Using A New Double-Coil TMS Method To Study Vulnerability Markers In Addictions

A dissertation presented

by

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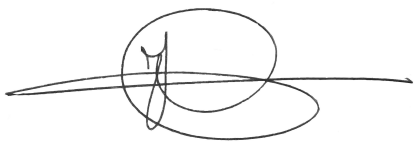
Declaration

I declare that this thesis is entirely my own work,
and except where otherwise stated,
describes my own research.



Grandjean Julien

For my Family;

For Etienne;

For Life;

For E.V.e.R.

Contents

Acknowledgments

"Gratitude unlocks the fullness of life. It turns what we have into enough, and more. It turns denial into acceptance, chaos to order, confusion to clarity. It can turn a meal into a feast, a house into a home, a stranger into a friend."

Melody Beattie

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Using A New Double-Coil TMS Method To Study Vulnerability Markers In Addictions

Abstract

The present thesis is articulated around three main axes. The first one focuses on assessing whether it is possible to obtain reliable motor-evoked potentials in both hands at once using a paired-pulse transcranial magnetic stimulation (TMS) method where the two primary motor cortices are stimulated with an inter-pulse interval as short as 1 ms (double-coil$_{1ms}$ TMS). The second axis assesses the function(s) of preparatory inhibition (i.e., the suppression of activity observed in the motor output pathway during the preparation of an action) and more specifically its suggested role for behavioural inhibition. The third one investigates with double-coil$_{1ms}$ TMS whether preparatory inhibition is altered in two distinct populations, that is, in one likely to suffer from alcohol-use disorder (i.e., binge-drinkers) and in one suffering from gambling disorder. Our results are threefold. First, they infer that double-coil$_{1ms}$ is a reliable TMS method that can be used both at rest and in the context of a task. Second, they support and extend previous work on the presence and role of preparatory inhibition. Last, they suggest abnormal preparatory activity in binge-drinkers but not in patients suffering from gambling disorder.

Une nouvelle technique de stimulation magnétique transcranienne pour étudier les marqueurs de vulnérabilité dans les addictions

Résumé

Cette thèse est articulée autour de trois grands axes. Le premier cherche à savoir s'il est possible d'obtenir de façon fiable des potentiels évoqués moteurs dans les deux mains en utilisant une technique de stimulation magnétique transcranienne stimulant le cortex moteur primaire de chaque hémisphère à un intervalle de 1 ms (double-coil$_{1ms}$). Le second axe s'intéresse à la fonction de l'inhibition préparatoire[1] et plus particulièrement à son rôle pour l'inhibition comportementale. Le troisième axe essaye de déterminer grâce à la technique de double-coil$_{1ms}$ si l'activité préparatoire observée au niveau de la voie de sortie motrice est altérée dans deux types de populations à savoir: dans une étant à risque de souffrir d'alcoolo-dépendance dans le futur (i.e., les *binge-drinkers*) et dans une autre souffrant d'addiction comportementale (i.e., les joueurs pathologiques). Nos résultats suggèrent que *double-coil*$_{1ms}$ permet d'acquérir des potentiels évoqués moteurs équivalents à une technique de stimulation simple, et ce, à la fois au repos et dans le contexte d'une tâche. En plus de cela, ils supportent et complètent les résultats d'études précédentes ayant investigué la présence et le rôle de l'inhibition préparatoire. Finalement, ils suggèrent une activité préparatoire anormale chez les binge-drinkers mais pas chez les joueurs pathologiques.

[1] L'inhibition préparatoire correspond à la suppression de l'excitabilité corticospinale observée lors de la préparation d'une action.

Abbreviations

AD ..... Alcohol-Dependent
ADI ..... Alcohol-Dependent Individual
ADM ..... Abductor Digitimi Minimi
ADP ..... Alcohol-Dependent Patient
ANOVA ..... Analysis of Variance
AP ..... Anterior-Posterior
APB ..... Abductor Pollicis Brevis
ARD ..... Alcohol-Related Disorder
AUD ..... Alcohol Use Disorder
AUDIT ..... Alcohol Use Disorders Identification Test
BA ..... Brodmann Area
BAC ..... Blood Alcohol Concentration
BD ..... Binge Drinker
BDI ..... Beck Depression Inventory
BG ..... Basal Ganglia
CB ..... Cerebellum
CC ..... Congruent Cue
CNS ..... Central Nervous System
CS ..... Corticospinal
CSE ..... Corticospinal Excitability
CV ..... Coefficient of Variation
DA ..... Dopamine

