UNIVERSITÉ DE SHERBROOKE
Faculté des sciences de l'activité physique
Département de kinanthropologie

L'influence de l'anticipation sur les modulations de puissance dans la bande de fréquence bêta durant la préparation du mouvement
et
L'effet de la variance dans les rétroactions sensorielles sur la rétention à court terme

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Mémoire par article présenté à la Faculté des sciences de l'activité physique
En vue de l'obtention du grade de maîtrise en sciences (M.Sc.)
M.Sc. en sciences de l'activité physique
Créneau de recherche en neuromécanique et ergonomie

Dépôt final effectué en septembre 2019

UNIVERSITÉ DE SHERBROOKE

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The influence of anticipation on power modulations in the beta-band during movement planning

and

The effect of variance in sensory feedback on short-term retention

Par

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Mémoire accepté le	05 septembre 2019

RÉSUMÉ

La production du mouvement est un aspect primordial de la vie qui permet aux organismes vivants d'interagir avec l'environnement. En ce sens, pour être efficaces, tous les mouvements doivent être planifiés et mis à jour en fonction de la complexité et de la variabilité de l'environnement. Des chercheurs du domaine du contrôle moteur ont étudié de manière approfondie les processus de planification et d'adaptation motrice. Puisque les processus de planification et d'adaptation motrice sont influencés par la variabilité de l'environnement, le présent mémoire cherche à fournir une compréhension plus profonde de ces deux processus moteurs à cet égard.

La première contribution scientifique présentée ici tire parti du fait que les temps de réaction (TR) sont réduits lorsqu'il est possible d'anticiper l'objectif moteur, afin de déterminer si les modulations de TR associées à l'anticipation spatiale et temporelle sont sous-tendues par une activité préparatoire similaire. Cela a été fait en utilisant l'électroencéphalographie (EEG) de surface pour analyser l'activité oscillatoire dans la bande de fréquence bêta (13 - 30 Hz) au cours de la période de planification du mouvement. Les résultats ont révélé que l'anticipation temporelle était associée à la désynchronisation de la bande bêta au-dessus des régions sensorimotrices controlatérales à la main effectrice, en particulier autour du moment prévu de l'apparition de la cible. L'ampleur de ces modulations était corrélée aux modulations de TR à travers les participants. En revanche, l'anticipation spatiale a augmenté de manière sélective la puissance de la bande bêta au-dessus des régions pariéto-occipitales bilatérales pendant toute la période de planification. Ces résultats suggèrent des états de préparation distinct en fonction de l'anticipation temporelle et spatiale.

D'un autre côté, le deuxième projet traite de la façon dont la variabilité de la rétroaction sensorielle interfère avec la rétention à court terme dans l'étude de l'adaptation motrice. Plus précisément, une tâche d'adaptation visuomotrice a été utilisée au cours de laquelle la variance des rotations a été manipulée de manière paramétrique à travers trois groupes, et ce, tout au long de la période d'acquisition. Par la suite, la rétention de cette nouvelle relation visuomotrice a été évaluée. Les résultats

ont révélé que, même si le processus d'adaptation était robuste à la manipulation de la variance, la rétention à court terme était altérée par des plus hauts niveaux de variance.

Finalement, la discussion a d'abord cherché à intégrer ces deux contributions en revisitant l'interprétation des résultats sous un angle centré sur l'incertitude et en fournissant un aperçu des potentielles représentations internes de l'incertitude susceptibles de sous-tendre les résultats expérimentaux observés. Par la suite, une partie de la discussion a été réservée à la manière dont le champ du contrôle moteur migre de plus en plus vers l'utilisation de tâches et d'approches expérimentales plus complexes, mais écologiques aux dépends des tâches simples, mais quelque peu dénaturées que l'on retrouve dans les laboratoires du domaine. La discussion a été couronnée par une brève proposition allant dans ce sens.

ABSTRACT

Motor behavior is a paramount aspect of life that enables the living to interact with the environment through the production of movement. In order to be efficient, movements need to be planned and updated according to the complexity and the ever-changing nature of the environment. Motor control experts have extensively investigated the planning and adaptation processes. Since both motor planning and motor adaptation processes are influenced by variability in the environment, the present thesis seeks to provide a deeper understanding of both these motor processes in this regard.

More specifically, the first scientific contribution presented herein leverages the fact that reaction times (RTs) are reduced when the anticipation of the motor goal is possible to elucidate whether the RT modulations associated with temporal and spatial anticipation are subtended by similar preparatory activity. This was done by using scalp electroencephalography (EEG) to analyze the oscillatory activity in the beta frequency band (13 – 30 Hz) during the planning period. Results revealed that temporal anticipation was associated with beta-band desynchronization over contralateral sensorimotor regions, specifically around the expected moment of target onset, the magnitude of which was correlated with RT modulations across participants. In contrast, spatial anticipation selectively increased beta-band power over bilateral parieto-occipital regions during the entire planning period, suggesting that distinct states of preparation are incurred by temporal and spatial anticipation.

Additionally, the second project addressed how variance in the sensory feedback interferes with short-term retention of motor adaptation. Specifically, a visuomotor adaptation task was used during which the variance of exposed rotation was parametrically manipulated across three groups, and retention of the adapted visuomotor relationship was assessed. Results revealed that, although the adaptation process was robust to the manipulation of variance, the short-term retention was impaired.

The discussion first sought to integrate these two projects by revisiting the interpretation of both projects under the scope of uncertainty and by providing an overview of the internal representation of uncertainty that might subtend the experimental results. Subsequently, a part of the discussion was reserved to allude how the motor control field is transitioning from laboratory-based tasks to more naturalistic paradigms by using approaches to move motor control research toward real-world conditions. The discussion culminates with a brief scientific proposal along those lines.

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1. PREFACE: THE STUDY OF MOTOR BEHAVIOR

1.1. Introduction

Movement is a paramount aspect of life, without which no interaction with the environment would be possible. The ability to generate movements is more than just a convenience that enables us to do basic things, like walking or manipulating objects; it is a critical component of the evolutionary development of living species. Some experts argue that movement is the main reason we have a nervous system (Wolpert, 2013; Wolpert, Ghahramani, & Flanagan, 2001).

Behavior results from a constant interaction between the living species and a complex environment (Cisek & Kalaska, 2010). For such interaction to take place, the brain is subject to a constant gathering of information about the environment, which affords a large variety of possibilities for action (Gibson, 2014). Since the environment is complex and susceptible to changes, the brain is compelled to the constant adaptation of behaviors depending on the constraints imposed by the outside world. From an evolutionary perspective, both humans and animals have developed the capacity to remain flexible enough to control and update their motor behavior within an inherently uncertain environment (Friston, Mattout, & Kilner, 2011; Sterling & Laughlin, 2015; Todorov & Jordan, 2002).

Broadly, studying motor behavior translates into investigating how the motor system controls its movements to interact with the outside world. Motor control experts have been interested in unraveling the intricacies by which the brain gathers external sensory information to execute and to update goal-directed movements in response to changes in the environment (Elliott et al., 2010; Schmidt & Lee, 2011; Scott, 2012). For this, *motor planning* and *motor adaptation* can be view as fundamental mechanisms that allow efficient interaction between the motor system and the world.

1.2. How to study motor behavior

Since the turn of the 19th century, motor control experts have developed distinct procedures and approaches that led to the increasing understanding of how humans and

animals behave (Rosenbaum, 1991; Schmidt & Lee, 2011; Scott, 2012; Woodworth, 1899). For that matter, two distinct levels of analysis commonly used in the field of motor control will be presented in the following lines.

1.2.1. Behavioral level of analysis

The first level alludes to the behavioral analysis and it can be understood as the quantification of the extent to which a movement is achieved related to an intended behavioral goal. Such quantification is often used in the assignment of scores in sports. For instance, an archer is evaluated based on the distance between his shots and the bullseye and a sprinter is qualified based on how fast he reacts and finishes his dash. These examples introduce two fundamental ways to assess behavior: the quantification of the 1) spatial accuracy and 2) timing of performance. Namely, end-point errors are often used to assess the spatial accuracy of a movement, whereas reaction times (RT) are often used to assess movement readiness (Schmidt & Lee, 2011). The topics of errors and RTs will be extensively discussed in the following parts of this manuscript.

1.2.2. Neurophysiological level of analysis

All behaviors are governed by the brain. Based on that simple premise, another way to further understand motor behavior is by analyzing the neurophysiological basis and mechanisms that subtend behavior. Historically, lesional studies allowed scientists to ascribe specific brain functions to specific brain regions. A classic case was the one of Phineas P. Gage (1823 - 1861), an American railroad foreman whose left frontal lobe was severely injured by an iron rod that pierced through his head. Reportedly, Gage's personality and social behavior drastically changed after the injury, which led scientists to suggest that damage to specific parts of the brain might induce specific changes in behavior (Harlow, 1848; Macmillan, 2000). Fortunately, today's neuroimaging modalities allow scientists to investigate the underlying neural processes of behavior without exclusively resorting to patients with brain lesions or diseases.

Amongst a plethora of approaches, electroencephalography (*i.e.,* EEG) allows investigating the electrical activity of cortical neuronal populations using surface electrodes positioned all over the head (Britton et al., 2016; Olejniczak, 2006). Under

controlled conditions, EEG can be used to record the neural activity associated with movement planning and execution with high temporal resolution (Berger, 1930; Buzsaki & Draguhn, 2004; Perfetti et al., 2011; Pfurtscheller & Lopes da Silva, 1999). The functional bases of EEG recording will be further explained in the second part of this document (cf. *Neural oscillations to investigate movement planning*).

1.3. Investigating motor behavior through motor planning and motor adaptation

Considering the variety of possible interactions with the outside world, it is crucial to understand how the various processes of motor control are influenced by the sensory information incoming from the environment. The present thesis presents two scientific contributions that lay their bases on the frameworks of motor planning and motor adaptation. Within their respective framework, the scientific projects presented here address how the motor system can be influenced by the reliability in the sensory information, using neurophysiological and behavioral levels of analysis. For a matter of concision, only the functional mechanisms of visually guided movements will be addressed in this manuscript.

The first part of this thesis will be dedicated to the concept of motor planning, referring to the process by which the key parameters of an upcoming movement are specified and readied for action execution (Gallivan, Chapman, Wolpert, & Flanagan, 2018). Here, we investigated how the simultaneous manipulation of spatial and temporal information of the behavioral goal, which are known to affect RTs in isolation (Hick, 1952; Niemi & Näätänen, 1981), influences the EEG dynamics during the preparatory period of reaching movements. The second part will be dedicated to the concept of motor adaptation, alluding to the behavioral processes that characterize the way that the motor system adapts its movements. Here, we investigated how motor adaptation is affected by the statistical characteristics of the sensory information that leads to adapted behavior. In conclusion, the last portion of the present work will be partly dedicated to a unifying discussion of the two scientific contributions. It will be

followed by a discussion of how the field of motor control is currently transitioning from laboratory-based tasks to more naturalistic paradigms.

2. PART I: INVESTIGATING MOTOR BEHAVIOR THROUGH MOTOR PLANNING

2.1. Operational framework of movement planning

Purposeful actions are often generated to interact with external objects in order to achieve a behavioral goal (Gallivan et al., 2018; Scott, 2016; Wong, Haith, & Krakauer, 2014). These actions are often referred to as goal-directed movements. In order to generate these types of movements, the brain needs to solve (at least) two fundamental problems. For one, the brain needs to specify the spatial parameters that determine how the movement will be accomplished in relation to the behavioral goal (Scott, 2016; Wong et al., 2014). Also, depending on a variety of action contingencies, the brain needs to determine when to execute its movement (Brass & Haggard, 2008; Haith, Pakpoor, & Krakauer, 2016).

Consider a simple movement such as reaching towards a visual target. For the brain to achieve that behavioral goal, it needs to specify where to produce the reach (Cisek & Kalaska, 2010; Scott, 2016; Wong et al., 2014). To do so, spatial information about the position of the target, which is acquired in a sensory format, needs to be reinterpreted in a motor format according to the position of the reaching hand. This process allows the motor system to define a directional vector from the hand to the target's location in space. This process is called **sensorimotor transformation**[1] (Andersen & Buneo, 2003; Andersen, Snyder, Bradley, & Xing, 1997; Kakei, Hoffman, & Strick, 2003; Kandel, 2013). As the sensorimotor transformation occurs along the dorsal processing pathways (*i.e.,* from dorsal parietal to premotor; Goodale & Milner, 1992; Ungerleider & Mishkin, 1982), neural representation of the motor plan that will allow to achieve the goal (i.e. neuronal activity of directionally tuned neurons) begin to emerge in the sensorimotor regions (Cisek, 2006; Cisek & Kalaska, 2010; Cui & Andersen, 2007; Nakayama, Yamagata, Tanji, & Hoshi, 2008).

[1] This refers to the series of processes by which extrinsic information about the state of world (*i.e.* spatial location of objects) and intrinsic information about our body (*i.e.* kinematic and kinetic information about our body) are transformed into potential motor plans (Kandel, 2013).

Simultaneously, the brain needs to gather evidence that will instruct the initiation of the reach (Klaus, Alves da Silva, & Costa, 2019). The reach onset can be triggered by an external stimulus, such as a go-cue, or it can be done endogenously, in the case of self-initiated movement (Brass & Haggard, 2008). The role of action initiation has long been conferred to the activity in basal ganglia neurons (Cui et al., 2013; Klaus et al., 2019). In the case of stimulus-triggered movements (*i.e.,* signaled by a go-cue), sensory information about that imperative signal is sufficient to elicit dopaminergic activity in the basal ganglia-cortical network, which will ensue in the initiation of the motor command (Jenkinson & Brown, 2011; Schultz, 1986; Schultz & Romo, 1990; see however Klaus et al., 2019). Specifically, the basal ganglia are known to "gate" movement (Brown, Bullock, & Grossberg, 2004; Grossberg, 2016; Zold et al., 2012) and the release of such gating, which is potentially mediated through the suppression of inhibitory cells that refrain existing motor plans (Thura & Cisek, 2017), results in action initiation.

2.2. Operational definition of movement planning

Although the example presented above is nothing but an oversimplification of the kind of situations that take place in real-life, it reliably depicts the following basic idea: Generation of purposeful movements involves simultaneous processes of action specification (Cisek & Kalaska, 2010; Wong et al., 2014) and action initiation (Brass & Haggard, 2008; Haith et al., 2016; Klaus et al., 2019). The framework presented above allows to broadly define **goal-directed movement planning as the processes by which the brain transforms sensory information from the environment to specify the potential actions and to determine when to initiate the movement**.

2.3. How to study movement planning

Classically, goal-directed movements can be conceptualized by two distinctive phases: a preparatory period and an execution period. Motor control researchers have extensively studied movement planning using laboratory tasks in which a **precue**

marks the start of a **delay period**[2] after which an imperative **go-cue** instructs the participants to initiate their movement. The use of delay periods enables to distinguish between preparatory-related from execution-related processes. Although preparatory- or execution-related processes are encoded within similar sensorimotor brain regions, there is evidence that some neurons are activated only during the delay period, others discharge during the execution period (Churchland, Cunningham, Kaufman, Ryu, & Shenoy, 2010; Crammond & Kalaska, 2000; Kaufman et al., 2016; Riehle & Requin, 1989), and some other neurons are activated during both planning and execution (Crammond & Kalaska, 2000). Neural activity during the delay period is referred to as preparatory activity (Svoboda & Li, 2018), during which the parameters of the upcoming movement are specified for it to be executed.

2.3.1. The use of reaction time to study motor planning

From a behavioral standpoint, the amount of task-relevant information that the precue provided (*i.e.,* location of a potential target or duration of the delay period) can influence movement performance (Rosenbaum, 1980, 1991; Schmidt & Lee, 2011; Woodworth, 1899), which can be quantified through measurements of RTs (cf. *Preface – How to study motor behavior – behavioral level of analysis*).

RTs have been used since the 19th century to investigate motor behavior (Cattell, 1886; Deary, Der, & Ford, 2001; Deary, Liewald, & Nissan, 2011; Jensen & Munro, 1979; Niemi & Näätänen, 1981; Posner, 1980). It can be conceptually defined as the time it takes to initiate a movement in response to a stimulus in the environment. RTs are considered a critical variable to study motor planning since they allow to infer the timing of all the ongoing neural processes that take place from the moment go-cue is delivered until its associated motor response is initiated (Marin & Danion, 2005; Schmidt & Lee, 2011). Interestingly, RTs can be highly influenced if the go-cue can be anticipated (Marin & Danion, 2005).

[2] For the sake of consistency preparatory period will be referred to as delay period from now on.

2.4. Factor influencing reaction times

2.4.1. Anticipation effects on RTs

RTs can be modulated according to the context in which a goal-directed reaching task is performed. One of the biggest influences over RTs is the ability to anticipate a sensory event that yields movement generation. Specifically, two forms of anticipation can be distinguished: spatial anticipation and temporal anticipation (Marin & Danion, 2005; Schmidt & Lee, 2011).

Spatial anticipation. Anticipating the spatial position of a target before reaching towards it (*i.e.,* where to move) can incur a significant reduction in RTs. In support, a classical experiment conducted by Rosenbaum (1980) demonstrated that RTs are faster (*i.e.,* reduced) when the direction of an upcoming target is precued as compare to when it is not (Rosenbaum, 1980). This demonstrates that providing directional information as to where to reach reduces RTs. Psychophysicists have established two main kinds of reaction time experiments based on this notion: simple reaction time (SRT) and choice reaction time (CRT) tasks (Luce, 1986; Welford, 1980).

Basically, in SRT reaching tasks, there is one target and consequently, one associated response, whereas in CRT, there are multiple targets, each requiring a different response. It has been well established that CRT is slower than SRT since there is no possibility to anticipate the spatial location of the reaching target before it has been specified by the imperative go-cue (Donders, 1868; O'Shea & Bashore, 2012). The relation between the number of targets and the RTs has been well established by the famous “Hick’s Law” (Hick, 1952).

Although very insightful, this relationship has been amended by subsequent work reporting that it is not the number of cues that determines RTs but rather the spatial separation that they subtend (Bock & Eversheim, 2000). Specifically, Bock and Eversheim (2000) showed that RTs are similar, whether two or more targets are precued within the same angular span. However, if two targets are placed closer together, then the RT is faster than if those two targets are far apart (Bock & Eversheim, 2000). These results have been interpreted using the action selection and specification

model (Cisek, 2006), suggesting that RTs are determined by the level of competition between motor plans to reach the potential targets. In other words, the farther apart the targets, the greater the competition between the distributed neural population encoding for each direction, thus requiring more time to select amongst opposing motor plans (Cisek, 2006), thus resulting in an inherent increase in RTs.

All in all, it is well established that anticipating the spatial position of a target leads to faster RTs, and that, in contrast, increasing the spatial separation between multiple targets leads to slower RTs.

Temporal anticipation. Anticipating the temporal occurrence of a go-cue instructing movement initiation (*i.e.,* when to move) can also incur a significant reduction in RTs. The length of the delay period can be used to manipulate temporal anticipation. In support, behavioral evidence has shown that a fixed delay period between the precue and the go-cue provides a temporal frame of reference that enables participants to promptly initiate their response (Niemi & Näätänen, 1981). Throughout several trials, participants can reliably estimate the length of the delay period, and likely anticipate the time at which a go-cue will be delivered, thus reducing their RTs (McMorris, 2014; Quesada & Schmidt, 1970; Rohenkohl, Cravo, Wyart, & Nobre, 2012). In contrast, for blocks of trials with variable delay periods (*i.e.,* delay periods for which the duration is inconsistent across trials), participants cannot successfully anticipate the go-cue, resulting in increased RTs (Niemi & Näätänen, 1981). These evidences suggest that the movement initiation can be anticipated if the participants can estimate the length of the delay period.

Estimating the length of the delay period implies that a representation of time needs to be internalized by the brain. In support for this assumption, there is evidence that the implementation of internal timing can be assured by internal models in the cerebellum (Ivry & Spencer, 2004; Perrett, Ruiz, & Mauk, 1993; Spencer, Zelaznik, Diedrichsen, & Ivry, 2003; Yamazaki & Tanaka, 2009) and then relayed to task-specific brain regions (Ivry, 1996; Ivry & Spencer, 2004; Leon & Shadlen, 2003), which include the cortico-basal ganglia network (Ferrandez et al., 2003; Klaus et al.,

2019; Thura & Cisek, 2017). This provides evidence highlighting the existence of neural processes dedicated to the internal representation of time, that might mediate the selection of when to initiate a movement.

In sum, temporal anticipation of the go-cue can facilitate movement initiation through the internalized representation of time in task-specific regions, resulting in reduced RTs.

2.5. Neural oscillations to investigate movement planning

From a neurophysiological standpoint, the preparatory processes that take place during the delay period can be recorded using brain imaging techniques such as EEG. Brain activity during the delay period has been associated with stereotyped patterns of neural oscillations (Adhikari, Shrestha, Mishra, Singh, & Timalsina, 2018; Perfetti et al., 2011; Pfurtscheller & Lopes da Silva, 1999; Shibasaki & Hallett, 2006). The following section will address the physiological bases of neural oscillations and how EEG recordings can be used to investigate motor planning.

2.5.1. Physiological bases of neural oscillations

The fundamental basis of neural oscillations resides in the coordinated spiking activity of a large number of neurons within the neuronal network (*i.e.,* neuronal population), which presumably guide functional activity and the evolution of the processes that are being encoded (Shenoy, Sahani, & Churchland, 2013). The synchronous activity of neuronal populations allows using non-invasive scalp EEG to investigate brain activity during movement preparation.

EEG indirectly captures extracellular fields resulting from superposed ionic contributions from all active cellular processes within a given brain region (Buzsáki, Anastassiou, & Koch, 2012). The contribution of cellular activity to EEG recordings is dependent on the distance between the source (*i.e.,* the cellular activity) and the sensor (*i.e.,* the EEG electrodes), as well as the structural arrangement of the neuronal population being recorded (Cohen, 2014). Thereby, the activity that is generated in the cortex contributes to a greater extent to the EEG signal than the activity generated in deeper structures of the brain (Murakami & Okada, 2006).

EEG reflects the **rhythmic changes** in the extracellular electrical fields that arise mainly (but not exclusively) from synaptic activity (Buzsáki et al., 2012). At the cellular level, synaptic activity refers to the dynamics of the ionic charges in the cellular membranes (Cohen, 2014). The passage of cation from extracellular to intracellular space generates an unbalanced charge that needs to be mediated by an opposing ionic flux from the intracellular to the extracellular space in order to preserve the electroneutrality of the cells (Cohen, 2014).

Unfortunately, scalp EEG cannot measure individual (*i.e.,* small-scale) synaptic events. However, it can indirectly measure the influence of small-scale events over meso- and macroscopic populations that produce large field potentials (Cohen, 2014). Indeed, when the spiking activity of a large neuronal population becomes synchronous, the sum of all electrical fields generated by individual neurons provides a signal powerful enough to be measured. At the systems level, rhythmicity can be observed as **neural oscillations**. The term oscillation refers to the rhythmic fluctuations in the excitability of neuronal populations, which can be extracted from raw EEG recordings through time-frequency decomposition (Cohen, 2014).

Although there are multiple mechanisms by which oscillations emerge from the brain, it is well accepted that oscillatory activity results from the constant interaction between excitatory pyramidal neurons and inhibitory GABAergic interneurons (Buzsaki, 2006; Cohen, 2014). Specifically, when a pyramidal cell becomes activated (e.g., from inputs provided from other brain areas), its increased excitation also influences cells in its vicinity, including inhibitory interneurons. As the activity of inhibitory interneurons increases, pyramidal neurons progressively become inhibited, which interactively decreases the activity of the inhibitory interneurons, allowing the activity of excitatory pyramidal cells to ramp up again. This “push-pull” between excitatory and inhibitory activity generates rhythmic fluctuations that are manifested as neural oscillations (Cohen, 2014).

