) can move and interact with the environment without a brain – this idea seems to hold true across animal species.

However, one problem the brain recurrently encounters when executing movements is the need to adapt and deal with ever-changing environments. Certainly, the incapacity of an organism's central nervous system to adapt to environmental perturbations/threats (i.e., to predators, but also to changing landscape such as strong winds, water, snow, rain, etc.) can result in its extinction (Sterling and Laughlin, 2015). From an evolutionary perspective, this adaptive pressure needed for survival is argued to be the cause that brought the brain to develop intricate plastic capacities to remain flexible enough to adapt and learn movements based on environmental needs (Sterling and Laughlin, 2015). As a result, to subtend increasingly larger behavioral repertoires, the brain grew increasingly complex and sophisticated with the "creation" of specialized neural networks that allow flexible behavior-environment interactions.

Sensory and motor neocortices are known to be markedly developed in mammals as compared to amphibians, reptiles, and birds (Shmuelof and Krakauer, 2011), perhaps because the possible number of interactions of the later with their respective environment is limited (Sterling and Laughlin, 2015). In the case of amphibians, reptiles, and birds, hard-wired encoded behaviors might suffice to ensure their survival (Shmuelof and Krakauer, 2011) and therefore limit their need to develop higher-order brain regions to support flexible adaptation and learning of novel

movements (Sterling and Laughlin, 2015). Hence, it might be that the evolutionary need for increased motor learning capabilities required a more specialized and sophisticated central nervous system, suggesting that there is an intricate and intimate relationship between the brain and motor learning.

1.2. Implications for humans

The intimate relationship between the brain and motor learning makes it hard to truly understand one without the other. Over the last two decades of research, technological advances in neuroimaging techniques now enable neuroscientists to study the relationship between behaviors and their respective neurophysiological underpinnings. Such advances in neuroscience are of tremendous importance for humans because motor learning is a major constituent of quality of life throughout the lifespan; from a child's motor babbling to elderlies' preservation of autonomy, from recreational sport practitioners to high-performance athletes and even from healthy beings to individuals suffering from brain traumas or neurodegeneration of the neuromotor network, understanding the neural bases of motor learning can help improve many people's life.

1.3. Operational definition of motor learning

Motor learning has recently been defined as "a blanket term for any practice-related change or improvement in motor performance for a defined variable of interest" (Shmuelof and Krakauer, 2011), which must manifest as "relatively permanent (i.e., long-lasting) changes in the capability for skilled behavior" (Schmidt and Lee, 2011). Hence, improvements in performance during a training session cannot be considered as motor learning because they cannot be deemed permanent (Soderstrom and Bjork, 2015). Depending on the nature of the task, one should assess performance at least after 6h of wakefulness once the initial training session ended or after a night of sleep (Breton and Robertson, 2014). Doing so would provide a better reflection of the stability and relative permanence of the performance improvements over time. In

conclusion, the terms “motor learning” refers to the relatively permanent changes in behavioral performance.

1.4. Difference between acquisition, consolidation and retention

Motor learning can be divided into three distinct conceptual phases: acquisition, consolidation, and retention. “Acquisition” refers to the initial portion of learning where the neural representation of a novel movement pattern is acquired (Luft and Buitrago, 2005). Once acquired, the neural representations are kept in a labile state within their respective neural networks and are susceptible to interference; for instance, the acquisition of a second movement’s neural representation that competes with the same neural network or the concomitant attempt to consolidate declarative knowledge can both disrupt the consolidation of a novel motor skill (Breton and Robertson, 2014). After a refractory time period of up to 6h (Muellbacher et al., 2002; Della-Maggiore et al., 2017), the neural representation eventually stabilizes and is stored as a memory. “Consolidation” refers to the time-dependent process that stabilizes the neural representation. Retention refers to the persistence of the motor memory, apparent as relatively permanent absolute or relative (i.e., compared to baseline performance during acquisition) behavioral improvements (Schmidt and Lee, 2011). To summarize, a novel motor behavior is first acquired and then consolidated to be retained.

Although these phases are conceptually distinct, neurophysiological data indicate that acquisition and consolidation can overlap (Luft and Buitrago, 2005; Dayan and Cohen, 2011; Hardwick et al., 2013). Acquisition has typically been divided into a fast and slow stage characterized by fast and slow performance improvements, respectively (Luft and Buitrago, 2005; Dayan and Cohen, 2011). Most importantly, depending on the nature of the skill being acquired (i.e., motor skill acquisition or motor adaptation; see section 1.5), the stages can be experienced within a few minutes during motor adaptation or may take up to several months in motor skill acquisition (Dayan and Cohen, 2011). Likewise, the slow stage of acquisition can be experienced a few minutes after the initiation of the practice session to multiple years (Dayan and Cohen, 2011).

Slow performance improvements where behavior has stabilized (i.e., during the attainment of a performance plateau within a given practice session) has been shown to initiate consolidation (Yin and Kitazawa, 2001; Hauptmann et al., 2005; Krakauer et al., 2005; Trempe and Proteau, 2010; Huberdeau et al., 2015), suggesting that the slow stage of acquisition and consolidation share common neural processes that ultimately give rise to retention. Although they should not, consolidation and retention are also terms that can be found to be exchanged with one another, in the motor learning and control literature. Although the proper definition of retention refers to the relatively permanent nature of the behavioral improvements, some studies assess performance gains immediately after the acquisition session ended as a reflection of "retention/consolidation" (Muellbacher, 2002; Galea et al., 2015; Krause et al., 2016; Pollok et al., 2015). Caution should be made when interpreting such findings because it has been shown that short-term and long-term improvements are most likely to be subtended by different neural underpinnings (Della-Maggiore et al., 2017; Kunori et al., 2014; Hosp and Luft, 2013; Dayan and Cohen, 2011; Luft and Buitrago, 2005), suggesting that findings on "immediate retention" does not necessarily apply to "long-term retention". Readers should be aware that the employed vocabulary sometimes lacks uniformity between studies which can add blurriness to their interpretation.

1.5. How is motor learning studied?

Two distinct types of motor learning are often studied: **motor adaptation** and **motor skill acquisition** (Kitago and Krakauer, 2013). In the former, the motor system responds to environmental perturbations initially causing errors in movements. No new movements are acquired per se, but rather a different relationship between the execution of a movement and its perceived consequences. Hence, during motor adaptation, participants seek **to return their performance to baseline level** and do so in a matter of a few to several minutes, making this approach useful in laboratories because "motor learning" can be studied on a short time-scale. The most commonly used tasks in laboratory settings are *visuomotor* and *force-field adaptation,* which respectively employs visual and kinetic (i.e., forces and torques) perturbations (Kitago

and Krakauer, 2013). Daily life examples include adapting gait to snowshoes during winter, adapting vision to a new pair of glasses or even modifying a slap shot technique based on the length of a hockey stick. Motor skill acquisition involves acquiring new patterns of muscle activation to **achieve higher levels of performance than baseline** where movements are executed more quickly, consistently and accurately with practice (Dayan and Cohen, 2011). Daily life examples include learning to ride a bike, to skate or even to play a musical instrument.

2. Psychophysical factors influencing motor learning

2.1. Increasing the amount of practice and motivation to enhance retention

Seeking to enhance performance during acquisition can be futile if what has been acquired cannot be retained. To this purpose, multiple parameters of practice (i.e., its length, its distribution across sessions, the amount of contextual interference, practicing skills as part vs whole, etc.) can be manipulated (Schmidt and Lee, 2011). However, consistent with neurophysiological studies (readers are referred to the sections 3. and beyond), the factors contributing to retention seem to depend more on the amount of practice (Schmidt and Lee, 2011) – and especially on the amount of practice spent at asymptote (Krakauer, 2009) – and on the motivational states of the learner (Wulf et al., 2010a). In the following sections, a global overview of those two psychophysical factors is provided.

2.2. Practicing beyond asymptote improves retention

The amount of practice is often considered as the most important factor contributing to motor learning (Schmidt and Lee, 2011). Schmidt and Lee (2011; p.347) called this the *law of practice*, referring to the idea that the execution of more acquisition trials should result in more learning. In its simplest form, a performance curve can be well modeled by a power or an exponential function, where iterative changes in behavior drive the large improvements early during acquisition (i.e., the fast

stage) and where behaviors repeat as performance stabilizes and reaches asymptote late in acquisition (i.e., the slow stage; Schmidt and Lee, 2011; Smith et al., 2006). Interestingly, psychophysical and computational work argued that the slow stage of acquisition accounts for the amount of long-term retention (Joiner and Smith, 2008; Dayan and Cohen, 2011), which could lead to conjecture that extending practice beyond the attainment of a performance asymptote during acquisition (referred to as "saturation in learning" by Krakauer, 2009) could result in increased retention.

In direct support, studies have shown that extending practice beyond the attainment of asymptote late in acquisition results in increased retention (Yin and Kitazawa, 2001; Hauptmann et al., 2005; Krakauer et al., 2005; Trempe and Proteau, 2010; Huberdeau et al., 2015). For instance, Krakauer et al. (2005) manipulated the amount of acquisition trials while participants had to learn a visuomotor adaptation task and were tested for after-effects (i.e., a measure of the internal model stability [i.e., retention]) either 5 min or 24h after the initial acquisition session. The results revealed that doubling the amount of initial acquisition trials enhanced the magnitude of the short- and long-term after-effects, where the memory traces of the newly acquired behaviors were found to be more resistant to interference. In sum, the amount of retention seems to be influenced by the amount of practice spent during the late stage of acquisition.

2.3. Practice is optimized if learners are motivated

The overall amount of practice could poorly contribute to retention if the "acquisition conditions" (i.e., challenge-point framework; see below) are not adapted to learners (Guadagnoli and Lee, 2004). Most likely, the misadaptation of acquisition conditions can impair the learners' motivational state, where a lack of motivation results in weaker long-term memory storage (Wulf et al., 2010a). To maintain the effectiveness and the engagement of learners over multiple practice sessions, the challenge point framework (Guadagnoli and Lee, 2004) posits that the degree of functional task difficulty must be adjusted to an individual's specific skill level and to its information-processing capabilities to optimize motor learning. Although this

framework seems somehow intuitive, it emphasizes that learners must be actively engaged in practice to facilitate performance at retention tests. Adjusting the difficulty of a practice could very well foster motor learning through enhanced motivation (Wulf et al., 2010a).

It should be noted that other approaches have been reported to enhance motor learning through greater engagement and motivation of learners: observational practice and self-controlled practice conditions (Wulf et al., 2010a). Observational practice usually occurs in dyad, where one learner observes the other as he practices and vice versa. In addition to optimizing time and available resources, the combination of observational practice with physical practice enhances retention (Wulf et al., 2010a). Self-controlled practice enhances the effectiveness of training when participants are given some degrees of control over practice conditions (i.e., deciding of feedback frequency, control of assistive devices, the request for additional information, etc.). Including a degree of learner control in practice can facilitate motor learning (Wulf et al., 2010a). In sum, motivation in learners can be enhanced through various means.

2.4. Motivational feedback: a powerful means to enhance retention

Motor learning depends upon the information provided by feedback. In its simplest form, feedback acts as a binary source of information about the performance or the outcome of a movement; either can it point to behaviors that need to be avoided (i.e., upon error commission) or to the ones that need to be repeated (i.e., upon successful movement execution). However, feedback does not merely provide objective information; it also carries a strong motivational content that importantly influences motor learning (Wulf et al., 2010a). Indeed, converging lines of evidence have shown that sources of augmented feedback that possess a motivational nature can provide additional guidance as to the behaviors to avoid or repeat by increasing the salience of feedback information; such impacts on motor learning have been reported for positive or negative social-comparative feedback (Lewthwaite and Wulf, 2010; Wulf et al., 2010b, 2014, 2017; Pascua et al., 2015) and monetary reward and punishment delivery based upon participants' accurate or inaccurate motor

performance (Abe et al., 2011; Dayan et al., 2014; Gajda et al., 2016; Galea et al., 2015; Hasson et al., 2015; Manley et al., 2014; Palminteri et al., 2011; Quattrocchi et al., 2017; Song and Smiley-Oyen, 2017; Steel et al., 2016; Wächter et al., 2009; Widmer et al., 2016).

Social-comparative feedback refers to the comparison of a learner's performance with an average (normative) performance score – *either real or bogus* – during motor learning (Wulf et al., 2010a). Multiple studies have shown that when learners are led to believe that their veridical performance during motor skill acquisition is consistently above an average score, retention is enhanced (Lewthwaite and Wulf, 2010; Wulf et al., 2010b, 2014, 2017; Pascua et al., 2015). For instance, Lewthwaite and Wulft (2010) had participants stood on a stability platform where the objective was to keep the platform in the horizontal position for as long as possible and they assessed retention 24h later. Importantly, their individual scores during acquisition were compared to a false normative average; scores were either veridical for a control group or manipulated to remain consistently above or below a false average for the better and worse group, respectively. During both acquisition and retention, the better group showed enhanced short-term performance and retention, respectively, as compared to both the worse and control groups. These results show that positive external feedback can facilitate both acquisition and retention of a novel motor skill.

Similar findings have been observed when monetary rewards (i.e., + 0.05 $) or punishments (i.e., - 0.05 $) are delivered based on accurate and inaccurate performance during the acquisition of a new motor behavior, respectively (Abe et al., 2011; Dayan et al., 2014; Gajda et al., 2016; Galea et al., 2015; Hasson et al., 2015; Manley et al., 2014; Palminteri et al., 2011; Quattrocchi et al., 2017; Song and Smiley-Oyen, 2017; Steel et al., 2016; Wächter et al., 2009; Widmer et al., 2016). Globally, monetary rewards are found to enhance retention (when assessed either immediately or 24h later; Abe et al., 2011; Dayan et al., 2014; Galea et al., 2015; Hasson et al., 2015; Manley et al., 2014; Palminteri et al., 2011; Quattrocchi et al., 2017; Song and Smiley-Oyen,

2017; Widmer et al., 2016), whereas monetary punishments have been found to foster short-term performance during acquisition (Wächter et al., 2009; Galea et al., 2015; Song and Smiley-Oyen, 2017; Steel et al., 2016). For instance, Galea et al. (2015) provided monetary rewards or punishments depending on task performance while participants acquired a novel upper limb reaching movement pattern. Compared to a control group receiving no monetary feedback, participants receiving monetary rewards following accurate performance showed improved short-term retention (i.e., assessed immediately after acquisition) but not improved short-term performance of the new movement pattern (see however Dayan et al., 2014; Gajda et al., 2016; Song and Smiley-Oyen, 2017; Quattrocchi et al., 2017 for conflicting results). Furthermore, participants receiving monetary punishments following inaccurate performance presented more rapid performance adjustments during acquisition but not improvements of short-term retention. Overall, these results suggest that monetary feedback adds to motor performance feedback and acts as a catalyst to promote motor learning.

2.5. Is retention only a function of repetition in behaviors and motivation?

A straightforward answer would be "most likely not" because retention seems to depend upon the nature of the tasks, that is whether the task has dominant motor or cognitive components (Lage et al., 2015). In tasks requiring more motor than cognitive engagement (i.e., sensorimotor adaptation, 100-meter sprints, Olympic weightlifting, etc.), caudal brain regions – that plan and execute motor behaviors – are mainly responsible for performance levels and motor memory formation (Lage et al., 2015). As argued in the previous sections, retention in these brain regions is likely to be a function of repetition at asymptote (Hamel et al., 2017) and motivation (i.e., through dopaminergic activity; Hosp and Luft, 2013), as well as their interaction (Mawase et al., 2017). In sum, if acquired motor abilities or practice sessions focus on motor components, then it is most likely that learners will benefit from extended repetitions and increased motivation.

However, in tasks where cognition dominates over motor components (i.e., jazz music artists during improvisation, most of team sports; hockey, soccer, football, etc.), motivation will still positively influence learning (Wulf et al., 2010a), whereas repetition will not necessarily benefit retention (Schmidt and Lee, 2011). When cognition dominates over motor components, it has repeatedly been shown that high levels of contextual interference will benefit retention (Schmidt and Lee, 2011). This may be because rostral brain regions (Lage et al., 2015) – such as the orbitofrontal, mid-frontal or dorsolateral prefrontal cortices – mediate cognitive computations and could regulate motor caudal regions in a top-down manner (Euston et al., 2012; Narayanan et al., 2013; Scangos et al., 2013; Miyachi et al., 2005, 2013). In support, Scangos et al. (2013) found that the neurons located in the medial wall of the prefrontal cortex (i.e., the supplementary and pre-supplementary motor areas) contain evaluative signals directly related to the mismatch between the intended and actual outcome (i.e., a reward prediction error [RPE]), which Narayanan et al. (2013) have found to directly mediate behavioral adjustments in response to errors within the primary motor cortex (M1). Hence, a likely possibility is that improving the ability to achieve top-down control over motor behaviors through practice in high levels of contextual interferences could subtend the classically observed retention improvements (Kantak et al., 2010; Schmidt and Lee, 2011). In sum, extending practice beyond asymptote may not improve retention if learners need to strategically adjust their behaviors in high contextual interference contexts.

3. Research problems

Although the above behavioral evidence converges on the idea that extending practice after asymptote and that the delivery of positive motivational feedback can both enhance retention, the underlying neural bases remain poorly understood in humans. Animal studies have provided a great deal of insight as to how motor

memories form and reviewing those findings is critical to understand how it might occur in humans. In this light, the next section provides an overview of the brain regions, the cellular and the learning mechanisms that subtend motor memory formation during motor skill acquisition.

3.1. The basic functional units: the neurons

All of the following information comes from Guyton and Hall (2011) and Kandel et al. (2000). Because the brain is the source of all behaviors, improvements, and retention of motor performance must translate into plastic changes in the brain's structure. The smallest functional unit subtending plastic changes are the neurons, where they interact with each other by transmitting action potentials via synapses. Regardless of the neuron size and shape, information signaling in neurons is organized in the same way and can be modeled as having four functional components: (1) an input region (i.e., entry of action potential information via dendrites on the post-synaptic neurons), (2) a trigger function (i.e., converging excitatory inputs eventually overcome the membrane potential threshold which triggers the release of a nerve action potential), (3) conduction capacities (i.e., transmission of the action potential along the membrane of the dendrites, the soma and the axon), and (4) an output region (i.e., transmission of action potential information via the synaptic boutons from a pre- to a post-synaptic neuron).

Nerve action potentials are the result of a transient unequal distribution of electrical charges around the neuron membrane where the intracellular space briefly becomes more positive than the extracellular space. At rest, a polarized neuron has a more negative intracellular electrical charge than the extracellular space surrounding it (i.e., a difference of ~ 60 to 70 mV). Once a neuron receives sufficient excitatory inputs, depolarization occurs through the rapid opening of voltage-gated Na^+ channels (i.e., at about ~55 mV) along the neuronal membrane, which allows Na^+ ions to diffuse from the extracellular to the intracellular space. In turn, the intracellular entry of Na^+ ions causes a positive increase in the net intracellular electrical charge (from ~ -55 mV to

+50 mV). Before polarization is restored by K^+ ions efflux to the extracellular space, this brief increase in intracellular electrical potential causes a chain reaction where the neighboring voltage-gated Na^+ channels open, causing the action potential to travel along the membrane from a neuron's post- to pre-synaptic terminals.

To propagate from a neuron to another, action potentials must be transmitted through synapses. Almost all of the synapses in the human central nervous system are chemical and allow the regulation of the synaptic weight attributed to action potential information by either blocking (i.e., inhibition) or facilitating (i.e., excitation) the transmission of action potentials. Once an action potential reaches pre-synaptic terminals, it causes the secretion of neurotransmitters in the synaptic cleft that act on receptor proteins in the membrane of the post-synaptic neurons. Neurotransmitters determine the sensitivity of the post-synaptic neuron to a given input, either by activating inhibitory or excitatory receptor proteins.

In motor learning, the most studied neurotransmitters include glutamate, gamma-Aminobutyric acid (GABA; Kida and Mitsushima, 2017) and dopamine (DA; Hosp and Luft, 2013), whereas the most studied receptor proteins include D1- and D2-type dopamine receptors (Hosp and Luft, 2013), N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors (Kida and Mitsushima, 2017).

3.2. The neural substrates of motor memory formation

Although no formal definition of "what is a motor memory" has been given yet, from a neurophysiological standpoint, motor memories could be defined as the brain plastic changes in the neural networks that subtend the lasting improvements of a given behavior. Motor memories are likely embedded in a widely distributed neural network which is mainly comprised of M1, dorsal premotor cortex (PMd), somatosensory cortex (S1), posterior parietal cortex (PPC), basal ganglia, and cerebellum (Doyon et al., 2009; Hardwick et al., 2013; Penhune and Steele, 2012; Della-Maggiore et al., 2017). Although one could also expect the plastic changes to occur in all of the above

brain regions, many studies have devoted attention to M1 because it is considered as a key motor region in both movement execution and memory formation (Della-Maggiore et al., 2017; Gabitov et al., 2014, 2015; Galea et al., 2011; Hadipour-Niktarash et al., 2007; Hayashi-Takagi et al., 2015; Kantak et al., 2010; Karni et al., 1995, 1998; Landi et al., 2011; Mandel-Blat Cerf et al., 2011; Manto et al., 2006; Mawase et al., 2017; Muellbacher et al., 2001, 2002; Overduin et al., 2009; Paz et al., 2003, 2005; Richardson et al., 2006, 2012; Rroji et al., 2015; Wise et al., 1998; Yu and Zuo, 2011; Fu et al., 1993, 1995; Sosnik et al., 2014; Stark et al., 2007; Li et al., 2015). Because plastic changes in M1 have been heavily studied, the following sections will provide a comprehensive overview of their contribution to retention.

3.3. The plastic changes in M1 induced by motor memory formation

The plastic changes induced by acquisition that are involved in M1 motor memory formation are diverse (Dayan and Cohen, 2011). However, they mainly involve the reconfiguration and the strengthening of synaptic connections between single neurons or neuronal populations during acquisition, which occur through synaptogenesis (Kleim et al., 2004; Yu and Zuo, 2011; Fu and Zuo, 2011; Fu et al., 2012; Rogerson et al., 2014) and dendritic spine formation and clustering (Xu et al., 2009; Yang et al., 2009, Rogerson et al., 2014; Hayashi-Takagi et al., 2015). Moreover, plastic changes also include increases in grey (Landi et al., 2011; Taubert et al., 2016) and white matter (i.e., axon myelination; Zatorre et al., 2012; Fields, 2005) as well as genesis of oligodendrocytes (Xiao et al., 2016) and astrocytes (Ota et al., 2013). Although increases in cerebrovasculature through angiogenesis have only been observed in the cerebellum (Black et al., 1990; Isaacs et al., 1992), it could also be conjectured that M1's capillary density could also increase due to the reorganization of the metabolic demands induced by the above plastic changes (Picard et al., 2013; Reber, 2013).

In light of the present literature, the initial neural events from which M1 plastic changes arise remain unclear (see section 3.4. for a description of early and late cellular

changes induced by Hebbian forms of learning at the synaptic level), one possibility is that they are first initiated by increases in corticospinal excitability (Bagce et al., 2013; Manto et al., 2006) and in changes of directional tuning of neuronal population (Wise et al., 1998; Paz et al., 2003, 2005; Mandel-Blat Cerf et al., 2011) during acquisition. These initial events could then induce changes in the expression of cellular receptors such as NMDA and AMPA-type glutamate receptors (Dayan et al., 2013; Volianskis et al., 2015), as well as changes in specific neurotransmitter activity such as glutamate (Kunori et al., 2014), GABA (Kida and Mitsushima, 2017) and DA (Hosp and Luft, 2013). Studies have also reported changes in learning-related genes (Hosp et al., 2013; Hertler et al., 2016; Diaz Heijtz and Forssberg, 2015; Cheung et al., 2013) and in the synthesis of learning-related proteins (Luft et al., 2004; Kleim et al., 2003) during or shortly after acquisition.

3.4. Long-term potentiation for motor memory formation

The most widely accepted cellular model for learning and memory is long-term potentiation (LTP; Nicoll and Roche, 2013). LTP is a form of synaptic plasticity where activity in neurons gives rise to an increase in synaptic strength that persists in a relatively permanent manner, ranging from many minutes (i.e., early LTP), to hours and days (i.e., late LTP; Abbas et al., 2015; Amtul and Atta-Ur-Rahman, 2015). Interestingly, there is now causal evidence that LTP is responsible for memory formation (Nabavi et al., 2014), which suggests that LTP might also be at play during motor learning.

Globally, the LTP-like plasticity subtending memory formation and task-related improvements are mostly dependent on the post-synaptic activation of NMDA receptors, intracellular entry of Ca^{2+}, activation of AMPA-type glutamate receptors as well as gene expressions and protein synthesis (Volianskis et al., 2015; Amtul and Atta-Ur-Rahman, 2015). More precisely, LTP occurs when the summation of potentials at the post-synaptic neuron is sufficient to remove the Mg^{2+} block from NMDA receptors, allowing intracellular entry of Ca^{2+} (Volianskis et al., 2015). Although Ca^{2+} can also

induce changes in the pre-synaptic neuron (Klomjai et al., 2015), post-synaptic intracellular entry of Ca^{2+} triggers both the activation of AMPA-type glutamate receptors and changes in the neuron morphology.

Referred to as *early LTP*, the expression of additional AMPA-type glutamate receptors on post-synaptic terminals is thought to be the main underlying mechanism subtending the increase in synaptic strength (Kida and Mitsushima, 2017; Amtul and Atta-Ur-Rahman, 2015) because action potential transmission between two glutamatergic neurons becomes facilitated. Referred to as *late LTP*, the intracellular entry of Ca^{2+} ions within the post-synaptic neuron also triggers gene expressions and protein synthesis (i.e., growth factor), which is necessary for synaptogenesis and dendritic spine formation (Amtul and Atta-Ur-Rahman, 2015).

Although the actual contribution of LTP-like plasticity to motor learning remains unknown, studies investigating the cellular mechanisms involved in M1 memory formation converge on the idea that two main learning mechanisms contribute to consolidation through LTP-like plasticity: (1) repetition-dependent mechanisms (i.e., referred to as use-dependent plasticity or Hebbian plasticity; Kida and Mitsushima, 2017) and (2) reward-based mechanisms that depend upon DA activity (Hosp and Luft, 2013). Although these two mechanisms likely interact together during motor memory formation (Mawase et al., 2017; Zhang et al., 2009; Ruan et al., 2014), these two learning mechanisms will be treated separately in the following sections.