DSM ..... Diagnostic and Statistical Manual of Mental Disorders

D-Wave ..... Direct-Wave

EEG ..... Electroencephalography

EMG ..... Electromyography

FDI ..... First Dorsal Interosseous

FSAS ..... Frequent Startling Acoustic Stimulus

GABA ..... Gamma-Aminobutyric Acid

GD ..... Gambling Disorder

GDP ..... Gambling Disorder Patient

HC ..... Healthy Control

H-Reflex ..... Hoffmann's reflex

ICF ..... Intracortical Facilitation

IFC ..... Inferior Frontal Cortex

IHF ..... Interhemispheric Facilitation

IncC ..... Incongruent Cue

ISI ..... Inter-Stimulus Interval

I-Wave ..... Indirect-Wave

LICI ..... Long Interval Intracortical Inhibition

LM ..... Lateromedial

LPFC ..... Lateral Prefrontal Cortex

LSD ..... Least Significant Difference

M1 ..... Primary Motor Cortex

MANOVA ..... Multivariate Analysis of Variance

MCQ ..... Monetary Choice Questionnaire

MEP ..... Motor-Evoked potential

MRI ..... Magnetic Resonance Imaging

NAc ..... Nucleus Accumbens

NC ..... No Cue
NMDA ..... N-Methyl-D-Aspartate
NSRD ..... Non-Substance-Related Disorder
OFC ..... Orbitofrontal Cortex
PA ..... Posterior-Anterior
PFC ..... Prefrontal Cortex
PMd ..... Dorsal Premotor Cortex
PMv ..... Ventral Premotor Cortex
PNS ..... Peripheral Nervous System
ppTMS ..... Paired-Pulse TMS
RM ..... Repeated Measure
rMT ..... Resting Motor Threshold
RSAS ..... Rare Startling Acoustic Stimulus
RT ..... Reaction time
rTMS ..... Repetitive Transcranial Magnetic Stimulation
SAS ..... Startling acoustic stimulus
SCM ..... Sternocleidomastoid
SD ..... Standard Deviation
SE ..... Standard Error
SICI ..... Short Interval Intracortical Inhibition
SMA ..... Supplementary Motor Area
SOGS ..... South Oaks Gambling Scale
spTMS ..... Single-pulse TMS
SRD ..... Substance-Related Disorder
SSD ..... Stop-Signal Delay
SSRT ..... Stop-Signal Reaction Time
STAI ..... State Trait Anxiety Inventory

SUD ..... Substance-Use Disorder

tDCS ..... Transcranial Direct Electrical Stimulation

TES ..... Transcranial Electrical Stimulation

TMS ..... Transcranial Magnetic Stimulation

TO ..... Time-Out

VTA ..... Ventral Tegmental Area

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General introduction

"If the human brain were so simple that we could understand it, we would be so simple that we couldn't."

Emerson W. Pugh

Picture yourself being at the dance floor on a Saturday night. The music is loud, the light dim. Whilst listening to the music and *following the beat*, you are making your best to display impressive dance moves. One step to the left, two to the right [...] *take it back now y'all. Left foot let's stomp, cha cha real smooth.*

This seemingly effortless act of dancing is a complex task. The amplitude, coordination and type of the movements you perform express your goal: do you want to impress your fellows or to have fun? Maybe both. It requires the integration of multiple visual and proprioceptive information; you need to be aware of your environment and of the space occupied by your own body. Minor adjustments as well as the maintenance of your heart rate, respiration, and numerous autonomic[2] functions are also essential; if they are not performed, you die.

All of these undertakings are coordinated by an organ, the brain, a *supercomputer* able to achieve amazing computational greatness that no current machine can even begin to approach. Particular regions carry out specific tasks. The well-known Broca's area, for instance, is responsible for language whilst, in the aforementioned example (i.e. dancing), the motor cortex fulfils a major role in the integration, preparation and execution of actions – may they be appropriate, or not.

For the last four years, I have engrossed in a better understanding of the processes guiding action preparation. To do so, I particularly looked into the activity of the motor output pathway through stimulating a *territory* of the motor cortex, viz., the primary motor cortex (M1), one of the prime brain areas involved in motor function. In the first part of my PhD, I developed

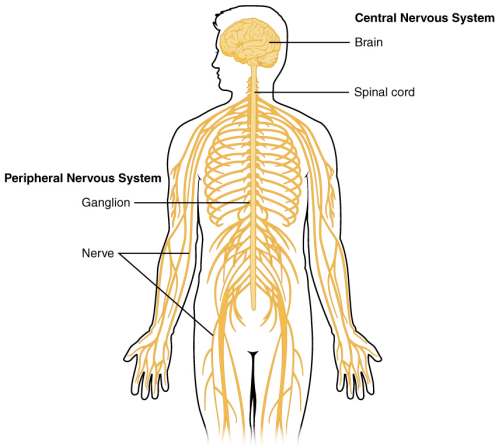
[2]Functions that are largely unconscious (e.g. heart rate, digestion, respiratory rate, pupillary response, etc.)

and validated a double-coil transcranial magnetic stimulation (TMS) method allowing one to assess the excitability of the corticospinal (CS) tract more efficiently. In the second part, using this method, I assessed whether preparatory inhibition (i.e., the suppression of activity observed in the motor output pathway during the preparation of an action) assists the generation of goal-directed behaviours. In the third part, I investigated the possible alteration of the activity of the motor output pathway in a couple of substance-related and non-substance-related disorders (SRDs and NSRDs, respectively).

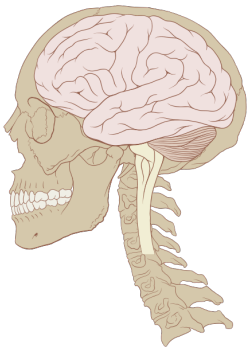
The following sections (1) summarise the basic neuroanatomy of the brain and its motor output pathway (section 0.1), (2) develop the basics of TMS and the role that it can play in investigating the state and activity of the motor system (section 0.2), (3) introduce the reader to the concept of motor-related inhibition (section 0.3) and (4), develop the proposed involvement of an alteration of the activity of the motor output pathway in mental disorders (section 0.4).