Oscillatory activity measured by scalp EEG can be considered as the reflection of synchronous activity amongst underlying cortical structures (Adhikari et al., 2018;

Palva & Palva, 2012; Pfurtscheller & Lopes da Silva, 1999; Singer, 2001; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Prevailing theories propose that oscillations might be the mechanism by which the motor system regulates local and network-wide neural communications (Buzsaki & Draguhn, 2004; Engel, Fries, & Singer, 2001; Palva & Palva, 2012). Importantly, neural oscillations seem to be ubiquitous across species, which highlights their evolutionary relevance (Buzsáki et al., 2012; Buzsaki & Draguhn, 2004).

2.5.2. Event-related spectral perturbations in the beta-band

A way to analyses EEG activity is by investigating event-related spectral perturbation (ERSP). ERSPs are defined as changes in the neural oscillations that are time-locked to a specific event, such as a precue stimulus or a go-cue signal. In the motor control domain, patterns of ERSP can be observed within distinct frequencies (*i.e.,* a measure of the number oscillatory cycles per second; Cohen [2014]) and can be quantified by the measurement of the amplitude of the oscillations, commonly expressed in terms of spectral power.

One of the frequency bands that has been classically associated with movement-related sensorimotor activity is the **beta-band** (Pfurtscheller, Stancak, & Neuper, 1996), reflecting oscillations occurring between 13 and 30 Hz (*i.e.,* cycles per second). When analyzing the oscillatory activity over sensorimotor regions contralateral to the moving arm, beta-band power is known to display a distinctive pattern of modulations respective to baseline activity (Baker, 2007; Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013; Leocani, Toro, Manganotti, Zhuang, & Hallett, 1997; Pfurtscheller et al., 1996). Specifically, during the delay period (*i.e.,* prior to movement initiation), the levels of beta-band activity gradually decline under baseline levels as a function of time (Pfurtscheller & Lopes da Silva, 1999). Upon movement initiation, a larger reduction in beta-band power can be observed, lingering until movement termination (Stancak & Pfurtscheller, 1996; Wheaton, Fridman, Bohlhalter, Vorbach, & Hallett, 2009). Once back at rest (*i.e.,* immobile), beta-band power prominently increases (*i.e.,* beta "rebound") before reverting to baseline levels (Kilavik et al., 2013).

Beta-band oscillations have served to infer the underlying cortical excitability during motor control, as activity in this frequency band has been shown to correlate with cortical inhibition (Baker & Baker, 2003; Jensen et al., 2005; Roopun et al., 2008; Roopun et al., 2006). In support, pharmacological administration of benzodiazepine, which is known to enhance GABAergic inhibitory activity, resulted in a beta-band power increase in healthy humans (Baker & Baker, 2003; Jensen et al., 2005). In a sense, higher levels of GABAergic inhibition are associated with increased beta-band power.

Alluding to its inhibitory nature, the stereotypical pattern of activation of beta-band power (*i.e.,* increased when maintaining posture and reduced when preparing and executing an action) is commonly assumed to be a signature of active processes that promote the existing motor state at the expense of new one – the *status-quo* hypothesis. (Engel & Fries, 2010; Gilbertson et al., 2005; Jenkinson & Brown, 2011). In support of this hypothesis, it was reported that experimentally increasing beta-band activity using transcranial alternating-current stimulation at 20 Hz resulted in slower tracking movements (Pogosyan, Gaynor, Eusebio, & Brown, 2009). Similarly, Gilbertson et al. (2005) also found that abductions of the index finger were slower when they were triggered during periods of enhanced cortical beta-band activity[3] compared to when they were triggered randomly (Gilbertson et al., 2005). Moreover, further support is provided by a recent study in which monkeys were trained to self-regulate their levels of beta-band activity through neurofeedback, while intra-cortical neural activity from neurons in the primary motor cortex and dorsal premotor cortex were recorded (Khanna & Carmena, 2017). The authors found that the monkeys took longer to initiate arm reaches when they had higher levels of beta-band power. They also provide evidence that beta-band power may reflect a change in the spiking activity of the neural population that influences movement initiation (Khanna & Carmena, 2017).

[3] This was indirectly assessed by finger microtremors in the beta band (Halliday, Conway, Farmer, & Rosenberg, 1998; McAuley, Rothwell, & Marsden, 1997), which are though to be attributable to synchronization between motor cortex neurons projecting to the spinal cord (Halliday et al., 1998; Kilner et al., 1999; Mima & Hallett, 1999; Mima, Simpkins, Oluwatimilehin, & Hallett, 1999).

In line with the above, it is known that pathological levels of beta-band activity are associated with motor impairments in Parkinson's disease patients (Brown, 2007; Kühn et al., 2004; Silberstein et al., 2005) and therapeutic reduction of beta-band activity through deep brain stimulation appears to elicit significant improvements in motor performance (Bronte-Stewart et al., 2009; Kogan, McGuire, & Riley, 2019; Kühn et al., 2008).

All this evidence endorses the *status quo* hypothesis, which posits that sensorimotor beta-band activity indexes the maintenance of an existing motor state while inhibiting the neural processing of a new one (Engel & Fries, 2010).

2.6. Research problem

2.6.1. Beta-band power modulations during the delay period: an interesting quandary

The beta-band activity during the delay period has gathered much attention from the scientific community (Baker, 2007; Bartolo & Merchant, 2015; Kilavik et al., 2012; Kilavik et al., 2013; Kilner, Mattout, Henson, & Friston, 2005; Pfurtscheller & Lopes da Silva, 1999). It has been commonly associated with ongoing preparatory activity in sensorimotor regions (Kilner et al., 2005; Stancak & Pfurtscheller, 1996; Wheaton et al., 2009). Thereby, beta-band activity has been used as an assessment of motor readiness – the likelihood to generate a movement (Doyle, Yarrow, & Brown, 2005; Jenkinson & Brown, 2011; Kilavik et al., 2013). Despite this, it remains unclear whether beta-band reduction indexes the processes pertaining to action specification (*i.e.,* where to reach) or to the selection of action initiation (*i.e.,* when to reach). Evidence for both these contentions can be found.

On the one hand, some authors have reported that beta-band power prior to movement initiation is influenced by the number of possible target directions (Tzagarakis, Ince, Leuthold, & Pellizzer, 2010; Tzagarakis, West, & Pellizzer, 2015) or by the extent of spatial separation between two alternative targets (Grent-'t-Jong, Oostenveld, Jensen, Medendorp, & Praamstra, 2014). Specifically, the greater the number of possible targets or the separation between two targets, the less the decrease

in beta-band power during the delay period. This provides support for the beta-band role in the spatial specification of the upcoming movement.

On the other hand, it has been suggested that beta-band activity during the delay period reflects the interactive processing between motor cortex and subcortical structures in the basal ganglia (Brittain, Sharott, & Brown, 2014), which acts to mediate movement initiation (Gurney, Prescott, & Redgrave, 2001; Hauber, 1998; Khanna & Carmena, 2017; Mink, 1996, 2003; Redgrave, Prescott, & Gurney, 1999). In light of the role of beta-band oscillations in time estimation (Arnal, 2012; Bartolo, Prado, & Merchant, 2014; Etchell, Johnson, & Sowman, 2015; Fujioka, Trainor, Large, & Ross, 2012; Heideman, 2017; Kononowicz & van Rijn, 2015), it has been shown that beta-band power is modulated by the temporal predictability of the upcoming go-cue instructing movement initiation (Alegre et al., 2003). Specifically, the more a go-cue signal is predictable, the greater the decrease in beta-band power prior to the movement onset, providing support for the role of beta-band in the objective evaluation of time that leads to movement initiation.

Keeping this in mind, studies have never assessed how the spatial specification of an upcoming reach direction and the temporal decision to initiate a movement are distinguished at the oscillatory level within the same experiment. This would provide better insights into the role of beta-band activity with respect to the timely initiation and spatial specification of an upcoming movement. It would also allow to investigate the potential interaction between these two types of processes, as well as the relations between the neurophysiological (*i.e.,* beta-band power) modulations and the respective behavioral (*i.e.,* RTs) enhancement incurred by these factors.

2.7. Research question

Alluding to the performance enhancements achievable through anticipation (cf. *Factors influencing reaction times*), the first scientific contribution presented here investigated **whether the RT modulations associated with spatial and temporal anticipation are subtended by similar preparatory activity in the beta-band**. This was done by manipulating both temporal and spatial anticipation as experimental

factors, incurring changes in RTs, and by analyzing their respective modulations in the beta-band using EEG. Moreover, this study **sought to elucidate the relationship between RTs and beta-band modulations incurred by the experimental factors**. This was done by investigating whether power modulations incurred by both factors were predictive (*i.e.,* correlated) of their respective RT modulations. Given the evidence in the reviewed literature (*cf. Beta-band power modulations during the delay period: an interesting quandary*), one could have hypothesized that the ability to anticipate both the occurrence of the cue and the reach direction would be associated with decreased power in the beta-band (Alegre et al., 2003; Tzagarakis et al., 2010). However, it remained exploratory to investigate the possibility of an interaction between factors and a potential relation between neurophysiological (*i.e.,* beta-band power) and behavioral (*i.e.,* RTs) modulations.

2.8. Submitted article in Journal of Cognitive Neuroscience

Please refer to section 7.1 for the authors' authorization to include this article in the present thesis.

2.9. Dissociation between temporal and spatial anticipation in the neural dynamics of goal-directed movement preparation

Abbreviated title:
EEG dynamics of temporal and spatial anticipation

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Number of pages:
(excluding Figure captions): 30 pages

Number of Figures: 7 Figures

Number of words:
Abstract: 248 words;
Introduction: 649 words;
Discussion: 1494 words.

Keywords: Reaction time, reaching, movement planning, humans, electroencephalography.
Conflict of interest: The authors declare no competing financial interests
Acknowledgments: This work was supported by the Natural Sciences and Engineering Research Council (grant number 418589). The authors thank François Thénault for his significant contribution to this work.

Abstract

It is well documented that providing advanced information regarding the spatial location of a target stimulus (*i.e.,* spatial anticipation) or its timing of occurrence (*i.e.* temporal anticipation) influences action preparation, reducing reaction times (RTs). Yet, it remains unknown whether the RT gains attributable to temporal and spatial anticipation are subtended by similar preparatory dynamics. Here this issue is addressed in humans by investigating EEG beta-band activity during movement preparation. Participants performed a reach RT task in which they initiated a movement as fast as possible toward visual targets following their appearance. Temporal anticipation was manipulated by having the target appear after a constant or variable foreperiod, whereas spatial anticipation was manipulated by precueing participants about the upcoming target location in advance or not. Results revealed that temporal and spatial anticipation both reduced reach RTs, with no interaction. Interestingly, temporal and spatial anticipation were associated with fundamentally different patterns of beta-band modulations. Temporal anticipation was associated with beta-band desynchronization over contralateral sensorimotor regions specifically around the expected moment of target onset, the magnitude of which was correlated with RT modulations across participants. In contrast, spatial anticipation did not influence sensorimotor activity, but rather led to increased beta-band power over bilateral parieto-occipital regions during the entire delay period. These results argue for distinct states of preparation incurred by temporal and spatial anticipation. In particular, sensorimotor beta-band desynchronization may reflect the timely disinhibition of movement-related neuronal ensembles at the expected time of movement initiation, without reflecting its spatial parameters *per se*.

Introduction

The time necessary to initiate a reaching movement toward an appearing stimulus, referred to as reaction time (RT), is known to be influenced by prior knowledge as to when and where it will appear. In support, studies manipulating the temporal predictability of an impending target have shown that RTs are faster as temporal anticipation increases (Niemi and Näätänen, 1981; Nobre et al., 2007). Similarly, studies manipulating the number of possible target locations have shown that RTs are faster as spatial anticipation increases (Hick, 1952; Schmidt and Lee, 2011). In spite of considerable work, it remains unclear whether the RT gains associated with spatial and temporal anticipation are subtended by similar preparatory dynamics at the neural level.

Of interest, recent behavioral work suggests that the mechanisms involved in the preparation of the spatial aspects of a movement (*i.e.* direction) are independent from those mediating its initiation (Haith et al., 2016). Specifically, these authors compared RTs in a task in which participants initiated reaching movements after target presentation to a task in which they were forced to initiate movements with lower-than-normal RTs using rhythmic cues. They showed that in the latter condition, participants reduced their RTs by ~80 ms, but strikingly were still able to produce spatially accurate movements. In further support, recent electrophysiological work in monkeys showed that movement initiation is accompanied by a large change in neural activity in primary motor (M1) and dorsal premotor (PMd) cortex that reflects when the movement will occur, but carries no essential information about reach direction (Kaufman et al., 2016). This indicates that separate "components" of the population response in these regions encode movement direction and timing. Overall, these studies suggest that RT gains associated with temporal and spatial anticipation may be subtended by distinct neural preparatory dynamics.

One method allowing to characterize preparatory activity with high temporal resolution is electroencephalography (EEG), with known modulations in many frequency bands. Most notable is the event-related desynchronization (ERD) in the beta-band (13-30 Hz) that is observed over contralateral sensorimotor regions before

and during movement (Pfurtscheller, 1981; Pfurtscheller and Lopes da Silva, 1999; Kilavik et al., 2013). While beta-band ERD has long been linked to "motor readiness," there remains ambiguity as to whether it relates more to the spatial specification of the movement or its initiation. For one, the *status quo* hypothesis, according to which reduced power reflects a release from inhibition necessary for a change in motor state (Gilbertson et al., 2005; Engel and Fries, 2010; Jenkinson and Brown, 2011; Perfetti et al., 2011), suggests that ERD is closely tied to movement initiation. As such, movements for which the go-cue is rhythmic are associated with greater pre-movement beta-band ERD than when the go-cue is unpredictable (Alegre et al., 2003). This possibility is further supported by a growing body of literature relating beta-band oscillations to predictive timing (Saleh et al., 2010; Arnal, 2012; Fujioka et al., 2012). However, there is also evidence that beta-band ERD is modulated by the degree of directional uncertainty of an upcoming movement, suggesting a possible role in encoding the spatial aspects of movements. For example, pre-movement beta-band ERD is greater when reducing the number of possible target directions (Tzagarakis et al., 2010) or the angle of separation between two alternative targets (Grent-'t-Jong et al., 2014).

Overall, these studies demonstrate that temporal and spatial precueing both influence the pattern of the beta-band ERD. However, direct comparison between the two types of precueing, as well as their possible interaction during reach preparation, has never been explicitly tested. Here this is addressed using a factorial design in a reach RT task. Temporal anticipation was manipulated by having separate blocks in which the foreperiod was either constant (*i.e.* 2 s) or variable (*i.e.* 1.25, 2 or 2.75 s). Spatial anticipation was manipulated by using spatial precues that were either informative (*i.e.* one location) or non-informative (*i.e.* three possible locations) as to the upcoming target location.

Materials and Methods

Participants

Twenty-seven young adults (23.1 ± 2.1 years old, 14 female and 13 male) without any known neurological or psychiatric condition took part in the experiment. They were all self-declared right-handed and had no visual impairment left uncorrected. All participants provided informed consent prior to the experiment by signing a consent form approved by the ethics committee of the Centre Hospitalier de l'Université de Sherbrooke and they all received a monetary compensation of 20 $ (CAD) for their participation.

Apparatus

Participants sat comfortably facing a CRT monitor and a digitizing tablet. The monitor (LG Studioworks 995E, Seoul, KR) was positioned ~77 cm in front of participants. The tablet (GTCO CalComp DB6 1218, Scottsdale, AZ, USA) was placed directly in front of participants and recorded the position of a hand-held stylus in real-time, which was presented as a cursor on the monitor (green circle; 0.5 cm in diameter). Participants were instructed to control the cursor by sliding the stylus across the tablet with the right hand. A custom-made box covered the digitizing tablet, such that participants could not see their arm while moving.

Stimuli and task

The experimental task consisted of center-out reaching movements toward one of three possible visual targets (see Figure 1). All movements were initiated from a starting circle (grey; 0.75 cm in diameter) located at the bottom of the screen. The targets (white circles; 1.65 cm in diameter) were situated 7 cm away from the starting circle, at 30°, 90° and 150° relative to the trigonometric circle (*i.e.* rightwards, straight-ahead and leftwards relative to midline, respectively). Participants were required to gaze at a fixation cross (red; 0.3 x 0.3 cm) situated 4 cm above the starting circle throughout the entire experiment to prevent eye movements.

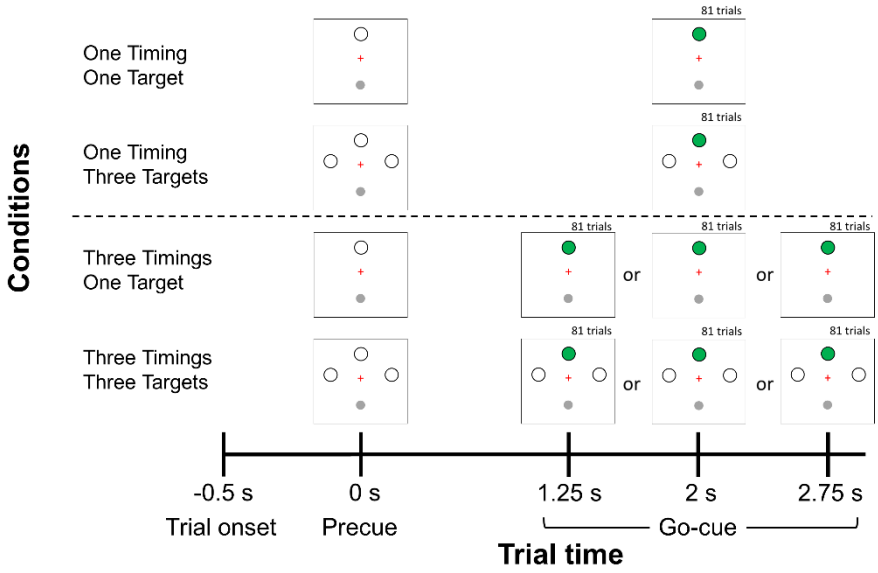

Figure 1. Trial sequence and experimental design. Temporal and Spatial anticipation were manipulated in four experimental conditions: 1) One Timing - One Target; 2) One Timing - Three Targets; 3) Three Timings - One Target; 4) Three Timings - Three Targets. Trials started with a 0.5 s baseline period after which a precue was provided. The precue consisted in the presentation of either a single target or three targets. The two levels of the factor Temporal anticipation were conducted in separate experimental blocks (One Timing; Three Timings). In the One Timing block (above dotted line), the timing of the go-cue (*i.e.,* target turning green) was constant at 2 s, whereas in the Three Timings block (below dotted line), it varied between 1.25, 2 or 2.75 s. Only trials for which the go-cue occurred at 2 s were kept for primary experimental analysis (n = 81 per participant per condition).

Figure 1 illustrates the sequence of events for a given trial. Participants brought the cursor into the starting circle to begin the trial. After a 0.5 s baseline period, a precue specifying the possible locations of the targets was presented, marking the beginning of the foreperiod. At the end of the foreperiod, a target turned green (*i.e.* go-cue), prompting participants to perform their reach towards it. Participants were instructed to initiate and execute their movements as fast and accurately as possible. They were told not to stop on the target but to "strike" through it with a single uncorrected movement. After movement completion, participants were instructed to hold their final hand position for 250 ms, after which the cursor disappeared, prompting the return to the starting circle for the initiation of the next trial.

Experimental design

The temporal and spatial anticipation of target onset were independently manipulated using a 2 × 2 factorial design (see Figure 1). Temporal anticipation was manipulated by having participants take part in two separate experimental blocks in which the duration of the foreperiod was either constant at 2 s (*i.e.* One Timing), or could vary pseudo-randomly between three possibilities (*i.e.* 1.25, 2 or 2.75 s; Three Timings). The objective of using repeated exposure to either constant or variable foreperiods was to manipulate participants' expectancy of the go-cue in order to build an internal representation of the moment of target onset (Niemi and Näätänen, 1981; Nobre et al., 2007). Although different approaches could have been used to influence temporal anticipation, such as rhythmic entrainment to a tone (Alegre et al., 2003), here the rationale for building a temporal prior of target onset was to keep the preparatory period exempt of additional sensory stimuli (*i.e.* rhythmic tones) which would have themselves influenced oscillatory activity and made it difficult to compare EEG modulations across conditions. Thus, in the present context, preparatory activity was identical from a sensory standpoint across the two levels of Temporal anticipation, therefore allowing to ascribe all spectral modulations to movement preparation only. Importantly, the ordering of the two blocks was counterbalanced across participants to rule out any ordering effect behavioral and EEG dependent variables.

Within each of the two experimental blocks, Spatial anticipation was manipulated by having the precue being fully informative as to the spatial location of the upcoming target (*i.e.* One Target; straight ahead) or not (*i.e.* Three Targets; leftwards, straight-ahead, and leftwards) (see Figure 1). The experiment thus consisted of four distinct conditions.

In a first block, participants could be submitted to either the One Timing - One Target condition or the One Timing - Three Targets condition. This block comprised a total of 178 trials: 81 for the former and 81 for the later (*i.e.* 27 trials per target), as well as 16 no-go trials. No-go trials were identical to the other trials with the exception that the go-cue was not presented. Participants were informed of these trials and were instructed not to move in this context. These trials served to prevent

participants from jumping the start, which was especially relevant for the One Timing - One Target condition since both spatial and temporal information were known in advance. In a second block, participants could be submitted to either the Three Timings - One Target condition or the Three Timings - Three Targets condition. This block comprised a total of 510 trials: 243 for the former (*i.e.* 81 trials per possible timing) and 243 for the later (*i.e.* 81 trials per possible timing, comprising 27 trials per target), as well as 24 no-go trials. Trials were pseudo-randomized throughout each experimental block. Overall, the experiment comprised 688 trials and lasted ~75 min.

By design, the One Timing conditions (One Timing - One Target and One Timing - Three Targets) only had data for the 2 s foreperiod. Hence, the primary experimental strategy was to compare preparatory activity across all four conditions using only trials in which the foreperiod was 2 s. Doing so ensured that the delay period was identical in every respect across the four conditions, such that any difference would be solely attributable to differential movement preparation incurred by Temporal or Spatial anticipation. In additional analyses, data from the 2.75 s foreperiods were used to provide further validation of the results obtained in the main 2 s foreperiod analysis.

To ensure that an internal representation of the timing of target onset (*i.e.* prior) would be achieved through repeated exposure to either constant or variable foreperiods (Temporal anticipation factor), it was decided a priori that the first 12 trials of each of the two One Timing conditions (One Timing - One Target and One Timing - Three Targets) would be discarded, as well as the first 36 trials of each of the two Three Timings conditions (12 trials per possible timing in both the Three Timings - One Target and the Three Timings - Three Targets conditions). This corresponded to 96 trials out of the 688 per participant (14 % of the trials).

Behavioral data recording and analysis

Visual stimuli were presented using functions from the psychophysics toolbox [Psychtoolbox (Brainard, 1997; Pelli, 1997)], which were run with MATLAB (v2014a, MathWorks, Natick, MA, USA) using the Windows 7 operating system (Microsoft, Redmond, WA, USA) on a desktop computer (Dell Optiplex 7010, Round Rock, TX, USA). All hand position-related data, obtained from the digitizing tablet, were recorded

at 100 Hz and analyzed offline with custom MATLAB routines. Movement initiation was defined as the moment when the stylus left the starting circle. RT was calculated as the time difference between the go-cue and movement initiation. Time to target was calculated as the time difference between movement initiation and the moment the radial distance between the stylus and the starting circle exceeded 7 cm. Endpoint error was defined as the Euclidian distance in cm between the location of the cursor at the 7 cm radial distance and the aiming target.

Outlier trials were rejected based on several criteria. First, trials for which 1) RT was under 160 or over 600 ms, 2) time to target exceeded 500 ms or 3) endpoint error was greater than 5 cm were discarded. In addition, trials for which RT and time to target were beyond ± 2 SD from a participant's mean were rejected. All these criteria led to the rejection of 21 ± 14 trials per participant (3.5% of the data).