3.5. LTP-like plasticity induced by repetition of behaviors

One way LTP-like plasticity can be induced is via use-dependent plasticity which refers to the enhanced synaptic efficacy and plastic changes induced by the repeated execution of a given behavior (Nudo et al., 1996; Classen et al., 1998; Bütefisch, 2000, 2004), likely occurring through Hebbian forms of learning (Hebb, 1949). Use-dependent activation of a movement neural representation has been shown to enlarge somatotopic movement representations in M1 (Nudo et al., 1996), to lead to increased corticospinal excitability (Classen et al., 1998; Mawase et al., 2017), and is

also thought to lead to motor memory formation (Bütefisch et al., 2004). An important feature of use-dependent plasticity is that acquisition of a novel movement has to occur in order to enhance corticospinal excitability; repeating movements for the sake of repeating does not seem to lead to enhanced corticospinal excitability (Mawase et al., 2017). Despite the transient nature of the increase in corticospinal excitability, this phenomenon has classically been regarded as the initial changes leading to LTP-like plastic changes in M1 (Classen et al., 1998; Manto et al., 2006).

At the neuronal level, animal work has shown that increases of corticospinal excitability are mediated by the glutamatergic projections of the ventral tegmental area (VTA) towards M1 (Kunori et al., 2014), resulting in a push-pull between increases in glutamate-mediated neuronal excitability and decreases in gamma-Aminobutyric acid (GABA)-mediated neuronal inhibition in M1 neuronal layers II/III (Kida and Mitsushima, 2017). Use-dependent plastic changes prominently manifest in synaptic reorganization within the neuronal layer V of M1 (Paz et al., 2009) where the strengthened synaptic connections allow the evolving movement representation during acquisition to be stored as a memory (Masamizu et al., 2014).

At the synaptic level, repeated execution of motor behaviors promote synaptogenesis through dendritic spine formation and clustering within M1 pyramidal neurons (Fu and Zuo, 2011; Yu and Zuo, 2011; Fu et al., 2012; Rogerson et al., 2014; Xu et al., 2009; Yang et al., 2009; Hayashi-Takagi et al., 2015). Interestingly, these newly formed dendritic spines are preferentially stabilized during prolonged training and are maintained long after training ended (Xu et al., 2009; Yang et al., 2009), suggesting that this specific type of synaptic plasticity is essential for use-dependent memory formation.

Although there is considerable evidence *suggesting or demonstrating* that use-dependent plasticity contributes to retention (Classen et al., 1998; Bütefisch, 2000, 2004; Mawase et al., 2017; Leow et al., 2014; Hirano et al., 2015; Gabitov et al., 2014, 2015, Rroji et al., 2015), one overlooked matter is the relationship that use-dependent

plasticity has with the early (i.e., fast) and late (i.e., slow) stages of acquisition. Because behaviors tend to repeat during the late stage of acquisition, M1 could likely initiate motor memory formation when asymptotic performance is reached (Hirano et al., 2015).

3.6. Converging to a hypothesis-driven research question on repetition-dependent mechanisms

Direct causal evidence demonstrating that repetition in behaviors during the late stage of acquisition is a direct contributor to long-term motor memory formation within M1 has yet to be provided. Thus, the first project of the present document sought to test the hypothesis that the human M1 causally contributes to retention when newly acquired behaviors reach asymptotic performance during acquisition.

3.7. Rewards and motivation potentiate LTP-like plasticity

The obtainment of a pleasant stimulus (i.e., a reward) or a stimulus of high motivational value can both trigger the release of DA within M1 during motor acquisition (Hosp and Luft, 2013), which reinforces the repetition of successful behaviors (Krakauer and Mazzoni, 2011) and potentiates Hebbian forms of learning (i.e., spike-timing-dependent plasticity [STDP]; Zhang et al., 2009; Ruan et al., 2014). During motor learning, DA is mostly released in M1 from VTA-M1 DA projections; about 73% of DA projections stem from the VTA and about 12% from the substantia nigra (Hosp and Luft, 2013). Based on the current evidence from the field of motor learning, DA is critical for motor memory formation in M1 because it enhances LTP-like plasticity by improving the regulation of spine dynamics (i.e., spine elimination and formation) and by inducing learning-relevant protein synthesis (i.e., c-fos), which ultimately leads to a stabilization of the synaptic movement representation (Hosp and Luft, 2013; Guo et al., 2015). Overall, DA leads to an overall strengthening of M1 synaptic connections between its neuronal layers (Hosp and Luft, 2013; Yagishita et al., 2014).

Interestingly, the enhancement of LTP-like plasticity through DA in M1 involves the activation of D1- and D2-type receptors (Molina-Luna et al., 2009; Hosp et al., 2009, 2011; Vitrac et al., 2014; Guo et al., 2015; Rioult-Pedotti et al., 2015), which suggests that additional cellular mechanisms than the ones involved in repetition-dependent mechanisms. Globally, when DA binds with D1 or D2 receptors, a greater number of Ca^{2+} ions enter the postsynaptic neuron (Chen et al., 2007; Hasbi et al., 2010), which could then potentiate use-dependent plastic changes (Kida and Mitsushima, 2017). In support, reward signals have been shown to potentiate use-dependent plasticity in M1 during acquisition (Mawase et al., 2017) and DA has been shown to potentiate Hebbian-like plasticity within the striatum (Yagishita et al., 2014). Hence, one possibility is that LTP-like plastic changes during motor acquisition result from the interaction between repeating motor behaviors (i.e., Hebbian learning) and rewards/motivation (Zhang et al., 2009; Ruan et al., 2014).

3.8. Converging to a hypothesis-driven research question on rewards and motor areas

Although the effects of DA on LTP-like plasticity within M1 have been documented in animals, whether DA indeed reaches M1 to trigger plastic changes upon reward delivery remains unknown in humans. In fact, there are reasons to believe that results from rodent studies might not apply to humans because there are substantial differences in the way the dopaminergic system is anatomically and functionally organized between these two species (Björklund and Dunnett, 2007a). As a result, it appears that the field of motor control and learning remains clueless as to whether DA indeed reaches human cortical motor areas – upon reward delivery – to potentiate plastic changes.

In humans, there is currently no evidence demonstrating that reward delivery influences neuronal activity within motor areas during a motor task. Seeking for evidence of reward processing in human motor areas appears as the first logical step to be taken before studies can address the possibility that reward signals – potentially under the form of DA releases – indeed reach motor areas to enhance motor

consolidation processes. Hence, in this light, the second research project of the present thesis used electroencephalography (EEG) recordings to test the hypothesis that reward processing influences neuronal activity over motor areas (potentially including – but not solely restricted to – M1) during the execution of upper limb reaching movements.

4. Conceptual framework of the first scientific contribution

4.1. Using single-pulse transcranial magnetic stimulation (TMS) to demonstrate the causal contribution of repetition-dependent mechanisms in M1 to motor memory formation

TMS is a non-invasive brain stimulation technique in which a strong current is quickly released through a coil that is placed against the scalp. The coil current generates a brief magnetic pulse that is used to non-invasively cross the skull and to induce an electrical field within a relatively focal targeted brain region (Dayan et al., 2013; Neggers et al., 2015). With high temporal and spatial resolutions, the induced electrical field disrupts ongoing neuronal activity by forcing depolarization in the neurons and axons it crosses (Neggers et al., 2015), which alters local information processing by adding noise in neuronal activity. At the cellular level, the single-pulse TMS-induced electrical fields are known to affect the 6 layers of the cortical grey matter if the orientation of the coil is perpendicular to their geometric orientation (Klomjai et al., 2015; Neggers et al., 2015). Although many efforts are devoted into understanding the biophysical effects of single-pulse TMS on brain tissue (Neggers et al., 2015), the disruptive nature of single pulses of TMS on neuronal information processing and, most importantly, their effects on plastic changes still remain elusive.

Of interest, one likely possibility is that single-pulse TMS can disrupt ongoing LTP-induced plastic changes, which is supported by a recent study showing that single-pulse TMS has a net suppression on dendritic activity in S1 (Murphy et al., 2016). More specifically, Murphy et al. (2016) found that TMS directly activates fibers within the upper neuronal layers, leading to the activation of dendrite-targeting GABA-mediated inhibitory neurons projecting to S1 pyramidal neuron layer V. The activation of these inhibitory neurons suppressed S1 dendritic activity, thereby providing a possible framework through which single-pulse TMS can inhibit LTP-induced synaptogenesis and dendritic spine formation and clustering. In light of the above framework on how LTP induces plastic changes, the results from Murphy et al. (2016) can lead to

conjecture that the LTP-dependent synaptic storage of motor memory within neuronal layer V could also be disrupted if TMS is applied over M1.

In support to this idea, Hadipour-Niktarash et al. (2007) used single-pulse TMS over M1 to demonstrate that short-term retention is dependent upon M1 immediate post-movement neuronal activity during the acquisition of novel upper limb movement patterns, suggesting that single-pulse TMS can indeed be used as a tool to disrupt plasticity within M1. Overall, a causal contribution of M1 to long-term motor memory formation could be revealed by using single-pulse TMS over M1 during the late stage of acquisition (to disrupt use-dependent plasticity), if applied immediately after movement end.

4.2. Published article in the *Journal of Neuroscience*

N.B. See section 8.1. for the authors' authorization to include this article in the present thesis.

Disruption of M1 activity during performance plateau impairs consolidation of motor memories

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Abstract

Upon exposure to a new sensorimotor relationship, motor behaviors iteratively change early in adaptation, but eventually stabilize as adaptation proceeds. Behavioral work suggests that motor memory consolidation is initiated upon the attainment of asymptotic levels of performance. Separate lines of evidence point to a critical role of the primary motor cortex (M1) in consolidation. However, a causal relationship between M1 activity during asymptote and consolidation has yet to be demonstrated. The present study investigated this issue in male and female participants using single-pulse transcranial magnetic stimulation (TMS) to interfere with post-movement activity in M1 in two behavioral phases of a ramp-and-hold visuomotor adaptation paradigm. TMS was either provided after each trial of the ramp phase of adaptation - when a gradual increase in the visuomotor rotation caused movements to be changing - or after each trial of the hold phase of adaptation - when the rotation was held constant and movements tended to stabilize. Consolidation was assessed by measuring performance on the same task 24h later. Results revealed that TMS did not influence adaptation to the new visuomotor relationship in either condition. Critically, however, TMS disruption of M1 activity selectively impaired consolidation of motor memories when it was provided during the hold phase of adaptation. This effect did not take place when TMS was delivered over adjacent dorsal premotor cortex (PMd) or when motor behaviors in late adaptation were prevented from plateauing. Together, these data suggest that the impaired consolidation stemmed from interference with mechanisms of repetition-dependent plasticity in M1.

Significance Statement

The present work demonstrates that TMS disruption of M1 activity impairs the consolidation of motor memories selectively when performance reaches asymptotic levels during sensorimotor adaptation. These findings provide evidence for a causal contribution of M1 to motor memory formation when movements tend to repeat, likely through mechanisms of repetition-dependent plasticity.

Introduction

Sensorimotor adaptation usually progresses through two typical phases. Upon initial exposure to a perturbation, errors drive the iterative updating of descending motor commands, causing movements to be gradually changing. Ultimately, with practice and feedback, motor performance improves and eventually stabilizes at a plateau.

Once acquired, the memory representation of a novel sensorimotor relationship is kept in a labile state before it is stored into long-term memory (Shadmehr and Holcomb, 1997; Krakauer et al., 2005). This is thought to occur through a time-dependent process called "consolidation". Evidence suggests that consolidation is initiated when performance reaches asymptotic levels during adaptation (Yin and Kitazawa, 2001; Hauptmann et al., 2005; Krakauer et al., 2005; Trempe and Proteau, 2010). For instance, Yin and Kitazawa (2001) showed that 250 trials of visuomotor adaptation yielded no significant aftereffects 24h later, whereas 250 additional trials of the same task led to persistent aftereffects. Given that performance had already plateaued by the 250th trial, the authors argued that additional repetitions of the stabilized behavior was critical to trigger consolidation. A similar finding was reported by Krakauer et al. (2005), whereby a newly learned visuomotor relationship became resistant to interference from a counter perturbation only in a condition in which an extensive period of training at asymptotic levels had occurred.

While neural plasticity associated with sensorimotor adaptation is broadly distributed (Doyon and Benali, 2005; Lalazar and Vaadia, 2008; Shadmehr et al., 2010), converging lines of evidence point to a critical role of the primary motor cortex (M1) (Richardson et al., 2006; Hadipour-Niktarash et al., 2007; Overduin et al., 2009; Galea et al., 2011; Della-Maggiore et al., 2015). For instance, Richardson et al. (2006) used repeated transcranial magnetic stimulation (rTMS) to disrupt M1 processing before force field adaptation. They showed that rTMS led to lower performance when re-tested 24h later, arguing that M1 would be critical for initiating the development of motor memories [see also Muellbacher et al. (2002) for a similar finding using a finger motor skill learning task]. Consistent with this, Hadipour-Niktarash et al. (2007)

applied single-pulse TMS over M1 at the end of every trial of a visuomotor adaptation protocol. They found that TMS led to a faster rate of forgetting during immediate de-adaptation, suggesting a more fragile memory trace.

While the preceding studies established a link between M1 and consolidation, they could not address whether its contribution differed between the early and late phases of adaptation. This is attributable in part to the fact that the neuromodulation techniques used (i.e. rTMS or tDCS; Muellbacher et al., 2002; Richardson et al., 2006; Overduin et al., 2009; Galea et al., 2011) induce changes in cortical excitability that outlast the stimulation period and persist for extended periods of time (Hallet, 2007). Hence, their influence on M1 could not be specifically constrained to the early or the late phase of adaptation. In this regard, accumulating evidence suggests that M1 undergoes structural changes predominantly when motor performance tends to plateau (Wise et al., 1998; Paz et al., 2003, 2005; Orban de Xivry et al., 2011; 2013). For instance, M1 neurons modulate their task-related firing activity mainly in the late stage of visuomotor adaptation, possibly reflecting the initiation of motor memory consolidation (Wise et al., 1998; Paz et al., 2003, 2005). Similarly, M1 cortiocospinal excitability is modulated during force field adaptation only in perturbation schedules that allow movements to stabilize at a plateau, which might be key for producing M1 plasticity (Orban de Xivry et al., 2011, 2013).

Together, these results point to a greater contribution of M1 to consolidation when motor performance reaches a plateau. However, a causal relationship between consolidation and M1 activity during asymptote has yet to be demonstrated in humans. In this light, the present work assessed consolidation by measuring reaching performance ~24h after exposure to a novel visuomotor relationship. A ramp-and-hold adaptation paradigm was used so that movements were either iteratively changing during the ramp phase (i.e., early in acquisition) or plateauing during the hold phase (i.e., late in acquisition). To probe the causal contribution of M1 to memory consolidation in the early or the late phase of adaptation, single-pulse TMS was used to interfere with M1 processing at the end of every movement of either the ramp phase or the hold phase of adaptation. It was hypothesized that disruption of M1 activity

would impair consolidation to a greater extent when applied during the hold phase as compared to the ramp phase. TMS was also delivered over adjacent dorsal premotor cortex (PMd) to act as a spatial control site.

Materials and Methods

Participants

Eighty-three healthy participants (22.1 ± 2.7 years, 44 females) with no self-reported neurological or psychiatric condition took part in the experiment. They were all self-declared right-handed with normal or corrected-to-normal vision. Participants provided written informed consent for their participation in the study. They were naive as to the purpose of the experiment and had no prior experience with the task. All received a monetary compensation of 20 $ CAD for their participation in the study. Experimental procedures were approved by the ethical committee of the Centre Hospitalier de l'Université de Sherbrooke (CHUS). One participant was excluded from all analyses for not following the experimental procedures.

Apparatus

The experimental setup consisted of a table supporting a computer monitor which projected visual stimuli on a mirror positioned horizontally in front of participants (Figure 1A). The monitor (20-inch Dell P1130; resolution: 1024 x 768; refresh rate: 150 Hz) was mounted face down 29 cm above the horizontal mirror and the mirror was mounted 29 cm above the table. Thus, the visual stimuli appeared to be projected directly onto the surface of the table on the same plane as the hand. Because of the mirror, participants could not see their hand. A 2-joint planar manipulandum was placed on the table and was held by participants via a stylus located at its mobile end. The manipulandum was custom-built with 2 lightweight metal rods (48 and 45 cm for the distal and proximal rods, respectively), with the fixed end attached to the upper left corner of the table. A thin sheet of smooth plastic covered the table surface and foam pads were installed under the hinges, allowing the manipulandum to be moved everywhere on the table with minimal inertia and friction.

Insert Figure 1 approximately here

Two potentiometers positioned in the joints of the manipulandum allowed the measurement of the angle of each segment at 1000 Hz from which the 2D position of the stylus was calculated. Raw kinematic data were spatially smoothed with a Kalman filter to estimate hand position in real time. This information was then used to project a cursor corresponding to participants' hand. The time lag between the measurement of the angles and the projection of the cursor was between 7 and 9 ms, as determined in separate pilot experiment using a high-speed camera (1000 Hz).

Procedures

Participants had to perform center-out reaching movements with their right hand toward one of ten visual targets (Figure 1B). All targets consisted of green circles of 0.5 cm radius. They were positioned along a circular array of 10 cm radius. At the center of the workspace a grey circle of 0.75 cm radius served as the starting point for every trial. It was located 30 cm in front of participants' chest along the midline. The cursor representing the hand position consisted of a red circle of 0.29 cm radius.

To initiate a trial, participants had to bring the cursor into the starting point and remain stationary within its boundary for one second. This prompted the disappearance of the starting point, which indicated the beginning of the trial. After 1.5 seconds, a target was presented, instructing participants to initiate their reaching movement. Target appearance was pseudo-randomized so that each target was presented once every 10 trials (i.e., cycle). Participants were asked to produce straight movements with minimal online corrections in a targeted movement time of 300 ms. This ensured that all participants had a similar speed-accuracy trade-off (Fitts, 1954). Movement end corresponded to when the tangential velocity of the cursor dropped below 0.05 cm/s. Vision of the cursor was provided only during the second half of the movement. Specifically, the cursor appeared once the hand crossed an imaginary 5 cm radius from the starting point. This corresponded to approximately 150 ms into the movement, and thus approximately 150 ms before movement end (see further for the rationale).

The target and final cursor positions remained displayed on the screen for 500 ms after movement completion, after which they disappeared. To limit exposure to the visuomotor rotation during the return to the starting point, the cursor was only provided when it was within an imaginary 1.79 cm radius around the starting point. On average, five seconds separated each trial.

All participants took part in an acquisition session and a retention session carried out on separate days and separated by ~24 hours (Figure 2). The acquisition session began with a familiarization phase allowing participants to learn the spatial and temporal requirements of the task. It consisted of nine cycles (90 trials) in which the mapping between the hand and the cursor was veridical. Then, participants performed 50 cycles (500 trials) over the course of which a visuomotor rotation was introduced between the hand and its corresponding cursor. Over cycles 1 to 25 (250 trials), a counterclockwise (CCW) visuomotor rotation was gradually introduced at a rate of +1° every cycle, up to 25° (hereafter called the "RampAdapt" phase). Then, over cycles 26 to 50 (250 trials), the visuomotor rotation remained constant at 25° (hereafter called the "HoldAdapt" phase). One-minute breaks were provided every 10 cycles to allow participants to rest. Upon completion of the acquisition session, participants were told to resume their daily activities and were invited to come back the next day for the retention session. Importantly, participants were not informed that a visuomotor rotation had been introduced, and none of them became consciously aware of it during the acquisition session, thus excluding the possibly that conscious strategies influenced the results.

Insert Figure 2 approximately here

Consolidation was assessed in the retention session, using three different tests that have been used in the literature. More specifically, participants performed 3 cycles (30 trials) with no visual feedback of the cursor and no endpoint feedback (hereafter called the "NoVision" phase). The persistence of the adapted behavior in absence of corrective visual feedback is thought to reflect the retention/consolidation of motor

memory (Galea et al., 2015). Then, participants performed 3 cycles (30 trials) in which they were re-exposed to the 25° visuomotor rotation (hereafter called the "Re-exp" phase). Participants' capacity to re-acquire the newly learned visuomotor relationship (i.e., savings) is also a reflection of the strength of a motor memory (Smith et al., 2006; Herzfeld et al., 2014). Finally, participants performed 3 cycles (30 trials) in which the mapping between the hand and the cursor was made veridical again (i.e., 0° visuomotor rotation; hereafter called the "De-adapt" phase). The presence of aftereffects in this context is yet another behavioral evidence of motor memory retention/consolidation (Hadipour-Niktarash et al., 2007; Trempe and Proteau, 2010; Landi et al., 2011). It was reasoned that if TMS interfered with consolidation of motor memories, it should lead to differences in each of these tests of retention/consolidation. The main statistical analysis thus exploited data from all of these phases to obtain the most comprehensive assessment of consolidation. Nevertheless, as a confirmatory analysis, performance was also compared across groups using only data from the NoVision phase, which can be taken as the most direct reflection of consolidation without any possible influence of being re-exposed to the visuomotor rotation.

TMS and EMG

To assess the causal role of M1 in the consolidation of motor memories, single-pulse TMS was used to interfere with contralateral (left) M1 activity in either one of two phases: (1) when movements were gradually changing (RampAdapt phase); or (2) when movements were stabilizing (HoldAdapt phase). This was done by creating two separate groups which differed with respect to the phase of the acquisition session in which TMS was delivered. Participants of the RampTMS group (n = 14) received single-pulse TMS over M1 at the end of each movement of the RampAdapt phase (i.e., cycles 1 to 25). Participants of the HoldTMS group (n = 13) received single-pulse TMS over M1 at the end of each movement of the HoldAdapt phase (i.e., cycles 26 to 50). Acting as a control, a third group (NoTMS; n = 14) received no TMS during the

acquisition session. Finally, a fourth group was used to act as a sham and to provide spatial specificity to the results obtained at M1. Specifically, participants of the HoldPMd group (n = 14) received single-pulse TMS over the contralateral (left) PMd at the end of each movement of the HoldAdapt phase. This controlled for the possibility that the TMS effect hypothesized to be observed over M1 might be attributable to current spread from M1 to PMd (Hadipour-Niktarash et al., 2007). This group also controlled for a possible effect of distraction produced by the stimulator during the critical HoldAdapt phase.

A MagStim 200 monophasic stimulator (MagStim Ltd., Whitland, UK) with a 70 mm diameter figure-of-8 coil was used. The coil was placed tangentially to the scalp with the handle pointing backwards at a 45° angle relative to the antero-posterior axis. Coil placement was determined by recording motor evoked potentials (MEPs) of the right first dorsal interosseous (FDI) muscle using surface electromyogram (EMG). The skin was first cleaned with alcohol swabs saturated with 70 % isopropyl alcohol to reduce electrode impedance. The reference electrode was placed on the lateral epicondyle of the right humerus. Prior to the beginning of the acquisition session, single-pulse TMS was delivered to the left M1 to localize the FDI motor "hot spot" (i.e., the site where maximal MEPs were elicited in the FDI at 50 ± 5 % of the maximum stimulator output). The resting motor threshold (RMT) at the motor hot spot was then defined as the minimum intensity required to elicit at least 5 MEPs out of 10 consecutive attempts in the FDI muscle. During the experiment, single-pulse TMS was delivered at 120 % RMT over the left FDI hot spot. The experimenter holding the TMS coil continuously monitored the MEPs in real-time via a computer monitor, ensuring correct positioning of the coil. Although EMG was only recorded for the FDI during the experiment, confirmatory tests were conducted to confirm that the TMS intensity and location used in the experiment also generated potent MEPs in the biceps muscle, a more proximal agonist in the present reaching task. In addition, using similar TMS parameters as used here, Schulze-Bonhage et al. (1998) demonstrated considerable overlap between the cortical areas from which MEPs could be evoked in the FDI and the deltoid, the latter also being recruited in the present task. In this light, the current

stimulation site over the FDI hot spot most likely also influenced proximal arm representations used for reaching.

For stimulation of the left PMd, the coil was positioned 2 cm rostral and 1 cm medial from the left FDI hot spot (Hadipour-Niktarash et al., 2007). This location was based on neuroimaging work demonstrating that PMd is located ~1.5-2.5 cm anterior to the hand area of the motor cortex (Fink et al., 1997; Picard and Strick, 2001). To simulate a coactivation of PMd induced by current spread from TMS over M1, the stimulation intensity over the PMd was reduced to correspond to ~ 90 % of the intensity used over M1 (Gerschlager et al., 2001; Hadipour-Niktarash et al., 2007). This incurred small but discernable MEPs in most participants. Across all participants, mean TMS output power was 52 ± 3 % and 46 ± 4 % over M1 and PMd, respectively.

The delivery of the TMS pulse was time-locked to the end of the movement (i.e., cursor velocity dropping below 0.05 cm/s). This particular timing was chosen because response-specific processing in motor areas has been shown to begin around 150 ms after the onset of a visual stimulus (Ledberg et al., 2007) and has been shown to contribute to short-term retention (Hadipour-Niktarash et al., 2007). Therefore, the delivery of TMS at movement end corresponded to approximately 150 ms after the hand cursor was provided. Importantly, TMS could not disrupt movement kinematics of an ongoing movement since it was provided after its completion (see Orban de Xivry et al., 2011).

Data Reduction

A custom-designed Matlab script (Version R2014a; MathWorks Inc.) was used to display and acquire kinematics and EMG data during the experiment. The cursor position data for each movement was acquired at 1 000 Hz and normalized over the movement time period (0 to 100 %).

To assess whether TMS affected movement kinematics, we first calculated participants' reaction time (RT, i.e., the time between target onset and movement onset), movement time (MT, i.e., the time between movement onset and movement end), time to peak tangential velocity (TtPV, i.e., the time between movement onset

and PV). In addition, we calculated the time between cursor onset and the TMS pulse (TCO-TMS) for participants in the RampTMS, HoldTMS, and PMdTMS groups.

Trials were excluded from all analyses if RT or MT were ±3 standard deviations around each participant's mean or if the absolute distance between the target and cursor endpoint was above 10 cm. Overall, 3 % of the trials were rejected.

Adaptation to the visuomotor rotation was assessed by measuring the hand direction at peak tangential velocity (PV). It was calculated as the angular difference between the reference vector joining the starting point and the target and the vector joining the starting base and the hand at PV. This early kinematic marker (M = 113 ms after movement onset; see results) was chosen because it is considered a reflection of the movement planning process (Carlton, 1992).

The extent to which reach directions changed across trials (hereby called "directional change") in each experimental phase was calculated by computing for each participant the slope of a linear regression using the hand direction at PV data over trials 1-250 (RampAdapt phase) and trials 251-500 (HoldAdapt phase), separately.

Success at achieving the target (hereby called "hit rate") was assessed by calculating the percentage of trials in which the cursor was in contact with the target at the end of the movement [i.e., the distance between the center of the cursor and the center of the target was below the sum of their radii (0.79 cm)]. This was computed over trials 1-250 (RampAdapt phase) and trials 251-500 (HoldAdapt phase), separately.