0.1 The human brain and its motor output pathway

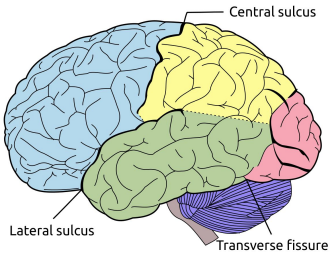
The human brain is part of the central nervous system (CNS) (Figure 0.1(i)). It is encased within the bones of the skull and the vertebral column and can be divided into three major parts, viz. the cerebrum, the cerebellum (CB) and the brain stem (Figure 0.1(ii) and Figure 0.1(iii)). The cerebrum is dominated by the two cerebral hemispheres which have their outer surface constituted of a narrow husk of grey matter: the cerebral cortex (Latin: cortex, *bark*), which is 2 - 4 mm thick. The cortex is moulded into distinct convolutions or gyri (singular: gyrus) isolated by grooves called sulci (singular: sulcus). Two of



(i) The human nervous system



(ii) The brain



(iii) Cerebral lobes

Figure 0.1: The human nervous system and the brain. (i) The human nervous system is composed of two main parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS is made up of the brain and spinal cord and represents the main integrating and decision-making centre of the nervous system. The PNS is made up of sensory and motor fibres passing to and from the CNS. It includes 31 pairs of spinal nerves and 12 pairs of cranial nerves. Its function is to transmit nerve impulses to and from the brain and spinal cord. (ii) The brain is encased within the bones of the skull and vertebral column. It is a pale pink organ with a mean mass of around 1.3 kg and a very soft, gelatinous consistency. (iii) The brain can be separated into three major parts: the cerebrum (consisting of the two cerebral hemisphere - i.e., the blue, yellow, pink and green regions - that are separated by the longitudinal fissure), the cerebellum (CB) (the purple region that is separated from the cerebrum by the transverse fissure) and the brain stem (the grey trunk). The CB can further been divided into four lobes, viz. the frontal lobe (i.e., the blue region), the parietal lobe (i.e., the yellow region), the temporal lobe (i.e., the green region) and the occipital lobe (i.e., the pink region). Note: no steady sulci on the lateral surface of the hemisphere help to clearly delineate the posterior lobar borders. Open source figures adapted from Wikipedia [1, 2, 3].

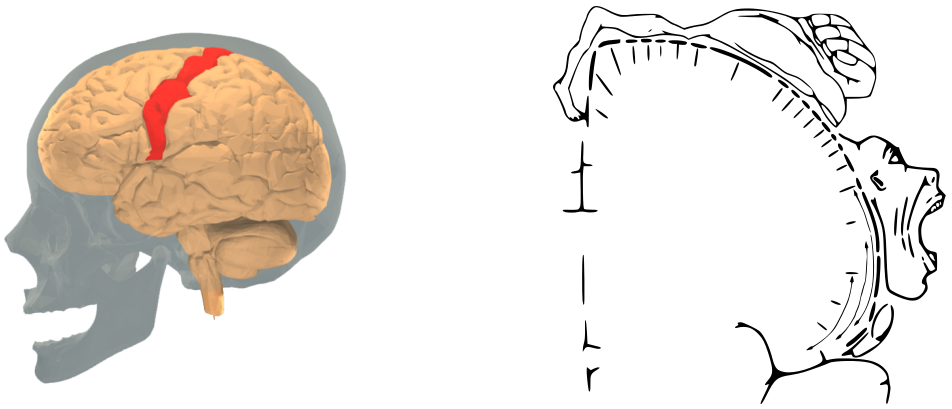
them, the lateral and the central sulcus, help to separate the hemispheres into frontal, parietal and temporal lobes (Figure 0.1(iii)) [4, 5]. The remaining lobe, the occipital one, is delineate by the preoccipital notch and the parieto-occipital sulcus; it stands posterior to them [6].

Before the central sulcus and above the lateral sulcus lies the frontal lobe which is the largest of the four lobes and accounts for around 40 % of the cortical surface area. It contains the precentral gyrus that is immediately anterior to the central sulcus (Figure 0.2(i)). The precentral gyrus corresponds to M1 (Brodmann area [BA] 4), a region which contains an inverted point-to-point somatotopic (Greek: soma, *body*; topos, *place*) map of the opposite half of the body that is proportional to the precision of movement control (Figure 0.2(ii)). The areas - or motor representations - for the hands, face and tongue are therefore disproportionally large whilst the arms and legs are less represented [4, 5, 7, 8]. Hence in humans, much of M1 is devoted to moving the finger muscles and those related to spoken language [4].

> "To move things is all that mankind can do, for such the sole executant is muscle, whether in whispering a syllable or in felling a forest."
>
> Sir Charles Scott Sherrington, 1924.

To control movements properly, the pathway making connections between upper and lower motor neurons ought to be intact[3]. This *final common pathway* [4], named the motor output pathway but also referred to as the pyramidal

[3]The term upper motor neurons refers to CS and corticobulbar tract neurons which have their cell bodies in the motor cortex of the frontal lobe whilst the term lower motor neuron is used to describe the motor neurons of the spinal cord and brain stem that innervate the skeletal musculature.