EEG data acquisition, processing and time-frequency decomposition

EEG recording and analysis

Scalp EEG data were recorded from a 64-electrode actiCAP (Brain Products, Gilching, Germany) and BrainAmp system (Brainproducts, Munich, Germany). Electrodes were positioned in accordance with the extended 10/20 system (Falk Minow Services, Herrsching-Breitbrunn, Germany) and it was ensured that the Cz electrode was at the participant's vertex. The reference electrode was located at FCz and impedances were kept below 20 kΩ. The EEG signals were digitized online (sampling rate 500 Hz; BrainVision Recorder 2.0) using a Laptop (Dell Latitude E6530, Round Rock, TX, USA) running on Windows 7 (Microsoft, Redmond, WA, USA).

All EEG analyses were done offline using custom MATLAB routines, as well as functions derived from the EEGLAB toolbox (Delorme and Makeig, 2004). First, trials that had been rejected based on movement kinematics were discarded from the EEG datasets. Then data were digitally bandpass-filtered between 1 – 55 Hz and epoched from -1000 ms to +3000 ms around precue onset for all conditions. EEG data were then baseline-corrected to the average potential recorded during the 500 ms preceding the precue. This period was chosen as a baseline since participants were motionless and the precue had not been presented yet. Cortical activity was thus

considered neutral at that moment. Thereafter, EEG epochs showing voltage values exceeding ± 80 μV were discarded. Based on this criterion, 47 ± 55 trials per participant (6.8 % of data) were discarded from further behavioral and EEG analyses.

In sum, after considering both kinematic-based and EEG-based trial rejections, all analyses (both EEG and movement kinematics) were conducted on a total of 62 ± 8, 64 ± 7, 60 ± 9, and 63 ± 8 trials per participant for One Timing - One Target, One Timing - Three Targets, Three Timings - One Target, and Three Timings - Three Targets, respectively.

The data were further inspected for artifacts with a procedure based on independent component (IC) analysis, a blind separation technique that decomposes the EEG signal into maximally independent components in order to remove artifacts from EEG activity without having to discard entire epochs (Makeig et al., 2002; Delorme and Makeig, 2004; Hammon et al., 2008; Gwin et al., 2010; Gwin and Ferris, 2012a,b). The 'runica' function in EEGLAB was applied to decompose EEG signals into statistically maximal ICs. ICs were analyzed with respect to scalp topography and frequency characteristics, and were identified as being artifactual and removed if they met two of the following three criteria: 1) their time-course showed spurious bursts of activity, 2) their spectral power did not generally decrease as a function of frequency, as expected for EEG spectral power (Buzsáki, 2006) and 3) their scalp map showed activity concentrated at the far edges of the scalp, which are often indicative of muscle and/or ocular artifacts (Jung et al., 2000). Cleaned EEG data were generated by projecting back the time-course of activity of the remaining ICs to the electrode space.

To assess time-frequency power modulations across experimental conditions, the EEG time-series of each electrode and trial were convolved with a series of complex Morlet wavelets (1-50 Hz, 1 Hz steps). Spectral power estimates were obtained by multiplying the resulting complex signal by its complex conjugate. Wavelet cycles were linearly increased from 3 - 7.9 in 0.1 steps to improve frequency resolution at higher frequencies (Cohen, 2014). The obtained power time-series were then baseline-normalized, and changes in power were expressed in decibels as follows:

$$\mathrm{dB} = 10\log_{10}\left(\frac{RP}{\overline{BP}}\right)$$

where dB corresponds to the decibel-converted mean power, RP corresponds to the mean power value at a given time point, and $\overline{\mathrm{BP}}$ corresponds to the average raw power during the baseline period, which was defined as the average power during the 500 ms preceding the precue. This measure was computed separately for each condition. Finally, the spectral power data were downsampled to 125 Hz.

Behavioral Statistical analysis

All behavioral dependant variables (*i.e.* RT, time to target and endpoint error) were submitted to separate 2 Temporal anticipation (One timing, Three timings) × 2 Spatial anticipation (One target, Three targets) repeated measures ANOVAs. All statistical tests were two-tailed and the threshold for significance was set to 0.05. Data normality was tested with the Shapiro-Wilk test prior to all analyses. The statistical analysis of the all behavioral dependent variables was done with IBM SPSS statistics (version 23, IBM Canada, ON, Canada). For all these analyses, the *F* statistic, statistical significance (p), effect size [partial eta squared, η_p^2 (Field, 2009)] and descriptive statistics (Mean ± Standard error of the mean) are reported in the text. According to Fritz and colleagues (2012), the thresholds past which η_p^2 denotes small, moderate and large effect sizes are 0.01, 0.06 and 0.14, respectively (Fritz et al., 2012).

EEG statistical analysis

Regarding EEG data, the goal was to assess whether beta-band power during the delay period was modulated by either Temporal or Spatial anticipation. To do so, non-parametric permutation tests were conducted to identify clusters of spatially and temporally adjacent electrode/time pairs showing statistically significant differences across conditions (Maris and Oostenveld, 2007). This method does not make assumptions about the distribution of the data and it provides an efficient solution to the multiple comparisons problem, making it particularly interesting for EEG analysis. Specifically, for each comparison, two-tailed dependent *t*-tests were computed for all electrode/time pairs in the true EEG data. Adjacent electrode/time pairs whose test statistic exceeded statistical significance threshold ($t(26) = 2.056$, $\alpha = 0.05$, two-tailed),

were then identified. To be considered as a cluster, at least three adjacent electrodes had to show statistically significant *t* values. The size of a cluster was obtained by summing the *t* values across all adjacent electrode/time pairs constituting the cluster. Then, permutations (N = 1000) were undertaken, which consisted of randomly shuffling the experimental condition labels across participants. Following each permutation, the largest permuted cluster was identified. Ultimately, a Monte Carlo estimate (*i.e.* the proportion of permuted clusters whose size was larger than the clusters identified in the true data) was used to yield *p* values for each cluster.

All non-parametric permutation tests were conducted over the entire delay period starting from the precue (0 ms) until trial end (3000 ms). To probe for differences across the Temporal anticipation factor, data were pooled across Spatial anticipation levels and dependent *t*-tests were used to compare the One Timing to the Three Timings trials. Similarly, to probe for differences across the Spatial anticipation factor, data were pooled across Temporal anticipation levels and dependent *t*-tests were used to compare the One target and the Three Targets trials. To probe for an interaction between the two factors, dependent *t*-tests were used to compare the differences between the One Target and the Three Targets trials across the two Temporal anticipation levels. Clusters were deemed statistically significant if their *p* value was smaller or equal to the significance threshold ($\alpha = 0.05$). All non-parametric permutation tests were done using the Fieldtrip toolbox (Oostenveld et al., 2011). For each identified cluster, the size, average statistic (*t*), statistical significance (*p*), and effect size (Cohen's d_z) are reported in the text. Cohen's d_z was calculated using the average *t*-value of a cluster (Rosenthal, 1986; Lakens, 2013). According to Cohen (1988), d_z is considered small, moderate, or large if it exceeds 0.2, 0.5 or 0.8, respectively.

Results

Behavioral results

Mean RT data for all conditions can be seen in Figure 2A. The ANOVA conducted on the RT data revealed both a significant main effect of Temporal and

Spatial anticipation. Specifically, as can be seen in Figure 2B, RTs were significantly faster in One Timing (321 ± 5 ms) as compared to Three Timings (326 ± 5 ms; $F_{(1,26)}$ = 5.478, p = 0.027, η_p^2 = 0.174). Similarly, as can be observed in Figure 2C, RTs were significantly faster in One Target (308 ± 5 ms) as compared to Three Targets (339 ± 5 ms; $F_{(1,26)}$ = 139.079, p < 0.001, η_p^2 = 0.842). Importantly, there was no significant interaction between factors ($F_{(1,26)}$ = 0.279, p = 0.602, η_p^2 = 0.011).

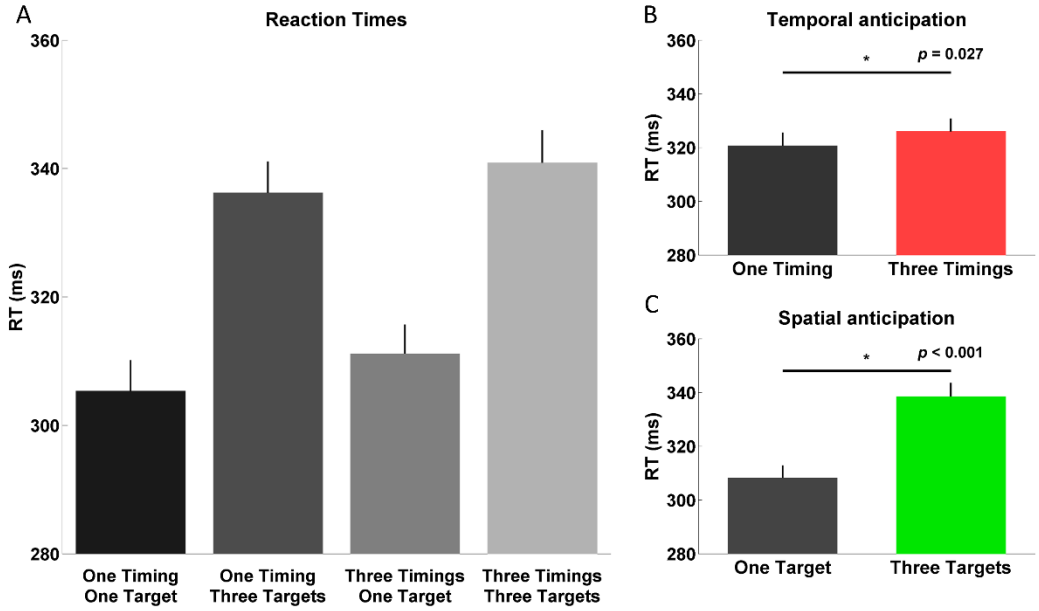

Figure 2. Reaction times **A.** Mean reaction times in each of the four conditions using only trials for which the go-cue occurred at 2 s. **B.** Main effect of Temporal anticipation. **C.** Main effect of Spatial anticipation. Error bars represent standard errors of the mean.

The ANOVA conducted on the time to target data revealed both a significant main effect of Temporal and Spatial anticipation. Specifically, time to target was slightly but significantly lower for One Timing (85 ± 2 ms) than for Three Timings (88 ± 3 ms; $F_{(1,26)}$ = 5.651, p = 0.025, η_p^2 = 0.179). Similarly, time to target was slightly but significantly lower for One Target (85 ± 2 ms) than for Three Targets (88 ± 2 ms; $F_{(1,26)}$ = 9.048, p = 0.006, η_p^2 = 0.258). There was no interaction between factors ($F_{(1, 26)}$ = 1.452, p = 0.239, η_p^2 = 0.053).

The ANOVA conducted on the endpoint error data revealed a significant main effect of Spatial anticipation, with errors being slightly but significantly lower in One

Target (0.508 ± 0.013 cm) as compared to Three Targets (0.592 ± 0.015 cm; $F_{(1,26)}$ = 9.048, $p < 0.001$, $\eta_p^2 = 0.596$). It should be noted that in spite of a significant main effect, the difference was extremely small (~0.8 mm) and unlikely to have any bearing on the EEG results. There was neither a main effect of Temporal anticipation ($F_{(1, 26)}$ = 0.152, $p = 0.700$, $\eta_p^2 = 0.006$) nor an interaction ($F_{(1, 26)} = 0.106$, $p = 0.748$, $\eta_p^2 = 0.004$).

Beta-band power results

The next analysis sought to investigate whether beta-band oscillatory power during the delay period was influenced by Temporal and Spatial anticipation or their interaction. For the Temporal anticipation factor, as can be seen in Figure 3A, a large cluster was observed over left (contralateral) fronto-central, central and centro-parietal scalp sites (size = 1372.11, average $t = 3.04$, $p = 0.022$, $d_z = 0.59$). This cluster was significant only for a transient period of time between 968 to 1376 ms after the precue. To appreciate the directionality of this effect, Figure 3B presents the time-course of beta-band activity across the two levels of the Temporal anticipation factor, obtained by averaging data over the 6 electrodes presenting the largest number of significant time-samples during the cluster period (FC1, FC3, C1, C3, CP1 and CP3; see inset for electrodes). As can be seen, beta-band power was significantly lower in Three Timings than in One Timing specifically around the moment of the first possible go-cue in the Three Timings conditions (*i.e.* 1 250 ms). In other words, there was greater beta-band ERD over contralateral sensorimotor regions when there was a possibility that a go-cue would occur.

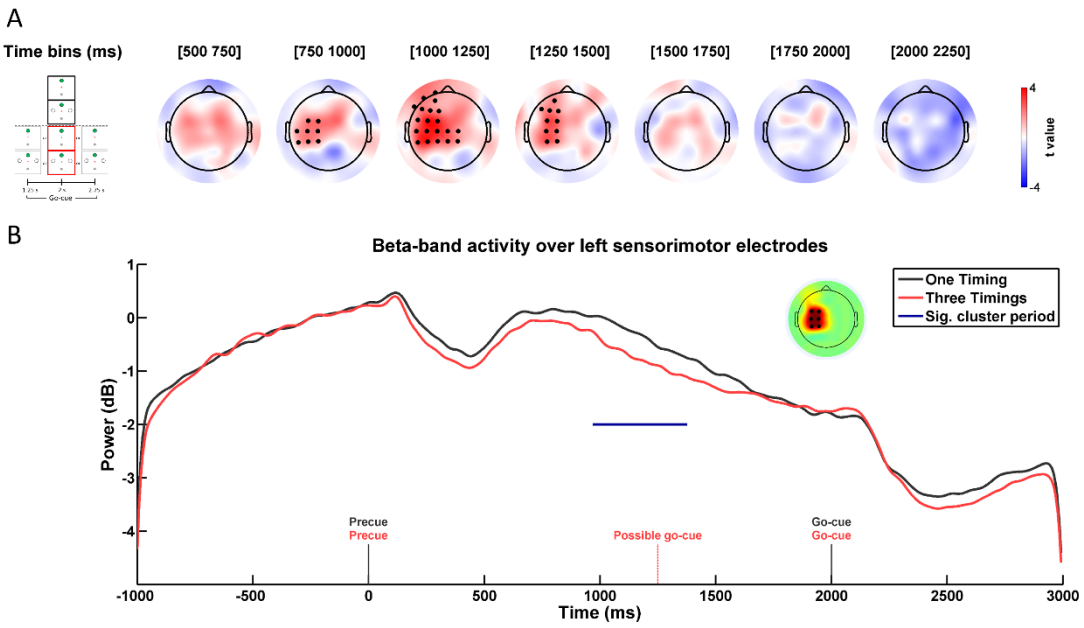

Figure 3. Main effect of Temporal anticipation on beta-band power. **A.** Paired comparisons of beta-band power across Temporal anticipation levels during the delay period for trials in which the go-cue occurred at 2 s (see inset). Black markers represent electrodes comprised in a significant cluster. **B.** Beta-band power time-course for One Timing conditions (black line) and Three Timings conditions (red line) during the delay period (obtained by averaging power values across the 6 electrodes presenting the largest number of significant time-samples during the cluster period; see inset). Horizontal blue line corresponds to the time period during which the cluster was significant (p = 0.022).

For the Spatial anticipation factor, two significant clusters were identified (Figure 4A). They were observed bilaterally over occipital, parieto-occipital, parietal and centro-parietal electrodes, although there was a right-hemisphere bias. The first cluster was observed between 136 and 568 ms after the precue (size = 5430.10, average t = 4.45, p = 0.004, d_z = 0.86), while the second cluster spanned between and 640 to 2312 ms (size = 1250.53, average t = 3.73, p = 0.002, d_z = 0.72). To better visualize this effect, the temporal evolution of beta-band activity across the two levels of Spatial anticipation are presented in Figure 4B. Time-courses were produced by averaging beta-band power over the six electrodes presenting the largest number of significant time-samples during the cluster periods (P1, Pz, P2, POz, PO4, and Oz; see inset for

electrodes). As can be seen, beta-band power was significantly lower in Three Targets than in One Target. This effect was sustained over the major part of the delay period.

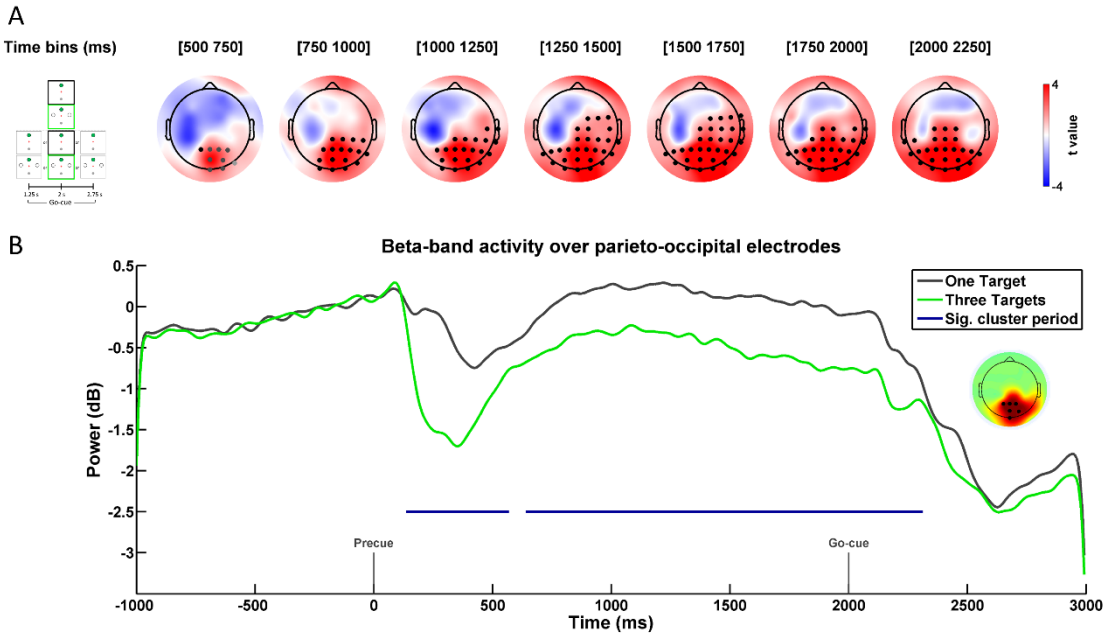

Figure 4. Main effect of Spatial anticipation on beta-band power. **A.** Paired comparisons of beta-band power across Spatial anticipation levels during the delay period for trials in which the go-cue occurred at 2 s (see inset). Black and pale grey markers represent distinct significant clusters, whereas dark gray markers denote electrodes common to both black and pale grey clusters (though at different time points). **B.** Beta-band power time-course for One Target conditions (black line) and Three Targets conditions (green line) during the delay period (obtained by averaging beta-band power values across the 6 electrodes presenting the largest number of significant time-samples during the clusters periods; see inset). Horizontal blue lines correspond to time periods during which the clusters were significant (both $p < 0.004$).

Finally, beta-band power differences between the two Spatial anticipation levels (One Target vs. Three Targets) were compared across the Temporal anticipation levels to probe for an interaction (see Experimental design and statistical analysis). This analysis revealed no significant interaction between factors (all clusters $p > 0.6$, one-tailed).

In sum, these results demonstrate that even though Temporal and Spatial anticipation both incurred RT gains, they were subtended by different modulations in beta-band activity. Specifically, power in the left sensorimotor electrodes was only

modulated by Temporal anticipation, whereas power in parieto-occipital electrodes was only modulated by Spatial anticipation.

Confirmatory analysis

To provide further support for the above-mentioned pattern of results, additional analyses were performed using trials for which the go-cue was presented at 2.75 s. Indeed, by using this new independent dataset, it was possible to conduct similar contrasts as those conducted for the primary analysis.

Firstly, to replicate the main effect of Temporal anticipation, all trials in the One Timing conditions were contrasted to those in the Three Timings conditions for which the go-cue was presented at 2.75 s (see inset of Figure 5A). This contrast engages the same neural events as the original contrast until 2 s, after which differences are expected due to the go-cue being presented only in the One Timing condition. Results were highly similar to those of the primary analysis. Specifically, as observed in Figure 5A, there was again a significant cluster over contralateral sensorimotor regions around the time of possible go-cue occurrence in the Three Timings conditions, from 784 to 1464 ms (size = 3601.45, average $t = 3.10$, $p = 0.026$, $d_z = 0.60$). As can be seen in the time-courses of Figure 5B, the same six electrodes as in the primary analysis were found to contribute most to the cluster, revealing that beta-band power was significantly reduced in the Three Timings as compared to the One Timing conditions. As expected, after the presentation of the go-cue in the One Timing conditions at 2 s, a second cluster was found over the same electrodes from 2160 to 2992 ms, showing much stronger beta-band ERD in One Timing than in Three Timings (size = -1884.56, average $t = -4.52$, $p = 0.002$, $d_z = 0.87$).

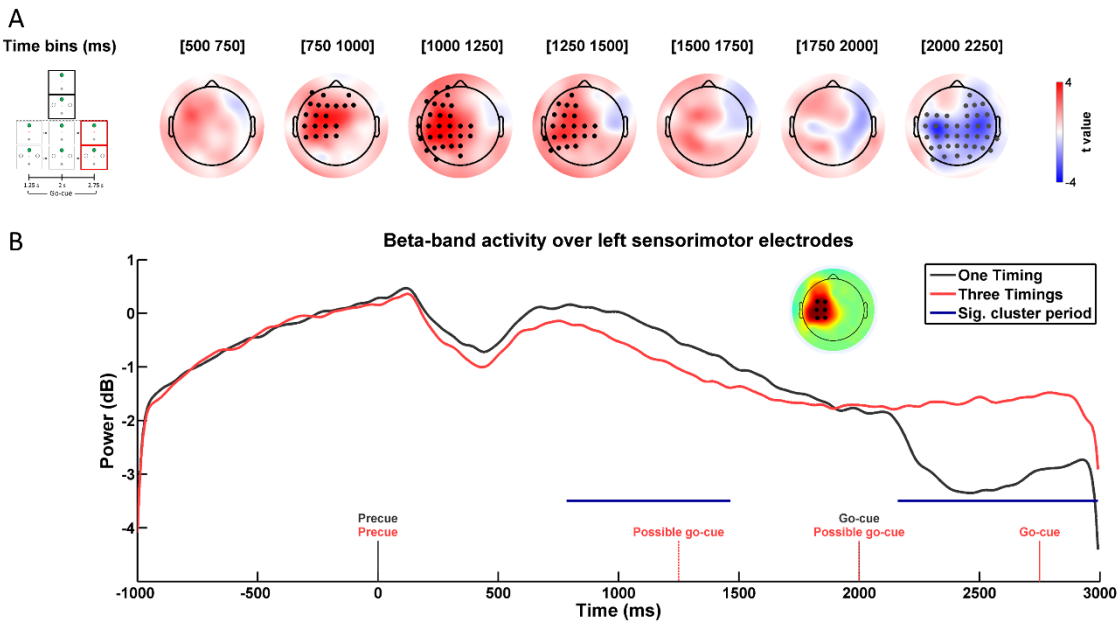

Figure 5. Additional analysis of the Main effect of Temporal anticipation on beta-band power. **A.** Paired comparisons of beta-band power across Temporal anticipation levels during the delay period for trials in which the go-cue occurred at 2 s for One Timing conditions, and at 2.75 s for Three Timings conditions (see inset). Black markers represent significant positive clusters, whereas grey markers represent significant negative clusters. **B.** Beta-band power time-course for One Timing conditions (black line) and Three Timings conditions (red line) during the delay period (obtained by averaging beta-band power values across the 6 electrodes presenting the largest number of significant time-samples during the clusters periods; see inset). Horizontal blue lines correspond to the time periods during which the clusters were significant ($p = 0.026$ and $p = 0.002$, respectively).