Statistical Analyses

The first analysis sought to assess whether TMS influenced reach kinematics and adaptation to the new visuomotor relationship during acquisition. This was done by submitting the RT, MT, TtPV, hand direction at PV, directional change and hit rate data to separate 4 Groups (NoTMS, RampTMS, HoldTMS, PMdTMS) x 2 Phases (RampAdapt, HoldAdapt) mixed-effects ANOVAs. To ensure the TMS pulses were delivered at the same time across groups, the TCO-TMS data were submitted to a 3 Groups one-way ANOVA comparing the RampTMS group (using data from the RampAdapt phase, i.e., when these participants received TMS), the HoldTMS group

(using data from the HoldAdapt phase) and the PMdTMS group (using data from the HoldAdapt phase).

The second analysis tested whether TMS influenced consolidation of the new visuomotor relationship. This was done by submitting the hand direction at PV data to a 4 Groups (NoTMS, RampTMS, HoldTMS, PMdTMS) x 3 Phases (NoVision, Re-exp, De-adapt) mixed-effects ANCOVA using the mean hand direction at PV over the last 30 trials of the HoldAdapt phase as a covariate. As a confirmatory analysis, the ANCOVA was also run using only data from the NoVision phase. Mean (*M*) and standard error of the mean (*SEM*) are reported throughout.

Results

To determine whether our experimental manipulation succeeded in creating two distinct phases (i.e., one in which movements were constantly changing and one in which movements stabilized), we compared the directional change in each phase. The analysis confirmed that mean directional change was greater in the RampAdapt phase (M = 0.083 ± 0.001°/trial) than in the HoldAdapt phase (M = 0.008 ± 0.001°/trial), as revealed by a significant main effect of Phase ($F(1, 51) = 2884{,}3$ $p < 0.001$, $\eta_p^2 = 0.98$; see Figure 3A and 3B). There was neither a main effect of Group (p = 0.65) nor an interaction (p = 0.32).

Insert Figure 3 approximately here

The first series of analyses sought to assess whether TMS influenced reach kinematics and adaptation to the new visuomotor relationship during the acquisition session. As can be seen in Figure 4A, the four groups showed a very similar pattern of adaptation during the acquisition session. Namely, the hand direction at PV gradually changed from ~-2° to ~19° in the RampAdapt phase and stabilized at ~21° in the HoldAdapt phase. This is supported by the ANOVA conducted on hand direction at PV which revealed a significant main effect of Phase ($F(1{,}51) = 11\ 741$, $p < 0.001$, $\eta_p^2 = 0.99$), with hand direction at PV being more shifted to the right in the HoldAdapt

phase (M = 20.3 ± 0.2°) as compared to the RampAdapt phase (M = 8.0 ± 0.2°). Most importantly, however, the ANOVA revealed no significant main effect of Group (p = 0.87) and no interaction (p = 0.28), suggesting that the four groups adapted to the new visuomotor relationship to the same extent during acquisition.

Insert Figure 4 approximately here

Separate ANOVAs conducted on RT, MT and TtPV were used to assess a potential influence of TMS on movement kinematics. Results revealed neither a significant main effect nor an interaction for RT (M = 367 ± 3 ms) and TtPV (M = 113 ± 1 ms). However, there was a significant interaction for MT (F(3,51) = 2.9, p < 0.04, η_p^2 = 0.15; M = 315 ± 3 ms). Breakdown of the interaction revealed that MT during the Ramp phase was longer for the NoTMS group (337 ± 9 ms) than for the RampTMS group (300 ± 9 ms). Importantly, there was no significant difference in TCO-TMS between groups (M = 166 ± 2 ms).

As for task success, the ANOVA carried out on the hit rate data revealed a significant main effect of Phase (F(1, 51) = 48.4, p < 0.001, η_p^2 = 0.49), suggesting that participants were significantly more accurate in the HoldAdapt phase as compared to the RampAdapt phase (M = 46 ± 2 % and 38 ± 2 %, respectively). However, there was neither a main effect of Group (p = 0.38), nor an interaction (p = 0.48).

Overall, these results suggest that post-movement TMS provided either in the RampAdapt or the HoldAdapt phase did not disrupt adaptation to the new visuomotor relationship or the movement kinematics and success rates.

The second analysis sought to assess whether TMS provided over M1 in the RampAdapt phase or over M1 or PMd during the HoldAdapt phase influenced the consolidation of the new visuomotor relationship 24h later. The hand direction at PV data across each cycle of the retention session is presented in Figure 4B. As can be seen, participants expressed approximately 1/3 of the adapted behavior in the NoVision condition, with hand directions at PV at ~6º. They then showed a rapid re-adaptation upon re-exposure to the rotation and the reverse effect upon removal of the rotation in

the de-adaptation phase. Most importantly, consistent with the hypothesis, the HoldTMS group showed impaired retention over all three phases as compared to the RampTMS, NoTMS and PMdTMS groups (Figure 4C). This was confirmed by the ANCOVA which revealed a significant main effect of Group ($F(3, 50) = 3.12$, $p = 0.03$, $\eta_p^2 = 0.16$). There was neither a main effect of Phase ($p = 0.5$) nor an interaction ($p = 0.9$). Holm-Bonferroni corrected pairwise comparisons revealed that hand direction at PV for the HoldTMS group (mean across the three phases of 8.4 ± 0.5°) was significantly lower than for the NoTMS group (M = 9.6 ± 0.5°; p = 0.02), the RampTMS group ($M = 9.5 \pm 0.6°$; $p = 0.03$) and the PMdTMS group ($M = 9.4 \pm 0.5°$; $p = 0.04$). No significant difference was observed between the NoTMS, RampTMS and PMdTMS groups (all $p > 0.6$).

As a confirmatory analysis, the ANCOVA was also carried out using only data from the NoVision phase. The pattern of results was the same, with a main effect of Group ($F(3, 50) = 2.79$, $p = 0.049$, $\eta_p^2 = 0.14$), and Holm-Bonferroni corrected pairwise comparisons revealing that the HoldTMS group presented significantly impaired consolidation as compared to each of the other three groups (all $p < 0.05$).

Control Experiment

Results from the main experiment suggest that TMS interfered with the consolidation of motor memories in M1 specifically when performance was plateauing in the HoldAdapt phase. However, an inherent feature of the present protocol is that TMS was delivered over M1 later in the acquisition session for the HoldTMS group than the RampTMS group. Hence it may be that TMS disrupted consolidation not because it was delivered when performance was plateauing, but because it was delivered at the end of the acquisition session. To test that, two additional groups were tested in a control experiment. They were submitted to a perturbation schedule in which visuomotor rotations kept changing both early (i.e., cycles 1 to 25; RampAdapt phase) and late (i.e., cycles 26 to 50; VarAdapt phase) in the acquisition session, thereby preventing performance from plateauing (see Figure 5A). Specifically, during the VarAdapt phase, visuomotor rotations gradually increased to 31° (i.e., cycle 32), then

decreased to 19° (i.e., cycle 44), then increased back to 25° (i.e., cycle 50) at the rate of ± 1° per 10 trials.

A first group ("VarTMS"; n = 14) received single-pulse TMS over M1 at the end of each trial of the VarAdapt phase. It was compared to a second group ("VarNoTMS"; n = 14) which did not receive TMS and thus acted as a control. The hypothesis that TMS over M1 interfered with consolidation specifically because of the performance plateau would be supported if consolidation did not differ between the VarTMS and VarNoTMS groups. This is because TMS would be delivered over M1 in a context in which motor behaviors did not plateau.

Insert Figure 5 approximately here

The same dependent variables were used as in the main experiment, with the exception of the calculation of directional change during the VarAdapt phase. Specifically, directional change was assessed by averaging the absolute values of the slopes of three linear regressions fitted over trials 251 to 320, 321 to 440 and 441 to 500. This was done to capture the perturbation schedule of the VarAdapt phase. A paired t-test comparing the slopes of all participants from the main experiment during the Hold phase and all participants from the control experiment during the VarAdapt phase confirmed that movements were indeed more continuously changing in the control experiment (M = 0.063 ± 0.014°/trial) as compared to the main experiment (0.008 ± 0.006°/trial) ($t(81) = 25.0$, $p < 0.001$; $d = 6.7$).

Results

As can be visually appreciated from Figure 5B, the manipulation of the perturbation schedule was successful in preventing a performance plateau, with motor behaviors continuously changing throughout the course of the acquisition session.

Analysis of the hand direction at PV revealed that the VarTMS and VarNoTMS groups adapted to the new visuomotor relationship to a similar extent. Indeed the ANOVA revealed only a main effect of Phase ($F(1, 26) = 6198.0$, $p < 0.001$, $\eta_p^2 = 0.99$),

with hand direction at PV being significantly more shifted to the right in the VarAdapt phase (M = 20.9 ± 0.3°) as compared to the RampAdapt phase (M = 8.1 ± 0.2°). However, the ANOVA revealed neither a significant main effect of Group (p = 0.28) nor an interaction (p = 0.22). Amongst the other dependent variables (RT, MT, TtPV, TCO-TMS, hit rate), only RT presented a significant main effect of Group during the acquisition session, with the VarTMS group initiating their movements slightly faster than the VarNoTMS group *(*M = 381 ± 10 ms and 412 ± 10 ms, respectively; $p < 0.05$). TCO-TMS in the VarTMS group was 172 ms ± 4 ms.

Most importantly, as can be seen in Figure 5C and 5D, there was no significant difference in consolidation between the VarNoTMS and VarTMS groups (M = 9.8 ± 0.4° and 9.9 ± 0.4°, respectively). This was confirmed by the ANCOVA which revealed no significant main effect of Group ($F(1, 25) = 0.02$, p = 0.88, η_p^2 = 0.001), no main effect of Phase (p = 0.47) and no interaction (p = 0.28). There was also no significant difference across groups when performing the ANCOVA using only trials from the NoVision phase (p = 0.36).

Overall the control experiment confirmed that the impaired retention presented by the HoldTMS group in the main experiment was specifically attributable to the fact that TMS was applied during a performance plateau and not simply because it was delivered late in the acquisition session.

Discussion

In this study, the contribution of M1 to the consolidation of motor memories was investigated in two characteristic behavioral phases of a ramp-and-hold visuomotor adaptation paradigm. Results revealed that TMS did not influence adaptation to the new visuomotor relationship during acquisition, but selectively impaired consolidation when it was provided during the hold phase of adaptation. This effect was specific to M1 as it was not observed when stimulating the PMd. A control experiment further confirmed the critical role of behavioral plateauing, since TMS did not impair consolidation when performance late in acquisition was prevented from plateauing. These findings extend a series of studies that have used neuromodulation

either before (Richardson et al., 2006) or during adaptation (Hadipour-Niktarash et al., 2007; Overduin et al., 2009; Galea et al., 2011; see also Muellbacher et al., 2002) to probe the contribution of M1 to motor memory formation. While these studies all pointed to a role of M1 in consolidation, the present results are the first to specifically attribute the contribution of M1 to the attainment of a performance plateau during visuomotor adaptation. In doing so, they provide causal evidence that processes associated with consolidation are engaged in M1 when performance reaches asymptotic levels.

The present protocol successfully allowed us to manipulate the degree to which movements were repeated across different phases of adaptation, with reach trajectories being more consistent during HoldAdapt as compared to RampAdapt. In this light, the most likely possibility accounting for the present results is that TMS interfered with mechanisms of repetition-dependent plasticity in M1 [also called Use-Dependent Plasticity (UDP) in recent literature]. Indeed, the repetition of movements is believed to strengthen existing neural connections and facilitate the creation of new ones within M1 through long-term potentiation-like mechanisms (Pascual-Leone et al., 1994; Bütefisch et al., 2000). While repetition-dependent plasticity has been well documented for simple finger movements (Classen et al., 1998; Bütefisch et al., 2000; Bütefisch et al., 2004), it has also recently been extended to more complex upper-limb reaching movements and proposed to contribute to sensorimotor adaptation (Diedrichsen et al., 2010; Huang et al., 2011; Verstynen and Sabes, 2011; McDougle et al., 2015). Specifically, the tight distribution of movement trajectories associated with a performance plateau would constitute a key step for the induction of UDP (Huang et al., 2011), biasing reach trajectories toward those converged upon during adaptation (Diedrichsen et al., 2010; Huang et al., 2011; Orban de Xivry et al., 2011, 2013; Verstynen and Sabes, 2011; Leow et al., 2014; Leow et al., 2016). In support, Leow et al. (2014) used anodal transcranial Direct Current Stimulation (tDCS) over M1, a technique known to facilitate synaptic plasticity and increase UDP, while participants adapted to a new visuomotor relationship. They found that it significantly impaired adaptation to a second distinct rotation (i.e., anterograde interference) but only when

the first rotation had been practiced extensively at asymptotic levels. In this light, TMS provided at movement end may have disrupted the direction-dependent memory trace that forms in M1 upon repeated movements (Classen et al., 1998), thus weakening the consolidation of the adapted reach trajectories.

While repetition-dependent plasticity is likely to account for the present results, several considerations should be raised. First, studies investigating UDP in the context of sensorimotor adaptation have used paradigms involving few targets restricted to a narrow area of space (Diedrichsen et al., 2010; Huang et al., 2011; Verstynen and Sabes, 2011; McDougle et al., 2015), unlike the multiple target directions used here. While it is reasonable to conjecture that the UDP mechanisms identified in these previous protocols would also take place for more numerous targets, the degree to which UDP contributes to sensorimotor adaptation when movements in a given direction repeat at a lesser rate remains unknown. Second, although UDP has been shown to exert a transient bias on reach trajectories (Diedrichsen et al., 2010; Huang et al., 2011; Verstynen and Sabes, 2011; McDougle et al., 2015), to our knowledge its influence on the long-term (i.e., 24h) retention of motor memories has not been specifically tested. Still, there is evidence that changes in the directional tuning of M1 neurons, which occur primarily during performance asymptote (Paz et al., 2003), persist across test sessions spanning several days (Mandelblat-Cerf et al., 2011; Richardson et al., 2012). This provides indirect evidence in favor of a contribution of repetition-dependent mechanisms in M1 to long-term memory consolidation. Thirdly, adaptation is sensitive to the type of perturbation schedule, with abrupt and gradual schedules having different contributions of error-based, strategic and repetition-dependent mechanisms (Huang et al., 2011; Taylor et al., 2014; Orban de Xivry and Lefèvre, 2015). While the neural correlates of adaptation to abrupt and gradual perturbations schedules may differ (Muellbacher et al., 2001; Werner et al., 2011; Schlerf et al., 2012), both have been found to produce a stabilized motor memory (Hadipour-Niktarash et al., 2007; Galea et al., 2011). Furthermore, abrupt schedules typically lead to more trials spent at asymptote, which has been shown to favor UDP mechanisms in M1 (Orban de Xivry et al., 2011; Orban de Xivry and Lefèvre, 2015).

Hence, it is likely that the results observed here would generalize to contexts in which a performance asymptote is reached following an abrupt perturbation. Finally, there was no influence of TMS on adjacent PMd (see also Hadipour-Niktarash et al., 2007), although neurons in this region show changes in directional tuning during force field adaptation (Xiao et al., 2006). Given that M1 is certainly not the sole contributor to consolidation (Herzfeld et al., 2014), it will be interesting to investigate repetition-dependent mechanisms in higher-order regions outside of M1.

It is important to note that the presence of a performance asymptote oftentimes correlates with an increased rate of task success. Indeed, as performance improves and movements become more repetitive, participants also tend to receive more frequent rewards (implicit or explicit). This was the case in the present work, as the HoldAdapt phase was associated with higher task success (i.e., hit rates) as compared to the RampAdapt phase. Interestingly, Huang et al. (2011) showed that UDP-induced reach biases are larger when movement repetitions take place within an adaptation paradigm in which movements are directed toward a goal as compared to repetitions alone (Verstynen and Sabes, 2011). They argued that repetitions in the context of reducing errors may itself constitute a reward signal that would modulate the efficacy of UDP. Similarly, recent studies using finger skill tasks have revealed changes in M1 excitability (Bagce et al., 2013) and increased UDP in M1 (Mawase et al., 2017) only in groups who successfully learned the skill as compared to groups that made comparable reaching actions without accumulating learning. In this context, a likely possibility is that repetition-dependent plasticity in the present experiment may have been potentiated by rewards associated with task success during asymptote.

Although the processes underlying consolidation may partly differ between sensorimotor adaptation and the learning of new motor skills (Baraduc et al., 2004; Doyon et al., 2009), the present results are consistent with findings stemming from the motor skill learning literature. Indeed, there is considerable evidence that late stages of learning are associated with increased M1 reorganization (Ungerleider, 2002; Rosenkranz et al., 2007; Masamizu et al., 2014). Importantly, the repetition of movements seems to be the key factor triggering consolidation and M1 reorganization

(Nudo et al., 1996; Karni et al., 1995, 1998; Kantak et al., 2010; Gabitov et al., 2014, 2015; Reis et al., 2015; Rroji et al., 2015). For instance, Kantak et al. (2010) showed that rTMS applied over M1 before training caused an impairment in retention under a constant practice structure but not under a variable practice structure. Similarly, Gabitov et al. (2014) trained participants on a finger-to-thumb opposition task while recording functional magnetic resonance imaging (fMRI) and found that M1 activity upon task repetition constituted a reliable neural signature for motor memory consolidation. Hence, the present work bridges a gap between the sensorimotor adaptation and motor skill learning literatures by showing that movements performed repeatedly during asymptote trigger important synaptic changes in M1.

At the cellular level, there is accumulating evidence that repeated motor experience promotes synaptogenesis and induces functional map reorganization within M1 that directly underlie motor memory formation (Kleim et al., 2004; Manto et al., 2006; Fu and Zuo, 2011; Yu and Zuo, 2011; Fu et al., 2012; Rogerson et al., 2014). Indeed, studies in rodents have demonstrated that motor skill learning leads to the formation and clustering of new dendritic spines in M1 pyramidal neurons (Xu et al., 2009; Yang et al., 2009; Rogerson et al., 2014; Hayashi-Takagi et al., 2015). Furthermore, these newly formed dentritic spines are preferentially stabilized during prolonged training and are maintained long after training is ended (Xu et al., 2009; Yang et al., 2009), suggesting a key role of synaptic structural plasticity in the formation and storage of long-term motor memories. Interestingly, given that single-pulse TMS has recently been shown to have a net suppression effect on dendritic activity of pyramidal neurons (Murphy et al., 2016), it is likely that in the present context TMS impaired consolidation by preventing the normal synaptic reorganization that occurs in M1 upon repeated motor exposure.

Together, our results demonstrate the causal contribution of M1 to the consolidation of motor memories when performance reaches a plateau during sensorimotor adaptation. These results suggest that repetition-dependent mechanisms within M1, possibly in conjunction with reward processing, fosters the long term storage of motor memories.

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Legends

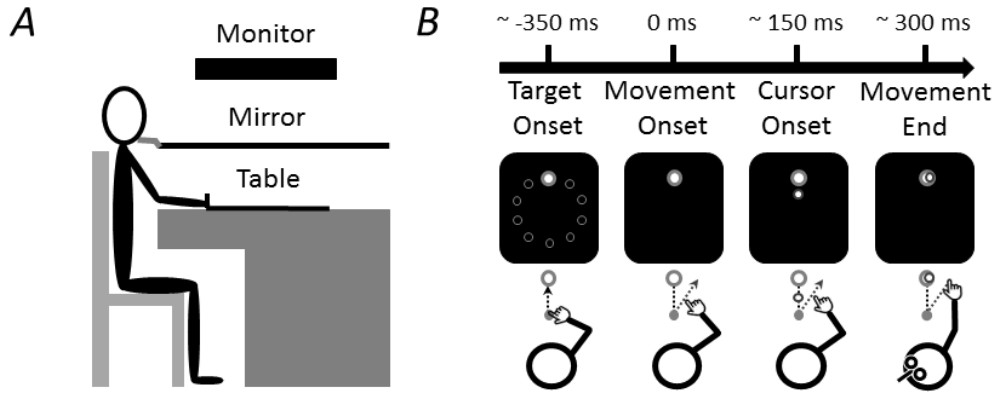

Figure 1. Schematic representation of the apparatus and experimental task. (A) Side view of the apparatus. (B) Chronology of a typical trial. Appearance of one of the ten targets indicated the beginning of a trial (Target Onset). Movement onset corresponded to when the hand left the starting point (Movement Onset). Vision of the cursor was only provided once the hand crossed the halfway point between the starting point and the target (Cursor Onset). The delivery of the TMS pulse over the left M1 was triggered at movement completion (Movement End).

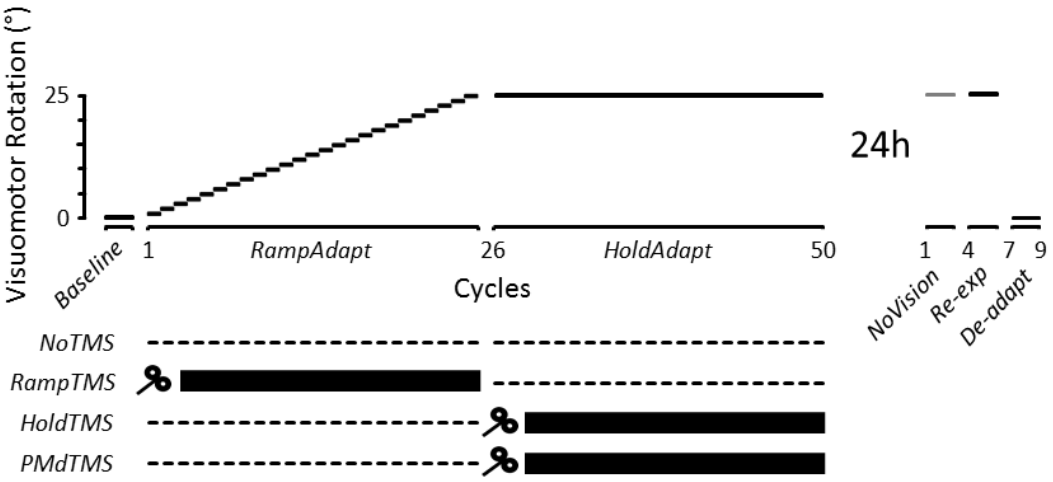

Figure 2. Time course of the main experimental protocol. On separate days (24h apart), participants performed an acquisition and a retention session of a visuomotor adaptation task. In RampAdapt, a counterclockwise (CCW) visuomotor rotation was gradually introduced at the rate of +1° per cycle from 1 to 25° over 25 cycles (250 trials). In HoldAdapt, the rotation was held at 25° CCW for 25 additional cycles (250 trials). Participants were separated into three groups and received (or not) TMS pulses in different phases of the acquisition session. Participants of the NoTMS group (n = 14) did not receive TMS during acquisition. Participants of the RampTMS (n = 14) and HoldTMS groups (n = 13) received single-pulse TMS over M1 after each trial of either the RampAdapt or HoldAdapt phase, respectively. Participants of the PMdTMS group (n = 14) received single-pulse TMS over the PMd after each trial of the HoldAdapt phase. The retention session was used to assess consolidation. The NoVision phase was performed without visual feedback of the hand. The Re-exp phase consisted in the re-exposure to the 25° CCW rotation, whereas the De-adapt phase was performed with veridical (i.e., non-rotated) visual feedback of the hand.

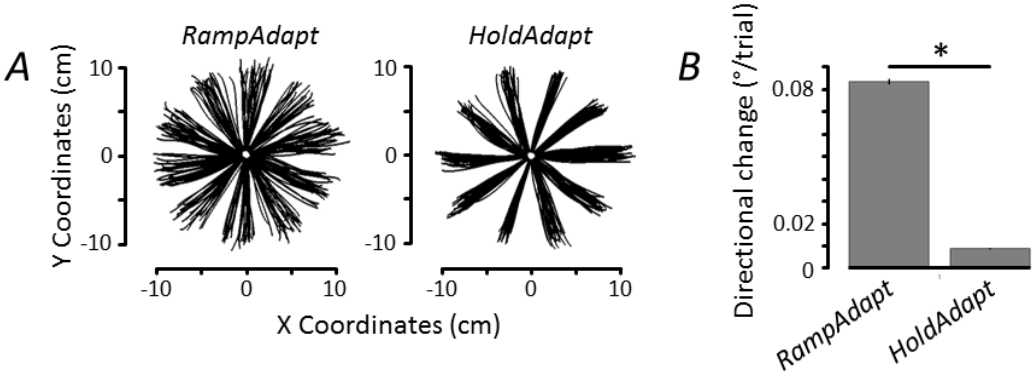

Figure 3. (A) Movement trajectories of a representative participant in the RampAdapt and HoldAdapt phases. (B) Mean change in reach directions across trials in each of the two phases of acquisition. RampAdapt yielded greater trial-by-trial changes in reach directions as compared to HoldAdapt ($p < 0.001$). Error bars represent the standard error of the mean (SEM).

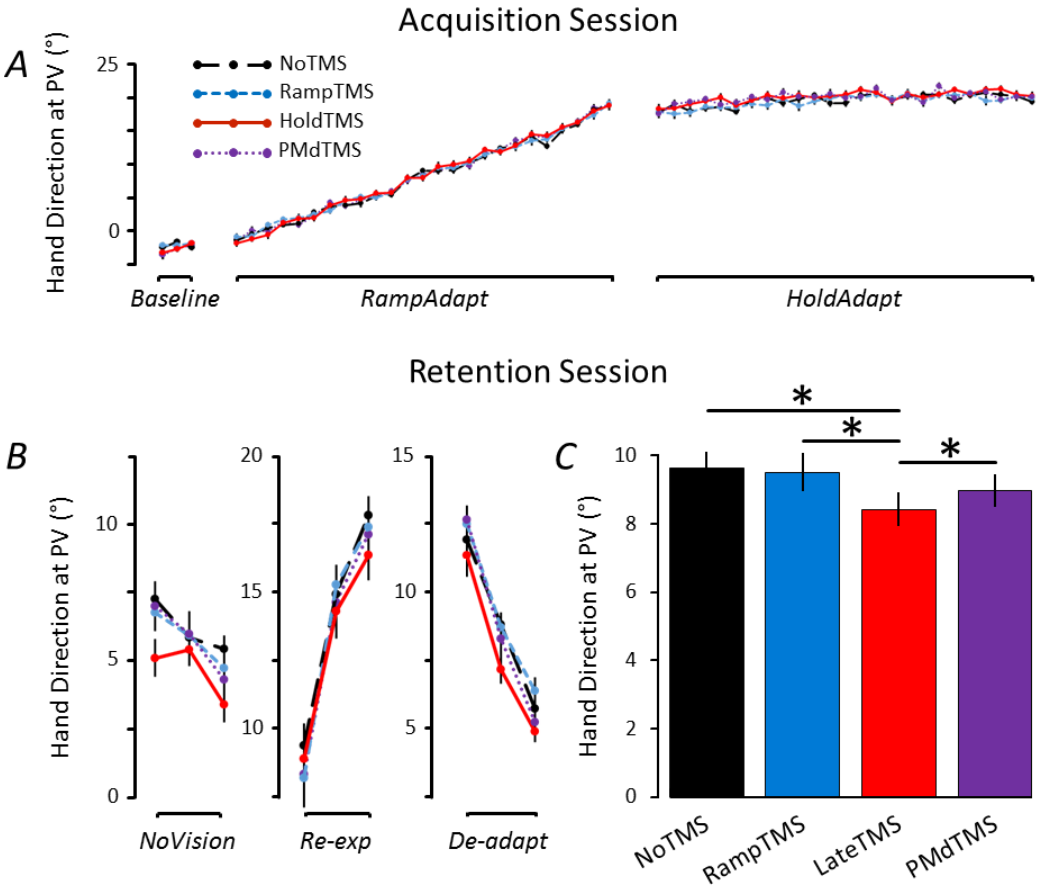

Figure 4. Main experiment results. (A) Mean hand direction at PV in each cycle of the acquisition session. The four groups did not differ in the extent of adaptation to the visuomotor rotation (p = 0.87). (B) Mean hand direction at PV in each cycle of the retention session. (C) Mean hand direction at PV of all trials performed in the retention session. The HoldTMS group showed impaired consolidation as compared to each of the other three groups (p < 0.05 Holm-Bonferroni corrected). Error bars represent the SEM.