(i) The precentral gyrus (ii) The cortical motor homunculus

Figure 0.2: The primary motor cortex and homunculus. (i) The primary motor cortex - represented by the red region in this figure - correspond to the precentral gyrus (BA 4; M1). It lies directly before the central sulcus and above the lateral sulcus. (ii) The primary motor cortex contains an orderly inverted point-to-point somatotopic portrait of the opposite half of the body going from the toes (medially) to the face and tongue (laterally). The importance of each muscle representation is function of the precision of motor control. As a result, the hands, face and tongue are overrepresented. Open source figures from Wikipedia [9, 10].

motor system or pyramidal tract is made of two components that originate in the cerebral cortex, viz. the corticobulbar tract and the CS tract [4, 5, 7, 11]. The first one terminates in the brainstem whilst the second one finishes in the spinal cord. The corticobulbar tract is responsible for innervating several cranial nerves and runs parallel to the CS tract as far as the brain stem. The CS tract is the main somatic motor pathway (Figure 0.3). It is highly critical for controlling and fine-tuning the voluntary movements of the distal limb musculature (e.g., hand motor function) [4, 5, 12]. The CS tract is the longest continuous white matter tract in the CNS. It is composed of more than a million myelinated axons on each side [4, 7] that - for the great majority - originate in the inferior part of cortical layer V [5, 13]. Two third of them arise from the primary motor area (BA 4), the premotor area (BA 6) and the

supplementary motor area (SMA; BA 6) of the frontal lobe [12, 14, 15]. The remaining third originates from the primary somatosensory cortex (BA 3, 1, 2) in the parietal lobe [12, 14, 15]. The CS tract descends through the internal capsule, crus cerebri of the midbrain, basilar pons and medullary pyramids. At the lower border of the medulla (i.e., the junction between the brain stem and the spinal cord), 75 - 90% of CS tract fibres cross the midline to enter the lateral CS tract of the spinal cord. This process is termed the pyramidal decussation [12, 16]. The remaining 10 - 25% of uncrossed fibres are a direct continuation of the medullary pyramids [7]. Most of them ultimately decussate and innervate the proximal and axial musculature [17]. Only a handful of CS tract axons make direct synaptic contact with spinal motor neurons, the majority finishes on interneuronal pools which influence spinal motor neurons indirectly [7]. Of note, because M1 is a significant source of descending motor commands for voluntary movements [18, 19, 20, 21], it has often been assumed that M1 is the *final common path* from the cerebral cortex to the motor neurons [4] and subsequently that its state/excitability represents the state/excitability of the CS tract. This is wrong. Indeed, as mentioned above, the CS tract is directly and indirectly influenced by distinct projections arriving from several premotor and parietal areas [4, 20] and its state/excitability represents the sum of the intracortical, transcortical, subcortical - but also spinal - contributions [22].

The awareness of a *path* between cortical structure and distant muscles is not new; it dates from 1804 when Giovanni Aldini stimulated - for the first time - the human cerebral cortex of one hemisphere and obtained facial muscle contractions on the contra-lateral side [24]. A century later, multiple attempts were made to electrically stimulate several regions of the brain in animals and, at the end of the 19^{th} century, G. Theodor Fritsch and Eduart Hitzig [25] as

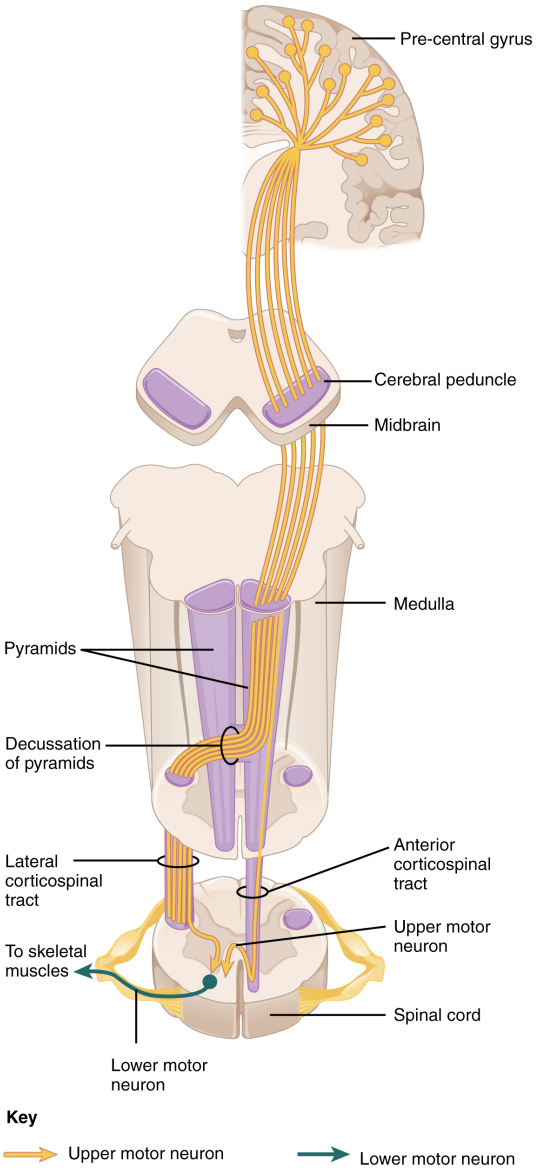


Figure 0.3: Origin and termination of the corticospinal (CS) tract. Axons composing the CS tract leave the cerebral cortex to pass the internal capsule and reach the crus cerebri in the anterior part of the midbrain. Having passed the midbrain and pons, around 75-90 % of the fibres decussate at the level of the medulla to enter the contralateral half the spinal cord. The pathway - named the lateral CS tract - then continues to mostly supply the distal limb musculature. Fibres that did not decussate - referred to as the anterior CS tract are a direct continuation of the medullary pyramids. At one point of the spinal cord, many of them ultimately decussate and essentially innervate the proximal and axial musculature. Open source figure from Wikipedia [23].

well as David Ferrier [26, 27, 28, 29] discovered that an electrical stimulation of the animal motor cortex induced evoked motor responses in the opposite half of the body [30]. The first map of cortical motor representations was issued at the beginning of the 20^{th} century when Wilder Penfield and Edwin Boldrey published a 55-page article presenting the somatic motor representation in the cerebral cortex of man [8]. However impressive, stimulating and/or investigating the motor cortex at that period was invasive (e.g., in 1874 Bartholow stimulated electrically the exposed cerebral cortex in a subject with cranial fracture) and painful (as you may imagine reading the former example). A breakthrough was made when transcranial electrical stimulation (TES) and TMS were invented in 1980 and 1985 respectively [31, 32]. These two techniques allow scientists to stimulate an intact human brain in a non-invasive manner.