Secondly, to replicate the main effect of Spatial anticipation, trials from the Three Timings – One Target condition for which the go-cue was presented at 2.75 s were compared to trials from the Three Timings – Three Targets condition for which the go-cue was presented at 2.75 s (see inset of Figure 6A). Again, this analysis revealed a very similar pattern of results as the primary analysis. As can be seen in Figure 6A, a large cluster over parieto-occipital electrodes was observed throughout the entire delay period until the go-cue, being significant between 120 to 2992 ms (size = 2.221.90, average $t = 3.99$, $p = 0.002$ $d_z = 0.76$). Once again, the same six electrodes as in the primary analysis were found to contribute most to the cluster, revealing that

beta-band power was significantly lower in the Three Targets than in the One Target condition (Figure 6B).

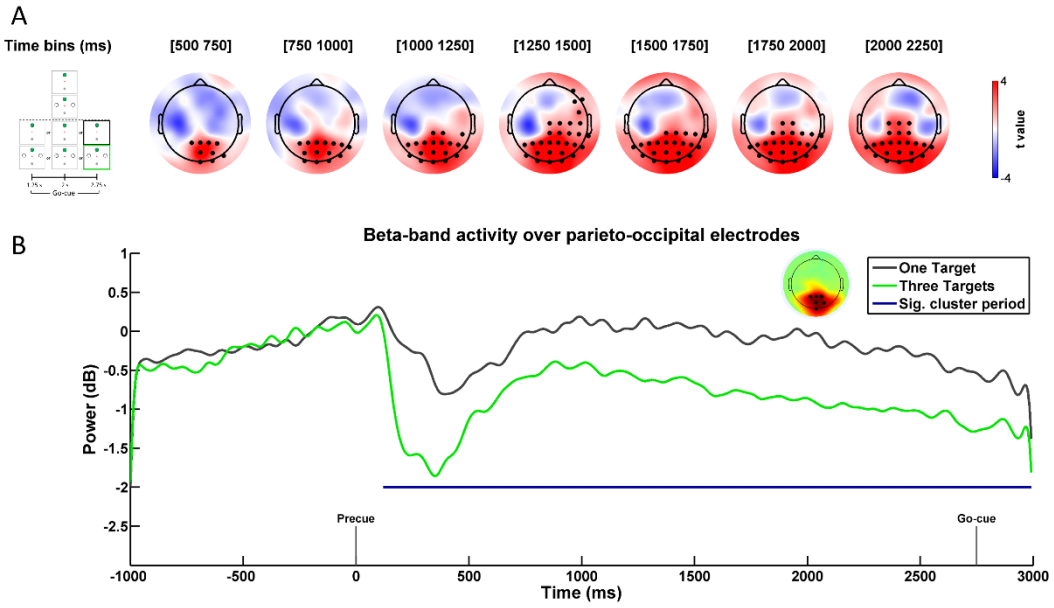

Figure 6. Additional analysis of the Main effect of Spatial anticipation on beta-band power. **A.** Paired comparisons of beta-band power across Spatial anticipation levels during the delay period for trials in which the go-cue occurred at 2.75 s. (see inset). Black markers represent electrodes comprised in a significant cluster. **B.** Beta-band power time-course for One Target conditions (black line) and Three Targets conditions (green line) during the delay period (obtained by averaging beta-band power values across the 6 electrodes presenting the largest number of significant time-samples during the clusters periods; see inset). Horizontal blue line corresponds to time period during which the clusters was significant (p = 0.002).

Relationship between beta-band power and reaction time

The analyses conducted on beta-band power revealed a clear dissociation, with Temporal anticipation being selectively associated with phasic modulations over left sensorimotor regions around moments of potential action, and Spatial anticipation being associated with tonic modulations over parieto-occipital regions over the entire delay period. An interesting contention is that these power modulations reflect distinct forms of preparation which may be related to the RT gains incurred by each factor. To further probe the link between neural activity and RTs, we next assessed whether individual power differences between factor levels during the delay period could explain the RT modulations.

To do so, beta-band power differences were extracted from the six electrodes that most strongly contributed to the significant clusters identified between factor levels (see Figures 3B and 4B insets). The resulting differential time-courses (Three Timings vs. One Timing and Three Targets vs. One Target) were then correlated at each time point with their corresponding RT differences. Thereafter, non-parametric analyses were used to identify significant correlation clusters, as described in the *EEG statistical analysis* section, with the two following variations. First, rather than dependent *t*-tests, Spearman's rank correlations were used as the test statistic. Second, clusters were defined as adjacent time-samples that exhibited a statistically significant correlation ($r_s(n = 27) = 0.382$, $p = 0.05$, two-tailed), with cluster size corresponding to the sum of the correlation coefficients within a cluster. The variable "r_s^{mean}," defined as the average correlation for a given cluster, is reported to provide an assessment of the strength of the correlation for an entire cluster.

Figure 7A presents the correlations between individual differences in beta-band power vs. differences in RT for the Temporal anticipation effect, using power data from the left sensorimotor electrodes (see inset for electrodes). As can be seen, the correlation between power modulations and RT modulations tended to increase over the course of the delay period, being maximal around the time of anticipated go-cue occurrence at 2 s. This was confirmed by a significant cluster spanning between 1912 and 2040 ms (size = 7,75, $p = 0.03$, $r_s^{mean} = 0.407$). This indicates that left sensorimotor beta-band power reflects a state of motor preparation whose relationship with RT peaks at the expected moment of go-cue. As a qualitative appreciation of the direction of the correlation, mean power modulations over the period of the significant cluster are plotted against RT modulations incurred by the Temporal anticipation factor, for each individual participant (Figure 7B). As can be seen, participants for whom beta-band activity was most reduced by Temporal anticipation tended to present the largest reductions in RTs, whereas those that presented the reverse pattern of beta-band modulations (*i.e.* increase in beta-band power under Temporal anticipation) presented increases in RTs. The direction of the effect is thus consistent and complementary with the previously reported main effect of Temporal anticipation observed at 1.25 s. In sum,

individual RT gains incurred through Temporal anticipation were well accounted for by differences in beta-band modulations in the left sensorimotor regions, specifically around the moment of go-cue.

Figure 7C presents the correlations between individual differences in beta-band power vs. differences in RTs for the Spatial anticipation effect, using power data from the parieto-occipital electrodes (see inset for electrodes). As can be seen, no significant correlation was observed at any time during the delay period. This suggests that parieto-occipital beta-band power is not linked to the timing of movement initiation.

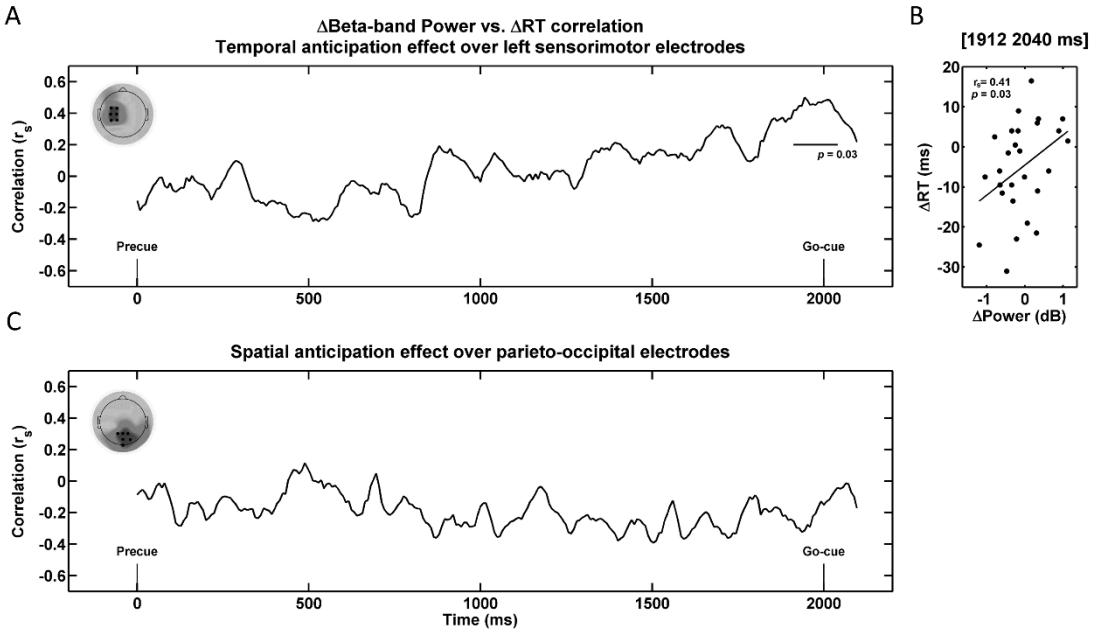

Figure 7. Correlations between beta-band power and RTs. **A.** Time-course of Spearman correlations between modulations in beta-band power incurred by Temporal anticipation and associated modulations in RT across participants. Six electrodes overlaying left sensorimotor regions were used (same as in Figure 3B; see inset). Horizontal line corresponds to the time period during which the cluster was significant (1912 to 2040 ms; p = 0.03). **B.** Mean power modulations over the period of the significant cluster plotted against RT modulations incurred by the Temporal anticipation factor, for each individual participant (n = 27). **C.** Time-course of Spearman correlations between modulations in beta-band power incurred by Spatial anticipation and associated modulations in RT across participants. Six electrodes overlaying parieto-occipital regions were used (same as in Figure 4B; see inset). No significant correlation was found.

Discussion

The present study investigated whether the RT gains incurred by temporal and spatial anticipation are subtended by similar beta-band modulations during movement preparation. To do so, EEG activity was recorded in a reach RT task in which knowledge of the target spatial location and timing of onset was manipulated. Results revealed that although Temporal and Spatial anticipation both led to significant RT gains, they were subtended by modulations in beta-band activity in distinct regions and different time periods. In particular, only Temporal anticipation incurred beta-band ERD over contralateral sensorimotor electrodes, the magnitude of which predicted RT modulations across participants. These findings argue for distinct states of motor preparation associated with temporal and spatial anticipation.

Temporal anticipation is associated with sensorimotor beta-band desynchronization

Temporal anticipation incurred greater beta-band ERD over contralateral sensorimotor regions specifically around the moment a go-cue was possible (*i.e.* ~1.25 s in the Three Timings conditions). Interestingly, the magnitude of these beta-band modulations around the time of actual target onset (*i.e.* 2 s) was correlated to the ensuing RT modulations across participants. These results are in line with the contention that beta-band oscillations signal the maintenance of the sensorimotor *status quo* (Engel and Fries, 2010), and conversely that a reduction in power indexes the degree to which a change is likely in the sensorimotor system (Jenkinson and Brown, 2011; Kilavik et al., 2013). In support, beta-band power over M1 has been shown to be progressively suppressed with the increasing likelihood of a go-cue instructing movement initiation (Schoffelen et al., 2005). It has been suggested that sensorimotor beta-band oscillations reflect interactions between the basal ganglia and M1 (Brittain et al., 2014), with desynchronization reflecting disinhibition and thus scaling with the time needed for movement initiation (Kuhn et al., 2004; Jenkinson and Brown, 2011). As such, Parkinson's disease, for which a cardinal symptom is a difficulty in initiating movement, is characterized by abnormally high beta-band oscillations in both basal ganglia and M1 (Brown, 2007). Drug-induced reduction in beta-band activity in basal ganglia (Kühn et al., 2006) and sensorimotor cortex (Devos et al., 2003; Silberstein et

al., 2005) is known to alleviate this symptom. Functionally, it has been proposed that pre-movement beta-band desynchronization allows to increase computational power and information coding within task-relevant neural ensembles (Brittain and Brown, 2014). As such, there is good evidence for an inverse relationship between firing rates within motor regions and beta-band power (Baker et al., 2001; Spinks et al., 2008; van Wijk et al., 2012). Given that M1 cells undergo the most important change in firing specifically at movement initiation (van Wijk et al., 2012; Shenoy et al., 2013), it is likely that the greater ERD observed over sensorimotor electrodes allowed for the timely allocation of neural resources at the critical moment associated with an imminent change in motor state.

The selective modulation of sensorimotor beta-band power with temporal anticipation of the upcoming target is particularly interesting in light of work from Kaufman et al. (2016) who found that the largest component of the neural response in M1 and PMd reflects the timing of transition from movement preparation to initiation, independently of movement direction. Similar to the present results, they also reported that the timing of the change in neural state space predicted much of the trial-by-trial variance in RTs. Hence a likely possibility is that sensorimotor beta-band activity is related to the temporally-sensitive neurons identified by Kaufman and colleagues, with ERD allowing neuronal activity to converge into a state necessary for movement to be generated, and thus correlating with RTs. In sum, the present findings support the view that beta-band ERD reflects processes that are needed to prompt responses to task-relevant stimuli (Perfetti et al., 2011), and marks the dissociation between movement preparation and initiation.

A null, yet equally important, result of this work is that Spatial anticipation did not impact pre-movement beta-band activity over contralateral sensorimotor regions, in spite of the fact that this factor led to more potent RT gains than Temporal anticipation. This provides strong evidence for the notion that sensorimotor beta-band desynchronization is more closely linked with movement initiation than with the encoding of the spatial aspects of movement. This view is consistent with evidence that EEG beta-band activity during the preparatory period yields poor directional decoding

accuracy of hand movement direction (Waldert et al., 2008) and is not influenced by upcoming visual feedback direction (Dufour et al., 2018). However, these results are inconsistent with those of Tzagarakis et al. (2010), who used magnetoencephalography (MEG) and found that beta-band desynchronization during planning negatively scaled with the directional uncertainty of an upcoming movement. One possible explanation lies in the different experimental designs. Indeed, in the present protocol, the target layout only spanned 120°, such that movements were systematically directed in the forward direction. This may have engaged neuronal ensembles broadly tuned to the forward direction to some extent in all conditions, even in the Three Targets condition (Cisek, 2006). In contrast, the target layout in Tzagarakis et al. (2010) spanned 360°, with targets being equally spaced around a circle. Such orthogonal target positioning likely prevented any possibility of encoding a movement vector in the high uncertainty context. As a result, the greater range of spatial uncertainty afforded by their design might have led to more potent beta-band modulations across conditions as compared to ours. Alternatively, it cannot be ruled out that the discrepant results stem from the different recording techniques, as EEG and MEG are sensitive to radial and tangential dipoles, respectively (Hämäläinen et al., 1993; Cohen, 2014). As such, it has been shown that the decoding of directional information during movement preparation differs between EEG and MEG (Waldert et al., 2008).

Spatial anticipation is associated with parieto-occipital beta-band synchronization

In further support for a dissociation between Temporal and Spatial anticipation, the latter incurred modulations at different scalp sites and with a different time-course. Namely, Spatial anticipation was associated with a sustained increase in beta-band power over parieto-occipital regions over the entire delay period, which was unrelated to ensuing RTs. This finding can be interpreted in light of the role of low beta-band oscillations [as well as alpha-band (8-12 Hz)] in regulating functional excitability within dorsal visual pathways for optimal task performance (Donner et al., 2007; Zhang et al., 2008; Jensen and Mazaheri, 2010). Specifically, when target location is precued, sensorimotor transformations can readily take place (Cappadocia et al., 2016), allowing to maintain a movement vector throughout the delay period (Andersen and Buneo,

2002; Buneo et al., 2002; Bernier et al., 2017). In this context, the go-cue carries no novel visuospatial information and merely acts as a trigger, in which case it has been shown to be processed outside of parietal regions (Snyder et al., 2006; Baldauf et al., 2008; Bernier et al., 2017). In this light, increased beta-band power may reflect functional disengagement of visuospatial attention processes within parieto-occipital cortex given that sensorimotor transformations have already been computed.

Temporal anticipation and RTs

Following the reasoning that Temporal anticipation acts to reduce beta-band power, ERD should have been greater in One timing as compared to Three Timings at ~2 s, since there was a 100% certainty of target onset in the former condition. However, the analysis revealed no significant cluster at that moment (see Figure 3A). This is likely attributable to the relatively small difference in RTs incurred by Temporal anticipation (5 ms; yet significant with an effect size deemed "large"), with a subset of participants even presenting the reverse effect (*i.e.* lower RTs in Three Timings; see y-axis of Figure 7B). In spite of evidence that constant foreperiods tend to reduce RTs as compared to variable foreperiods (Alegria, 1975; Johari and Behroozmand, 2017), one possibility is that the use of three fixed foreperiod durations with a constant interval was stereotyped enough to induce three distinct internal representations of go-cue occurrence. As a result, some participants might have entrained to multiple peaks of relatively high levels of preparation, consequently shortening their RTs. Yet, in spite of this behavioral reversal, it is noteworthy that these participants tended to present the reverse effect in sensorimotor beta-band activity (*i.e.* decreased beta-band power in Three Timings), as evidenced by the significant correlation between beta-band power and RT at ~2 s. Hence, even though the manipulation of Temporal anticipation had variable effects across participants, the entire dataset supports the existence of a link between sensorimotor beta-band ERD incurred by Temporal anticipation and associated RT modulations.

Conclusion

In conclusion, the present study provides evidence for a dissociation between the effects of Temporal and Spatial anticipation on beta-band activity during movement

planning. These data suggest that increasing "motor readiness" through spatial or temporal anticipation gives rise to fundamentally different brain states: one tonic process that is modulated by the spatial aspects of the movement and does not correlate with ensuing RTs, and one phasic process that reflects the temporal likelihood to initiate the movement and therefore predicts RTs. More generally, these results support the notion of independence between movement preparation and initiation.

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3. PART II: INVESTIGATING MOTOR BEHAVIOR THROUGH MOTOR ADAPTATION

3.1. Operational framework of motor adaptation: the theory of internal models

Prevailing computational theories of motor control posit that the brain is able to control and update its movements by modeling the physical laws that govern any interaction with the environment and by internalizing these interactions within complex neural networks (Honda et al., 2018; Kawato, Furawaka, & Suzuki, 1987; Lebon, Gueugneau, & Papaxanthis, 2013; McNamee & Wolpert, 2019; Wolpert, Ghahramani, & Jordan, 1995; Wolpert & M. Kawato, 1998). The use of **internal models** enables the brain and its motor system to efficiently control and adapt their movements (Wolpert et al., 1995).

Two types of internal models have been defined in the field of motor control: inverse models and forward models (Ito, 2008; Kawato, 1999; Kawato et al., 1987; Kawato & Wolpert, 1998; Miall & Wolpert, 1996; Wolpert et al., 1995; Wolpert & Kawato, 1998). Specifically, the brain resorts to **inverse models** that determine the required motor commands to achieve the desired motor goal (Shadmehr & Mussa-Ivaldi, 1994). An example of an inverse model is the sensorimotor transformation used to convert sensory coordinates of the motor goal into motor coordinates. In that sense, an inverse model can be viewed as a controller that commands the body. Also, the brain is able to predict the sensory consequences of its motor commands through **forward models**, which base their predictions on internal copies of the motor commands (Bubic, Von Cramon, & Schubotz, 2010; Miall & Wolpert, 1996; Wolpert et al., 1995). Importantly, the forward predictions are provided downstream of the internalized inverse models (Shadmehr & Krakauer, 2008) and are based upon the **prior beliefs** of the state of the body and the environment (Wolpert, Diedrichsen, & Flanagan, 2011).

In brief, the brain combines the predictions from a forward model with the sensory information from the environment to form an accurate estimation of the state

of the body and the world in order to efficiently control its movements (Shadmehr & Krakauer, 2008). In a sense, motor control can be view as an interplay between feedback processes and feedforward mechanisms (Cisek, 2005; Scott, 2016).

The combination of predictions with sensory information is a useful way to control movements unless the predictions are inaccurate (Shadmehr, Smith, & Krakauer, 2010). Namely, if there is a discrepancy between the predictions and sensory reafferences, it would mean that something about the prediction (*i.e.,* forward model) or the controller (*i.e.,* inverse model) is not quite right[4]. Thus, the internal models would need to be updated (*i.e.,* adapted) in such a way that its predictions would accurately match the sensory consequences of the motor commands. This translates into the recalibration of the mapping between desired movements and their respective motor commands (*i.e.,* **sensorimotor recalibration;** McDougle et al. (2016)). The updating of the internal models that generate accurate predictions respective to sensory feedback is the fundamental mechanism that defines **motor adaptation** (Krakauer et al., 2019; McDougle et al., 2016; Shadmehr et al., 2010).

3.2. Operational definition of motor adaptation

Motor adaptation is thought to be driven by sensory prediction errors (SPEs) (Izawa & Shadmehr, 2011; Lee, Oh, Izawa, & Schweighofer, 2018; Mazzoni & Krakauer, 2006; McDougle et al., 2016; Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). SPEs allow the brain to modify its motor commands in compensation to external perturbations in the environment (Krakauer et al., 2019; Shmuelof & Krakauer, 2011). In this sense, SPEs act as a teaching signal for sensorimotor recalibration. Some examples of motor adaptation in real life may include adapting gait while using boots during winter, adapting eye saccades when removing reading glasses, shifting speeds or using the brakes while driving an unfamiliar car, or even modifying serve technique when switching tennis rackets.

[4] The mismatch between the predictions and sensory feedback is known to elicit a sensory prediction error in the brain (Krakauer, Hadjiosif, Xu, Wong, & Haith, 2019; McDougle, Ivry, & Taylor, 2016; Shadmehr et al., 2010).

3.3. How to study motor adaptation

Motor adaptation can happen relatively quickly (*i.e.,* within a few minutes), which makes this approach adequate for experimental protocols in laboratories since it can be studied within a short timescale. To investigate motor adaptation, experts have used numerous approaches which vary depending on the type of perturbation to which the participants are exposed. The most common approaches are force-field adaptation and **visuomotor adaptation[5],** which are often used in the context of reaching movements (Krakauer et al., 2019). Briefly, force-field adaptation consists in introducing a mechanical force to the arm, altering its dynamics during movement, thus leading to compensatory forces to execute subsequent movements (Shadmehr & Mussa-Ivaldi, 1994; Smith, Ghazizadeh, & Shadmehr, 2006). On the other hand, visuomotor adaptation consists in introducing a perturbation of the visual consequences of reaching movement (typically by altering the relation between the position of the hand and the position of a cursor on a display screen) thus leading to compensatory movements in response to the visual perturbation (Galea, Mallia, Rothwell, & Diedrichsen, 2015; Krakauer, Ghilardi, & Ghez, 1999; Mazzoni & Krakauer, 2006). A common method to study visuomotor adaptation is by rotating the display of the cursor around the initial position of the hand, therefore inducing an angular deviation between the cursor's and the hand's displacement (i.e. visuomotor rotation [VMR]) (Krakauer et al., 2019; Krakauer, Pine, Ghilardi, & Ghez, 2000).

3.3.1. Phases of motor adaptation paradigms

Classically, motor adaptation paradigms can be described with a distinctive pattern (McDougle et al., 2016; Shadmehr et al., 2010). Initially, when first exposed to

[5] Other common approaches have been used to study motor adaptation, including vestibule-ocular reflex adaptation (Cohen & Raphan, 2004; Ito, 2002; Melvill Jones, Barlow, & Gaze, 1977), saccadic adaptation (Wong & Shelhamer, 2011), split-belt treadmill gait adaptation (Jayaram et al., 2012; Malone, Bastian, & Torres-Oviedo, 2012), and speech adaptation (Darainy, Vahdat, & Ostry, 2018; Parrell, Agnew, Nagarajan, Houde, & Ivry, 2017; Rochet-Capellan & Ostry, 2011).

a perturbation, participants tend to produce erratic movements[6], which elicit SPEs. Throughout adaptation, the sensorimotor recalibration gradually takes place, translating into an increase in performance from one trial to the next. The fraction of the error corrected from one trial to the next defines the **rate of adaptation** (also referred to as trial-by-trial sensitivity to error) (Marko, Haith, Harran, & Shadmehr, 2012; Wei & Kording, 2009). As the sensorimotor recalibration occurs, performance gradually reaches maximal levels, countering for most of the perturbation. Practicing at these asymptotic levels of adapted performance (*i.e.,* when performance tend to repeat, and no further adaptation is seen) is thought to strengthen the sensorimotor relationship (Huberdeau, Krakauer, & Haith, 2015; Krakauer, Ghez, & Ghilardi, 2005; Trempe & Proteau, 2010; Yin & Kitazawa, 2001). In effect, the strength of the sensorimotor recalibration can be assessed during a retention phase, when the perturbation is removed, resulting in a bias in subsequent reach performance opposing the perturbation (Krakauer et al., 1999; Krakauer et al., 2019). This phenomenon, commonly known as aftereffects, serves as a proxy of persistence of the adapted behavior and can be seen immediately after the adaptation, as an assessment of **short-term retention**, or several hours after the adaptation period, referring to long-term retention (Krakauer et al., 2005; Yin & Kitazawa, 2001).