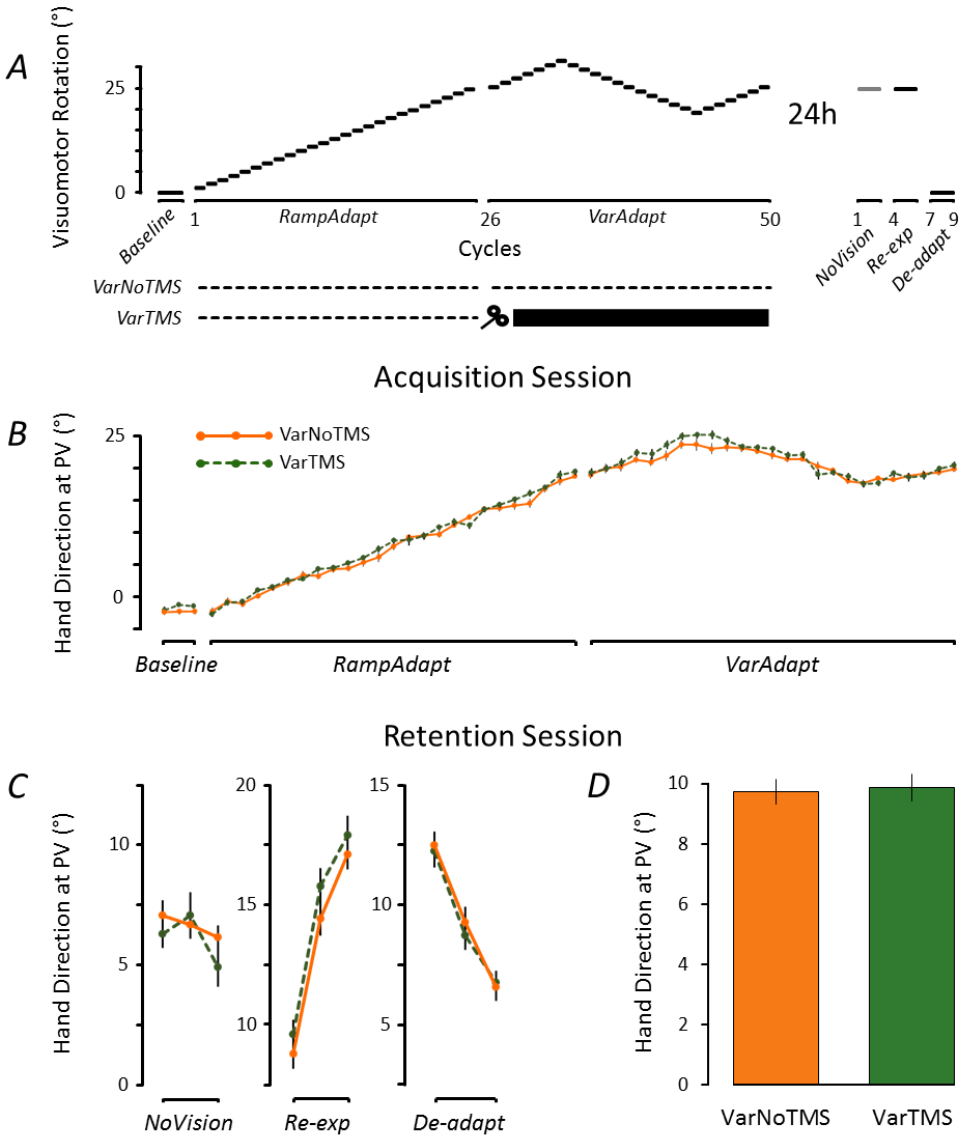

Figure 5. Control experiment. (A) Two additional groups were tested in a schedule in which visuomotor rotations kept iteratively changing both early and late in the acquisition session. Participants of the VarNoTMS group (n = 14) did not receive TMS whereas those of the VarTMS group (n = 14) received TMS after each trial of the VarAdapt phase. (B) Mean hand direction at PV in each cycle of the acquisition session. The VarNoTMS and VarTMS groups did not differ in the extent of adaptation to the visuomotor rotation (p = 0.28). (C) Mean hand direction at PV in each cycle of the retention session. (D) Mean hand direction at PV of all trials performed in the retention session. The VarNoTMS and VarTMS groups did not differ from each other (p = 0.88). Error bars represent the SEM.

5. Conceptual framework of the second scientific contribution

5.1. Studying human brain oscillations to investigate the neural bases of reward processing

Classically, reward processing occurs in a widely distributed mesolimbic network including the ventral striatum (Feingold et al., 2015; Lutz et al., 2012; Widmer et al., 2016), VTA (Hosp and Luft, 2013; Hosp et al., 2011), substantia nigra (Münte et al., 2008), and globus pallidus internus (Münte et al., 2017). In the context of a motor control task, recent animal studies have shown that neurons in cortical motor areas, such as the PMd, M1, and S1, also receive and encode reward signals (Saiki et al., 2014; Ramakrishnan et al., 2017; Ramkumar et al., 2016; Marsh et al., 2015). If the latter structures receive reward signals, then it implies that some form of functional interaction between the mesolimbic reward network and these cortical motor areas must occur to allow reward processing. However, these structures are anatomically distributed; the necessary functional binding of these neuronal assemblies to allow reward processing to emerge is a challenge that needs to be overcome by the system.

One way to establish functional communication between distant neural assemblies is to synchronize their neuronal oscillatory activity (Marco-Pallarés et al., 2015; Buszaki and Draguhn, 2004), therefore allowing the temporal, anatomical, and functional coordination of distributed neuronal populations (Palva and Palva, 2012; van der Meij al., 2015). As such, neuronal oscillations are thought to allow information processing across distant brain networks, making them likely candidates through which reward processing could occur (Marco-Pallarés et al., 2015).

5.2. Oscillations arise from micro, meso, and macroscopic neuronal activity

Rhythmic changes in the extracellular field electrical potentials, usually referred to as local field potential (LFP), arise from sub- and supra-threshold synaptic input and also *possibly* from non-synaptic activity (Watrous et al., 2015; Panzeri et al., 2015). Overall, oscillations in LFP arise from the synchronization of neuronal activity at a

micro (i.e., neuron), meso (i.e., a small patch of cortex) and macroscopical scale (i.e., between different brain areas). Although micro, meso, and macroscopical neuronal activity is likely to interact altogether, they will be addressed separately for conceptualization convenience.

At the **microscopic** level, neuronal membranes resonate through subthreshold fluctuation (meaning that it does not necessarily lead to the genesis of a nerve action potential) in the membrane potential (i.e., changes in the ion distribution around the membrane). This resonance in the membrane potential can result from the sub-threshold summation of post-synaptic potentials (Buzsáki et al., 2012).

At the **mesoscopic** level, oscillations arise from synaptic and *possibly* from non-synaptic (i.e., via ephaptic coupling) interactions in relatively small densely interconnected local neuronal assemblies (Buzsáki and Draguhn, 2004; Buzsáki et al., 2012).

Synaptic regulations of oscillatory activity occur through the balanced "push-and-pull" interactions of inhibitory interneurons and excitatory pyramidal cells, where inhibitory interneurons impose narrow time windows for excitatory pyramidal neurons to fire (Reato et al., 2013; Cohen, 2014). Globally, when a volley of post-synaptic potentials excites pyramidal neurons, they increasingly excite each other until inhibitory interneurons become activated. The activation of inhibitory neurons inhibits excitatory neurons until their activation decreases, allowing excitatory neurons to increase their activity again (Cohen, 2014). Hence, this shifting balance between excitation and inhibition is thought to give rise to oscillatory activity (Reato et al., 2013).

Non-synaptic regulations of oscillatory activity are thought to occur through *ephaptic coupling*, where spiking activity induces changes in extracellular fields which in turn alters neuronal membrane subthreshold potentials to facilitate or hamper spiking activity of nearby neurons (Anastassiou et al., 2011; Buzsáki et al., 2012). Even if the magnitude of the LFP voltage change can be fairly small (< 0.5 mV), it is enough to

significantly alter the neurons' spiking activity (Anastassiou et al., 2011; Buzsáki et al., 2012). During ephaptic coupling, spikes from single neurons unlikely affect the excitability of nearby neurons because the generated extracellular field is too weak. However, simultaneous activity of thousands of neurons can generate strong enough voltage gradients in their common extracellular field, which in turn can significantly alter their spiking activity (Anastassiou et al., 2011; Buzsáki et al., 2012; Reato et al., 2013; Anastassiou and Koch, 2015). Hence, one possibility is that rhythmic changes in LFP affect spiking activity through the extracellular medium, which in turn can also contribute to oscillations in LFP (Reato et al., 2013; Anastassiou and Koch, 2015), thus constituting an endogenous feedback loop where LFP alter the membrane potential of the neural assembly that gave rise to them in the first place (Anastassiou and Koch, 2015). Although the functional role of ephaptic coupling remains unknown (Anastassiou and Koch, 2015), the reciprocal relationship between spiking activity and LFP makes it plausible that oscillations can also be generated (or strengthened) via non-synaptic interactions.

At the **macroscopic** level, oscillations can also arise from long-distance functional interactions between neuronal assemblies (i.e., like during phase synchronization; see section 5.3.). The connections between separated brain regions are bidirectional, thus forming feedback loops. Those loops include the thalamo-cortical loop (Hunnicutt et al., 2014), the VTA-M1 loop (Hosp and Luft, 2013; Kunori et al., 2014), and even the fronto-striatal loop (Björklund and Dunnett, 2007b). Here, the sensorimotor-basal ganglia loop will be considered because they have been repeatedly shown to synchronize their oscillatory activity during the execution of motor behaviors (Ahn et al., 2015; Beck et al., 2016; Cassim et al., 2002; Delaville et al., 2014; Feingold et al., 2015; Kondabolu et al., 2016; McCairn and Turner, 2015; Tan et al., 2014; Vorobyov et al., 2003) and because they could be likely candidates through which reward processing could arise.

5.3. Parameters and functional processes of oscillations

An oscillation has multiple parameters, such as frequency (the number of oscillatory cycles per second, reported in Hz), power (a measure of the amplitude of the oscillation), and phase (the momentary deflection angle of an oscillation). All of these parameters are theoretically independent of one another, but their interaction is thought to support local and inter-areal interactions through the functional binding of neural assemblies (Watrous et al., 2015; Palva and Palva, 2012). More specifically, oscillations impose excitability and inhibitory windows (during the peak or the trough of the cycle, respectively) where neurons respectively rhythmically increase and decrease their spiking activity, hence facilitating or inhibiting interactions between neuronal populations (Palva and Palva, 2012; Reato et al., 2013). Interestingly, oscillations do not only allow the functional binding of distant neural assemblies but they could also participate in motor memory formation through LTP-like plastic changes. The rhythmic entrainment of spiking activity induced by oscillatory activity can lead to STDP (Jutras and Buffalo, 2010). That is because the synchronized activity between a pre and a post-synaptic neuron that falls within a critical time window (~ 10 ms) strengthens the connection between them (Jutras and Buffalo, 2010).

The most common frequency bands are canonically defined as follow: Delta (1 - 3 Hz), Theta (4 - 7 Hz), Alpha (8 - 12 Hz), Beta (13 - 30 Hz), Gamma (30 - 80 Hz; Chuderski, 2016). Over the past few decades, researchers have come to attribute different cognitive and/or motor functions to specific frequency bands. (1) *Delta* oscillations have been attributed an inhibitory function, where sustained delta oscillations prevent interferences (from sensory afferences for example) that could affect the performance of mental tasks (Harmony, 2013). (2) *Theta* oscillations have been involved in cognitive control, as they have been found to monitor performance and signal the need to modify a behavior (Cavanagh and Frank, 2014). (3) *Alpha* oscillations have been regarded as up- or down-regulating information processing, as they have been argued to actively regulate attention and memory retrieval (Klimesch, 2012). (4) *Beta* oscillations have been involved in the execution of motor behaviors

(Khanna and Carmena, 2015; Engel and Fries, 2010), but also in reward processing and *possibly* in learning (Marco-Pallarés et al., 2015). (5) *Gamma* oscillations have been regarded as a regulator of the activation of local cortical patches of brain tissues by regulating the balance between excitation and inhibition, but whether they are involved in information processing or storage remains an open question (Merker, 2013; Ray and Maunsell, 2015).

5.4. Multiplexing of information in oscillations

Because neuronal spiking activity is modulated by the frequency, power, and phase of an oscillation, neuronal information processing is thought to occur in multiplexed oscillatory activity (Watrous et al., 2015; Buzsáki and Draguhn, 2004; Buzsáki et al., 2012; Schyns et al., 2011). More precisely, the multiplexing of phase and power of different frequency bands is thought to allow for multiple information processing to occur simultaneously, thereby increasing the capacity of the network to code information in a cost-effective manner (Schnys et al., 2011; Watrous et al., 2015; Buzsáki and Draguhn, 2004). For instance, Schyns et al. (2011) showed that the conjunctive analysis of phase and power at theta (4 Hz) and low-beta (12 Hz) frequencies is ~ 3 times more informative than the analysis of power or phase alone to encode relevant visual information for the task that had to be performed. These results suggest that the decoding of oscillation functional meaning is likely to rely on the types of data analysis that can account for the multiplexing of information between frequency, power, and phase.

To this end, several methods to analyze EEG data to account for this multiplexing have emerged in last decades, allowing for various combinations of the coupled oscillatory parameters to be studied (referred to as "cross-frequency coupling"). The studied parameter combinations include (1) phase-amplitude coupling, during which the phase of slow oscillations determines the amplitude (power) of the fast oscillations (Sotero, 2015), (2) amplitude-amplitude coupling, where the power of the slow wave modulates the power of the fast oscillations, and (3) phase-phase

coupling, where the phase of the slow oscillations resets the phase of the fast oscillations (Chuderski, 2016). Globally, cross-frequency coupling is thought to enable the transfer of information from large-scale brain networks to local neural assemblies, hence allowing the integration of functional systems spatially, temporally, and functionally distributed (Canolty and Knight, 2010).

However, evidence supporting the involvement of coupled oscillatory parameters in information processing remain scarce (Chuderski, 2016), which regrettably hampers the ability to formulate hypothesis-driven questions and to eventually interpret such findings. Although many issues concerning functional interpretations remain to be resolved, the oscillatory parameters have been more studied in isolation (Watrous et al., 2015). As such, it is more straightforward to formulate a hypothesis-driven question with regards to power or phase and to interpret such findings. For this reason, the second scientific contribution presented in this document will focus on the analyses of oscillatory power.

5.5. Using scalp electroencephalography to record brain oscillations

Electroencephalography (EEG) is a montage consisting of several electrodes that are placed on the scalp used to record macroscopic changes in brain electrical activity. Globally, with a temporal resolution at the millisecond scale, EEG records an attenuated measure of the linear mixture of voltage changes in LFP that are believed to arise from every transmembrane current induced by ions influx or efflux in neurons, but also from glial cells (Buszaki et al., 2012). Artefactual electrophysiological activity generated by the eyes or muscles can also be captured by EEG electrodes (Onton et al., 2006; Urigüen and Garcia-Zapirain, 2015).

More precisely, EEG is believed to mainly record the summation of the electrical fields arising from synaptic currents within the radially oriented pyramidal neurons mainly located in cortical layers III, V, and VI (Olejniczak, 2006; Chuderski, 2016), mostly because synaptic currents are relatively slow events and because pyramidal cells are the most populous cell type (Olejniczak, 2006; Urigüen and Garcia-

Zapirain, 2015). Although nerve action potential firing also contributes to extracellular field currents, they do not produce sufficiently strong electrical fields and occur too quickly to be measured with scalp EEG (Buszaki et al., 2012). Thus, changes in LFP voltage are thought to stem from afferent input (i.e., via synapses) to a relatively small patch of cortex and not from its efferent output (Buszaki et al., 2012). However, many factors are known to affect the amplitude of the EEG signals recorded on the scalp and must be considered. Those include:

(1) Whether synaptic currents (input towards pyramidal cells) are synchronized or not because it gives rise to different magnitudes of electrical potentials (Buzsáki et al., 2012). Increases in synchronization can result in phase-locked or non-phase-locked power.
(2) Geometric factors like spatial neuronal layer orientation, which is dependent upon the highly folded nature of the human brain (Buzsáki et al., 2012). As mentioned above, EEG is thought to mainly capture extracellular electrical fields generated by radially oriented pyramidal cells relative to the cortical surface (Onton et al., 2006).
(3) Passive volume conduction of the extracellular medium, where brain tissues, skull bone, and the skin can inhomogeneously impede the conductivity of the current (Buzsáki et al., 2012).
(4) The distance of the cortical sources from the electrodes; the further the source, the weakest the recorded signals with a relationship of 1 / distance (Buzsáki et al., 2012).

It is important to keep in mind that EEG records a two-dimensional projection of three-dimensional synchronized slow voltage changes in LFPs (Olejniczak, 2006), implying that it is theoretically impossible to determine the location of the source without making some assumptions on the nature of the signals (i.e., like the source stationarity assumption in independent component analysis [ICA; Onton et al., 2006; Delorme et al., 2012]). EEG signals are believed to stem from relatively small densely interconnected patches of cortex depending on the frequency of the oscillation, where

slower and higher oscillations synchronize larger and smaller neuronal assemblies, respectively (Buzsáki and Draguhn, 2004; Buzsáki et al., 2012). Overall, because of all of the above factors that influence EEG signals, EEG has often been regarded as having a poor spatial resolution (> 1 cm on the scalp; Olejniczak, 2006), although new analysis methods are being developed to improve EEG's spatial resolution (Ball et al., 2016).

5.6. How to extract oscillations from raw EEG signals

Raw EEG signals have been thoroughly studied through their linear averaging across trials and time-locked to an event of interest (i.e., event-related potentials [ERPs]). However, because ERPs reflect the sum of all LFP oscillatory parameters, modulations in ERPs could be the result of increases/decreases in power and/or phase at single or multiple frequencies (Cohen, 2014). Although ERPs are better time-resolved than time-frequency analyses, ERPs are mainly constituted of phase-locked power, meaning that the phase of the signal is reset on every trial at the event of interest (Cohen, 2014). Phase-locked power is mainly constituted of the frequencies below ~ 15 Hz (Cohen, 2014).

ERPs are mainly deemed to comprise phase-locked power because non-phase-locked power – meaning that the phase of the signal is not affected by the event of interest – does not survive the ERP trial averaging (Cohen, 2014). Given that non-phase-locked power tends to be around or above ~ 15 Hz (Cohen, 2014), one limitation of ERPs is that its averaging prevents the comprehension of oscillatory activity above ~ 15 Hz. Given that it has been shown that relevant activity for reward processing and learning occurs at ~ 20 to 30 Hz (Marco-Pallarés et al., 2015), the study of brain signals through ERPs does not appear as the most suitable metric to document reward processing for the present research project.

One way to disentangle the contribution of LFP oscillatory activity to EEG raw signals and exploit the multiplexed information comprised in oscillations is time-frequency decomposition, where oscillatory information is "filtered" out of the raw EEG signals. More precisely, time-frequency decomposition can be performed by

complex Morelet wavelet convolution, where a kernel (i.e., a sinusoid of a given frequency is multiplied to a Gaussian window) is repeatedly multiplied with each EEG data samples along the time axis. The resulting complex number is then used to extract power and/or phase information for every given frequency (typically between 1 and 100 Hz) for almost each time points of the EEG raw data. This procedure is easily implemented in software like EEGLAB (Delorme and Makeig, 2004).

5.7. Submitted article in *NeuroImage*

N.B. See section 8.2. for the authors' authorization to include this article in the present thesis.

Added value of money on motor performance feedback: increased motor beta-band power for rewards and mid-frontal theta-band power for punishments

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Keywords: reaching, EEG, beta-band, theta-band, motor, mid-frontal, rewards, punishments.

Highlights

- Beta- and theta-band power encodes rewards and punishments in a motor task
- Monetary feedback entails greater oscillatory power than performance feedback alone
- Successful punishment avoidance entails similar beta-band power as rewards
- Beta-band power is greater after lowly probable than highly probable target hits
- Reward omissions entail similar mid-frontal theta-band power as punishments

Abstract

Monetary rewards and punishments have been shown to respectively enhance retention of motor memories and short-term motor performance, but their underlying neural bases in the context of motor control tasks remain unclear. Using EEG, the present study sought to test the hypothesis that monetary rewards and punishments are respectively reflected in post-feedback beta-band (20-30 Hz) and theta-band (3-8 Hz) oscillatory power. While participants performed upper limb reaching movements toward visual targets using their right hand, the delivery of monetary rewards and punishments was manipulated as well as their probability (i.e., by changing target size). Compared to unrewarded and unpunished trials, monetary rewards and the successful avoidance of punishments both entailed greater beta-band power at left contralateral motor electrodes, whereas monetary punishments and reward omission both entailed increased theta-band power at mid-frontal scalp sites. Additional analyses revealed that beta-band power was further increased when rewards were lowly probable. In light of previous work demonstrating similar beta-band modulations in basal ganglia during reward processing, the present results may reflect functional communication of reward-related information between the basal ganglia and motor cortical areas. In turn, the increase in mid-frontal theta-band power after monetary punishments may reflect an emphasized cognitive need for behavioral adjustments. Globally, the present work identifies neural substrates for the growing behavioral evidence showing beneficial effects of monetary feedback on motor learning and performance.

1. Introduction

Human motor performance and learning critically depends upon the processing of feedback. Beyond motor performance feedback, which informs of the accuracy of a movement (i.e., seeing oneself hitting or missing a target), external sources of feedback such as monetary rewards or punishments can provide additional guidance as to the behaviors to repeat or avoid. Support for this notion comes from converging lines of evidence showing that monetary feedback enhances short-term performance and retention of motor behaviors (Abe et al., 2011; Dayan et al., 2014; Gajda et al., 2016; Galea et al., 2015; Hasson et al., 2015; Manley et al., 2014; Palminteri et al., 2011; Quattrocchi et al., 2017; Song and Smiley-Oyen, 2017; Steel et al., 2016; Wächter et al., 2009; Widmer et al., 2016). For instance, Galea et al. (2015) provided monetary rewards or punishments depending on task performance while participants acquired a novel upper limb reaching movement pattern. Compared to a control group receiving no monetary feedback, participants receiving monetary rewards following accurate performance showed improved retention of the new movement pattern. Furthermore, participants receiving monetary punishments following inaccurate performance presented more rapid performance adjustments. These results suggest that monetary feedback provides added value to motor performance feedback and acts as a catalyst to promote motor learning and performance. Yet, the neural bases of monetary feedback processing in the context of motor control tasks remain unclear.

Several electroencephalography (EEG) and magnetoencephalography (MEG) studies investigating non-motor tasks such as gambling have provided evidence for

frequency-specific responses to monetary rewards and punishments in the high beta-band from 20 to 30 Hz (Andreou et al., 2017; Cohen et al., 2007; HajiHosseini and Holroyd, 2015a, 2015b; HajiHosseini et al., 2012; Marco-Pallares et al., 2008, 2009; Mas-Herrero et al., 2015) and theta-band from 3 to 8 Hz (Andreou et al., 2017; Cohen et al., 2007; De Pascalis et al., 2012; Doñamayor et al., 2011; 2012; Hajihosseini and Holroyd, 2013; Marco-Pallarés et al., 2008), respectively. These power modulations have been shown to occur mainly over mid-frontal regions in a time window ranging from about 200 to 600 ms post-feedback and to be enhanced when outcomes are lowly probable (Cohen et al., 2007; Doñamayor et al., 2012; HajiHosseini et al., 2012; Mas-Herrero and Marco-Pallarés, 2014). The role of mid-frontal brain regions in monetary feedback processing is further supported by electrophysiological and functional magnetic resonance imaging (fMRI) studies which have reported activity in both the mid-frontal cortex (Andreou et al., 2017; FitzGerald et al., 2012; Hester et al., 2010; Jarbo and Verstynen, 2015; Mas-Herrero and Marco-Pallarés, 2014; Mas-Herrero et al., 2015; Noonan et al. 2012; Rogers et al., 2004; Wrase et al., 2007) and orbitofrontal cortex (Abler et al., 2009; Camara et al., 2009; Kim et al., 2015; Klein-Flügge et al., 2013; Noonan et al., 2012; O'Doherty et al., 2001; Roesch and Olson, 2004; Rogers et al., 2004; Xue et al., 2013) following monetary feedback delivery.

Although the above-cited work argues for a frequency-specific signature for the processing of monetary rewards and punishments, it is unknown whether these oscillatory modulations also take place in the context of motor control tasks. In particular, unlike gambling paradigms, the delivery of monetary feedback in motor control tasks is contingent upon the accuracy of the movement and directly influences

subsequent behavioral adjustments. Furthermore, to have an impact on motor learning and performance, monetary feedback would be expected to influence activity in brain regions in which movements are planned and executed, namely in functionally lateralized motor regions such as dorsal premotor cortex (PMd) and primary motor cortex (M1) (Fu et al., 1993; 1995; Mandelblat-Cerf et al., 2009, 2011; Overduin et al., 2009; Paz et al., 2003, 2005; Pearce and Moran, 2012; Richardson et al., 2012; Sosnik et al., 2014; Stark et al., 2007; Wise et al., 1998; Xiao, 2005; Xiao et al., 2006). Interestingly, recent studies have provided support for the notion that motor cortical regions are involved in reward processing (Marsh et al., 2015; Ramakrishnan et al., 2017; Ramkumar et al., 2016; Saiki et al., 2014; Suzuki et al., 2014). Indeed, neurons in monkey PMd, M1, and primary somatosensory cortex (S1) have been shown to respond differently when an upper limb reaching movement successfully achieves a target and is rewarded with juice as compared to when a target is missed (Ramakrishnan et al., 2017; Ramkumar et al., 2016). These findings thus open up the possibility that oscillatory modulations associated with monetary feedback processing in the context of motor control tasks would be lateralized over motor cortical regions.