KEY POINTS

* The human brain can be divided into three major parts, viz. the cerebrum, the cerebellum and the brain stem.
* The cerebrum is made of the two cerebral hemispheres that have their outer surface composed of a narrow shell of grey matter: the cerebral cortex.
* The cerebral cortex is shaped by gyri and sulci that help delineate the cerebral hemispheres into frontal, parietal, temporal and occipital lobes.
* Just before the central sulcus lies the precentral gyrus that contains an inverted point-to-point somatotopic map of the opposite half of the body that is proportional to movement control. As a result, the cortical area accounting for the hands, face and tongue are disproportionally large.
* Some of the axons arising from the motor cortex and the primary somatosensory cortex form the corticospinal tract that is the longest continuous white matter tract in the central nervous system.
* The corticospinal tract is the principal somatic motor pathway making connections between upper and lower motor neurons. Its state results from many intracortical, transcortical, subcortical and spinal inputs. It is highly important for controlling and fine-tuning the voluntary movements of the distal limb musculature.

0.2 Transcranial magnetic stimulation

0.2.1 Context

40 years have now passed since Merton and Morton surprised the scientific community by showing that, through using TES, it was possible to stimulate the motor areas of an intact human brain. *"One of the most fertile methods of investigating the brain is to stimulate a part of it electrically and observe the results. [...] Much could be done, both with healthy subjects and with neurological patients, if it were feasible to stimulate through electrodes on the scalp, although the localisation of the stimulus on the cortex will always be much less sharp than with electrodes on the brain surface"* is what they wrote at the beginning of their article [31]. Up until that time, opening the skull surgically to apply the electrodes was the only way of investigating what happens under the cranium.

Their discovery implied the use of a brief, high voltage electric shock to activate the motor cortex and produce a relatively synchronous muscle response, the motor-evoked potential (MEP). New horizons were opened for a better understanding of the human brain. A problem persisted, however: TES was still painful - or at least induced discomfort - because of the activation of pain fibres in the scalp. Indeed, only a small portion of the current penetrates the brain and activates neurons, much of it travels along the scalp between the electrodes.

Five years after, Barker and colleagues made it possible to stimulate both nerve and brain using external magnetic stimulation without inducing any pain [32]. TMS was born. This method is now widely used both as a research and therapeutic tool whilst TES is employed for more selective purposes.

0.2.2 Physical principles and technical aspects of transcranial magnetic stimulation

TMS is based on the principle of electromagnetic induction discovered by Michael Faraday back in 1831 [33]. At that time, Faraday discovered that an alternating - but not constant - electric current in one conductor induces a current in the opposite direction in a nearby conductor. This law - naturally termed Faraday's law - was later generalized as one of the four Maxwell equations that were developed to explain the relationship between electricity and magnetism. One of these four, the Maxwell–Faraday equation (equation 1 in which $\vec{E}$ is the induced primary electric field, $\vec{B}$ is the magnetic field and t is the time)

$$\vec{\nabla} \times \vec{E} = -\frac{\partial \vec{B}}{\partial t} \tag{1}$$

clearly states that a time-varying magnetic field produces an electric field whose magnitude is proportional to the time rate of change of the magnetic field and, conversely, that an electric current in a conductor induces a proportional magnetic field around it [34]. It therefore implies that an electric field is induced in the brain tissue if an alternating current of adequate intensity is passed into a coil placed near a human head (Figure 0.4). At high enough intensity, the electric field induced can be sufficient to cause membrane depolarization in neuronal structures initiating action potential and neuronal activation. This stimulation technique is therefore unpainful as ions flow in the brain without the need for current to flow across the skull and without charged particles being injected into the scalp [35].

To reach a high intensity able to depolarize neurons, a TMS stimulation circuit requires several components: (a) a high-voltage power supply that charges (b) a capacitor that receives the current and stores the energy in the

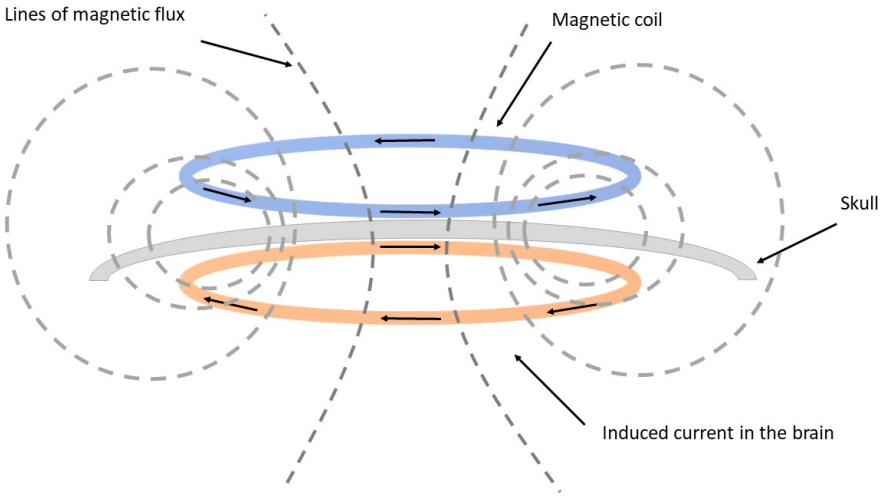


Figure 0.4: Schematic illustration of direction of current flows in a magnetic coil and the induced current in the brain. When an electric current flows through a coil, a magnetic field is produced with lines of flux passing perpendicularly to the plane of the coil. As a result, an electric field is induced perpendicularly to the magnetic field. In a homogeneous medium, the electric field will cause current to flow in loops parallel to the plane of the coil. The loops with the strongest current will be near the circumference of the coil itself. The current loops become weak near the centre of the coil, and there is no current at the centre itself. Figure adapted from Figure 1 in Hallett (2007) [36].