3.3.2. Multiple components of motor adaptation

During motor adaptation, performance follows a classical logarithmic curve, where it prominently increases during the initial trials of adaptation, and saturates towards the last trials, reaching a performance plateau (Krakauer et al., 1999; Krakauer et al., 2019). This stereotyped pattern of adaptation is largely consistent across participants and motor adaptation paradigms (Krakauer et al., 1999; Krakauer et al., 2019; Ostry & Gribble, 2016; Shadmehr & Mussa-Ivaldi, 1994; Smith et al., 2006). These regularities in the properties of adaptation prompted experts to derive adaptation

[6] This is true in the case of sudden and perceived perturbations (Galea et al., 2015; Mazzoni & Krakauer, 2006). When the perturbations are gradually introduced and too subtle to be consciously perceived, performance errors are not observed over the course of the adaptation (Hamel, Trempe, & Bernier, 2017). Importantly, adaptation, which is dependent on SPEs, occurs whether performance errors are present or not (Lee et al., 2018; Mazzoni & Krakauer, 2006; Taylor & Ivry, 2011).

into two separate processes (Huberdeau et al., 2015; McDougle et al., 2016; Taylor, Krakauer, & Ivry, 2014): a "fast" process that has high rates of adaptation, and a "slow" process that adapts slowly but account for most of the retention (Smith et al., 2006). These separate processes are though to distinctively rely on cognitive strategies (Martin, Keating, Goodkin, Bastian, & Thach, 1996; Mazzoni & Krakauer, 2006). Specifically, the "fast" component is thought to rely on explicit and conscious knowledge of errors that were made (*i.e.,* performance errors), whereas the "slow" component is thought to rely on the implicit and unperceived mismatch between sensory prediction and the sensory feedback, eliciting SPEs (Kim, Parvin, & Ivry, 2019; Krakauer et al., 2019; Mazzoni & Krakauer, 2006; McDougle et al., 2016; Taylor et al., 2014).

3.4. Factors influencing motor adaptation

3.4.1. The amount of practice at adapted performance asymptote

It has been shown that practicing at asymptotic levels of adapted performance leads to greater and more robust retention of a newly adapted state. For instance, (Krakauer et al., 2005) manipulated the amount trials while participants had to adapt to a visuomotor rotation and tested for aftereffects, measuring retention after 5 minutes (*i.e.,* an assessment of short-term retention) or 24 hours post-adaptation (*i.e.,* an assessment of long-term retention). Their results revealed an enhancement of both short- and long-term retention associated with doubling the number of trials of adaptation. Others have also obtained similar results (Huberdeau et al., 2015; Trempe & Proteau, 2010; Yin & Kitazawa, 2001). In sum, the amount of retention seems to be influenced by the amount of practice during the adaptation phase.

3.4.2. Reinforcement during adaptation

Providing reinforcement can also influence motor adaptation (Sutton & Barto, 1998). It is thought to act on the explicit component of adaptation (Bond & Taylor, 2015; see however Kim et al., 2019). Two basic forms of reinforcement can be distinguished: binary feedback about task success and monetary incentive.

Reinforcement through binary feedback about task success at adapted performance asymptote. Feedback of task outcome during adaptation can be provided in the form of a scalar error signal that does not inform about the directionality of the error. For instance, when someone reaches for a light switch in the dark and misses it, that person will be informed that the reach failed the target, but not in what direction the next reach would need to go in order to strike the switch. This is known as binary feedback (*i.e.,* success/failure) and it has been used to probe how this type of reinforcement can improve retention of a novel visuomotor rotation (Shmuelof et al., 2012). Specifically, Shmuelof et al. (2012) provided participants with binary feedback during the late (*i.e.,* asymptotic) portion of adaptation and showed that this type of feedback could enhance retention (Shmuelof et al., 2012). Although motor adaptation is dependent on SPEs rather than task errors (Mazzoni & Krakauer, 2006), binary feedback about performance error seems to influence the retention of an adapted state.

Reinforcement through monetary incentives. Rewarding performance through monetary incentives have been used to probe how reinforcement influences rates of adaptation (Galea et al., 2015; Nikooyan & Ahmed, 2015; Quattrocchi, Greenwood, Rothwell, Galea, & Bestmann, 2017) although there are some inconsistencies in the literature. For instance, Galea et al. (2015) reported that feedback in the form of punishment (*i.e.,* monetary loss for bad performance) accelerates the rate of adaptation but does not lead to greater levels of retention. They also reported that feedback in the form of reward (*i.e.,* monetary gain for good performance) did not influence rates of adaptation but led to greater levels of retention (Galea et al., 2015). In contrast, Nikooyan and Ahmed (2015) reported a beneficial effect of rewards on adaptation rate, specifically when they are coupled with visual feedback (Nikooyan & Ahmed, 2015). These findings suggest that reinforcement through monetary incentives influences rates of adaptation and retention, although more evidence is needed to clarify the selective effect of monetary rewards and punishments on adaptation phases.

3.5. Research problem

3.5.1. The presence of uncertainty during motor adaptation

When interacting with the world, the system has to deal with external objects which dynamics are often uncertain or even unknown. Uncertainty in the environment is a prominent feature of human behavior, as unexpected changes in the environment have played an essential role in honing the way we have evolved (Sterling & Laughlin, 2015). A critical consideration for motor control is conferred to the almost omnipresent noise and irregularities in environmental information (Cisek & Kalaska, 2010; Faisal, Selen, & Wolpert, 2008). In effect, uncertainty can arise from **noise in the sensory feedback.** In this case, the goal of the sensorimotor system is to transform noisy sensory information into the most appropriate actions. An example of this could be trying to drive a car with a foggy windshield.

In addition, another important type of uncertainty that needs to be considered when interacting with the environment is one that does not directly pertain to sensory afferences but is instead related to one own constructs (*i.e.,* priors) based on the sensory information. As posited by the theory of internal models, the environment shapes our own prior beliefs about the dynamics of our body (*i.e.,* state estimation), which allows us to make sensory predictions about our movements (Miall & Wolpert, 1996; Wolpert et al., 1995; Wolpert et al., 2011). Consequently, uncertainty in the environment could yield **uncertainty in the prior state estimation** (Wei & Kording, 2010). An example of this type of uncertainty is when one erratically lifts an object after misgauging its weight, such as a nearly empty milk pint in the fridge.

3.5.2. Bayesian integration to deal with uncertainty during motor adaptation

During the visuomotor adaptation, the brain has to deal with the inherent uncertainty in the sensory (*i.e.,* visual) feedback from the environment, as well as uncertainty in his internal models issuing the motor commands and their predictions (*i.e.,* the prior state estimation) (Faisal et al., 2008; Kording & Wolpert, 2004; Krakauer et al., 2019). In this regard, Bayesian frameworks posit that the motor system is able to construct estimates of the sensorimotor transformations, in the form of internal models,

and to represent the structure of the uncertainty in the sensory system, motor system and in the internal models themselves (Bernardo & Smith, 2009).

The probabilistic distribution of all types of uncertainties becomes crucial for proper sensorimotor adaptation. In support, Kording and Wolpert (2004) conducted a reaching experiment, in which participants were asked to perform visually guided reaching movements towards a target, while the virtual position of their index finger (provided via a cursor) was laterally shifted by 1 ± 0.5 cm to the right (*i.e.,* Gaussian distribution). The participants were first heavily trained to this new prior probability distribution of the lateral shift. Importantly, the visual feedback of the finger was only provided midway through the reaching movement, while the reliability of the feedback was manipulated by applying varying levels of blurriness to the cursor. The authors were interested in assessing the extent to which participants relied on sensory feedback to correct for an explicit lateral shift of the cursor. Results show that the relationship between the lateral shift and the deviations from target depends explicitly on the prior distribution and the uncertainties of feedback (*i.e.,* level of blurriness). Specifically, the influence of the feedback on the final pointing location decreases when its uncertainty increases. It appears that the brain internally represents the uncertainty in the prior and the sensory feedback, and then weighs them optimally to control its movement. This finding suggests that a probabilistic internal model may develop during motor adaptation.

This probabilistic view of internal models has been a fruitful framework in motor adaptation, leading to investigations on how uncertainty in the sensory feedback and the prior state estimation can affect the adaptation process (Huang, Haith, Mazzoni, & Krakauer, 2011; Scheidt, Dingwell, & Mussa-Ivaldi, 2001; Turnham, Braun, & Wolpert, 2012; Wei & Kording, 2010). For instance, Wei and Kording (2010) manipulated the uncertainty in the prior state estimation (in a similar fashion as in Kording and Wolpert [2004]; see above) and subsequently tested the trial-by-trial corrective behavior to random lateral perturbations. The authors found that the more uncertain the prior, the greater the trial-by-trial rate of adaptation to these random

perturbations. Similarly, Turnham et al. (2012) used a visuomotor rotation paradigm in which they conditioned participants by providing them with veridical visual feedback of the hand (*i.e.,* low prior uncertainty) or random perturbations (*i.e.,* high prior uncertainty) before assessing adaptation to +30° or -30° visuomotor rotations. They found that the rate of adaptation was higher in the random feedback group as compared to the veridical feedback group (Turnham et al., 2012). These results provide evidence suggesting that uncertainty in the prior state estimation influences the rate of adaptation. Specifically, the higher the prior uncertainty, the greater the amount of trial-by-trial correction to visuomotor perturbations.

In addition, the extent of adaptation in the context of uncertainty has also been subject to investigation (Huang et al., 2011; Scheidt et al., 2001). Briefly, it appears that when adapting to variable perturbations (*i.e.,* where the perturbation randomly varies from one trial to the next), the brain adapts to the approximate mean of the perturbations, without depending on their variance (*i.e.,* the statistical distribution of the perturbation). All in all, it is suggested by the Bayesian framework that the brain weights the uncertainty in both the internal models and the sensory evidence and exploits the mean of the statistical distribution of exposed perturbations to adapt its motor behavior.

3.6. Research question

In light of the Bayesian framework, prior uncertainty has been demonstrated to affect the rate at which one adapts to a visuomotor perturbation (Turnham et al., 2012; Wei & Kording, 2010). However, it is not clear whether uncertainty in the prior state estimation influences the strength of the newly adapted visuomotor relationship. In the following scientific contribution, it was asked **whether introducing variance in exposed visual perturbations interferes with the short-term retention of a new visuomotor relationship** while controlling potential confounding factors (cf. *Factors influencing visuomotor adaptation*). To address this question, visual perturbations of a VMR paradigm were parametrically manipulating in such a way that the variance in exposed rotations slightly increased across three groups, without affecting the mean of

the rotation during the acquisition phase. Subsequently, the aftereffects were measured during a no vision retention phase, therefore assessing the strength of the adapted state (Bernier, Chua, & Franks, 2005; Galea et al., 2015; 2011; Krakauer et al., 1999). It was hypothesized that training under a more variable perturbation schedule would increase the uncertainty of the adapted forward model and lead to weaker retention, despite not altering the extent to which participant adapted (Huang et al., 2011; Kording & Wolpert, 2004; Scheidt et al., 2001).

3.7. Published article in Journal of Neurophysiology

Please refer to section 7.2 for the authors' authorization to include this article in the present thesis.

3.8. Variance in exposed perturbations impairs retention of visuomotor adaptation

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Keywords: sensorimotor adaptation; visuomotor rotation; uncertainty; retention; arm reaching movement.

Running title: Forward model uncertainty modulates retention

Abstract

Sensorimotor control requires an accurate estimate of the state of the body. The brain optimizes state estimation by combining sensory signals with predictions of the sensory consequences of motor commands using a forward model. Given that both sensory signals and predictions are uncertain (*i.e.,* noisy), the brain optimally weights the relative reliance on each source of information during adaptation. In support, it is known that uncertainty in the sensory predictions influences the rate and generalization of visuomotor adaptation. We investigated whether uncertainty in the sensory predictions affects the retention of a new visuomotor relationship. This was done by exposing three separate groups to a visuomotor rotation whose mean was common at 15° CCW but whose variance around the mean differed (*i.e.,* SD of 0°, 3.2° or 4.5°). Retention was assessed by measuring the persistence of the adapted behaviour in a no vision phase. Results revealed that mean reach direction late in adaptation was similar across groups, suggesting it depended mainly upon the mean of exposed rotations and was robust to differences in variance. However, retention differed across groups, with higher levels of variance being associated with a more rapid reversion toward non-adapted behaviour. A control experiment ruled out that differences in retention were accounted for by differences in success rates. Exposure to variable rotations may have increased the uncertainty in sensory predictions, making the adapted forward model more labile and susceptible to change or decay.

New and noteworthy

The brain predicts the sensory consequences of motor commands through a forward model. These predictions are subject to uncertainty. Here we use visuomotor adaptation and modulate uncertainty in the sensory predictions by manipulating the variance in exposed rotations. Results revealed that variance does not influence the final extent of adaptation, but selectively impairs the retention of motor memories. These results suggest that a more uncertain forward model is more susceptible to change or decay.

Introduction

Efficient motor control requires an accurate estimate of the state of the body in real time, which is conveyed through sensory reafferent signals. The brain optimizes state estimation by combining these sensory signals with predictions concerning the sensory consequences of descending motor commands using a forward model (Wolpert et al. 1995). Considerable work has shown that these predictions are under adaptive control throughout development and ageing, underlying our capacity to interact accurately with the world despite changing sensorimotor contexts. Adaptation has been demonstrated across a wide range of tasks (Krakauer et al. 1999; Martin et al. 1996; Morton and Bastian 2004; Shadmehr and Mussa-Ivaldi 1994) and is thought to be driven by sensory prediction errors, which arise whenever a discrepancy is detected (consciously or not) between the predicted and actual sensory consequences of the movement (Izawa and Shadmehr 2011; Mazzoni and Krakauer 2006; Miall and Wolpert 1996; Wolpert et al. 1995).

Because sensory feedback and predictions are both inherently noisy and thus uncertain (Wei and Kording 2010), probabilistic Bayesian theory has provided a fruitful framework to study sensorimotor control. Seminal work has shown that for the control of reaching movements, the relative reliance on sensory predictions (*i.e.,* the prior) and sensory feedback (*i.e.,* the evidence) depends upon their uncertainty (Kording and Wolpert 2004). This framework has been extended to sensorimotor adaptation, with greater uncertainty in the prior being associated with a greater tendency to update motor behaviours given new sensory evidence. In support, Wei and Kording (2010) investigated the influence of uncertainty in the prior on the rate of adaptation to randomly changing perturbations. To manipulate uncertainty, they initially submitted participants to conditioning blocks in which they either reached with veridical visual feedback of the hand (low prior uncertainty), with no visual feedback of the hand (moderate prior uncertainty), or sat idle (high prior uncertainty). Afterwards participants performed reaches in a condition in which the cursor could be veridical or perturbed laterally by ±2 cm. The authors found that the more uncertain the prior, the greater the trial-by-trial rate of adaptation to these random perturbations. A similar

finding was reported by Turnham et al. (2012), who assessed adaptation to +30° or -30° visuomotor rotations after participants had underwent a conditioning phase in which they were either provided with veridical visual feedback of the hand (low prior uncertainty) or submitted to random perturbations between -60° and 60° (high prior uncertainty). They found that adaptation to +30° or -30° rotation was significantly faster for the random feedback group as compared to the veridical feedback group.

A separate line of work has investigated the influence of uncertainty in the prior on the generalization of visuomotor adaptation (Fernandes et al. 2014). These authors manipulated uncertainty by exposing participants to visuomotor rotations whose variance around the mean was varied parametrically across groups. They then measured the extent to which adaptation generalized from a learned reaching direction toward new directions. Interestingly, they found that the mean of the prior and the uncertainty in the prior presented different patterns of generalization. Indeed, although generalization of adaptation was local in the sense that it was greatest around the mean of the trained reaching direction (*i.e.,* width of ~30°), uncertainty in the prior had a much more global effect, influencing movements in all directions. The authors argued that the internal representation of the mean of a prior might be distinct from the representation of its uncertainty (see also Fernandes et al. 2012).

In light of these findings showing an influence of prior uncertainty on the rate and generalization of visuomotor adaptation, it is possible that variance in exposed rotations also influences the retention of a newly formed memory. Here we address this issue by parametrically manipulating the variance in exposed rotations, but not the mean, during an adaptation phase, and assessing retention through the persistence of the adapted behaviour in a no vision phase immediately following adaptation (Bernier et al. 2005; Galea et al. 2015; 2011; Krakauer et al. 1999). It was hypothesized that training under a more variable perturbation schedule would increase the uncertainty of the adapted forward model and lead to weaker retention.

Methods

Participants

A total of fifty-five healthy right-handed participants (22 males, 19-37 years old, mean: 22.2 ± 2.5) took part in the main (n = 32) and control (n = 23) experiments. They were all naïve as to the purpose of the experiment. All participants read and signed consent forms approved by the ethical committee of the Centre Hospitalier de l'Université de Sherbrooke (CHUS). They were encouraged to ask any question relative to the consent form if it was unclear.

Apparatus

The experimental setup consisted of a table supporting a computer monitor which projected visual stimuli on a semi-reflective mirror, preventing participants from seeing their hand (Fig. 1A). The monitor (20-inch Dell P1130; resolution: 1024x768; refresh rate: 150 Hz) was mounted face down 29 cm above the horizontal mirror. The mirror itself was mounted 29 cm above the table. With this setup the visual stimuli appeared to be projected directly onto the surface of the table on the same plane as the hand. Participants were instructed to rest their chin on a self-made cushion fixed above the mirror in order to prevent head motion during the experiment.

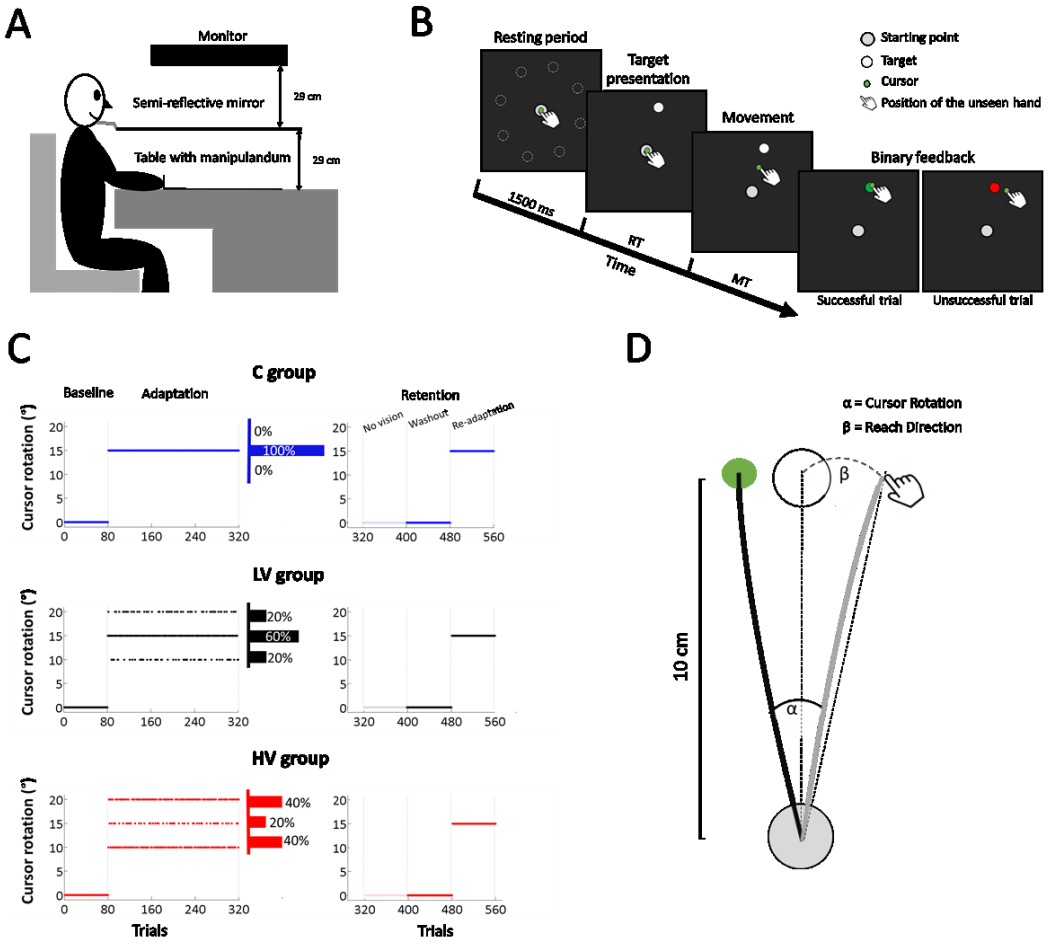

Figure 1. Apparatus and experimental procedures. (A) Side view of the apparatus. (B) Time sequence of a typical trial. (C) Experimental protocol. (D) Schematic of cursor and unseen hand trajectories. Cursor trajectory is the black trace, while unseen hand trajectory is the grey trace. Cursor rotation consisted of the angular difference between the trajectories of the cursor and the unseen hand (α). Reach direction was calculated as the angular difference between the unseen hand and the target at target radius (β). Figure not to scale.

Participants performed reaching movements using a 2-joint planar manipulandum placed on the table that they held with their right hand via a stylus located at its mobile end. The manipulandum was custom-built with 2 lightweight metal rods (48 and 45 cm respectively), with the fixed end attached to the upper left of the table. A thin sheet of smooth plastic was put on the table surface and foam pads were installed under the hinges, allowing the manipulandum to be moved anywhere on the table with minimal inertia and friction. Two potentiometers positioned in the joints

of the manipulandum allowed us to measure the angle of each segment, from which the kinematics of the stylus were estimated in the X (left, right) and Y (near, far) dimensions. This information was then used to project a cursor corresponding to participants' hand in real time on the mirror. During recording, raw kinematic data were spatially corrected with a Kalman filter to estimate hand position in real time. With this procedure, the total time necessary to collect the X- and Y-coordinates of the hand and present the corresponding visual cursor was estimated to be approximately 7-9 ms. The sampling rate of the manipulandum was 1000 Hz.

Task

Participants were instructed to make center-out reaching movements with the right hand, bringing the visual cursor (green circle; 6 mm in diameter) toward the visual targets. There were 8 targets (white circles, 15 mm in diameter, or 6°) displayed in a circular array 10 cm away from a starting point. The target array was offset counter-clockwise (CCW) by 22.5° from the X-axis (see Fig. 1B). The starting point was located at the center of the workspace and consisted of a circle (grey; 11 mm in diameter). Each target was presented once every 8 trials in a pseudorandom order, forming a cycle. Participants were instructed to make accurate movements toward the targets in a prescribed movement time of 150 ms. They were instructed not to stop on the targets but to "strike" through the targets with a single movement impulse, and to complete their movements approximately 5 cm beyond the target radius. There was no physical element stopping their movements. Fast, straight and ballistic movements were emphasized so that movement endpoints would reflect mainly the planning of the movement rather than visually-guided online corrections (Elliott et al. 2001; Khan et al. 2006; 2003; Woodworth 1899). Visual inspection of the data revealed that trajectories were very straight.