In light of the preceding evidence, the objective of this study was to test the hypothesis that beta- and theta-band oscillations respectively reflect monetary rewards and punishments in a motor control task. Moreover, it was hypothesized that the use of monetary feedback would result in greater oscillatory activity than motor performance feedback alone. Using EEG, participants performed goal-directed reaching movements toward visual targets while the delivery of monetary feedback as well as its probability were manipulated based on behavioral performance. To investigate the possibility that

monetary feedback processing entails lateralized responses, oscillatory activity was specifically assessed at electrodes overlaying the motor cortical regions bilaterally as well as over the mid-frontal cortical regions.

2. Materials and Methods

2.1. Participants

Twenty-three self-reported right-handed human participants (16 females; 22.3 ± 0.4 years old; all reported values are mean ± SEM) took part in the experiment. The number of participants was based on an a priori sample size estimation analysis which revealed that at least 22 participants were needed to achieve expected power based on previous studies (see below). Participants were neurologically healthy with normal or corrected-to-normal vision. They were initially offered 20 $ CAD for their participation and total earnings were adjusted according to their individual performance at the task. Upon completion of the experiment, participants received on average 19.3 ± 0.7 $ CAD. Informed consent forms approved by the ethical committee of the Centre Hospitalier de l'Université de Sherbrooke were signed prior to the start of the experiment.

The a priori sample size estimation analysis was conducted with G*Power3 (version 3.1.9.2; Faul et al., 2007) using an alpha value of 0.05, power of 80%, a within-factor design (two-way repeated measures ANOVAs) and effect sizes (partial eta-squared values) of 0.29 ± 0.05 for beta- and 0.42 ± 0.15 for theta-band power responses. Those values were calculated with the formulas provided by Fritz et al. (2011) based

on recent EEG studies investigating reward and punishment processing (Cohen et al., 2007; HajiHosseini et al., 2012, HajiHosseini and Holroyd, 2015a, 2015b; Marco-Pallarés et al., 2008, 2009; Mas-Herrero et al., 2015), and the resulting values were averaged.

2.2. Apparatus

The experimental setup consisted of a table supporting a computer monitor which projected visual stimuli on a mirror positioned horizontally in front of participants (see Figure 1a). The monitor (20-inch Dell P1130; resolution: 1024 x 768; refresh rate: 150 Hz) was mounted face down 29 cm above the horizontal mirror and the mirror was mounted 29 cm above the table. Thus, the visual stimuli appeared to be projected directly onto the surface of the table on the same plane as the hand. Because of the mirror, participants could not see their hand. A 2-joint planar manipulandum was placed on the table and was held by participants via a stylus located at its mobile end. The manipulandum was custom-built with 2 lightweight metal rods (48 and 45 cm for the distal and proximal rods, respectively), with the fixed end attached to the upper left corner of the table. A thin sheet of smooth plastic covered the table surface and foam pads were installed under the hinges allowing the manipulandum to be moved everywhere on the table with minimal inertia and friction. Two potentiometers positioned in the joints of the manipulandum allowed the measurement of the angle of each segment at 1000 Hz from which the 2D position of the stylus was calculated.

A 2 cm diameter grey circle served as the starting point for every trial. It was positioned at the center of the workspace 30 cm in front of participant's chest. The cursor representing hand position at movement end consisted of a 0.58 cm diameter

circle. The target to be achieved consisted of a small inner circle surrounded by an outer annulus (see Figure 1b and 1c). The color of the target and outer annulus informed of the reward/punishment contingency (green, red, and grey for rewards, punishments, and neutral, respectively; for details, see section 2.4). While the outer annulus had a consistent diameter of 2.47 cm, the diameter of the target was manipulated and ranged between ~ 0.8 and 1.5 cm across participants (for details, see section 2.5). Three targets were used, all located along a 10 cm radius semi-circular array in the upper quadrant of the workspace. Targets were separated by 4° and the middle target was located at 90° in line with participants' midline (only the middle target is shown in Figure 1b).

2.3. Procedures

Participants performed reaching movements with their right hand toward one of the three visual targets, without visual feedback of the cursor (see Figure 1b). Visual feedback of the final hand position was provided via the presentation of the cursor at the end of each movement (i.e., referred to as "motor performance feedback"). The mapping between the hand and the cursor remained veridical for the entire experiment.

To initiate a trial, participants had to bring the cursor into the starting point and remain stationary within its boundary for 500 ms. This prompted the appearance of a target, which indicated the beginning of the trial. After 2 000 ms, participants heard an auditory cue, prompting the initiation of the reach. The auditory cue was the same in each condition (see section 2.4 and 2.5) and consisted of a 300 ms tone (50 Hz). Participants were asked to produce straight movements with minimal online corrections in a targeted movement time of 300 ms. This ensured that all participants had a similar speed-accuracy trade-off (Fitts, 1954). Movements were deemed

completed when the velocity of the cursor dropped below 0.05 cm/s. At movement end, vision of the cursor and monetary feedback (in the form of "± 0.05 $") were simultaneously provided. Concomitantly, the target disappeared and was replaced by a red fixation cross at the same location, which participants were asked to fixate to avoid ocular saccades. The fixation cross, final cursor position and monetary feedback remained displayed on the screen for 1 500 ms, after which they disappeared, marking the end of the trial. On average, five seconds separated the beginning of each trial.

2.4. Manipulation of Monetary Feedback

Target hits (i.e., endpoints for which the cursor contacted the inner circle) could be either unrewarded or rewarded, whereas target misses (i.e., endpoints for which the cursor did not contact the inner circle, thus in the outer annulus or beyond) could be either unpunished or punished, resulting in three different Monetary Feedback conditions (see Figure 1c). In the Neutral condition, hits and misses were both associated with neutral monetary feedback (+ 0.00 $ CAD). In the Gain condition, hits were associated with monetary rewards (+ 0.05 $ CAD), whereas misses were associated with neutral monetary feedback. In the Loss condition, hits were associated with neutral monetary feedback, whereas misses were associated with monetary punishments (- 0.05 $ CAD). To make the monetary feedback more explicit, each type of monetary feedback as well as motor performance feedback (i.e., cursor) was presented in a specific color. Neutral monetary feedback was presented in grey, monetary rewards in green and monetary punishments in red.

2.5. Manipulation of hit rate probability

Because the processing of rewards and punishments has been shown to be modulated by outcome probability (Cohen et al., 2007; Doñamayor et al., 2012; HajiHosseini et al., 2012; Mas-Herrero and Marco-Pallarés, 2014; Ramakrishnan et al., 2017), the probability of hitting the target was also manipulated by using large or small targets (see Figure 1c). This was assessed through the Hit Rate, consisting in the percentage of trials in which the cursor was in contact with the inner circle at movement end. Our goal was for Hit Rates to be approximately ~70% for large targets (hereafter called "High Probability of Hit" condition), and ~30% for small targets (hereafter called "Low Probability of Hit" condition). The target sizes necessary to achieve these probabilities were adjusted for each individual participant based on their reaching accuracy. Specifically, prior to the main experiment, participants performed 120 baseline trials (see section 2.6) in which movement endpoints were recorded. On those data were fitted circles encompassing either 70% or 30% of movement endpoints using a custom-made MATLAB script (Version R2014a; MathWorks Inc.). These two circles were used to set the diameter of the targets in the High and Low Probability of Hit conditions, which were on average 1.49 ± 0.07 cm and 0.84 ± 0.04 cm, respectively. Target diameters remained constant during the entire experiment. Results revealed that this manipulation was successful as Hit Rates in the High and Low Probability of Hit conditions were 74.9 ± 2.1 % and 38.1 ± 1.7 %, respectively. This was confirmed by a 3 Monetary Feedback (Neutral, Gain, Loss) X 2 Probability (High, Low) repeated measures ANOVA conducted on the Hit Rate data which yielded a significant main effect of Probability ($F(1,22) = 344.42$, $p < 0.001$, $\eta_p^2 = 0.94$).

[Color should be used for Figure 1]

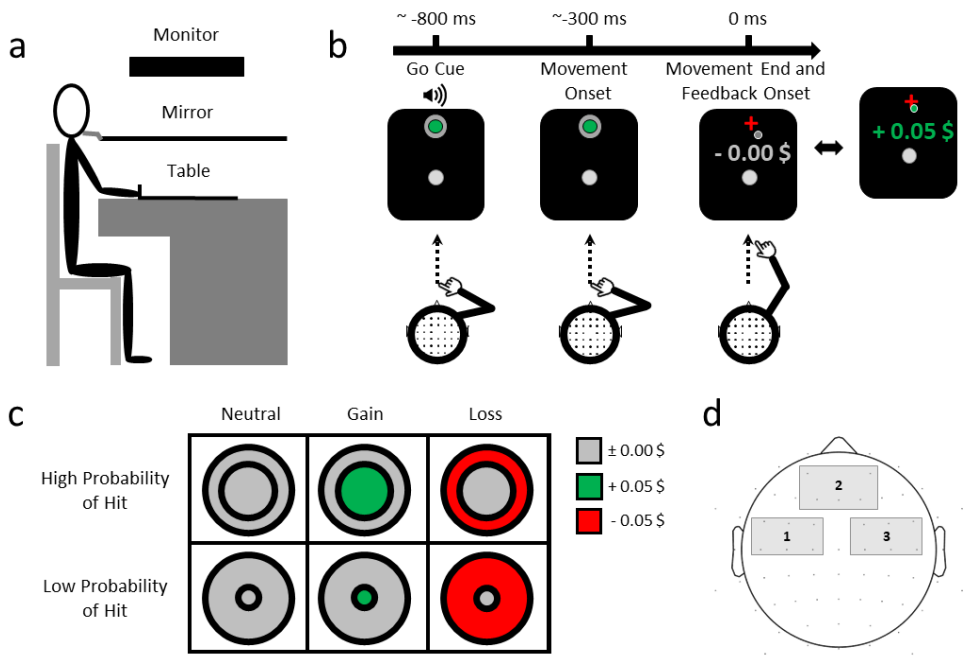

Figure 1. *Schematic representation of the apparatus and methodological procedures. (a) Side view of the apparatus. (b) Chronology of a typical trial. An auditory tone prompted the beginning of a trial (Go Cue). Movement Onset corresponded to when the hand left the starting point (Movement Onset). Vision of the cursor and monetary feedback based on performance were only and simultaneously provided at movement end (Movement End and Feedback Onset). Trial outcomes were binary: targets were either hit –accompanied by neutral monetary feedback (i.e., + 0.00 $ CAD) or monetary rewards (i.e., +0.05 $ CAD) – or missed –accompanied by neutral monetary feedback (i.e., - 0.00 $ CAD) or monetary punishments (i.e., – 0.05 $ CAD). (c) Schematic representation of the six experimental conditions. (d) Scalp localization of the three regions of interest (ROIs): (1) Left Motor, (2) Mid-frontal, (3) Right Motor.*

2.6. Experimental sessions

All participants took part in a single experimental session. The session began with a 30-trial practice phase allowing participants to familiarize with both the spatial and temporal requirements of the task. Then, participants underwent a 120-trial baseline phase in which they reached toward grey targets of 1 cm diameter. There was no manipulation of monetary feedback in the practice and baseline phases, and EEG data were not recorded. Kinematic data from the baseline phase were used to determine target sizes for the High and Low Probability of Hit conditions. Following this, the EEG cap was put on and the main experiment began. Participants executed a total of 432 trials which were equally divided into 8 blocks and interleaved with one-minute breaks. The order of presentation of the conditions was pseudo-randomized so that each of the six conditions was presented 9 times per experimental block.

2.7. Kinematic Data Reduction

A custom-made MATLAB script was used to display and acquire kinematic data during the experiment. The cursor position data was acquired at 1 000 Hz. To assess whether the experimental conditions influenced movement kinematics, endpoint accuracy (i.e., the absolute distance in cm between the center of the cursor and the center of the target), reaction time (RT; i.e., the time between the go cue and movement onset), and movement time (MT; i.e., the time between movement onset and movement end) were calculated. Trials were excluded from all analyses if RT or MT were ± 3 standard deviations beyond each participant's mean or if the absolute distance between

target and cursor endpoint was beyond 10 cm. Overall, this resulted in the rejection of 239 trials across all participants (~ 2.5 % of all trials).

2.8. EEG recordings

EEG data were acquired with a 64-channel BrainAmp system (Brainproducts, Munich, Germany) along with the BrainCap electrode cap (Falk Minow Services, Herrsching-Breitbrunn, Germany). The cap was affixed to participants' head and the Cz electrode was placed at the vertex. The electrodes were ring-type sintered nonmagnetic Ag-AgCl electrodes and were positioned in accordance with the extended 10/20 system. Continuous EEG signals were recorded using BrainVision Recorder (© Brain Products, version 2.0) at 500 Hz and impedances were kept below 20 kΩ. All EEG channels were referenced to the FCz electrode during recordings. Following data collection, data were downsampled to 256 Hz, bandpass filtered from 1 to 50 Hz, and transformed to the average reference (Gwin and Ferris, 2012a, 2012b; Gwin et al., 2010). Data were epoched from -1 000 ms to 1 500 ms around feedback onset (defined as time 0) to ensure that edge artifacts stemming from time-frequency analyses would not contaminate activities of interest. Afterwards, artefactual signals were removed based on visual inspection of individual EEG data scrolls, resulting in a total rejection of 141 trials (~ 1.5% of the total trials). The data were then further inspected for artifacts with a procedure based on independent component analysis (ICA), a standard method for removal of artifacts from EEG (Delorme and Makeig, 2004; Gwin and Ferris, 2012a, 2012b; Gwin et al., 2010; Hammon et al., 2008; Makeig et al., 2002). The 'runica' procedure in EEGLAB was applied to decompose EEG signals into statistically maximal independent components (ICs). ICs were analyzed with respect

to scalp topography, frequency and time-activation characteristics and those that displayed features indicative of artifacts were removed. More precisely, ICs were considered as artifactual on the basis of the combination of the following features: (a) scalp maps localizing signal sources outside of the scalp surface (suggestive of non-cortical activity), (b) abnormal Fourier transforms that did not respect the 1/frequency relationship and (c) source activation time-courses showing spurious and transient bursts of activity. Cleaned EEG data were generated by projecting back the time course of activity of the remaining ICs to electrode space. This procedure allows the removal of artifacts from the EEG without having to reject the entire trial during which an artifact occurred (Jung et al., 2000; Whittingstall et al., 2010).

2.9. Time-Frequency Analyses

EEG spectral activity was assessed by using a sinusoidal wavelet as implemented in EEGLAB (Delorme and Makeig, 2004). This procedure involves convolving the time domain signal with a complex sinusoidal wavelet. The number of cycles for the lowest frequency was set to 3 and increased linearly with frequency (factor 0.8). The resulting complex signal was then used to provide an estimate of instantaneous power for each time point and frequency ranging from 3 to 50 Hz. Power values were normalized into a decibel scale ($10*\log_{10}$ of the signal) using movement offset (i.e., time 0) as a baseline, thus avoiding contamination of movement-related activity in feedback-induced spectra. This procedure was repeated on every trial of every condition and power values were then averaged across conditions. For statistical analyses, EEG data were binned into 50-ms epochs.

The oscillations of interest were selected based on previous EEG research using gambling tasks which revealed modulations in the high beta- (20-30 Hz) and theta-bands (3-8 Hz) for the processing of rewards and punishments, respectively (Andreou et al., 2017; Cohen et al., 2007; De Pascalis et al., 2012; Doñamayor et al., 2011, 2012; Hajihosseini and Holroyd, 2013, 2015a, 2015b; Hajihosseini et al., 2012; Marco-Pallares et al., 2008, 2009; Mas-Herrero et al., 2015). These studies further showed that modulations in EEG spectra would occur approximately ~200 to 600 ms after feedback delivery, with time-windows for analysis ranging from 250 to 600 ms. In the present work, consistent with the aforementioned studies, all experimental conditions revealed beta- and theta-band modulations ~ 250 to 600 ms after feedback delivery. Hence, this hypothesis-driven time window was used to conduct statistical analyses.

2.10. Regions of Interest

For EEG data analyses, three regions of interest (ROIs) were defined (see Figure 1d). First, based on several fMRI studies pointing to activity in mid-frontal regions (Andreou et al., 2017; FitzGerald et al., 2012; Hester et al., 2010; Mas-Herrero and Marco-Pallarés, 2014, 2016; Mas-Herrero et al., 2015; Noonan et al., 2012; Rogers et al., 2004; Wrase et al., 2007) and orbitofrontal cortex (Abler et al., 2009; Camara et al., 2009; Jarbo and Verstynen, 2015; Kim et al., 2015; Klein-Flügge et al., 2013; Noonan et al., 2012; O'Doherty et al., 2001; Roesch and Olson, 2004; Rogers et al., 2004; Wrase et al., 2007; Xue et al., 2013) during reward and punishment processing, a Mid-Frontal ROI consisting of a cluster of five electrodes (F1, Fz, F2, AF3 and AF4) was defined. Second, given the hypothesis that rewards would entail lateralized brain activity over premotor and primary motor regions (Marsh et al., 2015; Ramakrishnan

et al., 2017; Ramkumar et al., 2016; Saiki et al., 2014; Suzuki et al., 2014), a Left Motor ROI (FC1, FC3, FC5, C1, C3 and C5) and a Right Motor ROI (FC2, FC4, FC6, C2, C4 and C6) were defined. These clusters of electrodes were chosen based on MRI studies showing their localization to be above the midfrontal and motor regions of interest (Jurcak et al., 2007; Okamoto et al., 2004).

2.11. Main Analyses

Prior to all analyses, Shapiro-Wilk tests were used to assess whether data were normally distributed. Non-parametric tests were conducted on non-normal samples using a Wilcoxon's signed rank test instead of a pairwise *t*-test. Post-hoc comparisons were conducted using pairwise comparisons with False Discovery Rate (FDR) correction (also known as the Benjamini and Hochberg procedure [1995]). Briefly, this type of correction is used in neuroimaging studies (see Chumbley et al., 2010; Genovese et al., 2002) to protect against type I errors by adjusting the alpha value according to the number of remaining pairwise comparisons to be conducted in a given analysis. For convenience, all *p* values reported below have been corrected to allow the reader to compare them to a fixed alpha value of 0.05 (see Tables 2 and 3).

The first series of analyses assessed whether kinematic data differed across conditions (see Manohar et al., 2015). To do so, the endpoint accuracy, RT and MT data were submitted to separate 2 Outcome (Hit, Miss) X 3 Monetary Feedback (Neutral, Gain, Loss) X 2 Probability (High, Low) repeated measures ANOVAs.

Similar to the "gain vs loss" contrast typically used in gambling tasks (Andreou et al., 2017; Cohen et al., 2007; De Pascalis et al., 2012; Doñamayor et al., 2011, 2012; Hajihosseini and Holroyd, 2013, 2015a, 2015b; Hajihosseini et al., 2012; Marco-

Pallares et al., 2008, 2009; Mas-Herrero et al., 2015), the second analysis sought to assess if beta- and theta-band power was modulated as a function of target hits and misses specifically when monetary feedback was present (i.e., Gain and Loss conditions). For this purpose, the beta- and theta-band power was pooled across the two Probability levels and submitted to separate 2 Outcome (Hit, Miss) X 2 Monetary Feedback (Gain, Loss) repeated measures ANOVAs. Furthermore, to evaluate whether beta- and theta-band power was modulated as a function of target hits and misses in absence of monetary feedback (i.e., Neutral condition), these data were pooled across the two Probability levels and compared between Hits and Misses using paiwise *t*-tests. ANOVAs (or paiwise *t*-tests) were run on each of the the seven 50-ms time bins spanning 250 and 600 ms, with FDR correction implemented on those seven time-bins. These analyses were done for each ROI, and only those ROIs showing significant differences in spectral power were kept for further analysis.

The third analysis sought to assess if beta- and theta-band power differed across the factor Monetary Feedback. For beta-band power, data from target hits were pooled across the two Probability levels and submitted to 3 Monetary Feedback (Neutral, Gain, Loss) repeated measures ANOVAs on each of the seven 50-ms time bins spanning 250 and 600 ms, with FDR correction implemented on those seven time-bins. For theta-band power, the same analysis was conducted but using data from target misses.

The fourth analysis sought to assess if beta- and theta-band power differed across the factor Probability. For beta-band power, data from targets hits were pooled across the three Monetary Feedback levels and compared between the Low Probability and High Probability conditions using paiwise *t*-tests on each of the seven 50-ms time

bins spanning 250 and 600 ms, with FDR correction implemented on those seven time-bins. For theta-band power, the same analysis was conducted but using data from target misses. It should be noted that in this context, the Low and High Probability of Hit conditions (i.e., small and large targets, respectively) refer to a high and low probability of missing the target, respectively.

2.12. Additional analyses

A first additional analysis was conducted to address the possibility that participants accumulated fatigue over the course of the experiment. To do so, kinematic data (i.e., endpoint accuracy, RT and MT) were pooled into 2 temporal epochs (i.e., Early [blocks 1, 2, 3 and 4] vs Late [blocks 5, 6, 7 and 8]) and compared using pairwise comparisons. Similarly, to evaluate the stability of the EEG data across the experiment, beta- and theta-band power within the Left Motor and Mid-Frontal ROIs were also submitted to 2 Outcome (Hit, Miss) X 2 Monetary Feedback (Gain, Loss) X 2 Epoch (Early, Late) repeated measures ANOVAs.

A second additional analysis sought to rule out the possibility that differences in EEG power were attributable to differences in movement kinematics. Hence, whenever significant power differences were found between conditions, bivariate correlations (Pearson's product-moment or Spearman's rank correlations, depending on data normality) were conducted between these differences and their corresponding differences in RT and MT data (see Bernier et al., 2012 for similar analysis). Power differences were not correlated to endpoint accuracy differences because the EEG data were binned according to this variable (i.e., whether trials were hits or misses). The

FDR correction procedure was applied accross the two correlation *p* values obtained per EEG dependent variable.

A third additional analysis addressed the possibility that the processing of rewards and punishments depended upon whether the preceding trial was a hit or a miss. To do so, rewarded (i.e., target hits in the Gain condition) and punished trials (i.e., target misses in the Loss condition) were binned separately according to the previous trial (Hit or Miss), and beta-band power in the Left Motor ROI was compared using 2 Preceding Outcome (Hit, Miss) X 2 Monetary Outcome (Reward, Punishment) repeated measures ANOVAs. Similarly, theta-band power in the Mid-frontal ROI was compared using 2 Preceding Outcome (Hit, Miss) X 2 Monetary Outcome (Reward, Punishment) repeated measures ANOVAs. To maximize SNR, all preceding hits or misses were pooled irrespective of Monetary Feedback condition (i.e., Neutral, Gain, Loss). These ANOVAs were run on each of the seven 50-ms time bins spanning 250 and 600 ms, with FDR correction implemented on those seven time-bins.

3.1. Behavioral results

3.1.1. Endpoint accuracy

The ANOVA conducted on the endpoint accuracy data revealed a significant Outcome X Monetary Feedback X Probability three-way interaction ($F(2,44) = 6.522$, $p = 0.003$, $\eta_p^2 = 0.23$), a significant Outcome X Probability two-way interaction ($F(1,22) = 29.955$, $p < 0.001$, $\eta_p^2 = 0.58$), a main effect of Outcome ($F(1,22) = 126.707$, $p < 0.001$, $\eta_p^2 = 0.85$) and a main effect of Probability ($F(1,22) = 81.402$, $p < 0.001$, η_p^2

= 0.79). The analysis revealed no effect of Monetary Feedback ($F(2,44) = 1.715$, $p = 0.192$, $\eta_p^2 = 0.07$) and no other significant two-way interactions (all $F(2,44) > 0.376$ and < 0.729, all $p > 0.485$, all $\eta_p^2 > 0.02$ and < 0.03).

The three-way interaction was decomposed by conducting two separate 3 Monetary Feedback (Neutral, Gain, Loss) X 2 Probability (High, Low) repeated measures ANOVAs on each level of the Outcome factor (Hits, Misses). For target hits, the ANOVA revealed a significant interaction ($F(2,44) = 5.703$, $p = 0.006$, $\eta_p^2 = 0.21$), with a significant main effect of Probability ($F(1,22) = 66.345$, $p < 0.001$, $\eta_p^2 = 0.75$) and no effect of Monetary Feedback ($F(2,44) = 3.185$, $p = 0.051$, $\eta_p^2 = 0.13$). Breakdown of the interaction revealed that, in the High Probability condition, participants were more accurate in the Gain condition as compared to both the Neutral ($t(22) = 2.606$, $p = 0.024$, r = 0.48) and Loss conditions ($t(22) = 3.651$, $p = 0.002$, r = 0.61), with the Neutral and Loss conditions not differing from one another ($t(22) = 0.067$, $p = 0.947$, r = 0.01). As for the Low Probability condition, pairwise comparisons revealed no difference between any of the conditions (all $t(22) > 0.312$ and < 2.040, all $p > 0.101$, all r > 0.07 and < 0.40), suggesting participants were similarly accurate across Monetary Feedback conditions.

For target misses, the ANOVA revealed a significant interaction ($F(2,44) = 3.276$, $p = 0.047$, $\eta_p^2 = 0.13$), with a significant main effect of Probability ($F(1,22) = 77.888$, $p < 0.001$, $\eta_p^2 = 0.78$) and no effect of Monetary Feedback ($F(2,44) = 0.712$, $p = 0.496$, $\eta_p^2 = 0.03$). Breakdown of the interaction revealed that, in the High Probability condition, endpoint accuracy did not differ between any of the Monetary Feedback

factors (all $t(22) > 0.187$ and < 0.658, all $p > 0.854$, all $r > 0.04$ and < 0.14). As for the Low Probability condition, pairwise comparisons revealed that participants were more accurate in the Gain condition as compared to both the Neutral ($t(22) = 3.665$, $p = 0.002$, $r = 0.62$) and the Loss conditions ($t(22) = 2.924$, $p = 0.012$, $r = 0.53$), with the Neutral and Loss conditions not differing from one another ($t(22) = 0.365$, $p = 0.718$, $r = 0.08$).

3.1.2. Reaction Time

The ANOVA conducted on the RT data revealed a main effect of Outcome ($F(1,22) = 4.884$, $p = 0.038$, $\eta_p^2 = 0.18$), with participants being faster to initiate their reaches on Hits as compared to Misses (see Table 1). There was also a main effect of Monetary Feedback ($F(2,44) = 6.063$, $p = 0.011$, $\eta_p^2 = 0.22$), with RTs being slower in the Loss condition than in the Neutral ($t(22) = 2.638$, $p = 0.020$, $r = 0.49$) and Gain conditions ($t(22) = 4.982$, $p < 0.001$, $r = 0.73$). Finally, no main effect of Probability ($F(1,22) = 0.026$, $p = 0.874$, $\eta_p^2 < 0.01$) and no interaction between any of the factors (both two- and three-way) were found (all F values > 0.029 and < 2.184, all $p > 0.058$, all $\eta_p^2 > 0.01$ and < 0.15).