form of electric charge which is then rapidly discharged via a (c) fast electronic switch into a (d) TMS coil consisting of, for instance, multiple wound copper wires in order to create the briefly changing magnetic field pulse [34, 37]. This pulse is usually of a very short duration ($\sim$200 μs) and can reach up to about 2 Tesla, an intensity similar to that of the static field utilised in magnetic resonance imaging [35].

Interestingly, the current pulse waveform delivered by the stimulator can be of two types [38, 39, 40]. It can either have a monophasic (i.e., unidirectional) or a biphasic (bi-directional) charge-balanced shape. Monophasic pulses are conventionally used for single pulse TMS (spTMS) in the assess-

ment of CS tract excitability (CSE) and integrity. It consists of a fast rising, high amplitude, and short duration flow of current in one direction followed by a smaller but longer duration flow in the opposite direction. Biphasic pulses - however sometimes used for the assessment of CSE - are commonly employed for repetitive TMS (rTMS) for reasons of lower energy requirements and because of their ability to achieve repetitive stimulation trains with frequencies of up to 50 Hz. They consist in two phases of equal amplitude and duration. The purpose of these trains is to modulate the excitability of cortical areas both for scientific and therapeutic reasons. These different patterns of stimulation are later developed in section 0.2.5.

Beside the shape of the pulse generated, one critical aspect of a TMS stimulator is the form of the coil used [34, 41]. TMS was first introduced using large circular coils of wires with a diameter of around 10 cm. When such a coil is placed over the scalp of a subject, the site of stimulation is very large but the depth of penetration into the brain is small as the intensity of the induced current falls proportionally with the distance. Through overlapping two small round coils with opposite directed currents into a figure-of-eight shape, shallower stimulation with more intense focal neural stimulation can be achieved [39, 42]. With this configuration, the induced current under the point where the coil windings overlap is approximately twice that of the coil edges, and thus stimulation can be considered to occur within that smaller area [43]. The smaller the diameter the more focal the TMS but the more rapidly the coil heats up during repetitive stimulation.

Figure-of-eight coils are now classically used to stimulate a given brain region more selectively. These are the ones I have been using for my thesis. If the reader is interested in literature assessing the electric field focality and depth of penetration of more than 50 TMS coils, I invite him to read the

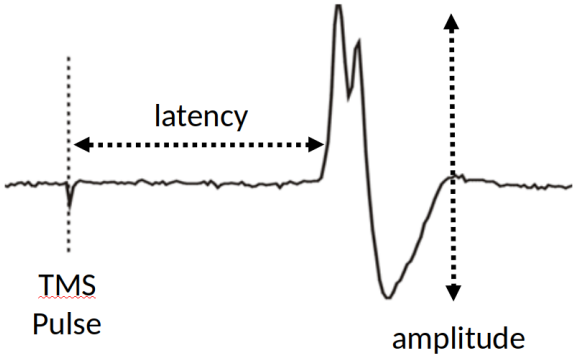
thorough review written by Deng et al. 2013 [44].

0.2.3 Corticospinal tract assessment through using transcranial magnetic stimulation

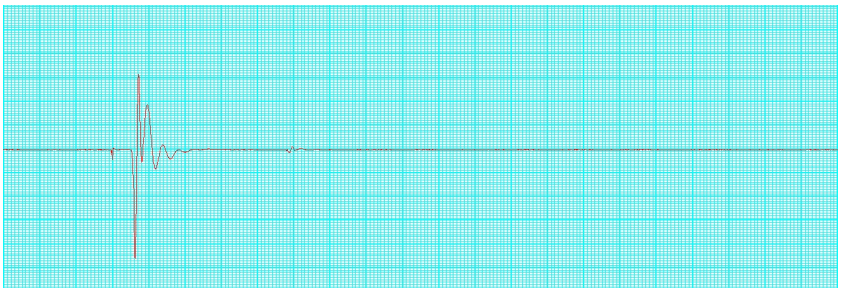
The integrity and excitability of the CS tract can be investigated through using TMS [45, 46]. When the stimulating coil is placed over M1, TMS elicits descending volleys in the CS fibres that synapse on spinal motoneurons [47]. These motoneurons innervate peripheral muscles contralateral to the stimulation site. The evoked response, the MEP (Figure 0.5(i) and 0.5(ii)), can easily be recorded using surface electromyography (EMG). Of note, applying TMS over other cortical areas that contribute to the CS tract is not expected to elicit MEPs [35]. This is due - at least in part - to the fact that the axons constituting the cells of these regions mainly project to interneurons instead of directly influencing spinal motor neurons.

Many interesting measurements related to the CS tract can be obtained with MEPs. The most obvious one is the corticomotor conduction time which is the time from the motor cortex to the motor neuron pool in the spinal cord or brainstem [36]. Another one is mapping which consists of assessing motor representation by moving the TMS coil over the surface of the scalp and recording MEPs from different muscles. These measurements, however fascinating, are not the focus of the present thesis and will therefore not be discussed. In the following pages, I present the reader with one interesting aspect of the CS tract, that is, the assessment of CSE.