Figure 1B illustrates the sequence of events for a single trial. Participants brought the cursor into the starting point to begin a trial. After a 1500 ms resting period, a target was presented, prompting participants to perform the fast reaching movement. The end of the movement was defined as the time when the cursor crossed the target

radius, 10 cm away from the starting point. Binary feedback regarding task success was provided immediately at movement end, *i.e.,* at the crossing of the target radius, hence while in motion. The target turned green if participants successfully achieved the target, or turned red if they missed it (see "Success Rate" below for more details). Visual feedback of the cursor was provided throughout the entire trial, except during the No vision phase (see below). At the end of the trial, participants were instructed to stay still until the target disappeared (500 ms after movement end), at which point they could return to the starting point to initiate the next trial. Visual feedback of the cursor was removed for the return phase.

Main experiment

Before the experiment, participants practiced the task for 80 trials to get acquainted with the timing of the movement. Then they took part in the main experiment. In the Baseline phase, participants performed 80 trials with veridical (non-rotated) feedback of the cursor. Then, in the Adaptation phase, participants were exposed to a new visuomotor relationship for 240 trials. This was done through a cursor rotation, which generates a mismatch between the predicted visual feedback and the actual visual reafferent feedback *i.e.,* sensory prediction error. Participants were divided into three groups according to the variance in cursor rotations they experienced during the Adaptation phase. Figure 1C shows the distribution of cursor rotations in each group. In the Constant (C) group (n = 10; 4 males, mean age: 23.3 ± 5.0), the cursor rotations were constant at 15º CCW throughout the Adaptation phase. In the Low Variance (LV) group (n = 11; 3 males, mean age: 21.8 ± 1.5), the cursor rotations pseudo-randomly varied between 10º CCW (20% of trials), 15º CCW (60% of trials) and 20º CCW (20% of trials) throughout the Adaptation phase. This corresponds to a standard deviation (SD) of 3.2°. In the High Variance (HV) group (n = 11; 3 males, mean age: 21.9 ± 1.8), the cursor rotations pseudo-randomly varied between 10º CCW (40% of trials), 15º CCW (20% of trials) and 20º CCW (40% of trials) throughout the Adaptation phase. This corresponds to a SD of 4.5°. Importantly, the mean of exposed cursor rotations (15º) was identical across groups. An important aspect of the chosen

rotations, which was validated by pilot testing, is that although participants would consciously perceive the presence of visuomotor rotations, they would neither perceive their different levels (10º, 15º or 20º) nor that they could vary on a trial-by-trial basis. Also, because random rotations directly impact the endpoint error between the cursor and the target, the target sizes were specifically chosen to allow maximal control over success rates across the three groups. Indeed, pilot testing allowed us to adjust the target size so that if participants fully compensated for the cursor rotation (*i.e.,* reaching 15º CW with respect to the targets), then cursor rotations of 15º CCW would lead to hitting the target, whereas cursor rotations of 10º and 20º CCW would be associated with missing the target. This was done so that the three groups would present reliable (and thus experimentally tractable) differences in success rates during adaptation.

Immediately after the Adaptation phase, participants took part in a No vision phase, a Washout phase and a Re-adaptation phase. These allowed us to assess retention and savings of the newly acquired visuomotor relationship (Galea et al. 2015; 2011; Smith et al. 2006; Taylor et al. 2014). All three phases consisted of 80 trials and were identical for the three groups. In the No vision phase, the cursor was not provided and there was no binary feedback regarding task success. Participants were simply instructed to reach to the targets as accurately as possible. In the Washout phase, veridical (non-rotated) feedback of the cursor was provided. Finally, in the Re-adaptation phase, all participants were submitted to a constant 15º CCW cursor rotation. Breaks of ~1 minute were given between each phase. Overall, the experiment comprised 560 trials and lasted ~55 minutes.

Reaction Time

Reaction time (RT) was calculated as the time between target onset and movement onset, which was defined as the moment when the distance between the manipulandum and the starting point exceeded 2 mm. In a first rejection phase, trials for which RT was smaller than 100 ms or larger than 1000 ms were discarded. In a second phase, trials were rejected on a per-participant basis. Specifically, trials for

which RT was beyond ±3 SD from a participant's mean were rejected. This corresponded to 1.6% of the data across participants (492 trials).

Movement Time

Movement time (MT) was calculated as the time between movement onset and movement end, which corresponded to the moment the cursor crossed the 10 cm target radius. In a first rejection phase, trials for which MT was smaller than 50 ms or larger than 500 ms were discarded. In a second rejection phase, trials were rejected on a per-participant basis. Specifically, trials for which MT was beyond ±3 SD from a participant's mean were rejected. This corresponded to 2.0% of the data across participants (607 trials).

Reach direction

Reach direction was defined as the angular difference between the physical location of the unseen hand at movement end and the target. This was done by subtracting the angle subtended by the X- and Y-coordinates of the hand at movement end from that of the target (Fig. 1D). Trials for which reach directions were beyond ±100° were considered abnormal and were rejected. This corresponded to 0.5% of the data across participants (146 trials). Overall, a total of 4.1% of the data were rejected.

Variability in reach direction

It was hypothesized that uncertainty of the forward (*i.e.,* inverse) model would be influenced by variance in exposed rotations. As a proxy for uncertainty, the variability in reach directions was measured, since it reflects the level of noise in motor commands (Bays and Wolpert 2007; Harris and Wolpert 1998; Izawa and Shadmehr 2011). Specifically, the SD of reach directions was computed over the last 40 trials of the Baseline phase (cycles 6-10), providing a baseline assessment of variability, and over the last 40 trials of the Adaptation phase (*i.e.,* cycles 36-40), when participants were adapted to the visual perturbation.

Success rate

In order to provide feedback regarding task success, the angular difference between the cursor and the target at movement end was computed. Specifically, a successful trial was defined as a trial for which the angular difference was less than that subtended by the radii of the cursor and the target (*i.e.,* there was physical overlap between the cursor and the target). Note that the position of the cursor is the product of both the physical location of the unseen hand and the experimentally-induced visuomotor rotation, which could vary on a trial-by-trial basis. Success rates were assessed by calculating the percentage of successful trials over the last 40 trials of the Baseline phase (*i.e.,* cycles 6-10), providing a baseline assessment of success rates, and over the last 40 trials of the Adaptation phase (*i.e.,* cycles 36-40), when participants were adapted to the visual perturbation.

Statistical analyses

A preliminary analysis sought to confirm that RT and MT did not differ across groups over the course of the experiment. This was done by conducting a 3 Groups (C, LV, HV) x 5 Phases (Baseline, Adaptation, No vision, Washout, Re-adapt) mixed-effects analysis of variance (ANOVA).

Another analysis sought to confirm that movements did not differ across groups during baseline. To do so, reach directions, variability in reach directions and success rates were measured over the last 40 trials of the Baseline phase (*i.e.,* cycles 6-10). These data were submitted to separate 3 Groups (C, LV, HV) one-way ANOVAs.

The next analysis sought to evaluate the influence of variance in exposed rotations on the initial rate of adaptation to the new visuomotor relationship. This was calculated in two ways. First, adaptation rates were measured for each participant by fitting an exponential function over all trials of the Adaptation phase (Huang et al. 2011; Morehead et al. 2015). The function had the following form:

$$y = a - b * e^{x * c}$$

Parameter fitting was implemented using the MATLAB function fminbnd to minimize squared error (y). The asymptotic performance parameter, *a*, was set to the mean of the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40). The parameter corresponding to the total amount of adaptation, *b*, was taken as the difference between the mean of the last 5 cycles of the Adaptation phase and the mean of the last 5 cycles of the Baseline phase. The variable *x* refers to the trial number and *c* is the adaptation rate constant, which was the only free parameter in the equation (Huang et al. 2011).

This analysis was supplemented by a model-free analysis in which mean reach direction over the first 5 cycles of the Adaptation phase (*i.e.,* cycles 11-15) was compared across groups. This form of analysis has been shown to reliably capture initial adaptation in similar paradigms (Galea et al. 2011; Krakauer et al. 2005; Morehead et al. 2015). This window of trials was chosen because it captured the bulk of the changes in reach direction up to the point where participants reached asymptotic levels. To control for inter-individual differences in baseline performance, mean reach direction in the last 5 cycles of the Baseline phase was subtracted for each participant (see Morehead et al. 2015). Separate 3 Groups (C, LV, HV) one-way ANOVAs were conducted on the adaptation rate and mean reach direction data.

The final extent of adaptation was assessed by comparing mean reach direction between groups over the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40). To do so, the mean reach direction data were submitted to a 3 Groups (C, LV, HV) one-way ANOVA. To evaluate whether exposure to different levels of variance in rotations influenced the variability in reach directions as well as success rates, these data were measured over the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40) and submitted to separate 3 Groups (C, LV, HV) one-way ANOVAs.

Finally, a last set of analyses assessed the influence of variance in exposed rotations on the retention of the new visuomotor relationship. The main test of retention consisted of the No vision phase, which immediately followed adaptation. Indeed, in the absence of corrective feedback, the persistence of the adapted behaviour can be

taken as evidence for retention (Galea et al. 2011; 2015). Some participants did not present a reliable drift in reach directions during No vision. As a result, not every participants' data were well fit by an exponential function, such that a "decay rate" analysis was not used. Rather, reach directions were averaged over the first 5 cycles (*i.e.,* cycles 41-45; Early No vision) and the last 5 cycles of the No vision phase (*i.e.,* cycles 46-50; Late No vision). This allowed us to capture possible changes over the course of the No vision phase (Galea et al. 2011). These data were then submitted to a 3 Groups (C, LV, HV) x 2 Epochs (Early No vision, Late No vision) mixed-effects ANOVA. To evaluate a possible direction dependency associated with the use of multiple targets during this critical phase, a 3 Groups (C, LV, HV) x 8 Targets repeated-measures ANOVA with target as a within-participant factor was also conducted on the reach direction data from that phase (Hadipour-Niktarash et al. 2007).

As for the Washout and Re-adaptation phases, the de-adaptation rates (*i.e.,* during Washout), and re-adaptation rates (*i.e.,* during Re-adapt) were assessed. In both cases, parameter *a* was set to the last cycle of each phase, and parameter *b* was taken as the difference between the last cycle of each phase and the last cycle of the previous phase. These analyses were supplemented by a 3 Groups (C, LV, HV) x 2 Epochs (Early, Late) mixed-effects ANOVA conducted on the reach direction data. Finally, to assess savings (*i.e.,* more rapid adaptation upon second exposure to the perturbation as compared to the first), the adaptation rates were compared to the re-adaptation rates using a 3 Groups (C, LV, HV) x 2 Phases (Adaptation, Re-adaptation) mixed-effects ANOVA.

It should be noted that the potential influence of variance in exposed rotations was expected to attenuate over the Washout and Re-adaptation phases, since variance was not manipulated across groups anymore. Hence, while the Re-adaptation phase allowed us to assess savings, it did not constitute the key condition on which differences in retention would be assessed across conditions. All effects were deemed significant at $P < 0.05$, and Tukey's test was used for post-hoc comparisons.

Results

Verbal debriefing with participants after the experiment confirmed that although they did perceive the suddenly introduced visuomotor rotations, they neither perceived their different levels (10º, 15º or 20º) nor that they could vary on a trial-by-trial basis.

Before assessing whether variance in exposed rotations influenced the acquisition and retention of the new visuomotor relationship, the RT and MT data were compared to ensure that they did not differ across groups. This was confirmed. Indeed, the ANOVA conducted on the RT data only revealed a main effect of Phase ($F_{(4, 116)}$ = 8.4; $P < 0.001$; η_p^2 = 0.22), with RTs tending to increase over the course of the experiment. However, it neither revealed a main effect of Group (448 ± 17 ms, 406 ± 16 ms and 426 ± 16 ms for the C, LV and HV groups, respectively; P = 0.24; η_p^2 = 0.09) nor an interaction (P = 0.53; η_p^2 = 0.06). Similarly, the ANOVA conducted on the MT data also revealed only a main effect of Phase ($F_{(4, 116)}$ = 5.7; $P < 0.001$; η_p^2 = 0.17), with MTs being slightly higher in the Baseline phase as compared to the other phases. Most importantly, it neither revealed a main effect of Group (151 ± 5 ms, 152 ± 5 ms and 151 ± 5 ms for the C, LV and HV groups, respectively; P = 0.98; η_p^2 = 0.001) nor an interaction (P = 0.72; η_p^2 = 0.04).

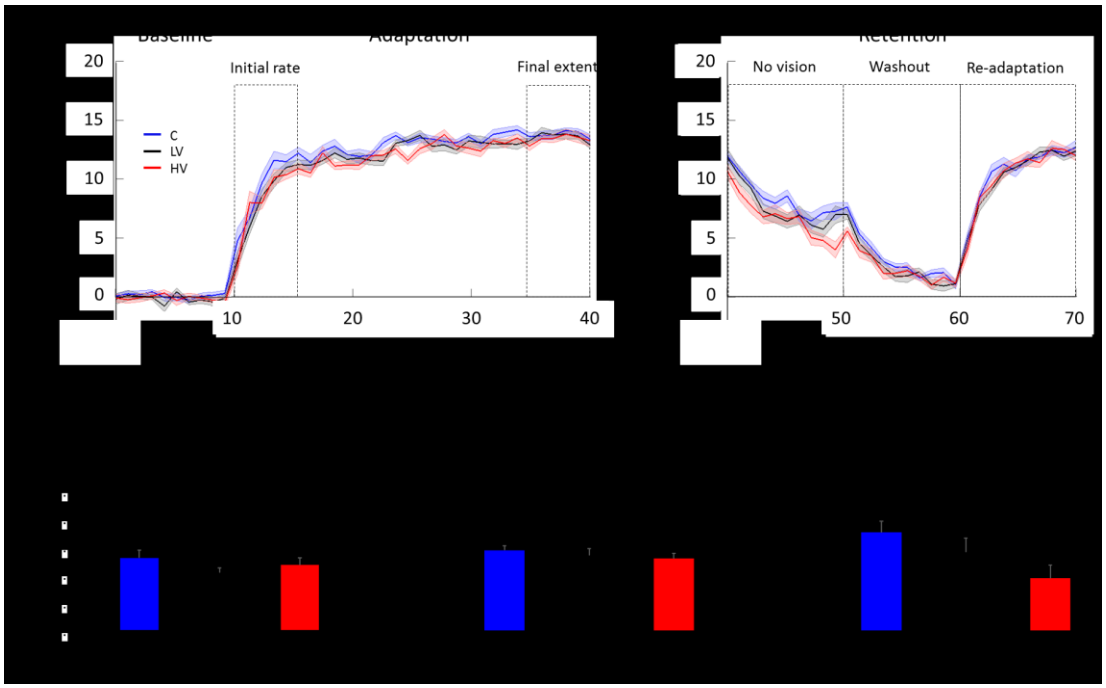

Figure 2. Main experiment results. (A) Time course of reach directions for each group during adaptation, with data binned in cycles (8 trials). (B) Initial rate of adaptation, as measured by fitting an exponential function over all trials of the Adaptation phase. Variance in exposed rotations did not influence the initial rate of adaptation. (C) Final extent of adaptation, as measured by mean reach direction over the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40). Variance in exposed rotations did not influence the final extent of adaptation. (D) Time course of reach directions for each group during retention. (E) Retention of the new visuomotor relationship, as measured by mean reach direction in the No vision phase. Higher variance in exposed rotations was associated with lower retention. Error bars represent S.E.M. Asterisk denotes a $P < 0.05$.

Adaptation

The mean reach directions in the three groups across each cycle of the Adaptation phase are presented in Figure 2A. As can be seen, the three groups did not differ significantly during baseline. Indeed, the ANOVA carried out on the Baseline phase data revealed no significant difference in mean reach direction (M = -0.1 ± 0.1°; $F_{(2, 29)} = 1.1$; $P = 0.35$; $\eta_p^2 = 0.07$), variability in reach directions (M = 2.7 ± 0.1°; $F_{(2, 29)} = 2.1$; $P = 0.14$; $\eta_p^2 = 0.13$), as well as success rates (M = 89.0 ± 1.5%; $F_{(2, 29)} = 0.02$; $P = 0.98$; $\eta_p^2 = 0.001$).

Figure 2A also shows that the three groups adapted to the new visuomotor relationship rapidly, reaching near-asymptotic levels within ~5 cycles. As can be seen on Figure 2B, adaptation rates were similar across groups, with the C, LV and HV groups presenting values of 0.05 ± 0.01, 0.04 ± 0.003 and 0.05 ± 0.01, respectively. This was confirmed by the ANOVA which revealed no significant difference across groups ($F_{(2, 29)} = 1.2$; $P = 0.32$; $\eta_p^2 = 0.08$). The same conclusion emerged from the analysis of the mean reach direction over the first 5 cycles of the adaptation phase ($M = 8.3 \pm 0.5°$; $F_{(2, 29)} = 1.1$; $P = 0.34$; $\eta_p^2 = 0.07$). Overall, these data suggest that the initial rate of adaptation was unaffected by variance in exposed rotations.

As can also be seen in Figure 2A, the three groups tended to plateau at a similar level of performance (~14°) late in adaptation, compensating near fully for the mean rotation of 15° CCW to which they were exposed. To assess the final extent of adaptation, mean reach direction over the last 5 cycles of the Adaptation phase was compared across groups. As can be seen in Figure 2C, there was minimal difference across groups, with the C, LV and HV groups presenting mean reach directions of 13.9 ± 0.1°, 13.7 ± 0.2° and 13.6 ± 0.2° respectively. Accordingly, the ANOVA revealed no significant difference across groups ($F_{(2, 29)} = 0.55$; $P = 0.6$; $\eta_p^2 = 0.04$). This indicates that variance in exposed rotations did not affect the final extent of adaptation.

Retention

Reach directions in each cycle of the No vision, Washout and Re-adaptation phases are presented in Figure 2D. As can be seen, movements were still biased toward the adapted reach direction in the No vision phase, demonstrating retention. However, reach directions tended to drift over that phase, going from ~14° to ~6°. Retention of the newly acquired visuomotor relationship was primarily assessed through reach directions in the No vision phase, which are presented in Figure 2E. Critically, mean reach direction during that phase tended to be graded across groups, with the C group showing the highest mean reach direction during No vision (*i.e.,* better retention). This

was confirmed by the ANOVA which revealed a significant main effect of Group ($F_{(2, 29)} = 3.4$; $P = 0.04$; $\eta_p^2 = 0.19$). Post-hoc comparisons revealed that mean reach direction in the C group ($M = 8.5 \pm 0.5°$) was significantly greater than in the HV group ($M = 6.8 \pm 0.5°$; $P = 0.04$). The LV group was intermediate ($M = 7.8 \pm 0.5°$) but did not differ significantly from the two other groups (both $P > 0.1$). There was also a significant main effect of Epoch ($F_{(1, 29)} = 181.6$; $P < 0.001$; $\eta_p^2 = 0.86$), with reach directions decreasing significantly between Early No vision (cycles 41-45; $M = 9.0 \pm 0.3°$) and Late No vision (cycles 46-50; $M = 6.4 \pm 0.3°$). Importantly, there was no Group x Epoch interaction ($F_{(2, 29)} = 0.2$; $P = 0.8$; $\eta_p^2 = 0.01$), suggesting that the differences across groups were maintained throughout the No vision phase. In sum, these data indicate that as variance in exposed rotations increased, retention decreased.

To evaluate a possible direction dependency during the critical No vision phase, reach directions were also compared across targets. The ANOVA again revealed a main effect of Group ($F_{(2, 29)} = 3.5$; $P = 0.04$; $\eta_p^2 = 0.19$), with the C group again presenting significantly better retention than the HV group ($P = 0.03$). The LV group was intermediate but did not differ significantly from the two other groups (both $P > 0.2$). There was also a main effect of Target ($F_{(7, 203)} = 14.4$; $P < 0.001$; $\eta_p^2 = 0.33$), with reach directions differing across targets, possibly attributable to biomechanical constraints. Critically, however, there was no Group x Target interaction ($F_{(14, 203)} = 0.9$; $P = 0.6$; $\eta_p^2 = 0.06$).

Reach directions gradually reverted back from ~6° to ~1° during the Washout phase. This was confirmed by the ANOVA, which revealed a significant main effect of Epoch ($F_{(1, 29)} = 385.2$; $P < 0.001$; $\eta_p^2 = 0.93$). Although mean reach direction tended to be slightly graded across groups during this phase (3.2 ± 0.3°, 2.6 ± 0.3° and 2.5 ± 0.3° for the C, LV and HV groups, respectively), there was no significant main effect of Group ($F_{(2, 29)} = 1.8$; $P = 0.19$; $\eta_p^2 = 0.11$). Similarly, the ANOVA carried out on the de-adaptation rates did not show a significant main effect of Group ($M = 0.05 \pm 0.01$; $F_{(2, 28)} = 1.2$; $P = 0.31$; $\eta_p^2 = 0.08$).

As for the Re-adaptation phase, participants rapidly re-acquired the new relationship, with reach directions going from ~1° to ~14°. The ANOVA carried out on the reach direction data revealed a significant main effect of Epoch ($F_{(1, 29)}$ = 308.5; $P < 0.001$; $\eta_p^2 = 0.91$). However, there was no significant main effect of Group (10.8 ± 0.3°, 10.5 ± 0.3° and 10.5 ± 0.3° for the C, LV and HV groups, respectively; $F_{(2, 29)}$ = 0.35; $P = 0.7$; $\eta_p^2 = 0.02$). Similarly, the ANOVA carried out on the re-adaptation rates did not show a significant main effect of Group ($M = 0.08 \pm 0.01$; $F_{(2, 28)} = 0.27$; $P = 0.76$; $\eta_p^2 = 0.02$). Even though re-adaptation was similar across groups, there was evidence for savings, as the re-adaptation rates ($M = 0.08 \pm 0.01$) were significantly greater than the initial adaptation rates ($M = 0.05 \pm 0.005$; $F_{(1, 26)} = 28.9$; $P < 0.001$; $\eta_p^2 = 0.53$). This suggests a persistent memory representation of the adapted forward model in all three groups (Smith et al. 2006).

Variability in reach directions and success rates

Although participants' mean reach direction did not differ across groups late in the Adaptation phase, they may have presented different levels of variability in reach directions. To visually represent this, the distributions of reach directions of all trials in the last 5 cycles of the Adaptation phase were averaged across participants and are presented in Figure 3A. As can be seen, the three groups presented unimodal distributions with a mean at ~14°. This is consistent with the finding that the three groups adapted their mean reach direction similarly. Interestingly, however, there was a tendency for the variance groups (LV and HV) to be associated with broader distributions (*i.e.,* more variability in reach directions). This was confirmed by the ANOVA conducted on the SD of reach directions in the last 5 cycles of the Adaptation phase, which revealed a significant main effect of Group ($F_{(2,29)} = 4.9$; $P = 0.02$; $\eta_p^2 = 0.25$; see Figure 3B). Post-hoc comparisons revealed that SD in the C group (2.8 ± 0.2°) was significantly smaller than in HV group (3.6 ± 0.2°; $P = 0.01$), whereas the LV group (3.1 ± 0.2°) was intermediate but did not differ significantly from the other groups (both $P > 0.1$).