3.1.3. Movement Time

The ANOVA conducted on the MT data revealed no main effect of Outcome ($F(1,22) = 0.882$, $p = 0.358$, $\eta_p^2 = 0.04$), but a significant main effect of Monetary Feedback ($F(2,44) = 26.544$, $p < 0.001$, $\eta_p^2 = 0.55$) as well as a significant Outcome X Monetary Feedback interaction ($F(2,44) = 4.679$, $p = 0.022$, $\eta_p^2 = 0.18$). Breakdown of the interaction revealed that when targets were hit, participants were faster in the Gain

condition as compared to both the Neutral ($t(22) = 5.482$, $p < 0.001$, r = 0.76) and the Loss conditions ($t(22) = 3.995$, $p = 0.001$, r = 0.65). Participants were also faster in the Loss as compared to the Neutral condition ($t(22) = 3.330$, $p = 0.003$, r = 0.58). When targets were missed, participants were faster in the Gain ($t(22) = 3.904$, $p = 0.002$, r = 0.64) and Loss conditions ($t(22) = 6.321$, $p < 0.001$, r = 0.80) as compared to the Neutral condition, but the Gain and Loss conditions did not differ from each other ($t(22) = 0.483$, $p = 0.634$, r = 0.10).

The ANOVA also revealed a main effect of Probability ($F(1,22) = 5.518$, $p = 0.028$, $\eta_p^2 = 0.20$), with participants being faster in the High as compared to the Low Probability of Hit conditions. All other interactions (both two- and three-way) were not significant (all $F > 0.597$ and < 3.698, all $p > 0.068$, all $\eta_p^2 > 0.04$ and < 0.14).

Kinematic Data			
Endpoint Accuracy (mm)		**High Probability**	**Low Probability**
Hits	Neutral	4.9 ± 0.3	3.3 ± 0.3
	Gain	4.6 ± 0.2	3.3 ± 0.3
	Loss	4.9 ± 0.3	3.1 ± 0.2
Misses	Neutral	10.2 ± 0.6	7.9 ± 0.4
	Gain	10.3 ± 0.6	7.5 ± 0.4
	Loss	10.2 ± 0.6	7.0 ± 0.4
RT (ms)			
Hits	Neutral	474 ± 28	482 ± 31
	Gain	474 ± 30	476 ± 33
	Loss	483 ± 32	496 ± 33
Misses	Neutral	495 ± 33	488 ± 30
	Gain	496 ± 33	485 ± 32
	Loss	505 ± 34	503 ± 32
MT (ms)			
Hits	Neutral	284 ± 8	285 ± 9
	Gain	275 ± 9	273 ± 9
	Loss	278 ± 9	281 ± 10

Misses	Neutral	282 ± 7	285 ± 8
	Gain	272 ± 8	279 ± 9
	Loss	272 ± 8	277 ± 8

Table 1. *Descriptive statistics of endpoint accuracy, RT and MT for the three factors (Outcome, Monetary Feedback and Probability). Reported values represent Mean ± SEM.*

3.2. EEG Results

3.2.1. Greater beta-band power in the Left Motor ROI after target hits with monetary incentives

The first EEG analysis sought to determine if beta-band power was enhanced following target hits as compared to misses when monetary feedback was present (i.e., Gain and Loss conditions). The time-courses of beta-band modulations following target hits and misses in each ROI are presented in Figure 2a. As can be seen, beta-band power was greater following hits than misses. This was confirmed statistically by the ANOVAs, which revealed a significant main effect of Outcome in the Left Motor ROI from 300 to 400 ms (all $F(1,22) > 8.024$ and < 11.505, all $p < 0.034$, all $\eta_p^2 > 0.27$ and < 0.34; see Table 2 for p values and effect sizes). There were no main effects of Monetary Feedback (all $F(1,22) > 0.081$ and < 1.390, all $p > 0.850$, all $\eta_p^2 < 0.06$) and no interactions (all $F(1,22) > 0.027$ and < 0.302, all $p > 0.871$, all $\eta_p^2 < 0.01$).

As monetary feedback systematically covaried with movement outcome (hits vs misses), it is possible that differences in beta-band activity were not driven by the presence of monetary feedback but merely by hitting the target. To address this, a contrast between hits and misses was conducted using only data from the Neutral condition in which no monetary feedback was delivered. As can be seen in Figure 2b,

there was no difference in beta-band power between hits and misses in any of the ROIs (all $t(22) > 0.040$ and < 1.870, all $p > 0.524$, all $r > 0.01$ and < 0.37). This suggests that the beta-band modulations observed in the preceding analysis were specifically attributable to the presence of monetary incentives. Overall, given that the influence of monetary feedback on beta-band power was restricted to the Left Motor ROI, only this ROI was used for subsequent analyses.

[Color should be used for Figure 2]

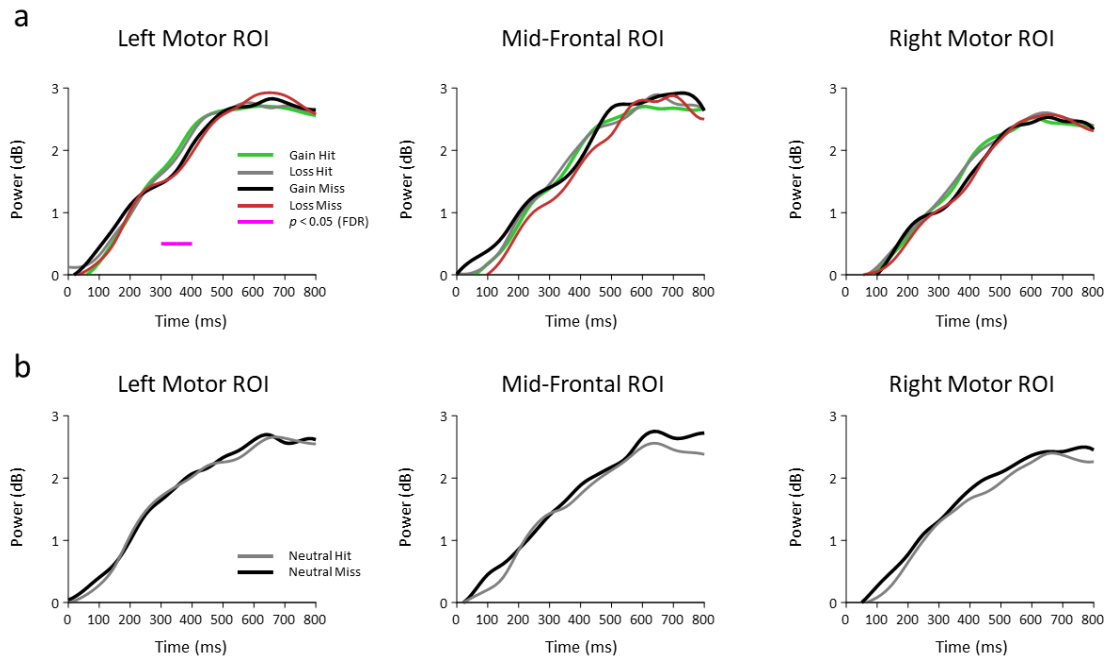

Figure 2. *Beta-band (20-30 Hz) power modulations following feedback delivery. (a) Time-courses of beta-band power following target hits and misses when monetary feedback was present (i.e., Gain and Loss conditions) in each ROI. On average, there were 41 ± 1, 39 ± 1, 29 ± 1 and 30 ± 1 trials per participant for the Gain Hit, Loss Hit, Gain Miss and Loss Miss conditions, respectively. Hitting the target with the presence of monetary incentives incurred a significant increase in beta-band power selectively*

in the Left Motor ROI from 300 to 400 ms. (b) Time-courses of beta-band power following target hits and misses when monetary feedback was not present (i.e., Neutral condition) in each ROI. On average, there were 38 ± 1 and 31 ± 1 trials per participant for the Neutral Hit and Neutral Miss conditions, respectively. There was no difference in any of the ROIs.

3.2.2. Effects of Monetary Feedback and Probability on beta-band power in Left Motor ROI

The next analysis sought to determine if beta-band power in the Left Motor ROI differed across the three Monetary Feedback conditions. Specifically, target hits in the Neutral, Gain, and Loss conditions were compared and the time-courses are presented in Figure 3a. FDR-corrected repeated measures ANOVAs conducted on each 50-ms time bin revealed that beta-band power significantly differed across feedback conditions in three time bins corresponding to 400 to 550 ms (all $F(2,44) > 4.634$ and < 8.296, all $p < 0.035$, all $\eta_p^2 > 0.17$ and < 0.27; see Table 2 for p values and effect sizes). Post-hoc comparisons revealed that beta-band power was significantly greater in the Gain ($t(22) = 3.221$, $p = 0.006$, r = 0.57) and Loss conditions ($t(22) = 2.799$, $p = 0.016$, r = 0.51) as compared to the Neutral condition (Figure 3b). Importantly, the Gain and Loss conditions did not differ from each other ($t(22) = 0.149$, $p = 0.883$, r = 0.03). To confirm that the reported difference in the Left Motor ROI was not attributable to a phenomenon occurring elsewhere on the scalp, the associated scalp map shows the differential beta-band activity resulting from the contrast Gain & Loss vs Neutral

between 400 and 550 ms. As can be seen, the differential activity between conditions was largely confined to the left motor electrodes.

The last analysis sought to test whether beta-band power in the Left Motor ROI was modulated by the Probability of Hit. To do so, target hits in the High and Low Probability conditions were compared and the time-courses are presented in Figure 3c. Using FDR-corrected pairwise *t*-tests, results revealed a significant difference in one time bin corresponding to 500 to 550 ms ($t(22) = 2.945$, $p = 0.049$, $r = 0.53$; see Table 2 for *p* values and effect sizes). Specifically, target hits in the Low Probability condition incurred a stronger beta-band response than in the High Probability condition. The associated scalp map shows the differential beta-band activity across the two Probability conditions between 500 and 550 ms. As can be qualitatively appreciated, differential activity was largely confined to the left motor electrodes, confirming that the reported statistical difference in the Left Motor ROI was not attributable to a phenomenon occurring elsewhere on the scalp.

[Color should be used for Figure 3]

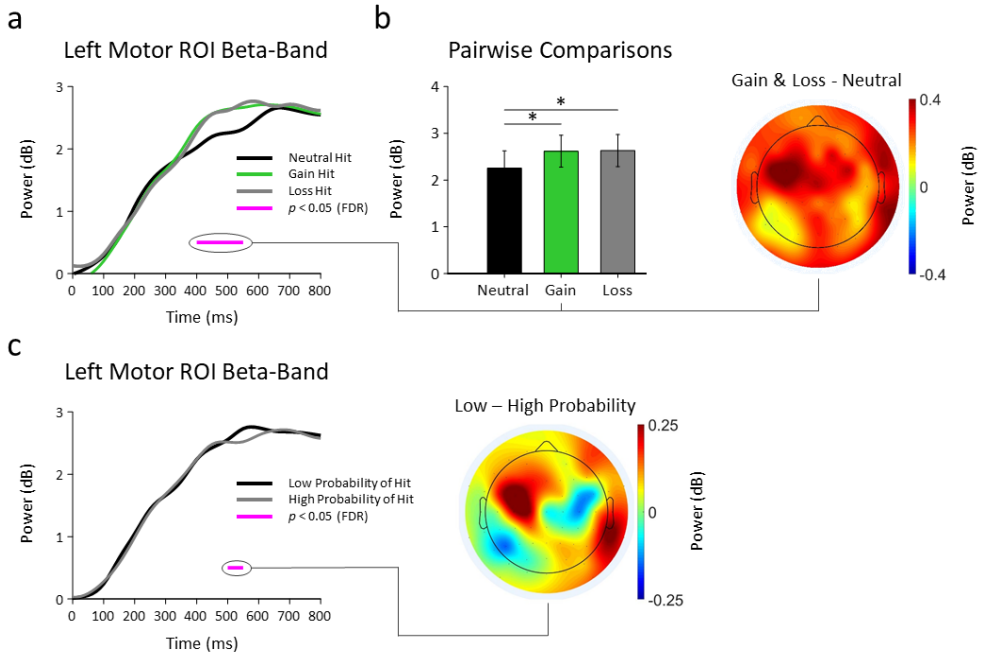

Figure 3. *Beta-band (20-30 Hz) power modulations in Left Motor ROI following feedback delivery, using data from target hits only. (a) Beta-band power modulations across the three levels of Monetary Feedback. On average, there were 38 ± 1, 41 ± 1 and 39 ± 1 trials per participant for the Neutral Hit, Gain Hit and Loss Hit conditions, respectively. There was a significant difference across conditions between 400 and 550 ms. (b) Pairwise t-tests revealed that both the Gain and Loss conditions yielded greater beta-band power than the Neutral condition. The scalp map shows the differential beta-band activity resulting from the contrast Gain & Loss vs Neutral, between 400 and 550 ms. (c) Beta-band power modulations across the two levels of Probability. On average, there were 52 ± 2 and 26 ± 1 trials per participant for the High and Low Probability conditions, respectively. The Low Probability condition yielded greater beta-band power than the High Probability condition between 500 and 550 ms. The scalp map*

shows the differential beta-band activity resulting from the contrast between the Low and High Probability conditions, between 500 and 550 ms.

Beta-Band Power – FDR-Corrected P Values (Effect sizes)									
			250 - 300 ms	300 - 350 ms	350 - 400 ms	400 - 450 ms	450 - 500 ms	500 - 550 ms	550 - 600 ms
Fig 2a	**Main effect of Outcome (Hits, Misses)**								
	(Partial Eta-Squared)	Left Motor	0.182 (0.13)	**0.009 (0.34)**	**0.034 (0.27)**	0.202 (0.11)	0.943 (< 0.01)	0.989 (< 0.01)	0.839 (0.01)
		Mid-Frontal	0.718 (0.05)	0.254 (0.14)	0.498 (0.14)	0.642 (0.04)	0.968 (< 0.01)	0.826 (0.01)	0.914 (< 0.01)
		Right Motor	0.291 (0.09)	0.117 (0.19)	0.097 (0.25)	0.277 (0.11)	0.882 (< 0.01)	0.984 (< 0.01)	0.976 (0.01)
	Main effect of Monetary Feedback (Gain, Loss)								
	(Partial Eta-Squared)	Left Motor	0.850 (< 0.01)	0.991 (0.03)	0.991 (0.05)	0.908 (< 0.01)	1.000 (0.01)	1.000 (0.01)	1.000 (0.06)
		Mid-Frontal	0.902 (0.03)	0.846 (< 0.01)	0.846 (0.01)	0.670 (0.08)	0.131 (0.23)	0.828 (0.02)	0.950 (0.01)
		Right Motor	1.000 (0.01)	0.733 (0.01)	1.000 (0.03)	0.842 (0.01)	1.000 (0.01)	0.953 (0.01)	1.000 (0.02)
	Interaction (Outcome x Monetary Feedback)								
	(Partial Eta-Squared)	Left Motor	1.000 (0.01)	1.000 (< 0.01)	0.973 (< 0.01)	1.000 (0.01)	0.871 (< 0.01)	1.000 (0.01)	1.000 (0.01)
		Mid-Frontal	0.360 (0.12)	0.247 (0.11)	0.620 (0.03)	0.305 (0.08)	0.359 (0.02)	0.954 (< 0.01)	0.914 (< 0.01)
		Right Motor	1.000 (< 0.01)	1.000 (0.02)	1.000 (0.01)	1.000 (0.01)	0.992 (< 0.01)	1.000 (< 0.01)	1.000 (< 0.01)
Fig 2b	**Neutral Hits vs Misses**								
	(Pearson's r)	Left Motor	1.000 (0.12)	0.969 (0.01)	0.919 (0.10	0.875 (0.07)	1.000 (0.11)	1.000 (0.17)	1.000 (0.18)
		Mid-Frontal	0.893 (0.03)	1.000 (0.14)	1.000 (0.18)	1.000 (0.12)	1.000 (0.06)	0.963 (0.05)	1.000 (0.20)
		Right Motor	0.893 (0.04)	0.754 (0.17)	0.609 (0.24)	0.524 (0.37)	0.841 (0.25)	0.554 (0.15)	0.606 (0.17)
Fig 3a and Fig 3b	**Monetary Feedback**								**Average from 400 to 550 ms**
	(Partial Eta-Squared)	Main Effect	0.764 (0.01)	0.756 (0.02)	0.054 (0.15)	**0.035 (0.17)**	**0.019 (0.20)**	**0.002 (0.27)**	0.133 (0.11)	**0.003 (0.24)**
	(Pearson's r)	Neutral vs Gain	0.747 (0.07)	1.000 (0.19)	**0.019 (0.53)**	**0.023 (0.53)**	**0.005 (0.57)**	**0.013 (0.52)**	0.258 (0.29)	**0.006 (0.57)**
		Neutral vs Loss	1.000 (0.16)	0.920 (0.02)	0.126 (0.36)	0.054 (0.43)	**0.050 (0.44)**	**0.002 (0.61)**	0.077 (0.45)	**0.016 (0.51)**
		Gain vs Loss	1.000 (0.08)	0.741 (0.15)	0.526 (0.14)	0.974 (0.01)	0.850 (0.04)	0.446 (0.16)	0.582 (0.12)	**0.883 (0.03)**
Fig 3c	**Probability**								
	(Pearson's r)	High vs Low	0.944 (0.05)	1.000 (0.13)	0.974 (0.01)	1.000 (0.11)	1.000 (0.07)	**0.049 (0.53)**	0.403 (0.33)	

Table 2. *FDR-corrected p values with their corresponding effect sizes for every statistical test conducted on beta-band power. In bold are the time bins where significant differences were observed. The variable used to report effect sizes is specified in parantheses (either partial eta-squared or Pearson's r). For partial eta-squared, benchmark values of 0.06 and 0.14 have been suggested to represent medium and large effect sizes, respectively, whereas for Pearson's r, values of 0.3 and 0.5 can be considered as medium and large effect sizes, respectively (Fritz et al., 2011).*

3.2.3. Greater theta-band power in Mid-Frontal ROI following target misses

This EEG data analysis sought to determine if theta-band power was enhanced following target misses as compared to target hits when monetary feedback was present (i.e., Gain and Loss conditions). The time-courses of theta-band modulations for each ROI are presented in Figure 4a. As can be seen, theta-band power was greater following misses than hits. This was confirmed by the ANOVAs, which revealed a significant main effect of Outcome between 250 and 600 ms for the Left Motor and Mid-Frontal ROIs and between 250 to 550 ms for the Right Motor ROI (all $F(1,22) > 4.661$ and < 43.956, all $p < 0.042$, all $\eta_p^2 > 0.17$ and < 0.67; see Table 3 for p values and effect sizes). There was also a main effect of Monetary Feedback from 250 to 400 ms as well as from 500 to 600 ms in the Mid-frontal ROI only (all $F(1,22) > 5.662$ and < 15.062, all $p < 0.037$, all $\eta_p^2 > 0.20$ and < 0.41) and no interaction in the three ROIs (all $F(1,22) > 0.007$ and < 6.072, all $p > 0.154$, all $\eta_p^2 > 0.01$ and < 0.22).

As monetary feedback systematically covaried with movement outcome (hits vs misses), it is possible that differences in theta-band activity were not driven by the presence of monetary feedback but merely by missing the target. To address this, a contrast between hits and misses was conducted using only data from the Neutral condition in which no monetary feedback was delivered. As can be seen in Figure 4b, there were differences in theta-band power between hits and misses in the three ROIs from 250 to 600 ms in the Left and Right Motor ROIs and from 300 to 500 ms in the Mid-Frontal ROI (all $t(22) > 2.437$ and < 4.516, all $p < 0.027$, all $r > 0.46$ and < 0.69; see Table 3 for p values and effect sizes). Because previous studies have documented

mid-frontal theta-band modulations in punishment processing (Cohen et al., 2007; Marco-Pallarés et al., 2008; De Pascalis et al., 2012; Andreou et al., 2017) and in negative performance feedback processing (Cavanagh et al., 2010; van de Vijver et al., 2011; Luft et al., 2013; Mas-Herrero and Marco-Pallarés, 2014; Arrighi et al., 2016), only the Mid-Frontal ROI was kept for further analyses.

[Color should be used for Figure 4]

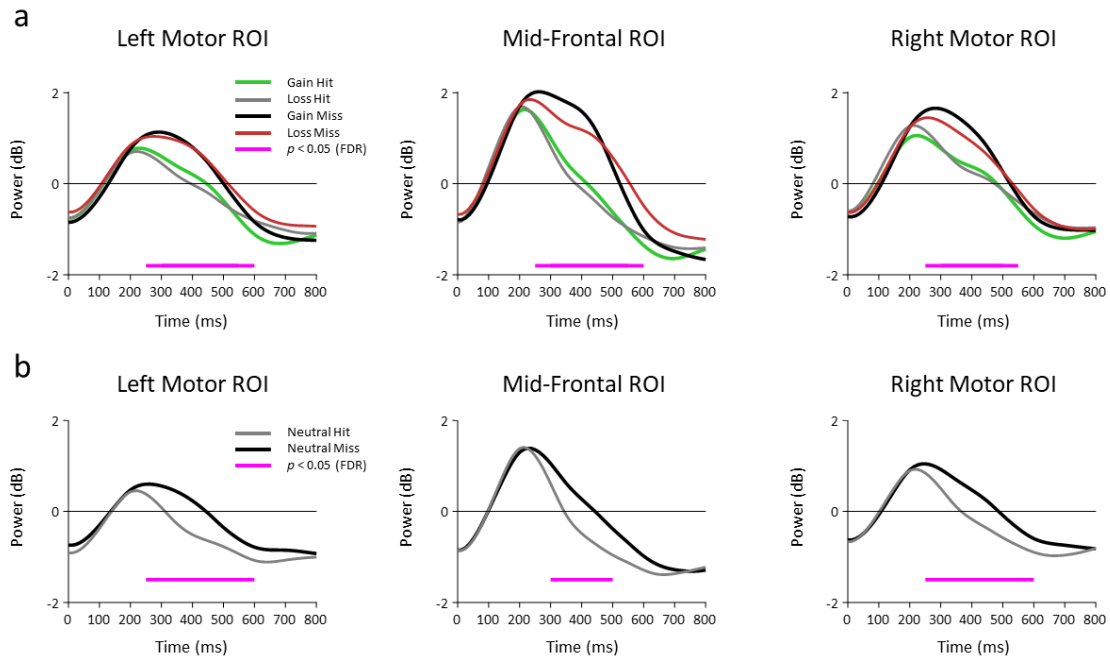

Figure 4. *Theta-band (3-8 Hz) power modulations following feedback delivery. (a) Time-courses of theta-band power following target hits and misses when monetary feedback was present (i.e., Gain and Loss conditions) in each ROI. On average, there were 41 ± 1, 39 ± 1, 29 ± 1 and 30 ± 1 trials per participant for the Gain Hit, Loss Hit, Gain Miss and Loss Miss conditions, respectively. Missing the target with the presence of monetary incentives incurred a significant increase in theta-band power in all ROIs*

between 250 to 600 ms. (b) Time-courses of theta-band power following targets hits and misses when monetary feedback was not present (i.e., Neutral condition) in each ROI. On average, there were 38 ± 1 and 31 ± 1 trials per participant for the Neutral Hit and Neutral Miss conditions, respectively. Significant differences were found in each ROI between 250 to 600 ms.

3.2.4. Effects of Monetary Feedback and Probability on theta-band power in Mid-Frontal ROI

The next analysis sought to determine if theta-band power in the Mid-Frontal ROI differed across the three Monetary Feedback conditions. Specifically, target misses in the Neutral, Gain, and Loss conditions were compared and the time-courses are presented in Figure 5a. FDR-corrected repeated measures ANOVAs conducted on each 50-ms time bin revealed that theta-band power significant differed across feedback conditions between 250 and 600 ms (all $F(2,44) > 6.417$ and < 18.196, all $p < 0.006$, all $\eta_p^2 > 0.23$ and < 0.45; see Table 3 for p values and effect sizes). Post-hoc comparisons revealed that theta-band power was significantly greater in the Loss ($t(22) = 3.863$, $p = 0.001$, r = 0.64) and Gain conditions ($t(22) = 4.619$, $p < 0.001$, r = 0.70) as compared to the Neutral condition (Figure 5b). Importantly, the Gain and Loss conditions did not differ from each other ($t(22) = 0.181$, $p = 0.858$, r = 0.04). To confirm that the reported difference in the Mid-Frontal ROI was not attributable to a phenomenon occurring elsewhere on the scalp, the associated scalp map shows the differential theta-band activity resulting from the contrast Gain & Loss vs Neutral

between 250 and 600 ms. As can be seen, the differential activity between conditions was largely confined to mid-frontal electrodes.

The last analysis sought to test whether theta-band power in the Mid-Frontal ROI was modulated by the Probability of Hit. To do so, target misses in the High and Low Probability conditions were compared and the time-courses are presented in Figure 5c. As can be seen, there was a tendency for lowly probable target misses (i.e., High Probability of Hit conditions) to yield greater theta-band responses. However, pairwise *t*-tests revealed no significant difference between the High and Low Probability of Hit conditions in any of the time bins (all $t(22) > 1.114$ and < 2.266, all $p > 0.127$, all $r > 0.23$ and < 0.44).