MEPs elicited through using spTMS represent a valuable indicator of CSE at the time of stimulation and their amplitude can be compared at different moments within a given condition [48, 49] and between different states [48, 50,



(i) Schematic representation of a MEP.



(ii) Screenshot of a MEP recorded in an experiment.

Figure 0.5: (i) Schematic and (ii) actual representation of a motor-evoked potential (MEP). The MEP is a biphasic response recorded from a targeted muscle via electrodes placed on the surface of the skin. It has a latency of approximately 18 ms after the TMS pulse when elicited in hand muscles. While the latency is relatively invariant, the peak-to-peak amplitude fluctuates, reflecting the sum of cortical, subcortical, and spinal contributions to the descending signals to the muscle.

51]. The MEP measured with surface EMG represents the net effect of cortical, spinal and peripheral neuromuscular inputs [52]. It is a signal resulting from a series of complex waves that descend through the CS tract [43, 53]. The MEP increases in size and is followed by later volleys as the intensity of stimulation increases [54, 55, 56]. The first motor unit recruited during minimal voluntary contraction is also that engaged by TMS. The subsequent ones are equivalent with TMS and with voluntary contraction [54] with the sequence of activation being in accordance with the Henneman's size principle where the smallest

motor unit are recruited first [57]. As a matter of fact, MEPs are also larger and elicited earlier when the muscle is contracting as opposed to when it is at rest [58, 59]. This is mainly due to the fact that the motor neuron pool is at a higher level of activity and it is easier to provoke stronger CS activation [36].

To be able to assess CSE, one first needs to measure the resting motor threshold (rMT), that is, the minimal TMS intensity required to evoked MEPs of about 50 μV peak-to-peak in the relaxed targeted muscle in at least 5 out of 10 consecutive trials [39, 60]. The centre of the coil is placed over a so-called *hotspot* which is defined as the site at which the stimulation elicits the largest MEP in the aimed effector for a given intensity. The lowest threshold for the hand area can usually be established by orienting the coil 45° towards the contralateral forehead in order to guarantee the current to stream relatively perpendicular to the central sulcus [39]. Orientation is critical, at least as much as position [61]. Stimulations are usually described as a percentage of the rMT. The ones above 100% of the rMT are called "supra-threshold" stimulations whilst stimulations below 100% are called "sub-threshold" stimulations.

Supra-threshold TMS pulses evoke a series of descending CS volleys that make up different components of the MEP (Figure 0.6). The first volley is termed the direct (D-; i.e., resulting from direct depolarization) wave whilst subsequent volleys are termed indirect (I-; i.e., resulting from indirect depolarization) waves [43, 62]. The first I-wave is usually named I_1 whilst later I-waves are numbered in order of their appearance (i.e., I_2, I_3, etc., I_n). Early D-wave is thought to result from direct depolarization of the initial axonal segment of the CS neuron [39, 51]. I-waves - following the D-wave sequentially with a periodicity of $\sim$1.5 ms which indicates a discharge frequency of about 600 Hz - are thought to reflect the delay required for synaptic discharge [63]. Only I-waves are evoked when a threshold intensity sufficient to evoke a

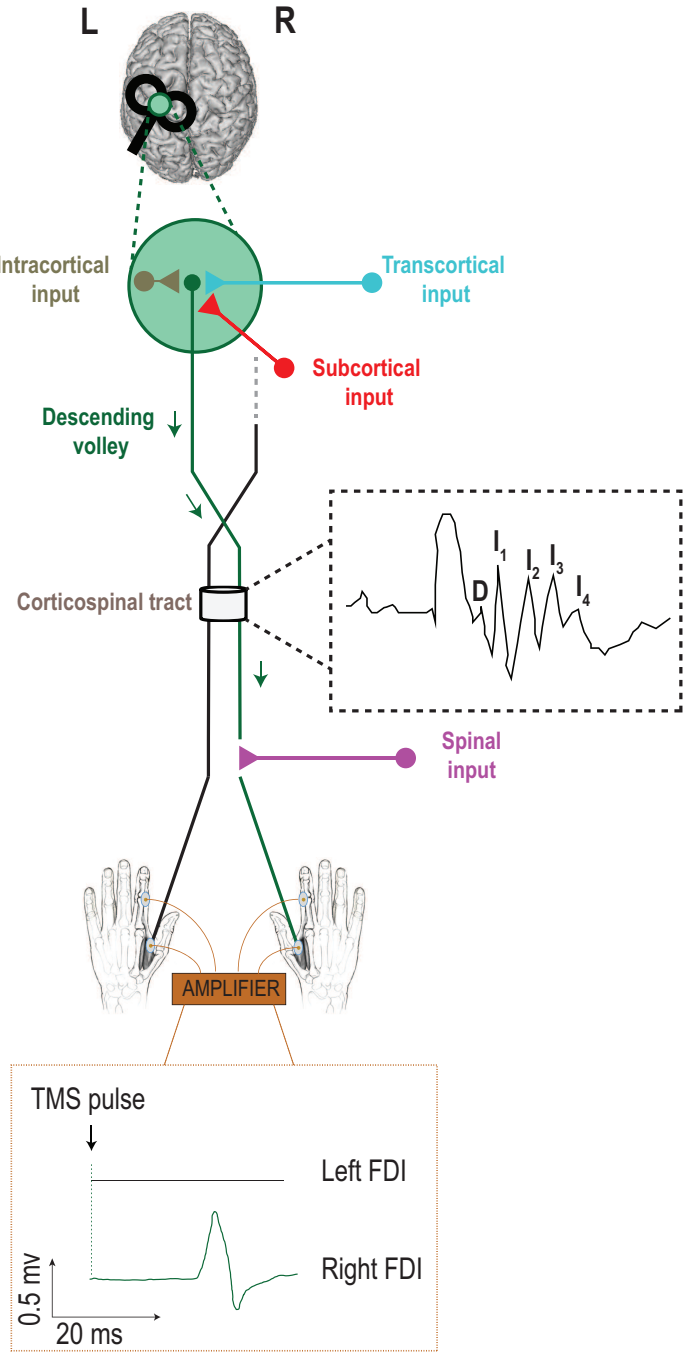


Figure 0.6: (Continued on the following page).