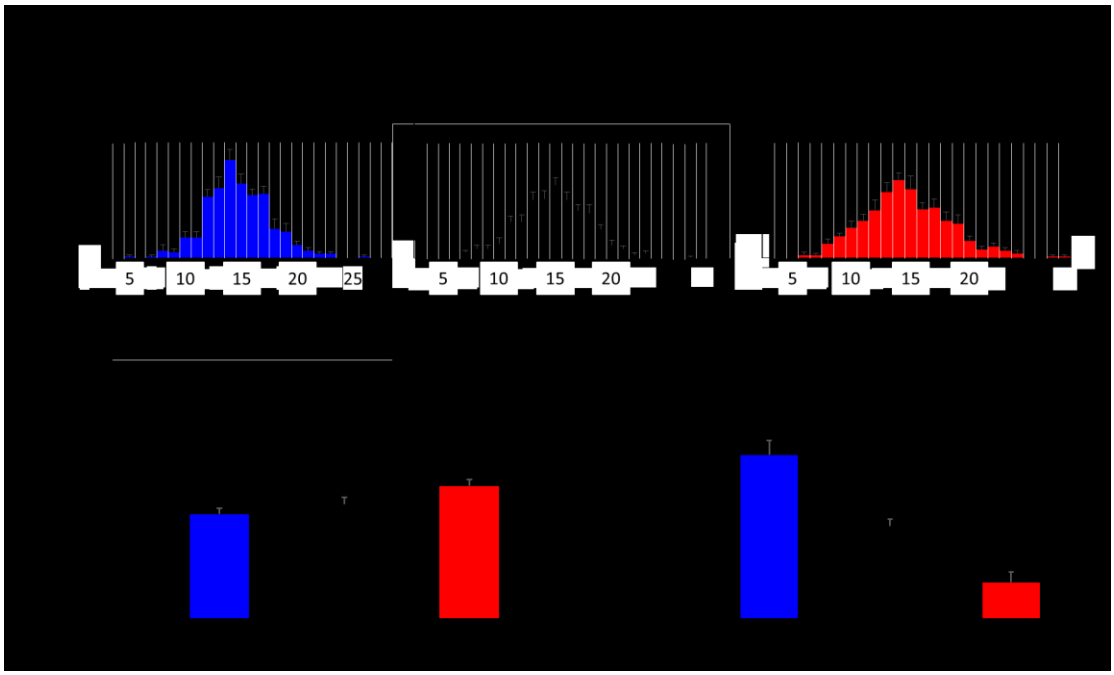

Figure 3. Main experiment results. (A) Distributions of reach directions of all trials in the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40), averaged across participants and presented for each group. (B) Mean variability in reach directions for each group, assessed by calculating the SD of reach directions over the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40). Higher variance in exposed rotations was associated with higher variability in reach directions. (C) Mean success rates for each group over the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40). Higher variance in exposed rotations was associated with lower success rates. Error bars represent S.E.M. Asterisks denote a $P < 0.05$.

Success rates in the last 5 cycles of the adaptation phase were also compared across groups and are presented in Figure 3C. The ANOVA again revealed a significant main effect of Group ($F_{(2,29)} = 33.8$; $P < 0.001$; $\eta_p^2 = 0.7$), with the highest success rates for the C group (84.0 ± 4.0%) followed by the LV group (64.9 ± 1.8%) and the HV group (50.0 ± 2.7%). Post-hoc comparisons revealed that all three groups differed significantly from each other (all $P < 0.005$). This was expected, given that participants' mean reach direction was ~14° in all three groups, hence leading to target hits whenever the cursor rotation was 15° CCW, but misses whenever the rotation was 10° CCW or 20° CCW.

Control Experiment

Results from the main experiment revealed that retention of the new visuomotor relationship differed across groups in the No vision phase (Fig. 2E). While this suggests that variance in exposed rotations was the key factor influencing retention, a possible confound is the fact that the three groups also differed in terms of overall success rates (see Fig. 3C). In light of recent work showing that rewards impact the retention of a new visuomotor relationship (Galea et al. 2015), it was important to confirm that the observed group differences in retention were not merely accounted for by differences in success rates. To do so, two additional groups were created (C-Control; n = 11; 6 males, mean age: 22.1 ± 1.1, and HV-Control; n = 12; 6 males, mean age: 22.2 ± 1.2), for which the size of the targets was manipulated to modulate success rates. Identical to the C group, the C-Control group had no variance in exposed rotations (*i.e.,* constant 15° CCW), but was presented with smaller targets (10 mm in diameter), thereby decreasing success rates. This target size was chosen so that the success rates would approximate those of the HV group late in adaptation (*i.e.,* 50%). On the other hand, the HV-Control group was submitted to the same high variance perturbation schedule as the HV group, but was provided with larger targets (24 mm in diameter), thereby increasing success rates. This target size was chosen so that the success rates would approximate those of the C group late in adaptation (*i.e.,* 84%). All other features of the control experiment were identical to the main experiment. If the C-control group still presented better retention than the HV-control group, then it would rule out that the differences in retention observed in the main experiment were merely accounted for by differences in success rates.

Results

Success rates were first assessed to confirm the effectiveness of the target size manipulation. This was the case, as an independent-samples t-test conducted on the success rates late in the Adaptation phase revealed that the C-Control group presented significantly lower success rates than the HV-Control group (43.0 ± 2.1% and 86.0 ± 2.3%, respectively; $t_{(21)} = 13.6$; $P < 0.001$).

The mean reach directions across each cycle of the Adaptation phase are presented in Figure 4A. The two groups did not differ significantly during baseline in any of the dependent variables (all $P > 0.4$). As can be seen on Figure 4B, the initial rate of adaptation was similar across groups. This was confirmed by independent samples t-tests which revealed no significant difference across groups both for the adaptation rates ($M = 0.06 \pm 0.02$; $P = 0.8$) and the mean reach direction over the first 5 cycles of the Adaptation phase ($M = 8.8 \pm 0.7°$; $P = 0.9$).

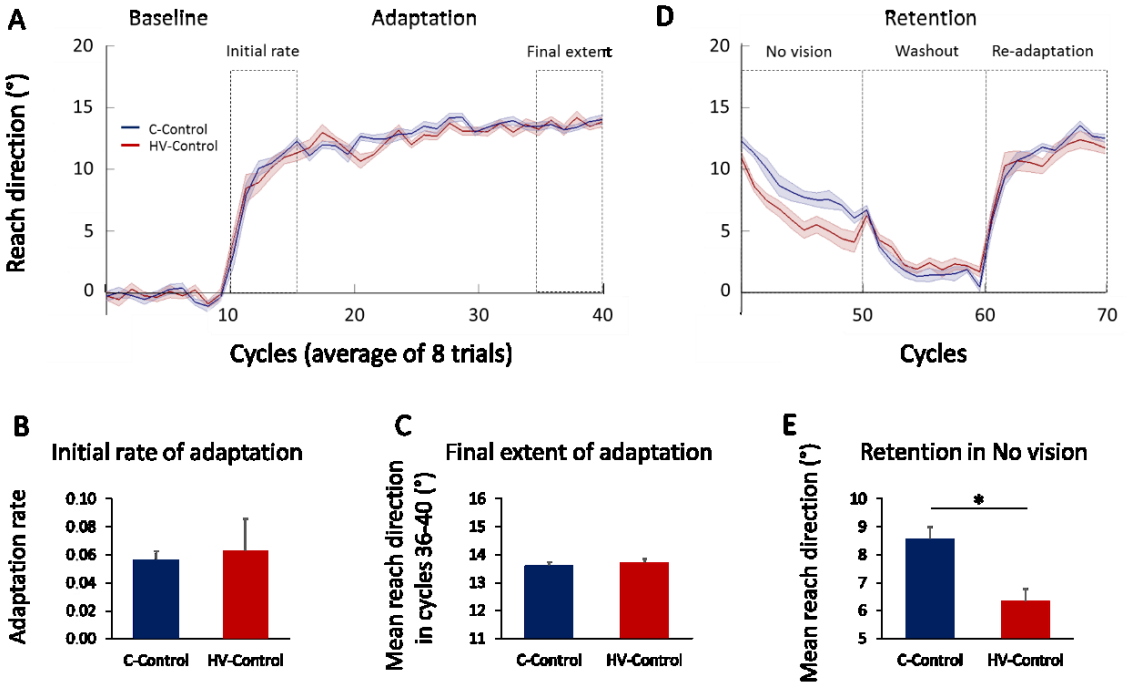

Figure 4. Control experiment results. (A) Time course of reach directions for each group during adaptation, with data binned in cycles (8 trials). (B) Initial rate of adaptation, as measured by fitting an exponential function over all trials of the Adaptation phase. Variance in exposed rotations did not influence the initial rate of adaptation. (C) Final extent of adaptation, as measured by mean reach direction over the last 5 cycles of the Adaptation phase (*i.e.,* cycles 36-40). Variance in exposed rotations did not influence the final extent of adaptation. (D) Time course of reach directions for each group during retention. (E) Retention of the new visuomotor relationship, as measured by mean reach direction in the No vision phase. Higher variance in exposed rotations was associated with lower retention. Error bars represent S.E.M. Asterisk denotes a $P < 0.05$.

The final extent of adaptation was also similar across groups (Figure 4C). Indeed, the t-test conducted on the mean reach direction over the last 5 cycles of the

Adaptation phase revealed no significant difference across groups (M = 13.7 ± 0.1°; P = 0.6). As for variability in reach directions late in the Adaptation phase, the HV-Control presented higher variability as compared to the C-Control group (3.6 ± 0.2° and 3.2 ± 0.1°, respectively), although this did not reach statistically significant levels (P = 0.4).

Figures 4D and 4E present the mean reach direction in the No vision phase, used to assess retention. Critically, retention was better in the C-Control group than in the HV-Control group (8.6 ± 0.4° and 6.3 ± 0.4°; respectively), as confirmed by the ANOVA which revealed a significant main effect of Group ($F_{(1, 21)}$ = 13.0; P = 0.002; η_p^2 = 0.38). There was also a significant main effect of Epoch ($F_{(1, 21)}$ = 113.8; P < 0.001; η_p^2 = 0.84), with reach directions decreasing between Early No vision (M = 9.0 ± 0.5°) and Late No vision (M = 6.0 ± 0.6°). Again, there was no Group x Epoch interaction ($F_{(1, 21)}$ = 0.1; P = 0.7; η_p^2 = 0.01), indicating that the group differences were maintained across the No vision phase. There were no differences across groups during the Washout and the Re-adaptation phases, in either the mean reach direction analyses or the rate analyses (all P > 0.2).

In sum, using independent datasets, the control experiment replicates the findings of the main experiment, in that variance in exposed rotations did not influence adaptation but selectively impaired retention of the new visuomotor relationship. Importantly, it confirms that in the present context, retention was mainly influenced by variance in exposed rotation and not by different success rates.

Discussion

The present study investigated the influence of uncertainty in the sensory predictions on the retention of a new visuomotor relationship. This was done by parametrically manipulating the variance in exposed rotations but not the mean during visuomotor adaptation, and then measuring the persistence of the adapted behaviour in a no vision phase. Results revealed that mean reach direction was similar across groups late in adaptation. Interestingly, however, retention differed across groups, with increased variance being associated with a more rapid reversion toward non-adapted behaviour (*i.e.,* weaker retention). A control experiment confirmed that differences in retention were not attributable to differences in success rates during adaptation. These results suggest that exposure to more variable rotations increased the uncertainty of the adapted forward model, making it more labile and susceptible to change or decay.

Variance in exposed rotations does not influence the mean of the adapted forward model but its uncertainty

Results revealed that the initial rate of adaptation and the final extent of adaptation were not influenced by variance in exposed rotations. This supports previous work from Burge et al. (2008) and Scheidt et al. (2001), who also found that random variability in exposed perturbations had no effect on adaptation in humans. However, this is in contrast to Fernandes et al. (2012), who reported slower and less complete adaptation under high variance conditions. It is possible that the difference between the present results and those of Fernandes et al. (2012) is attributable to the fact that the variances used here (SDs of 0º, 3.2º, 4.5º) were much smaller than theirs (SDs of 0º, 4º and 12º). In this regard, it should be reiterated that the goal here was for participants not to consciously perceive the induced variance in rotations, which was indeed the case. The fact that mean reach direction was similar across groups late in training thus suggests that adaptation was robust to differences in variance (at least in the range tested here) and was rather dependent upon the mean of exposed perturbations.

Interestingly, even though the three groups similarly adjusted their mean reach direction toward 15° during adaptation, exposure to higher levels of variance impacted the trial-to-trial variability of those movements. Indeed, variability (SD) in reach directions significantly differed across groups late in adaptation, being largest in the HV group, intermediate in the LV group, and smallest in the C group (see Fig. 3B). This suggests a more uncertain estimate of the adapted forward model upon exposure to variance, since more variable movements are thought to underline a more uncertain forward (and inverse) model (Bays and Wolpert 2007). The increased variability in reach directions is unlikely to have reflected a strategy of offsetting the perturbations by aiming at 10° or 20°, or the separate adaptation to three independent rotations, since the distributions of reach directions were clearly unimodal with a peak near 15° in all three groups (Fig. 3A). This is especially striking for the HV group, whose schedule of perturbations was bimodal, suggesting that participants adapted to the mean and not to the most likely rotation [see also Scheidt et al. (2001) for similar observation]. Overall this result points to variability in reach directions as truly reflecting uncertainty around the mean. This is consistent with previous work showing that adding variance around a perturbation acts to increase the uncertainty of the adapted forward model (Fernandes et al. 2012; 2014; Tan et al. 2016).

Together, these findings indicate that the rate and extent to which the adapted forward model "shifted" from 0° to 15° depended upon the mean evidence sampled over the course of the adaptation phase. In contrast, variance in exposed rotations acted to increase the uncertainty (*i.e.,* noise) around this new mean.

Variance in exposed rotations influences the retention of the adapted forward model

The main finding of the present work is that despite the fact that the three groups presented similar mean reach directions late in adaptation, variance in exposed rotations influenced the retention of the new visuomotor relationship. This effect was specific to the No vision phase. Indeed, although there was significant savings upon re-exposure to the rotation in the Re-adapt phase, there was no difference across groups

in that phase. A similar finding was recently reported by Maeda et al. (2017), who also found no difference in the re-learning of a visually guided walking task between groups that had trained under a constant vs. noisy visuomotor mapping. Still, it is possible that the absence of group effect during re-adaptation is simply attributable to the fact that the influence of variance in exposed rotations had washed away during the Washout phase.

In light of the preceding evidence for differences in uncertainty, a first possibility accounting for the differential retention during no vision derives from the Bayesian framework, which suggests that greater uncertainty in the prior is associated with a greater tendency to adjust motor behaviours given new sensory evidence (Wei and Kording 2010). Indeed, the present adaptation phase could be considered as a conditioning phase, effectively modulating uncertainty of the adapted forward model. The retention phase, in turn, would reflect participants' tendency to change their behaviour given new sensory evidence. While a no vision condition is generally considered as providing no feedback and thus no "new sensory evidence" with which to adjust behaviour, participants could still rely on proprioceptive information to plan, control and evaluate the outcome of their movements. Interestingly, it is well documented that visuomotor adaptation is accompanied by proprioception recalibration (Simani et al. 2007; Cressman and Henriques 2009), and a recent study showed that variance in exposed rotations tends to reduce the degree of proprioceptive recalibration (Saijo and Gomi 2012). Specifically, the authors investigated proprioceptively-guided online control by using probe trials in which vision was unpredictably removed. They found that reaches during probe trials were more biased toward the actual (*i.e.,* non-rotated) target location when variance in exposed rotations was high, suggesting that proprioceptive recalibration was reduced by variance. In this light, the drift toward baseline during the present No vision phase may have been attributable to a proprioceptively-driven task error (*i.e.,* the comparison between final hand position and target position), and the different rate at which this occurred across groups may have been a result of differences in proprioceptive recalibration. In this framework, given that variance in exposed rotations: i) makes the sensorimotor system

rely less on the prior and more on new sensory evidence (Wei and Kording 2010), and ii) reduces the degree of proprioceptive recalibration (Saijo and Gomi 2012), it would follow that higher levels of variance in exposed rotations led to a faster reversion toward non-adapted behaviour.

Alternatively, it is possible that the differences observed in the No vision phase were due to a competition between two visuomotor memories: the adapted forward model at 15° CCW and the "original" forward model at 0°. In support, Shmuelof et al. (2012) proposed that the drift toward baseline observed in no vision or error-clamp conditions is the reflection of a gradual reversion toward the original well learnt forward model. In this light, increased uncertainty in the adapted prior may have led the sensorimotor system to attribute a greater weight to the original prior, thus explaining the more rapid drift.

Another possibility is that the different retention across groups reflected differences in the stability of the new motor memory (Vaswani and Shadmehr 2013), perhaps driven by different rates of forgetting of the adapted forward models. Specifically, variance in exposed rotations may have influenced the relative contribution of the fast and slow components of adaptation across groups, which show differential adaptation rates and capacity for retention (Joiner and Smith 2008; Shadmehr et al. 2010; Smith et al. 2006). Namely, the fast component shows high adaptation rates but poor retention, whereas the slow component shows low adaptation rates but high retention. A key element is that uncertainty in the prior has previously been associated with faster adaptation rates (Wei and Kording 2010, Turnham et al. 2012), a sign that the fast component is exacerbated in this context. In turn, higher variance may have been associated with a proportionally lesser contribution of the slow component to adaptation, accounting for the weaker retention of the adapted forward model in this context.

Finally, the differences in retention may have been partly attributable to the fact that movements were more repetitive (smaller SD) in the C group than the LV and HV groups (see Fig. 3B), leading to use-dependent plasticity (UDP). Indeed, the repetition of movements in a given direction fosters the formation of a stronger memory trace by

the creation and strengthening of neural connections through Hebbian processes (Diedrichsen et al. 2010; Huang et al. 2011; Kantak et al. 2013; Rroji et al. 2015; Verstynen and Sabes 2011). While UDP is a possibility, it has been shown to contribute to retention mainly in contexts in which a single or few targets are used. To our knowledge it remains to be demonstrated whether UDP plays a significant role when there is inherent variability in motor commands across trials given the large number of targets.

Retention was not modulated by task success

In the main experiment, variance in exposed rotations covaried with success rates, making it possible that the graded retention was attributable to differences in rewards across groups (Galea et al. 2015). However, a control experiment in which success rates were independently manipulated by changing target size confirmed that differences in retention were uniquely attributable to variance in exposed rotations. These results demonstrate that in the present context, behavioural success did not have a significant bearing on the retention of the new visuomotor relationship. In support of the present results, a recent study tested how external reward feedback affects sensorimotor adaptation (Nikooyan and Ahmed 2015). They found that while it is possible to learn from reward feedback alone, it does not lead to a remapping of the visuomotor relationship, which is necessary to drive aftereffects and retention (see also van der Kooij and Overvliet 2016). Similarly, Izawa and Shadmehr (2011) reported that, while sensory and reward prediction errors can both lead to changes in motor commands during adaptation, only sensory prediction errors alter the predicted consequences of motor commands and cause sensory remapping. These interpretations are in line with the present results, in that feedback about task success was not the defining factor of retention.

Conclusion

In conclusion, the present study suggests a dissociation between the influence of variance in exposed rotations on the mean reach direction late in adaptation vs. the

retention of a new visuomotor relationship. This extends previous work suggesting differential internal representations of the mean and uncertainty of priors (Fernandes et al. 2014). These results may have implications in rehabilitation settings involving virtual reality, where visual reafferent feedback can be manipulated. Efforts should focus on developing interfaces that minimize variability in the feedback being delivered to patients, hence fostering the long-term storage of motor memories.

Acknowledgements

This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada (NSERC). The authors declare no competing financial interests

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4. DISCUSSION

4.1. Integrating the two scientific contributions

4.1.1. Manipulation of uncertainty

In this thesis, two very distinct projects with their respective frameworks were presented. The first one was devoted to movement planning, alluding to the processes by which the brain spatially and temporally prepares its movement before its execution. Specifically, it was asked how the pre-movement beta-band dynamics were modulated by the manipulation of the amount of spatial and temporal information provided before the execution of a reach movement. On the other hand, the second part of the thesis focused on motor adaptation, pertaining to the process by which the brain updates its internal models in response to environmental perturbation. Specifically, it was asked how retention in the short-term is modulated by the manipulation of the variance around the mean of the perturbations during a visuomotor adaptation task.

Although there is a noticeable distinction in the nature of these two scientific contributions, both projects consisted of manipulating task-specific information, which in a sense, could be viewed as manipulating the uncertainty in task-specific contingencies within each protocol. For instance, in the first experiment, the spatiotemporal anticipation could be view as the opposite of spatiotemporal uncertainty. Thus, participants prepared target-directed reach movements while being uncertain about the target location (spatial) and imperative go-cue (temporal). Conditions were designs in such a way that spatiotemporal uncertainty was either nulled (One Target, One Timing) or increased (Three Targets, Three Timings). When considering the presence of uncertainty, the behavioral results could be reinterpreted as follows: higher levels of spatiotemporal uncertainty about the reaching target led to higher RTs.

On the other hand, in the second experiment, the participants adapted to a mean rotation of 15°, while uncertainty in the sensory feedback was manipulated by changing the variance of the rotation across groups. The results could be reinterpreted as follows:

adaptation to perturbation with higher variance, which probably led to the update of an uncertain internal model, was associated with reduced levels of short-term retention. Following this perspective, both these experiments comprised variations in task-specific contingencies that increased uncertainty in distinctive and specific ways, which led to significant decay in behavioral performance.

4.1.2. Representation of spatial uncertainty during the planning of reaching movements

In the first project, the spatial uncertainty was manipulated through the number of potential targets during the delay period. It is possible that this manipulation could have incurred multiple motor plans (Cisek & Kalaska, 2002), which neural representations entrained a competition through mutual inhibition (Bastian, Schöner, & Riehle, 2003; Cisek & Kalaska, 2005). Alluding to this inhibitory nature of beta-band activity (Baker & Baker, 2003; Jensen et al., 2005; Roopun et al., 2008; Roopun et al., 2006), an expected result would have been higher levels of beta-band power during movement planning associated with higher levels of directional uncertainty, as it has previously been reported (Tzagarakis et al., 2010; Tzagarakis et al., 2015). This phenomenon was not seen in the present results. The discrepancy between results could potentially be ascribed to different degrees of cortical inhibition across experiments. It is possible that the degree of cortical inhibition might depend on the degree of interference between the directionally-tuned neural populations representing each movement vector (*i.e.,* motor plan) for each potential target. In that sense, the more distributed the targets, the more competition between neural activities. This interpretation is supported by monkey studies showing that activity of directionally-tuned neurons encoding for two reaching targets was discrete and separate when the targets were far apart but could merge into a continuous pattern when closer together (Bastian et al., 2003; Cisek & Kalaska, 2005). These studies have reported that the distribution patterns of such neuronal activations tend to reduce when there is greater competition (*i.e.,* inhibition) across motor plans (Bastian et al., 2003; Cisek & Kalaska, 2005). This can be accounted for by biased competition mechanisms in which

directionally-tuned neurons with similar preferred directions excite each other, whereas neurons with distinct directional preferences tend to inhibit each other (Cisek, 2007). In other words, the greater the space between competing targets, the more the mutual inhibition between the neural representations of their motor plans. Considering its inhibitory nature, beta-band power over sensorimotor regions might thus reflect the degree of competition between motor plans. A great way to elucidate this contention is simply by recording EEG activity while having participants preparing reach movement toward a set of three potential targets and comparing beta-band activity across two separate conditions: one where targets are spread across the workspace (akin the three targets condition in Tzagarakis et al. [2010]) and the other where targets are much closer together. Based on work showing that cortical activity during movement planning is influenced by the layout of the targets in the workspace (Grent-'t-Jong et al., 2014), it can be hypothesized that the former condition would elicit greater competition, which would translate in higher levels of beta-band synchrony.

4.1.3. Representation of temporal anticipation during the planning of reaching movements

The neural representation of time remains an elusive concept in modern neuroscience. For instance, it remains unclear whether time perception is subtended by specialized neural populations or rather by a distributed network in the brain (Eagleman et al., 2005; Ivry & Spencer, 2004; Karmarkar & Buonomano, 2007). Evidence from single-cell recordings appears to favor the latter proposition (Kilavik, Confais, & Riehle, 2014). Specifically, neurons in many cortical areas, including SMA (Cui, Stetson, Montague, & Eagleman, 2009; Jahanshahi et al., 1995; Lewis & Miall, 2003), the parietal cortex (Janssen & Shadlen, 2005; Leon & Shadlen, 2003), and the primary motor and premotor cortices (Crammond & Kalaska, 2000; Lebedev, O'doherty, & Nicolelis, 2008; Roux, Coulmance, & Riehle, 2003) change their firing rates progressively during the preparatory delay, in a context (*i.e.* task) specific manner. Even though these distributed changes in neural activation can be the reflection of task-relevant time-keeping processes, they do not seem to be self-sufficient mechanisms

responsible for tracking time (Lebedev et al., 2008). Instead, this activity might be embedded in a context-dependent timing network (Ivry & Spencer, 2004; Mauk & Buonomano, 2004; Merchant, Harrington, & Meck, 2013). With respect to this "timing network," accumulating evidence has indicated that both the cerebellum and the basal ganglia may play a critical role in temporal processing of events (Ivry & Spencer, 2004; Sokolov, Miall, & Ivry, 2017).