[Color should be used for Figure 5]

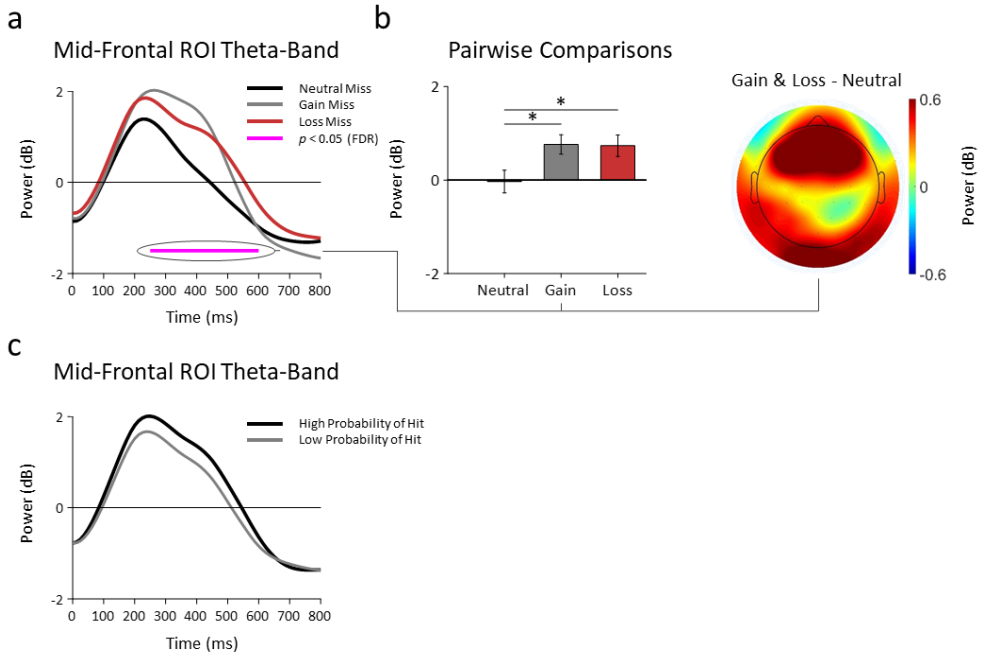

Figure 5. *Theta-band (3-8 Hz) power modulations in Mid-Frontal ROI following feedback delivery, using data from target misses only. (a) Theta-band power*

modulations across the three levels of Monetary Feedback. On average, there were 31 ± 1, 29 ± 1 and 30 ± 1 trials per participant for the Neutral Miss, Gain Miss and Loss Miss conditions, respectively. There was a significant difference across conditions between 250 and 600 ms. (b) Pairwise t-tests revealed that the Gain and Loss conditions yielded greater theta-band power than the Neutral condition. The scalp map shows the differential theta-band activity resulting from the contrast Gain & Loss vs Neutral, between 250 and 600 ms. (c) Theta-band power modulations across the two levels of Probability. On average, there were 43 ± 1 and 17 ± 1 trials per participant for the High Probability of Hit (i.e., lowly probable misses) and Low Probability of Hit conditions (i.e., highly probable misses), respectively. FDR-corrected pairwise t-tests revealed no significant differences across conditions.

Theta-Band Power – FDR-Corrected P Values (Effect sizes)									
			250 - 300 ms	300 - 350 ms	350 - 400 ms	400 - 450 ms	450 - 500 ms	500 - 550 ms	550 - 600 ms	
Fig 4a	**Main effect of Outcome (Hits, Misses)**									
	(Partial Eta-Squared)	Left Motor	**< 0.001 (0.44)**	**< 0.001 (0.49)**	**< 0.001 (0.28)**	**0.001 (0.42)**	**0.003 (0.34)**	**0.010 (0.26)**	**0.042 (0.17)**	
		Mid-Frontal	**< 0.001 (0.49)**	**< 0.001 (0.54)**	**< 0.001 (0.58)**	**<0.001 (0.63)**	**< 0.001 (0.67)**	**< 0.001 (0.64)**	**< 0.001 (0.49)**	
		Right Motor	**< 0.001 (0.54)**	**< 0.001 (0.54)**	**< 0.001 (0.47)**	**0.002 (0.38)**	**0.007 (0.30)**	**0.024 (0.22)**	0.142 (0.10)	
	Main effect of Monetary Feedback (Gain, Loss)									
	(Partial Eta-Squared)	Left Motor	0.376 (0.07)	0.440 (0.08)	0.399 (0.05)	0.601 (0.02)	0.863 (0.00)	0.624 (0.08)	0.170 (0.21)	
		Mid-Frontal	**0.023 (0.23)**	**0.011 (0.28)**	**0.026 (0.23)**	0.203 (0.08)	0.670 (0.01)	**0.037 (0.20)**	**0.001 (0.41)**	
		Right Motor	0.343 (0.05)	0.196 (0.13)	0.259 (0.14)	0.277 (0.07)	0.989 (0.00)	0.291 (0.09)	0.228 (0.19)	
	Interaction Outcome x Monetary Feedback									
	(Partial Eta-Squared)	Left Motor	0.812 (0.00)	0.741 (0.03)	0.602 (0.08)	0.868 (0.10)	0.435 (0.08)	0.825 (0.01)	0.862 (0.01)	
		Mid-Frontal	0.505 (0.03)	0.444 (0.06)	0.492 (0.04)	0.781 (0.00)	0.273 (0.13)	0.154 (0.22)	0.182 (0.13)	
		Right Motor	0.916 (0.10)	0.500 (0.09)	0.752 (0.04)	0.808 (0.01)	1.000 (0.00)	0.932 (0.00)	0.774 (0.03)	
Fig 4b	**Neutral Hits vs Misses**									
	(Pearson's r)	Left Motor	**0.009 (0.52)**	**0.001 (0.65)**	**< 0.001 (0.69)**	**< 0.001 (0.66)**	**0.005 (0.55)**	**0.016 (0.49)**	**0.021 (0.47)**	
		Mid-Frontal	0.064 (0.40)	**0.009 (0.55)**	**0.004 (0.59)**	**0.007 (0.57)**	**0.027 (0.49)**	0.063 (0.41)	0.082 (0.36)	
		Right Motor	**0.014 (0.49)**	**0.002 (0.60)**	**0.001 (0.63)**	**< 0.001 (0.66)**	**0.001 (0.62)**	**0.007 (0.54)**	**0.023 (0.46)**	
Fig 5a and Fig 5b	**Monetary Feedback**									**Average from 250 to 600 ms**
	(Partial Eta-Squared)	Main Effect	**< 0.001 (0.30)**	**< 0.001 (0.40)**	**< 0.001 (0.45)**	**< 0.001 (0.44)**	**< 0.001 (0.35)**	**0.003 (0.27)**	**0.006 (0.23)**	**< 0.001 (0.38)**
	(Pearson's r)	Neutral vs Gain	**0.002 (0.63)**	**< 0.001 (0.71)**	**< 0.001 (0.76)**	**< 0.001 (0.76)**	**0.001 (0.64)**	0.111 (0.33)	0.791 (0.06)	**< 0.001 (0.70)**
		Neutral vs Loss	**0.022 (0.49)**	**0.003 (0.58)**	**0.001(0.63)**	**0.001 (0.65)**	**0.002 (0.62)**	**0.006 (0.57)**	**0.029 (0.47)**	**0.001 (0.64)**
		Gain vs Loss	0.062 (0.39)	**0.025 (0.46)**	**0.047 (0.41)**	0.424 (0.17)	0.221 (0.26)	**0.010 (0.54)**	**0.002 (0.61)**	**0.858 (0.04)**
Fig 5c	**Probability**									
	(Pearson's r)	High vs Low	0.235 (0.44)	0.214 (0.39)	0.212 (0.35)	0.176 (0.34)	0.144 (0.34)	0.127 (0.34)	0.277 (0.23)	

Table 3. *FDR-corrected p values with their corresponding effect sizes for every statistical test conducted on theta-band power. In bold are the time bins where significant differences were observed. The variable used to report effect sizes is specified in parantheses (either partial eta-squared or Pearson's r). For partial eta-squared, benchmark values of 0.06 and 0.14 have been suggested to represent medium and large effect sizes, respectively, whereas for Pearson's r, values of 0.3 and 0.5 can be considered as medium and large effect sizes, respectively (Fritz et al., 2011).*

3.3. Additional kinematic and EEG analyses

3.3.1. Adressing the possible emergence of fatigue in kinematic and EEG data

To verify the possibility that participants accumulated fatigue over the course of the experiment, pairwise comparisons (Early vs Late epochs) were conducted on the endpoint accuracy, RT, and MT data. Results revealed no difference for RT ($Z = 0.091$, $p = 0.927$, r = 0.01) and MT ($t(22) = 0.329$, $p = 0.577$, r = 0.07). As for endpoint accuracy, the analysis revealed a slight but significant difference across epochs ($Z = 3.133$, $p = 0.002$, r = 0.46), with participants being 0.5 ± 0.1 mm more accurate late as compared to early. Overall, these data suggest that fatigue was not an issue in the present experiment.

The next analysis evaluated the stability of the EEG data over the course of the experiment. To do so, a 2 Outcome (Hit, Miss) X 2 Monetary Feedback (Gain, Loss) X 2 Epoch (Early, Late) repeated measures ANOVA was conducted on the data from the significant time bins from Figure 2a (Left Motor beta-band power, from 300 to 400 ms) and Figure 4a (Mid-Frontal theta-band power, from 250 to 600 ms). Concerning the Left Motor beta-band power, the ANOVA revealed no main effect of Epoch ($F(1,22) = 0.486$, $p = 0.493$, $\eta_p^2 = 0.02$) but still showed a significant main effect of Outcome ($F(1,22) = 12.631$, $p = 0.002$, $\eta_p^2 = 0.37$). No main effect of Monetary Feedback ($F(1,22) = 0.222$, $p = 0.642$, $\eta_p^2 = 0.01$) and no interaction were found (all $F(1,22) > 0.014$ and < 1.382, all $p > 0.252$, all $\eta_p^2 > 0.01$ and < 0.06). As for Mid-Frontal theta-band power, the ANOVA revealed a similar pattern of results: no main effect of Epoch ($F(1,22) = 0.134$, $p = 0.718$, $\eta_p^2 = 0.01$) but a significant main effect

of Outcome ($F(1,22) = 37.981$, $p < 0.001$, $\eta_p^2 = 0.63$). No main effect of Monetary Feedback ($F(1,22) = 0.979$, $p = 0.333$, $\eta_p^2 = 0.04$) and no interaction were found (all $F(1,22) > 0.284$ and < 2.877, all $p > 0.104$, all $\eta_p^2 < 0.12$). Overall, these analyses confirm that the observed differences in both beta- and theta-band power were consistent across the experiment.

3.3.2. Assessing the correlation between kinematic and EEG data

The next analysis sought to evaluate whether differences in EEG power across conditions were related to differences in movement kinematics across conditions. To do so, the EEG power data were averaged over the time bins that presented a significant difference between conditions (for both Left Motor beta- and Mid-Frontal theta-band power) and were correlated with their corresponding differences in MT and RT data. Specifically, for Left Motor beta-band power, the averaged time bins used for this analysis were 300 to 400 ms for the Main effect of Outcome (Hits vs Misses; Figure 2a), 400 to 550 ms for the Main effect of Monetary Feedback (Gain & Loss vs Neutral; Figure 3a) and 500 to 550 ms for the Probability effect (Figure 3c). As for Mid-Frontal theta-band power, the averaged time bins used for this analysis were 250 to 600 ms for the main effect of Outcome (Hits vs Misses; Figure 4a), 300 to 500 ms for the effect of Neutral Hits vs Misses (Figure 4b), as well as 250 to 600 ms for the main effect of Monetary Feedback (Gain & Loss vs Neutral; Figure 5a).

Results revealed no significant correlation between Left Motor beta-band power and RT as well as MT (all $r(21)$ or $r_s(21) > 0.106$ and < 0.286, all $p > 0.372$). Similarly, there was no significant correlation between Mid-Frontal theta-band power and RT as

well as MT (all r(21) or $r_s(21)$ > 0.059 and < 0.269, all p > 0.428). This suggests that kinematic differences are not related to the observed differences in beta- and theta-band activity.

3.3.3. The influence of the preceding trial on reward and punishment processing

To evaluate a potential influence of the preceding trial on the processing of rewards (i.e., target hit in the Gain condition) and punishments (i.e., target misses in the Loss condition), the EEG data of Gain Hit and Loss Miss trials were binned separately depending on whether they were preceded by a target hit or a target miss. This resulted in four new conditions: rewards preceded by a hit (50 ± 3 trials), rewards preceded by a miss (30 ± 1 trials), punishments preceded by a hit (29 ± 1 trials) and punishments preceded by a miss (27 ± 2 trials).

The Left Motor beta- and Mid-Frontal theta-band power responses were submitted to 2 Preceding Outcome (Hit, Miss) X 2 Monetary Outcome (Reward, Punishment) repeated measures ANOVAs on each of the seven time-bins spanning 250 to 600 ms, with FDR correction implemented on those seven time-bins. For Left Motor beta-band power, the ANOVAs revealed a main effect of Monetary Outcome from 300 to 400 ms (all $F(1,22)$ >8.149 and < 11.732, all p < 0.032, all η_p^2 > 0.27 and < 0.35), with beta-band power being greater after rewards than punishments. More importantly, no main effect of Preceding Outcome (all $F(1,22)$ > 0.105 and < 1.624, all p > 0.748, all η_p^2 < 0.07) and no interaction were found (all $F(1,22)$ > 0.105 and < 1.299, all p values > 0.749, all η_p^2 < 0.06).

For Mid-Frontal theta-band power, the ANOVAs revealed a significant main effect of Monetary Outcome from 250 to 600 ms (all $F(1,22) > 8.994$ and < 30.948, all $p < 0.007$, all $\eta_p^2 > 0.29$ and < 0.58), with theta-band power being greater after punishments than rewards. There was no main effect of Preceding Outcome (all $F(1,22) > 0.004$ and < 0.688, all $p > 0.966$, all $\eta_p^2 > 0.01$ and < 0.03), but there was a significant interaction from 300 to 600 ms (all $F(1,22) > 4.872$ and < 15.526, all $p < 0.044$, all $\eta_p^2 > 0.18$ and < 0.41). Breakdown of the interaction revealed that theta-band activity following punishments was greater when the preceding trial was a hit as compared to when it was a miss ($t(22) = 2.594$, $p = 0.034$, r = 0.48), whereas theta-band activity following rewards did not differ as a function of the preceding trial ($t(22) = 1.965$, $p = 0.061$, r = 0.39). Overall, these results suggest that in the present experimental context, there was an effect of the preceding trial on theta-band activity during punishment processing, but not on beta-band activity.

4. Discussion

The present study sought to test the hypothesis that beta- and theta-band oscillations respectively reflect monetary rewards and punishments in a goal-directed reaching task, and that monetary feedback results in greater oscillatory activity than motor performance feedback alone. EEG time-frequency analyses revealed a double dissociation between target hits and misses when monetary incentives were provided. Namely, target hits associated with contextually positive outcomes (i.e., reward or punishment avoidance) incurred greater beta-band power over contralateral motor

regions, whereas target misses associated with contextually negative outcomes (i.e., punishment or reward omission) incurred greater theta-band power over mid-frontal regions. Results further revealed that beta-band activity was also modulated according to the probability of hitting the target.

4.1. Beta-band power over contralateral motor regions for rewards

One of the main novel findings of the present work is that monetary rewards induced greater oscillatory activity in the beta-band selectively at left motor electrodes. This observation adds to recent studies that have used non-motor tasks such as gambling (Andreou et al., 2017; Cohen et al., 2007; HajiHosseini and Holroyd, 2015a, 2015b; HajiHosseini et al., 2012; Marco-Pallarés et al., 2008, 2009; Mas-Herrero et al., 2015), suggesting that this frequency band constitutes a marker of monetary reward processing across a broad range of behaviors. Interestingly, unlike these previous studies, the present beta-band modulations were strongly lateralized, suggesting that monetary reward processing implicated motor cortical regions linked with movement planning and execution. This finding is consistent with recent evidence stemming from animal work and human neuroimaging which have reported potent modulations in motor cortical activity for reward processing in the context of motor tasks (Marsh et al., 2015; Ramakrishnan et al., 2017; Ramkumar et al., 2016; Saiki et al., 2014; Suzuki et al., 2014). For instance, Saiki et al. (2014) reported that M1 neurons of rodents represented both reward- and motor-related information when they obtained liquid rewards following successful performance of a forelimb movement task. Similarly, Ramkumar et al. (2016) recorded single-cell activity of PMd and M1 neurons while monkeys obtained a juice reward based on accurate performance in a goal-directed

reaching task very similar to the one used here. They found that neuronal activity reflected reward processing in both regions, arguing that the availability of this information within motor regions was critical for reward-based learning. In light of these findings, the present beta-band modulations over motor cortical regions are likely to constitute a scalp electrophysiological manifestation of reward-related processing within PMd and/or M1.

The finding that beta-band power over contralateral motor regions was greater when target hits were rewarded (i.e., Gain condition [+ 0.05$]) as compared to when target hits were unrewarded (i.e., Neutral condition [+ 0.00$]) speaks to the added value of monetary rewards on positive motor performance feedback. This finding is consistent with recent work from Widmer et al. (2016) who recorded fMRI while participants acquired an upper-limb arc-tracking task which could be either supplemented with monetary rewards or not. They found that adding monetary rewards after positive motor performance feedback led to a greater blood-oxygen-level dependent (BOLD) response in the ventral striatum during acquisition and better retention of the motor skill when assessed 24h later, as compared to motor performance feedback alone (see also Lutz et al. [2012] for similar findings). Reward valuation in the ventral striatum is critical for reward-based learning (for a review, see Daniel and Pollmann, 2014) and reward signals must reach task-relevant brain regions to shape behaviors (Pessoa and Engelmman, 2010). Based on the known projections from reward-related brain areas, such as the ventral tegmental area (VTA) and substantia nigra (SN), to primary motor areas (Hosp and Luft, 2013), the present increase in beta-

band activity following rewards is likely to reflect a greater engagement of the reward network, possibly mediating the improvements in motor memory formation.

4.2. Beta-band power over contralateral motor regions for successful punishment avoidance

Another important finding is that target hits that allowed to avoid monetary punishments (i.e., Loss Condition [+ 0.00$]) entailed similar beta-band power over left motor regions as target hits with monetary rewards (i.e., Gain Condition [+ 0.05$]). This indicates that beta-band power does not reflect the absolute value of a monetary reward, but rather an outcome that acquires a positive value as a function of the context. Interestingly, several fMRI studies have reported that the reward network is engaged similarly for monetary rewards and punishment avoidance, two contexts in which the outcome is perceived as being desirable (Knutson et al., 2000; Kim et al., 2006; Nieuwenhuis et al., 2005; Palminteri et al., 2012, 2015; Pessiglione et al., 2006). For instance, Palminteri et al. (2015) used fMRI in a task in which participants could get monetary rewards or punishments while learning arbitrary stimulus-outcome pairings. They showed that the BOLD response related to monetary punishments in the anterior insula shifted to the ventral striatum when punishments were avoided, thus eliciting similar activation of the reward network as reward delivery. In the same vein, Knutson et al. (2000) used a monetary incentive delay task and reported similar heightened BOLD responses in the left M1 for conditions involving monetary rewards or punishments, as compared to a neutral condition where stimuli lacked an incentive value. Furthermore, recent psychophysical work has shown that retention of a visuomotor perturbation can be enhanced by monetary punishments (Song and Smiley-

Oyen, 2017). Namely, these authors demonstrated that participants who received monetary punishments on 50% of the trials or rewards on 100% of the trials during acquisition demonstrated equivalent relearning rates upon reexposure to the visual perturbation. In sum, the present results support the notion that in contexts where the desirable outcome is to avoid being punished, punishment avoidance acts as a reinforcement.

4.3. Beta-band power for lowly probable target hits

Beta-band power over left motor regions was greater when target hits were lowly probable (i.e., small target) as compared to when they were highly probable (i.e., large targets). Such sensitivity of motor cortical regions to reward probability finds echo in recent work from Ramakrishnan et al. (2017) who demonstrated that monkey M1 and S1 neurons respond differently to unexpected changes in reward magnitude (i.e., reward prediction error [RPE]) in a reaching task. These results suggest that lowly expected target hits entail greater engagement of the reward network, an interpretation supported by the fact that midbrain dopaminergic neurons are also known to be sensitive to RPEs (for recent reviews, see Schultz, 2016a, 2016b). Interestingly, Dayan et al. (2014) showed that providing rewards in a stochastic (i.e., unexpected) manner benefited both the acquisition and long-term retention of a new visuomotor task. One possibility is that the increase in beta-band power reflects the additional recruitment of the reward network for the storage of relevant information for goal-directed behaviors, providing neurophysiological grounds to the Ramakrishnan et al. (2017) and Dayan et al. (2014) findings.

Additional analyses revealed that the present beta-band responses during reward processing were not influenced by whether the preceding trial was a hit or or a miss [see Ramkumar et al. (2016) for similar observation]. This lack of sensitivity to reward/punishment history could be a by-product of the experimental procedures (i.e., the pseudo-randomization of conditions, limiting the opportunity to transfer knowledge from one trial to another) or it could indicate that this frequency band is modulated independently of the history of preceding trials. Work is underway to specifically test if reward signals in the beta-band are dependent upon the recent history of outcomes and memory formation in a learning paradigm.

4.4. Functional interpretation of beta-band activity: possible interaction with the basal ganglia

It is likely that the present beta-band modulations following rewards implicated the basal ganglia. Although EEG cannot assess the contribution of deep brain structures, the similarities between the present results and known patterns of reward processing in the basal ganglia open up the possibility that there is a link between the two. Indeed, reward processing in the basal ganglia has been shown to be subtended by beta-band oscillations (Courtemanche et al., 2003; Feingold et al., 2015; Münte et al., 2008, 2017). Furthermore, functional communication between motor cortical regions and the basal ganglia occurs largely in a beta-band channel (Ahn et al., 2015; Beck et al., 2016; Cassim et al., 2002; Delaville et al., 2014; Feingold et al., 2015; Kondabolu et al., 2016; McCairn and Turner, 2015; Tan et al., 2014; Vorobyov et al., 2003), with cells in both regions co-representing movement- and reward-related information (Ramakrishnan et al., 2017; Puryear et al., 2010; Isomura et al., 2013). These reward-

related signals originating from the basal ganglia, manifesting in the form of phasic dopaminergic activity, would be critical for triggering plastic changes subtending motor memory formation within M1 (Guo et al., 2015; Hosp et al., 2009, 2011; Molina-Luna et al., 2009; Rioult-Pedotti et al., 2015; Vitrac et al., 2014). This is further supported by the fact that cortical beta-band power in response to monetary rewards is modulated by genetic differences in dopamine-related enzymatic activity (Marco-Pallarés et al., 2009). In this light, it is likely that the present contralateralized beta-band modulations constitute the neurophysiological underpinning of reward-based motor memory enhancements.

4.5. Theta-band power over mid-frontal regions for negative motor performance feedback and punishments

In the Neutral condition, thus in absence of monetary feedback, theta-band power over mid-frontal regions was greater after target misses than target hits. This finding replicates previous results revealing the implication of theta-band activity in negative performance monitoring (Cavanagh and Frank, 2014; Luft et al., 2013; van de Vijver et al., 2011; Cavanagh et al., 2010; Mas-Herrero and Marco-Pallarés, 2014; Arrighi et al., 2016). Interestingly, some of these studies have shown that the magnitude of theta-band power after negative performance feedback positively correlates with performance improvements on subsequent trials, suggesting that feedback giving rise to the largest theta-band responses might be most beneficial to performance. Along this line, a novelty of the present work is the increased theta-band response following monetary punishments (i.e., target misses in the Loss condition [- 0.05 $]) as compared to negative performance feedback alone (i.e., target misses in the Neutral condition [-

0.00 $]). This suggests that monetary punishments may signal an emphasized need for behavioral adjustments on subsequent trials, thus providing a neurophysiological basis to behavioral reports showing a beneficial effect of monetary punishments on short-term motor performance (Galea et al., 2015; Steel et al., 2016; Song and Smiley-Oyen, 2017; Wächter et al., 2009). Further support for this comes from the additional analysis addressing the influence of the preceding trial on punishment processing. Namely, theta-band power during punishment processing was found to be greater when the preceding trial was a hit as compared to when it was a miss, suggesting that this frequency band is sensitive to reward/punishment history.

4.6. Theta-band power over mid-frontal regions for reward omission

Theta-band power was also found to be greater when rewards were not obtained (i.e., reward omissions, referring to target misses in the Gain condition [- 0.00 $]) as compared to negative performance feedback alone (i.e., target misses in the Neutral condition [- 0.00 $]). This indicates that theta-band power does not reflect absolute monetary outcome processing, but rather monetary outcomes that acquire a context-dependent negative value. In support, Wrase et al. (2007) recorded fMRI and showed that monetary punishments and reward omissions gave rise to similar orbitofrontal cortex activity, suggesting that frontal brain regions evaluate monetary outcomes in a context-dependent manner. The present results thus open up the possibility that reward omissions might be beneficial to performance by increasing theta-band activity.

4.7. Functional interpretation of theta-band activity: possible reflection of noradrenergic phasic activity in medial frontal regions to optimize performance

Although speculative, it is possible that the present theta-band responses reflect phasic norepinephrine (NE) activity in medial frontal regions, a neuromodulator directly involved in performance optimization of ensuing behaviors (see Aston-Jones and Cohen, 2005; Uematsu et al., 2015). In support, several recent studies using pupillometry, fMRI, EEG, computational and/or psychopharmacological approaches have linked this neurobiological system to performance optimization (Browning et al., 2015; Chmielewski et al., 2017; Ebitz and Platt, 2015; Eldar et al., 2013; Howlet et al., 2017; Mückschel et al., 2017a, 2017b; Payzan-LeNestour et al., 2013). Interestingly, an association between NE activity and mid-frontal theta-band activity has been proposed (Dippel et al., 2017; Zitnik et al., 2016). Namely, Dippel et al. (2017) recorded EEG and pupillometry data and found that pupil dilatation (i.e., a reflection of NE activity) strongly correlated with mid-frontal theta-band (4-7 Hz) responses when participants had to volitionally withhold a keypress, suggesting that theta-band activity during cognitive control tasks matches patterns of NE activity in the mid-frontal cortex. Hence, because theta-band responses play a key role in the processing of negative feedback and in the updating of performance (see Frank and Cavanagh, 2014), one possibility is that the present theta-band activity reflects phasic NE activity in mid-frontal brain regions, thereby increasing the efficiency of the neuronal units that mediate performance of subsequent behaviors. Future studies should address the possible relationship between short-term performance improvements, theta-band and phasic NE activity in mid-frontal brain regions.

4.8. Conclusion

Overall, the present work characterizes the EEG oscillatory signatures of positive and negative monetary feedback processing in the context of goal-directed reaching movements. The identified changes in oscillatory power constitute plausible neural substrates for the documented effects of monetary incentives on motor learning and performance.

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6. Discussion: how can we go further?

6.1. Integrating the two scientific contributions: behavioral and neurophysiological perspectives

The two present scientific contributions have provided evidence that both behavioral repetitions and reward processing have a bearing on neuronal activity in cortical motor areas (i.e., under the form of disrupted consolidation and greater reward-related oscillatory power responses in the beta-band, respectively). Although the nature of their reported effects on cortical activity appears to differ at first sight, at the cellular level, both behavioral repetitions and oscillatory activity have been argued to influence spike-timing-dependent activity (Frémaux and Gerstner, 2016; Masquelier, 2014; Jutras and Buffalo, 2010). The effects of repetition-dependent and reward processing on spike-timing-dependent activity are worth considering because this framework allows formulating predictions on the interaction between behavioral repetitions and reward processing (i.e., from a behavioral perspective) and on their potential synergistic influence on neuronal activity in motor areas (i.e., a system's level neurophysiological perspective).