In the context of sensorimotor control, the cerebellum plays a significant role in temporal processing (Ivry & Keele, 1989; Sokolov et al., 2017). Cerebellar dysfunction is canonically related to loss of sensorimotor coordination. In effect, cardinal symptoms of cerebellar ataxia are related to uncoordinated muscular patterns attributable to delayed latencies in the recruitment of antagonist muscles (Bastian, Martin, Keating, & Thach, 1996; Hore, Wild, & Diener, 1991). This makes sense in light of the predictive role of the cerebellum, alluding to its contribution in the operation of a forward model (Ebner, Hewitt, & Popa, 2011; Ishikawa, Tomatsu, Izawa, & Kakei, 2016; Liu, Robertson, & Miall, 2003; Miall, Christensen, Cain, & Stanley, 2007; Nowak, Topka, Timmann, Boecker, & Hermsdörfer, 2007; Shadmehr et al., 2010; Wolpert & Kawato, 1998). Sensory predictions generated by the cerebellum can be used to coordinate motor outputs (Ebner et al., 2011; Liu et al., 2003) and provide a means to anticipate the consequences of motor commands (Wolpert & Kawato, 1998). An important consideration of sensorimotor predictions is that they are temporally precise; sensory predictions do not only represent what the sensory consequences of motor commands will be but also when these reafferences are going to happen with relatively short time intervals (Sokolov et al., 2017). In addition, the cerebellum is highly interconnected with motor cortical structures (Dum & Strick, 2003; Kelly & Strick, 2003; O'Reilly, Mesulam, & Nobre, 2008; Ramnani, 2006; Salmi et al., 2010), all of which have been reported to be activated by temporal processing in a task-specific manner (Ivry & Spencer, 2004; Jahanshahi et al., 1995). The dense connectivity between the cerebellum and cortical motor regions constitutes a great signaling pathway by which sensory predictions allow for timely coordination of motor actions.

All in all, the cerebellum is critical for representing the precise temporal relationship between task-relevant events (Moberget et al., 2008).

In addition to its high reciprocity with cortical structures, the cerebellum is also in interplay with thalamic and subcortical structures (Bostan, Dum, & Strick, 2010; Bostan & Strick, 2010; Hoshi, Tremblay, Féger, Carras, & Strick, 2005; Mori, Okada, Nomura, & Kobayashi, 2016). As introduced in Part I, the basal ganglia are known to play a major role in the timely initiation of motor actions. These subcortical structures are proposed to keep downstream motor centers under tonic inhibitory control (Ivry & Spencer, 2004; Redgrave et al., 1999), initially preventing for the occurrence of involuntary movements and then providing a temporal frame to signal the initiation of a selected motor response (Gaidica, Hurst, Cyr, & Leventhal, 2018; Thura & Cisek, 2017). This "gating" is thought to be dependent on complex connectivity between the basal ganglia and other brain regions (Alexander & Crutcher, 1990; Grossberg, 2016; Ivry & Spencer, 2004), including cerebellar inputs through thalamic and subthalamic pathways (Bostan et al., 2010; Bostan & Strick, 2010; Gaidica et al., 2018; Hoshi et al., 2005; Mori et al., 2016). However, it is not clear how the cerebellum and the basal ganglia interact to mediate initiation of movement (see however Mori et al. [2016]).

In the first project, temporal anticipation was manipulated by varying the length of the delay period, in such a way that the go-cue could be predictable (2 s) or not (1.25, 2 or 2.75 s) across trials. When comparing the oscillatory activity during the delay period across conditions, there was a greater reduction in beta-band power around the time of an expected and potential go-cue (at ~ 1.25 s). suggests that participants in the "unpredictable block" were able to build up an internal representation of preceding possible go-cue occurrence (at ~ 1.25 s). This prospective release of inhibition could result from predictive signals coming from internal models in the cerebellum that mediate sub-cortical activity preparing for a change of motor state. This hypothesis is in line with the suggested interplay between cerebellar and basal ganglia functions in predictive timing tasks (Bares et al., 2011; Lungu et al., 2016). Recording EEG activity from cerebellar and PD patients performing predictive timing task such as the one used

in the first project could be a potential way to investigate whether the putative preparatory beta-band reduction is mediated by a functional interplay between these neural structures.

4.1.4. Concluding remarks on the first scientific contribution

Building over these results, it is precocious to affirm that high beta-band power could index the level of uncertainty about movement initiation (Palmer, Zapparoli, & Kilner, 2016). In effect, it is possible that the activity signaled by beta-band oscillation might be much more multiplexed, encompassing both motor and cognitive functions of the brain (Arnal, 2012). Indeed, there is evidence that beta-band activity recorded over sensorimotor regions might also reflect the allocation of attentional resources to information related to an upcoming motor task (Fetz, 2013; Kilavik et al., 2013; Murthy & Fetz, 1996; Saleh, Reimer, Penn, Ojakangas, & Hatsopoulos, 2010; Sanes & Donoghue, 1993). In support, Saleh et al. (2010) developed a task that isolates attention from motor-related processes. In their study, participants were asked to observe five sequential precues, each of which instructs a different target. After an imperative go-cue, the participant was requested to reach toward the target presented at the fourth precue, thus having to keep count of the previous three and the last. The results revealed transient increases in beta-band activity just before the first through fourth precues (Saleh et al., 2010). These findings suggest that beta-band activity can be interpreted as a proxy for time-resolved attentional deployment to process precues that need to be counted (*i.e.,* first through third) and precues that provide task-relevant instructions (*i.e.,* the fourth), upon which preparatory dynamics can take place. These results can be viewed as increased alertness in anticipation of task-relevant sensory precues. Saleh and colleagues' work conflicts with the notion that higher levels of beta-band are present during rest and hold periods, as suggested by the status quo framework (Engel & Fries, 2010). Instead, beta-band power during postural maintenance seems to reflect up-regulation in anticipation of task-relevant cues that will prompt preparation processes, potentially driven by frontal cognitive regions (Buschman & Miller, 2007, 2009).

The extent to which beta-band activity reflects mostly preparatory or attentional related processes remains largely unknown, let alone the way these distinct processes interact with each other. So far, evidence suggests that beta-band activity acts as a likely functional mechanism by which the system pauses the neural populations implicated in the movement (Khanna & Carmena, 2017), perhaps to remain sensitive to upcoming task-relevant information (Saleh et al., 2010).

4.1.5. Second project: Neurophysiological correlates of internal models

The main results of the second project revealed lesser levels of short-term retention associated with adaptation to a variable rather than a fixed practice schedule of VMRs, despite achieving similar extents of adaptation between the two contexts. The prevailing interpretation of these results is that adapting to variable perturbations may have led the motor system to rely more on new sensory evidence rather than on an uncertain prior (Wei & Kording, 2010). Given that retention was assessed during a no-visual feedback period, new sensory evidence could only be from proprioceptive signals. Specifically, because proprioceptive recalibration has been shown to be robust to uncertainty in visual perturbations (Saijo & Gomi, 2012), proprioceptive feedback during the retention phase could have acted as an error signal driving behavior to the original prior levels (see however Shmuelof et al., 2012).

From a neurophysiological perspective, this type of short-term retention can result from complex changes in the population interactions within the motor network. In support, short-term plasticity has been associated with changes in the recruitment of M1 neurons by upstream premotor neurons (Perich, Gallego, & Miller, 2018). In other words, PMd neurons could formulate new motor plans reflecting the adapted state, which are then sent to M1 to generate the motor command (Perich et al., 2018). Now, these new motor plans could have been issued from a certain and stable motor state estimation built upon precise predictions (such as in CV condition), or from an uncertain estimate of the adapted forward model upon exposure to variance (such as in HV condition). In the latter case, both the adapted inverse (“controller”) and forward

model could have become less reliable, thus susceptible to revert to the "unadapted" state.

Although we did not measure neurophysiological activity during this experiment, one could argue that both the cerebellum and the parietal cortex could be strongly implicated in providing the prediction to update the state estimation during the adaptation phase (Krakauer et al., 2019). Indeed, as it has been mentioned before, the cerebellum plays a critical role in processing the sensory prediction and is thought to be the center of the forward model (Ebner et al., 2011; Ishikawa et al., 2016; Liu et al., 2003; Miall et al., 2007; Nowak et al., 2007; Shadmehr et al., 2010; Wolpert & Kawato, 1998). On the other hand, parietal structures are known to integrate visual and proprioceptive information of moving effectors (Graziano, Cooke, & Taylor, 2000; Limanowski & Blankenburg, 2016; Rushworth, Nixon, & Passingham, 1997a, 1997b; Sakata, Takaoka, Kawarasaki, & Shibutani, 1973), thus providing the instantaneous estimation of the state of the body and its environment (Mulliken, Musallam, & Andersen, 2008).

However, it remains unclear whether the behavioral results obtained during the retention phase could be subtended by distinctive neuronal activations in sensorimotor and cerebellar regions. Interestingly, the role of oscillatory activity in the formation of motor memories has been suggested since they are thought to induce synchronized firing between neuronal ensembles (Buzsaki & Draguhn, 2004), which shapes spike-timing-dependent plasticity (Hanslmayr, Staudigl, & Fellner, 2012; Hebb, 2005; Amtul, 2015). In this light, some studies have exploited the beta-band dynamics over sensorimotor regions during motor adaptation paradigms (Özdenizci et al., 2017; Tan, Wade, & Brown, 2016; Torrecillos, Alayrangues, Kilavik, & Malfait, 2015). Specifically, Tan et al. (2016) have reported that the post-movement beta-band synchronization (PMBS) over motor regions is negatively correlated with the uncertainty in the estimations of the internal (*i.e.,* forward) model after motor adaptation (Tan et al., 2016). Although, it remains unclear whether the PMBS is more strongly related to the stabilization of inhibitory mechanisms that contribute to the

maintenance of a motor state (Engel & Fries, 2010) or to the processing of movement-related sensory afference after movement execution (Alegre et al., 2002; Cassim et al., 2001; Tan, Jenkinson, & Brown, 2014), this evidence allows to suggest that beta-band activity could be related to the reliance on top-down (*i.e.,* feedforward) internal representations that are created to properly interact with the environment (see however Bressler & Richter, 2015). Thus, trial-by-trial pre-movement beta-band activity during the retention phase could be used as a proxy of the reliance on the updated forward model. It can be hypothesized that the greater the uncertainty in the forward model, the lesser the reduction in pre-movement beta-band power.

4.2. Going further

4.2.1. Transitioning from laboratory-based designs to real-world-like situation

Classical experimental protocols to investigate motor control, such as the ones that were used in the present studies, often involve simple and well-trained tasks. The conformity of using such elementary tasks is that they reduce confounding variability that can be found in more complex designs, which might potentially pollute the results. Thus, simple tasks enable to ascribe the experimental results to the variables that were manipulated, allowing for a better interpretation of findings. However, one can argue that the results obtained using these simple laboratory designs might be context-specific to the constraints imposed in the laboratory. Thereby, it is possible to question to what extent the results found under these simple conditions can be generalized to more complex environments. In effect, laboratory-based designs could potentially corner our comprehension about how the brain controls its movement in controlled environments.

It was recently exposed by motor control experts during the *28th Annual Meeting of the Society for Neural Control of Movement* in May 2018 (for the proceedings of the meeting, see Mazurek et al., 2018) that the field is transitioning toward the implication of complex dynamics in movement, which would extend the understanding of how the brain controls its movement in uncertain environments. Scientists are findings ways to make "real-world" behaviors quantifiable and controlled

by loosening the constraints on well-defined laboratory-based paradigms allowing for more degrees of freedom in movement (Maruzek et al., 2018). For instance, studies on motor control have been introducing innovative tasks in which participants have to interact with dynamical objects, such as bouncing balls (Sternad, Duarte, Katsumata, & Schaal, 2000) and moving targets (Danion, Mathew, & Flanagan, 2017; Ghez et al., 1997; Soechting, Rao, & Juveli, 2010), or through the production of complex movement, such as ballistic throws (Müller & Sternad, 2009) and the use of cart-and-pendulum models (Hasson, Shen, & Sternad, 2012; Maurice, Hogan, & Sternad, 2018). The latter consist in carrying a virtual ball into a sleigh in the shape of a cup, which mimicked the dynamics of transporting water on a tray platter (Hasson et al., 2012; Maurice et al., 2018). Moreover, the use of sophisticated tools, such as virtual reality to improve decision-making skills in athletes (Pagé, Bernier & Trempe, 2019) and fMRI-compatible musical instrument to investigate motor learning in musicians (Hollinger, Steele, Penhune, Zatorre, & Wanderley, 2007) has also been reported. These experimental methods and tools go beyond the neural control of point-to-point movement by adding a chaotic component during the physical interaction with objects akin to what happens in real-world situations. Experimental protocols exploiting the continuous interaction with an object (with dynamic properties) gives a better window to understand the underlying strategies of motor control.

4.2.2. Challenges of taking the real-world to the laboratory

Following these ideas, understanding motor control is about investigating how the brain exploits the dynamics of its body and those of external objects in the environment to interact with them (Beer, 2009). The challenge is now to find clever ways to study these ecological interactions by analyzing the brain under controlled experimental conditions without denaturalizing the parameter of everyday situations. Precisely, a particular challenge is to obtain reliable measurements of behavioral parameters in unconstrained experimental environments and to perform sophisticated behavioral analysis in order to capture the complexity of such behavioral data. Additionally, from a neurophysiological standpoint, the genesis of complex

movements interferes with neural recordings, which hinders their analysis. Therefore, another challenge would be to analyze neural data from unstructured (*i.e.,* trials without a clearly defined starting and ending points) and unwell-trained (*i.e.,* nonrepetitive) behavior. Generalizing experimental findings from simplistic tasks in the laboratory to complex real-world situations remains highly challenging (Mazurek et al., 2018) given the increased variability coming from the environment, the motor commands and their respective neural representations (Faisal, 2008).

Hopefully, a great starting point would be to bring "nuggets" (or "chunks") of naturalistic situations into controlled laboratory environments, as it was proposed during the 28th NCM annual meeting, in 2018 (Mazurek et al., 2018). In this light, the following sections will present a simple experimental proposal harnessing the use of real-world-like paradigms to address research questions pertaining to motor control.

4.2.3. Investigating action preparation while already in motion

Movement planning is classically studied through protocols where participants are immobile during a delay period and wait for an imperative cue to produce their movement, akin to what has been done in the present thesis. These well-controlled paradigms enable to associate any underlying neural activity during the delay period to preparatory processes of the upcoming movement (Churchland et al., 2010; Riehle & Requin, 1989). However, these types of paradigms have the disadvantage of being simplistic and less generalizable to movement planning in real-life situations. One could argue that neural phenomena during the delay period can be ascribed to condition-irrelevant inhibitory mechanisms, refraining any type of movement before the go-cue is delivered, irrespective of what the action would be (Davranche et al., 2007; Ficarella & Battelli, 2019). In real-life situations, instead of being completely immobile, humans are most of the time already moving while planning their subsequent movements. They might even be moving the same limb that will subsequently be recruited to perform another action. This happens all the time in sports, like while a player handles the puck before shooting in hockey, or while playing any musical instruments, where a musician sequentially recruits its muscles to play all the notes in

a chord progression coordinately. Thus, investigating movement planning while the body is already in motion could help to elucidate the mechanisms by which the brain plans and decide to generate movement, distinguishing them from purely inhibitory mechanisms.

4.2.4. Assessing movement preparation through corticospinal excitability (CSE) while moving

Action preparation while already in action can be studied by analyzing corticospinal excitability (CSE). This mechanism has been used as a proxy of the physiological state changes in human motor system (Bestmann & Krakauer, 2015) both during movement preparation and execution (Bestmann et al., 2008; Duque & Ivry, 2009; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010; Hasbroucq, Kaneko, Akamatsu, & Possamai, 1997; Mars et al., 2008). CSE can be assessed through the measurement of the amplitude of motor evoked potential (MEP) after transcranial magnetic stimulation (TMS). Briefly, TMS is a non-invasive stimulation of the human cortex that induces a sudden and short-lived (200 μs) disruption in the membrane's potential of the underlying cortical neural population (Bestmann, 2008; Bestmann & Krakauer, 2015). When applied over motor regions at the appropriate intensity, TMS transsynaptically (*i.e.,*, indirectly) activates the corticospinal tract producing muscle responses (*i.e.,* MEPs), which amplitude (a measurement of peak-to-peak between maximal and minimal values of potentials evoked by the stimulation) is known to be proportional to cortical excitability and can be recorded with electromyography over targeted muscles (Bestmann, 2008; Bestmann & Krakauer, 2015; Hess, Mills, & Murray, 1986). Importantly, MEP amplitude depends not only on the excitability of the corticospinal tract but also on the excitability of downstream motoneurons, which are highly recruited during movement execution (Hess et al., 1986; Kujirai et al., 1993; MacKinnon & Rothwell, 2000; Thompson et al., 1991). A way to distinguish cortical from motoneurons' activity is by averaging EMG activity during movement execution and by normalizing the MEP amplitudes according to the background EMG activity (Gritsenko, Kalaska, & Cisek, 2011). Interestingly, the contribution of preparatory

mechanisms to the CSE modulation while the body is already in motion has never been assessed. Therefore, one could ask **how the time course of CSE evolves throughout the period where an ongoing (*i.e.*, background) action is susceptible to switch to another potential movement.**

Proposed task, protocol and data analysis. To address this issue, a task can be designed where participants have the possibility to prepare a movement midway through the course of an ongoing action. One way to do so is to have participants perform a tracking task where they will be asked to follow a moving target with a virtual cursor while EMG activity from task-related muscles is recorded. The moving target will be programmed to follow a pseudorandom path, forcing the participants' cursor to eventually pass through one of four predetermined paths (Figure 1). Each pass through a predetermined path will be called a repetition, for the sake of clarity.

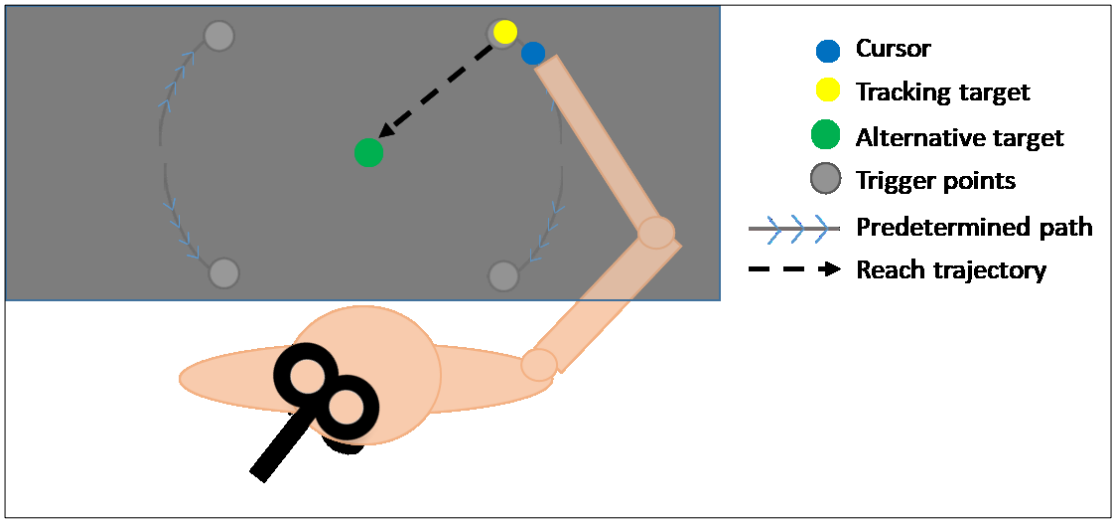

Figure 1. Overview of the experimental setup of the proposed real-world-like task.
Participants follow a moving target (yellow circle) with a cursor (blue circle). Once the cursor passes through a trigger point (grey circle) at the end of one of four predetermined paths (example displaying upper-right), an alternative target (green or red circle) appear at the center of the screen, prompting a reaching response. Single-pulse TMS will be delivered at various moments related to the passage through the trigger points. EMG activity will be recorded (not depicted in the figure).

Participants will be submitted to two distinct conditions. In the experimental condition, participants will be forced to perform a subsequent movement, distinct from

their ongoing motion. Specifically, as the cursor reaches a specific point (*i.e.,* trigger points, see Figure 1) at the end of either one of the four predetermined paths, a second (*i.e.,* alternative) target (*i.e.,* green circle) could appear (50 % of the times) at the center of the workspace, prompting participants to switch their behavior and reach to the alternative target and pursue its trajectory. The remaining 50 % of the time, the alternative target would appear red (no-go condition), informing the participants to pursue their ongoing movement.

Since the update of a control policy based on visual feedback can be performed within ~120 ms (Scott, 2016), single-pulse TMS will be deliver at either one of five distinct moments (-160, -80, 0, 80, or, 160 ms) throughout the experiment, time-locked to the moment at which the participants' cursor passes through the trigger points. The elicited MEPs will be recorded using EMG electrodes placed over task-related muscles (*i.e., biceps brachii*, *brachioradialis*, *triceps brachii*, *pectoralis major*, and posterior deltoid).

Generalizing from classic experiments, it can be hypothesized that agonist and antagonist muscles respective to the location of the trigger point will be characterized by a progressively increased and decreased CSE before the switch onset in both experimental conditions, respectively (Ficarella and Battelli, 2019). However, the no-go condition should elicit lesser CSE compared to the switch condition at the last stimulation timing, associated with cortical inhibition of subsequent movement plan (Duque & Ivry, 2009; Ficarella & Battelli, 2019; Hasbroucq et al., 1997; Kujirai et al., 1993; van Elswijk, Schot, Stegeman, & Overeem, 2008).

This experimental proposal is a simple way to challenge our understanding of how the brain interacts with its environment in its natural context. Results from studies harnessing this idea will help for a better understanding of motor behavior. Although much work remains to be done, it is encouraging that the field is willing to transition from purely laboratory-based paradigms to more real-world experimental protocols.

5. CONCLUSION

The understanding of how the brain works is one of the greatest modern scientific quests, that incentivizes the work of neuroscientists across a variety of domains. A common problem shared by all these neuroscientists in order to understand how the brain works and why it does so, is that they need to analyze the details of its structures and functions in relation to its behaviors. This remains true in the field of motor control, where experimental approaches derived from behavioral and neurophysiological levels of analysis can be leveraged to that matter. In a sense, this was the goal of both scientific contributions presented herein.

Understanding how the brain controls its behaviors implies the understanding of how the nervous system has evolved in the presence of the complexity and the uncertainty in the environment. The results of the scientific contributions presented in this thesis reveal that the fundamental processes of motor planning and adaptation are sensitive to that uncertainty, and its manifestation can be reflected in their underlying neural and behavioral underpinnings.

I believe that the investigation of the motor processes in the face of uncertainty could be beneficial to the field of motor control. The fact that the field is now focusing on the underlying neural processes related to the control of movements in uncertain real-world situations is a testament that progress in motor control has been made. Nevertheless, further work needs to be done to generalize experimental findings using simple tasks to complex real-world situations. The manipulation of uncertainty, akin to what has been done in both scientific contributions included in this thesis, is a step toward that goal. As a concluding remark, I firmly believe that investigating motor control through naturalistic approaches that capture the essence of the evolutionary interactions with the environment would constitute a holistic approach that surely will allow for a better understanding of the intricacies of the brain. After all, as the famous biologist Theodosius Dobzhansky mentioned in 1973: "Nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973).

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