Namely, cellular work has shown that the release of extracellular dopamine potentiates STDP mainly by widening the critical time-window necessary to temporally integrate pre and postsynaptic spikes (Zhang et al., 2009; Ruan et al., 2014), which is crucial for Hebbian learning to occur (Amtul and Atta-Ur-Rahman, 2015). More specifically, without dopamine, this time-window is of ~ 10 ms, but when dopamine is present, this time-window widens to ~ 45 to 60 ms (Zhang et al., 2009; Ruan et al., 2014). Moreover, Zhang et al. (2009) reported that lower number of repetitive pairings are necessary to trigger LTP and that the effect of dopamine on STDP was dependent on DA D1-like receptors (i.e., the receptors that are sensitive to phasic dopaminergic responses). Overall, dopamine appears to bias STDP mechanisms toward potentiation.

From a behavioral perspective, considering the above cellular evidence, the delivery of monetary rewards while behaviors are repeating during the attainment of a performance plateau should promote consolidation processes as compared to the effects of reward delivery or repetitions alone. This hypothesis could easily be tested by having 6 groups of participants adapting to a visual deviation while manipulating the delivery of monetary rewards based on accurate performance during asymptote (rewarded, neutral trials) as well as the number of trials executed at performance asymptote during acquisition (short, medium, long). To infer an effect on consolidation processes, behavioral performance levels would need to be measured in a retention session, 24 hours later. A between-group interaction should be expected in performance levels at retention, where the group that received rewards while experiencing the longest asymptote (i.e., a greater number of repeating trials) should outperform all of the other groups. This would provide evidence that rewards and behavioral repetitions interact to benefit consolidation processes.

From a neurophysiological perspective, building on the two present scientific contributions and the above reported cellular work, the expected interaction between repetitions and rewards could have a bearing on cortical motor area neuronal activity. One way to test this could be to deliver TMS single-pulses over task-relevant muscle representations in M1 (i.e., the bicep and deltoid muscle representations) and to measure motor evoked potentials (MEPs) through electromyogram recordings (Kantak et al., 2013) during visuomotor adaptation. More specifically, using the same experimental design briefly described above, MEPs could be expected to be of higher amplitude (Hirano et al., 2015) when behaviors are being both repeating and rewarded during asymptote, which would suggest a facilitation/potentiation of the corticospinal projections from M1 to task-relevant muscles (Carson et al., 2016). In support, a recent study provided evidence of the interaction between repetitions and rewards during acquisition (Mawase et al., 2017), but the effects on increased excitability in M1 on consolidation processes remain unknown. One way to demonstrate this would be to measure behavioral performance levels during a retention session, 24h later, to which

would be correlated the MEP amplitude changes induced by the repeating and rewarded conditions during acquisition. This project would build upon the present thesis by providing evidence that repetition-dependent and reward-based mechanisms can interact during acquisition (by means of MEP recordings), which improves consolidation processes.

6.2. Testing the hypothesis that post-movement beta-band power over motor areas is predictive of the amount of retention 24h later

As acquisition proceeds and performance reaches asymptote, EEG studies have shown attenuations in post-movement ERPs (i.e., the error-related negativity and the P300) in the slow as compared to the fast stage of acquisition (Beaulieu et al., 2014; Quinlivan et al., 2014; Bednark et al., 2013; Padrão et al., 2014). For instance, Quinlivan et al. (2014) had participants undergo a goal-directed reaching task in which the objective was to learn the location of hidden targets while EEG data were recorded. When comparing EEG data from the last to the first block of 30 acquisition trials, results revealed an attenuation of the P300 ERP component. Analyses performed on a control condition revealed that behavioral improvements need to occur in order for the P300 to decline as a function of acquisition. Interestingly, recent EEG studies investigating oscillatory power have found similar results, suggesting that changes in motor beta-band power during acquisition could perhaps be predictive of retention (Torrecillos et al., 2015; Tan et al., 2016; Özdenizci et al., 2017). For instance, Torrecillos et al. (2015) have shown that foreperiod (i.e., before the movement is executed) motor beta-band power is enhanced when no errors are made during force-field adaptation, a behavior typically occurring during the slow stage of acquisition. Interestingly, Tan et al. (2016) showed that post-movement beta-band power increases as movements become more successful during visuomotor adaptation. Also using force-field adaptation, Özdenizci et al. (2017) have shown that participants with higher and lower adaptation rates respectively showed decreases and increases in the foreperiod beta-band power over sensorimotor regions. Although these later studies used a limited number of practice trials during adaptation, which hinders their possible

direct translation to consolidation processes, they nonetheless suggest that the investigations of EEG oscillatory activity, and potentially beta-band power, during acquisition could be linked to consolidation.

Because rewards facilitate the formation of motor memories, their influence on motor cortical activity should be apparent when motor memory starts to consolidate, that is during the slow stage of acquisition. Converging lines of evidence now suggest that reward-based motor memory formation entails changes in M1 reward activity (Ramkumar et al., 2016; Ramkumar et al., 2017), likely during the slow stage of acquisition (Hamel et al., 2017). Moreover, it is important to consider that as implicit memory forms, that is with extended practice during the slow stage, the efficiency of the neural networks that mediate motor performance should increase (Reber 2013), which should result in decreased metabolic demands (Picard et al., 2013) and decreased brain-evoked activity (Gobel et al., 2011). In support, with respect to reward processing, phasic dopaminergic activity has been shown to return to baseline levels at reward delivery as acquisition proceeds and rewards can be expected (for a review, see Keiflin and Janak, 2015). Thus, when considering these evidence, reward-related evoked patterns of brain activity could be expected to decrease as implicit memory forms. As a result, it is possible that reward-based motor memory formation manifests as decreasing EEG activity over motor areas as acquisition proceeds during the slow stage of acquisition. These decreases in motor reward activity during the execution of motor behaviors should be apparent in motor beta-band power (Hamel et al., submitted in *NeuroImage*). As a result, the extent of motor beta-band decreases during the slow stage of acquisition when rewards are provided could be predictive of long-term retention.

Therefore, **a testable hypothesis would be that the reduction in the amplitude of contralateral motor beta-band power upon reward delivery in the slow stage of acquisition negatively correlates with retention (assessed 24h later).** These changes in beta-band power would be interpreted as being the result of waning phasic dopaminergic activity (i.e., a decreasing RPE at reward delivery, meaning that the

"surprise" of behavioral success / reward delivery is no more) within motor areas as acquisition proceeds, which triggered the necessary plastic changes for motor memory formation.

However, the above hypothesis would not allow addressing the possible causal contribution of beta-band power and dopamine to motor memory formation, mainly because of the correlational nature of the design employed. To address this confound, beta transcranial alternating current stimulation (i.e., tACS) could be used over M1 upon reward delivery during motor acquisition to demonstrate the causal contribution of motor beta-band power to long-term retention. This matter is the focus of section "6.2.". To determine the contribution of dopamine in motor memory formation and to the EEG signals, participants could be divided into sub-groups based on their genetic functional variations in DA-related gene alleles. This consideration is the focus of sections "6.4." and "6.5.".

6.3. Using transcranial magnetic or electrical stimulation techniques as a non-invasive means to determine the contribution of cortical motor regions to reward processing and memory formation

One methodological approach to test the hypothesis that contralateral motor beta-band *causally* contributes to reward-related motor memory enhancements is the use of transcranial alternating current stimulation (tACS) in beta-band frequencies (~ 25 Hz) over M1. Globally, tACS shares the same electrode montage as transcranial direct current stimulation (tDCS), but tACS uses sinusoidal alternating rather than a continuous current (Antal and Herrmann, 2016; Fröhlich et al., 2015; Reato et al., 2013; Woods et al., 2016). During tDCS, the anode and the cathode do not switch their polarity; however, during tACS one electrode serves as the anode and the other as the cathode *for half of a sinusoidal cycle* and their polarity switches again for the remaining half cycle, and so on. Thus, on average over a cycle, membrane potentials are unaffected by tACS, as compared to anodal and cathodal tDCS which monotonously respectively increase or decrease the mean firing rate of a targeted neural assembly through the modulation of membrane potentials. *Instead, the purpose of tACS is to*

entrain the neural assemblies underneath both the electrodes to oscillate at a targeted frequency (where one assembly oscillates in anti-phase to the other), causing neurons to preferentially increase and decrease their spiking activity in the peak and trough of the generated oscillations (Antal and Herrmann, 2016; Reato et al., 2013). Because tACS has been shown to effectively modulate the power of brain oscillatory rhythms (Antal and Herrmann, 2016), tACS thus allows to causally demonstrate the contribution of oscillatory activity recorded with EEG to behaviors.

Based on the present EEG results, beta-band tACS (25 Hz) could be applied 250 ms after "rewarding trials" offset (i.e., both target hits and monetary rewards) for a duration of about 350 ms and while participants undergo a reward-based motor learning protocol. The purpose of this research project would be to *test the hypothesis that post-movement beta-band power changes in brain activity during acquisition causally contribute to motor memory formation*. Control groups would be needed to test for the spatial and frequency specificity of the hypothesis by demonstrating that beta tACS of the ipsilateral M1 or that theta (~5 Hz) tACS over contralateral M1 do not alter memory formation. Overall, this project could establish the causal contribution of beta-band EEG oscillatory rhythms to reward-based motor memory formation.

Other neuromodulation means could also be employed to demonstrate the contribution of M1 to reward-based motor memory enhancements (*but not of beta-band*). For instance, a future research project could use single-pulse TMS after the movement offset of rewarded trials only **to test the hypothesis that M1 forms motor memory based on rewarded trials during acquisition.** Similar to Hamel et al. (2017), single-pulse TMS could be delivered over M1 250 ms after movement completion, rather than immediately following movement completion, with the objective to specifically disrupt reward-related (i.e., after a reward) rather than repetition-dependent neuronal activity (i.e., after movements during the performance plateau). The latency of 250 ms is based on the present EEG results (Hamel et al., submitted in *NeuroImage*) and on the findings from Ramkumar et al., 2016. Overall, this project could demonstrate that (1) M1 forms memory based on the rewarded outcomes experienced

during acquisition and (2) with a latency consistent with the engagement of the reward network (Schultz, 2016a, 2016b). It would also provide causal evidence for the involvement of M1 in reward-based motor memory formation.

6.4. Ultrasonic neurostimulation to non-invasively determine the involvement of the basal ganglia in the motor beta-band responses

Magnetic- and electrical-based neurostimulation has a limited focusing capacity and lacks brain penetration power since its influence on neuronal activity is restrained to peripheral brain regions. To overcome this limitation, increasing interest is now devoted to transcranial ultrasonic stimulation (TUS), a type of neuromodulation that non-invasively sends ultrasound through the skull to interfere with neuronal activity through changes in extracellular acoustic pressure (Tyler, 2011). The major advantages of TUS are its increased spatial resolution (millimeter-scale precision) as compared to TMS, tACS, or transcranial direct current stimulation (tDCS; Tufail et al., 2011; Panczykowski et al., 2014), and its increased depth control (Lee et al., 2015).

Instead of altering endogenous membrane potentials through exogenously triggered electrical currents (like TMS, tACS or tDCS), TUS mainly acts on non-thermal neuronal membrane mechanoreceptors. Specifically, *by inducing changes in acoustic neuronal membrane tension, it is capable of triggering the opening of voltage-gated Na^+ channel sufficiently to evoke action potentials and trigger synaptic transmission* (Tyler, 2011). The feasibility of TUS to modulate neuronal spiking activity in alert behaving monkeys has been shown by Wattiez et al. (2017) in which they showed that TUS over the frontal eye field while monkeys performed an antisaccade task increased spiking activity of neurons located in the supplementary eye field. Using a similar antisaccade task, Deffieux et al. (2013) have shown that TUS over the frontal eye field causally modulates monkey behaviors, a finding which opens the possibility that TUS could also be used in humans to modulate both behavior and neuronal activity.

Because TUS does not operate through electromagnetic means, TUS can be coupled with EEG recordings (Mueller et al., 2014; Legon et al., 2014; Lee et al., 2015).

For instance, Legon et al. (2014) delivered focused TUS over S1 at electrode site CP3 while participants were receiving electrical stimulation of the median nerve (causing sensory-evoked potentials [SEPs]) and while EEG data of electrode C3, P3, CP1, and CP5 were recorded. Overall, following SEPs, results showed spatially restricted, transient, and reversible decreases in EEG oscillatory power in alpha- (7-12 Hz) and beta-band (13-30 Hz). Moreover, results revealed that decreases in oscillatory power did not take place if the acoustic beam was displaced anteriorly or posteriorly of 1 cm on the scalp, which argues that TUS-induced disruption is spatially constrained. Although the physiological mechanisms underlying the effects of focused TUS remain largely unknown, the authors argued that focused TUS increased local inhibition by acting on mechanical sensitive neuronal components (i.e., cell membranes and ion channels) to shift the balance between excitation and inhibition. Globally, these results suggest that focused TUS can simultaneously be used with EEG to interfere with ongoing oscillatory activity.

Another advantage of TUS over magnetic- and electrical-based neurostimulation is that it could be used *to non-invasively interfere with deep brain regions*, as current efforts are devoted to the development of this technology (Robertson et al., 2017). In relation with the second scientific contribution presented in the present document (Hamel et al., submitted in *NeuroImage*), the development of such technology could allow to causally test the speculated contribution of the basal ganglia to scalp EEG signals recorded over M1 during reward processing. Given that TUS can be fairly easily implemented in laboratory settings (Tufail et al., 2011), TUS is likely to gain popularity in the future to non-invasively investigate the function of specific neural assemblies.

6.5. Genetic variations in a DA-related gene as potential candidates to explain interindividual differences in motor acquisition and M1's capacity for plastic changes

One increasingly studied mechanism to highlight the role of cortical DA signaling in motor memory formation in humans is the study of genetic variations in dopaminergic reinforcement signaling. One important gene regulating prefrontal cortex

(PFC) dopamine levels is catechol-O-methyltransferase (COMT), which codes for catabolic catecholamine enzyme activity (Tunbridge et al., 2012; Witte and Floël, 2012). The human COMT gene contains functional polymorphisms in its sequence (i.e., variations in the expression of a gene) that directly affect dopamine catabolism in the synaptic clefts of the PFC (Tunbridge et al., 2012). For instance, homozygous Val/Val allele carriers have ~ 40% higher enzymatic activity (i.e., more DA catabolic activity) as compared to carriers homozygous for the Met/Met allele (i.e., meaning that Met/Met have less catabolic activity; Tunbridge et al., 2012; Witte and Floël, 2012). Heterozygote carriers (Val/Met) are typically considered as having *intermediate* enzymatic activity (Tunbridge et al., 2012; Witte and Floël, 2012).

Studies in rodents have shown that COMT regulates dopamine turnover within the PFC (Yavich et al., 2007; Tunbridge et al., 2004; Kaënmaki et al., 2010) and that genetic or pharmacologic manipulation of COMT activity does not affect dopamine levels in the striatum (Tunbridge et al., 2012). As such, a recent meta-analysis has shown that individual differences in COMT gene has a direct bearing on reward processing (Corral-Frias et al., 2016), where homozygosity for the Met allele is generally found to increase response bias towards the most rewarded cues as compared to Val/Val carriers during probabilistic reward learning tasks. *Most importantly*, individual differences in COMT gene polymorphisms also influence individual motor sequence skill acquisition and motor adaptation capacities (Baetu et al., 2015; Noohi et al., 2014, 2016; Pearson-Fuhrhop et al., 2013); Val/Val participants showed poorer performance during the motor sequence acquisition and visuomotor adaptation as compared to both Val/Met and Met/Met participants (Noohi et al., 2014). Interestingly, a recent study has shown that Met/Met carriers of the COMT gene have increased motor cortical plasticity if they also carry the Val/Val alleles of the BDNF gene (Witte et al., 2012). These results suggest that reported individual differences in COMT gene polymorphisms could affect motor acquisition capabilities through an alteration of M1 plasticity. Therefore, the COMT gene could regulate both reward processing and motor acquisition, possibly by modulating M1 plastic changes.

6.6. Testing the hypothesis that genetic variations in COMT polymorphisms account for (1) the amount of EEG beta-band power upon reward delivery during acquisition and (2) the extent of retention 24h later

The increases in motor beta-band power following reward deliveries are likely to reflect DA signaling in motor areas (Hamel et al., submitted in *NeuroImage*), which have been related to interindividual differences in the expression of the COMT gene functional polymorphisms (Marco-Pallarés et al., 2009). Specifically, Marco-Pallarés et al. (2009) recorded EEG data while groups of 24 participants of Val/Val and Met/Met participants performed a gambling task. Results revealed that participants homozygous for the Val/Val variant of the COMT gene showed greater beta-band (20-30 Hz) power in response to monetary rewards as compared to Met/Met participants. The authors argued that because Val/Val participants have higher DA catabolic activity, phasic DA activity in response to acute rewards might be higher in these participants, which resulted in higher beta-band responses after rewards. Overall, this study suggests that the variance in the COMT gene polymorphisms could explain differences in beta-band power following reward delivery.

One remaining unknown key issue is the involvement of the COMT gene in contexts involving *both* rewards and motor acquisition. Given that it is well known that rewards based on accurate motor performance lead to increased long-term retention of novel motor behaviors (Abe et al., 2011; Dayan et al., 2014; Galea et al., 2015; Hasson et al., 2015; Manley et al., 2014; Palminteri et al., 2011; Quattrocchi et al., 2017; Song and Smiley-Oyen, 2017; Widmer et al., 2016), functional polymorphisms in the COMT gene are likely to play a role in reward-based motor memory formation because of its regulatory action on PFC DA signaling.

As a result, the scientific project planning to use EEG to assess beta-band power changes during motor adaptation for the purpose of predicting the amount of retention 24h later *could establish a link between DA activity during acquisition, beta-band power, and retention.* Specifically, not only could the between-session changes in beta-band power be explained by variance in the COMT gene, but they could both account

for the amount of long-term retention assessed 24h later. Hence, dividing participants according to the functional COMT gene polymorphisms they carry will allow gaining insights into the interindividual differences in both EEG signals and retention. Hence, a strong link between beta-band power, retention, and dopamine could be demonstrated.

6.7. Testing the hypothesis that replacing monetary rewards with positive social-comparative feedback would have the same effects on (1) motor beta-band power during acquisition and (2) 24h retention

On the field or in clinical contexts, using monetary incentives to boost participants/patients motivation – by giving or withdrawing money based on performance – is hardly implementable. To overcome this limitation, practitioners would need to employ external feedback sources that both effectively influence motivation and are unrelated to money. In this light, many psychophysical studies have shown that using positive social-comparative feedback could yield the same beneficial effects on retention as monetary rewards (Lewthwaite and Wulf, 2010; Wulf et al., 2010b, 2014, 2017; Pascua et al., 2015), which could very well also be subtended by mesolimbic dopaminergic activity (Burkett and Young, 2012; Leblois, 2013; Love, 2014). As compared to monetary incentives, using of social comparison as external sources of motivational feedback thus appear cost- and time-effective and easily implementable on the field and in clinics. However, although this approach could hold great promises to optimize motor learning strategies, its neurophysiological bases remain largely unknown.

Based on the present findings showing that motor beta-band power reflects subjective and context-dependent outcome processing in the context of motor control, replacing monetary rewards with positive social comparative feedback could give rise to highly similar brain activity. More precisely, during a reward-based motor learning protocol, *a testable hypothesis could be that motor beta-band activity in the post-movement period of target hit trials encodes motivational significance*. Then, this activity could be related to the amount of retention 24h later.

The expected finding that positive social comparisons give rise to motor beta-band activity (similar to what is documented in the second scientific contribution of the present document) is bound to make an important scientific contribution. **From a fundamental perspective**, it would build on the idea that the reward network may not care much about the nature of the feedback, but rather encodes its motivational significance (Bischoff-Grethe et al., 2009). It would also suggest that motivation enhances neuronal activity to increase signal processing in task-relevant neural assemblies (Pessoa and Engelmann, 2010), which are contralateral motor regions in this case. *Stated differently, it would mean that the reward network "cares" more about the nature of task – because different tasks involve different neural substrates – more than it "cares" about the nature of the feedback – as long as it is rewarding based on context.* **From a clinical perspective**, this would provide a strategy (i.e., positive social comparison), medium (i.e., beta-band power) and brain region (i.e., cortical motor regions) to target with neuromodulation tools during acquisition to foster motor memory formation. Because neuromodulation tools are inexpensive and easily implementable in clinical or on-the-field settings, these findings could lead to significant improvements in current motor learning practices.

6.8. Mobile EEG and neurostimulation to transfer findings from the laboratory to real-world settings

The traditional approach to study and understand human behaviors has been the empirical collection of laboratory findings, where experiments take place in static and often simulated settings. The strength of this approach is that experimenters can control multiple confounding factors. However, doing so comes with the cost of reduced ecological validity, leaving experimenters empty-handed as to the transferability of laboratory findings in real-world settings. This concern mostly stems from the idea that the human brain interacts with complex and ever-changing environments, for which laboratory settings may be ill-equipped to study (Ladouce et al., 2017). Thus, research projects conducted in laboratory settings could benefit from findings stemming from

on-the-field and clinical studies – and vice-versa – because their combination would result in heightened ecological validity.

To address that issue, increased interest is now devoted to the development of mobile cognition approaches to study human behaviors in real-world settings. These approaches include the use of transcranial magnetic or direct-current stimulation techniques (Woods et al., 2016) and/or mobile EEG (Park et al., 2015). Concerning transcranial brain stimulation, growing body of data now suggests that motor learning can benefit from the application of tDCS in healthy and clinical populations (Ammann et al., 2016) but also in athletes (Kaminski et al., 2016; Borducchi et al., 2016; Okano et al., 2015). However, using brain stimulation to enhance physical and mental performance raises ethical issues in sports because it can be considered as an illegitimate form of doping similar to the use of unauthorized pharmacological drugs (Davis, 2013). Overall, although brain stimulation holds great promises to understand and enhance motor learning in real-world situations, the ethics of doing so to enhance performance must be carefully considered.

Recording EEG data while one performs a sports activity generally does not lead to ethical issues. That is because EEG does not modulate cortical activity, it only records electrophysiological signals that stem from the brain. As such, mobile EEG could prove an effective way to test laboratory findings in "real-life" sports situations without raising ethical issues. Overall, mobile EEG records both brain and body dynamics by combining the recordings of classical EEG data *and* head and/or whole body motion data (Kranczioch et al., 2014). Moreover, to date, it appears to be the only neuroimaging tools in which head and body movements can be allowed (Kranczioch et al., 2014). However, developing mobile EEG approaches to study "real-world motor learning" leads to novel methodological challenges and will require innovation to deal with mechanical and motion artifacts in the EEG signals to ensure their reliability (Kranczioch et al., 2014).

The feasibility of using mobile EEG systems (even with only 64 electrodes) during treadmill walking has been shown by several studies (Wagner et al., 2016; Gwin et al., 2010, 2011; Snyder et al., 2015; Nathan et al., 2016). For instance, Nathan et al. (2016) sought to examine the potential contributions of physiological and non-physiological motion artifacts in scalp EEG during treadmill walking. Specifically, the authors used a wireless 64 channel EEG system and a wireless inertial sensor attached to the subject's head while the participants were walking at three different speeds (1.5, 3.0, and 4.5 km/h). Contrary to prior expectations, head motions during treadmill walking did not significantly affect the EEG signals recorded during treadmill walking. Overall, although running at 6.8 km/h was found to severely compromise EEG signals (Gwin et al., 2010), results from Nathan et al. (2016) suggest that mobile EEG recordings can provide reliable information during relatively slow unconstrained body movements.

Thus, mobile EEG appears to be a methodological approach suitable to test laboratory findings to real-world settings, thereby addressing the issue of ecological validity and adding significant value to traditional laboratory methods. This approach is bound to increase in popularity in the future because it offers a great level of understanding of the neurophysiological underpinnings at play in human movement execution on the field.

7. Conclusion

The last few decades indeed gave birth to great achievements in many neuroscience research fields. However, a great deal of accomplishments remains to be realized before neuroscience can conclude on the understanding of the intricate relationship between the nervous system and motor behaviors.

Similar to some of the most successful methodological approaches used in the past, it is of my opinion that some of the greatest future advancements will arise from the conjugation of body of knowledge originating from different research fields mainly

because they provide a more holistic comprehension of motor behaviors and their neurophysiology; examples include studies combining genetics and electrophysiology, simultaneous pharmacological and non-invasive brain stimulation interventions, as well as studies investigating both behaviors and their cellular and/or molecular underpinnings. Moreover, I believe that the formulation of hypothesis-driven research questions in a researcher's respective field of research can greatly benefit from the investigation of orthogonal – but related – body of literature; using a holistic view of the brain certainly promotes the overcoming of interpretational issues (i.e., due to a lack of evidence in a given field) and leads to address issues that remain largely unexplored.

In a near or distant future, research in neuroscience will certainly need to reconcile and unify all existing data and prevailing theories on the brain that originate from the abounding different research fields. As final words, I would like to leave readers with the idea that this challenge could believably be overcome by the opening of – sometimes isolated – research fields to new ideas or methodological approaches as well as the translation of knowledge from one field towards another.

8. Annexes

8.1. Authorization to integrate the article published in the *Journal of Neuroscience* to the present thesis

UNIVERSITÉ DE SHERBROOKE

ANNEXE 2.5

Faculté des sciences de l'activité physique
Département de kinanthropologie
Programme de maîtrise en sciences de l'activité physique

Autorisation d'intégrer un article dans un mémoire

Par la présente, chacune et chacun des coauteurs de l'article intitulé et dont le nom et les signatures sont apposés ci-contre :

Titre de l'article :
Disruption of M1 activity during performance plateau impairs consolidation of motor memories

Acceptent que celui-ci soit intégré au mémoire de maîtrise de Nom de l'étudiante ou de l'étudiant du programme de maîtrise en sciences de l'activité physique de la Faculté des sciences de l'activité physique de l'Université de Sherbrooke.

Nom :	Raphaël Hamel	Date :	26 mars 2018
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Signature :	Maxime Trempe		

Nom :	Pierre-Michel Bernier	Date :	26 mars 2018
Signature :	Pierre-Michel Bernier		

Nom :		Date :	
Signature :			

Nom :		Date :	
Signature :			

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Signature :			

Nom :		Date :	
Signature :			

Guide des études du programme de maîtrise en sciences de l'activité physique **52**

8.2. Authorization to integrate the article submitted to *NeuroImage* to the present thesis

UNIVERSITÉ DE SHERBROOKE

ANNEXE 2.5

Faculté des sciences de l'activité physique
Département de kinanthropologie
Programme de maîtrise en sciences de l'activité physique

Autorisation d'intégrer un article dans un mémoire

Par la présente, chacune et chacun des coauteurs de l'article intitulé et dont le nom et les signatures sont apposés ci-contre :

Titre de l'article :
Added value of money on motor performance feedback: increased motor beta-band power for rewards and mid-frontal theta-band power for punishments

Acceptent que celui-ci soit intégré au mémoire de maîtrise de Nom de l'étudiante ou de l'étudiant du programme de maîtrise en sciences de l'activité physique de la Faculté des sciences de l'activité physique de l'Université de Sherbrooke.

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