Figure 0.6: Transcranial magnetic stimulation (TMS) as a probe of corticospinal (CS) tract excitability (CSE). To probe CSE, a TMS coil need to be placed over the primary motor cortex (M1) at the hotspot (depicted in green) of the targeted muscle. There, the largest MEPs can be recorded in the electromyography (EMG) signal. The amplitude of the MEP depends of the CS neurons that are activated directly or indirectly via the stimulation of intracortical circuits to which they are connected. Transcortical inputs from premotor, prefrontal, and parietal cortices, as well as axons of subcortical cells projecting onto M1, are also activated by TMS over M1. Depending on the direction of the pulse and of the intensity of stimulation, a series of descending volleys named direct (D-) wave and indirect (I-) wave are transmitted from M1 to the motor neurons in the spinal cord. These signals are further influenced by inputs at the spinal level before they jointly give rise to an MEP in the targeted, contralateral muscle (the right first dorsal interosseous [FDI] in the present example). Figure adapted from Figure 1 in Duque et al. (2017) [22].

muscle twitch is used with a coil inducing a posterior-anterior (PA) current in the brain. D-waves are elicited at much higher intensities of stimulation [43].

Not only the intensity of stimulation but also the orientation of the current induced by the TMS coil alters the onset and shape of the MEP [43, 61, 64]. The lowest threshold for activation of the hand area of the motor cortex occurs when the TMS pulse is aligned to induce current perpendicularly to the line of the central sulcus (approximately PA in the brain; Figure 0.7). This stimulation evokes the earliest I-wave (I_1) in the CS tract. In contrast, when the TMS pulse is aligned to induce current parallel to the line of the central sulcus (approximately lateromedial [LM] in the brain; Figure 0.7), a D-wave is recruited even at low intensities of stimulation. Finally, if the orientation of the induced current is kept perpendicular to the line of the central sulcus but is reversed (approximately anterior-posterior [AP] in the brain; Figure 0.7), then the lowest threshold response occurs later than the I_1 wave evoked by PA stimulation; it mainly produces late I_2, I_3, ... , I_n waves. This means that depending on whether the TMS pulse is oriented PA or AP, it can activate different sets of inputs that arrive at the CS neurons several

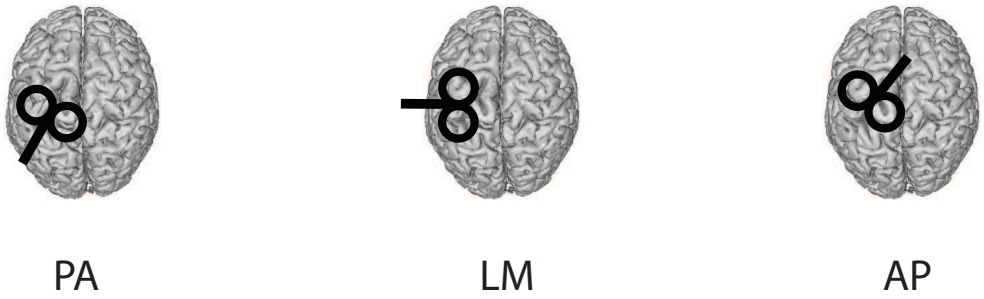


Figure 0.7: Possible TMS current orientations. TMS coils can induce either posterior-anterior (PA), lateromedial (LM) or anterior-posterior (AP) currents in the brain. Each one induces distinct types of descending volleys. Of note, manufacturers have recently given the opportunity to choose the direction of the current flowing through the TMS coil. As such, currents with different directions can be induced into the brain without changing the orientation of the TMS coil.

milliseconds apart [65]. Since the I-wave activity produced by AP stimulation is less synchronized and has peak latencies later than those seen after PA stimulation and since the order of recruitment of the descending corticospinal waves may change with the direction of the current used, one can speculate that PA and AP stimulation activate different sets of inputs to CS neurons - or the same population but at different sites - that are preferentially tuned to different frequencies and arrive at the CS neurons several milliseconds apart [66].

0.2.4 Cortical and neuronal loci of transcranial magnetic stimulation over the primary motor cortex

Despite the common employment of TMS in many experimental settings, the neural types and neural elements that it activates remain largely unknown [67]. For instance, since Barker and colleagues introduced TMS and showed that targetting M1 produces a MEP in the contralateral hand [32], it is still unclear which neural structure(s) is (are) most targetted by the TMS magnetic

field and underlying electric current. This is surprising as the coil configuration (coil design, orientation, etc.) associated with the optimal effect can be accurately identified [39, 43, 44, 68]. At a macroscopic level, are radial cells in the adjacent sulcal walls most stimulated or rather tangential structures in gyral crowns? The question stands also at a cellular level. Is the axon hillock, the bends or terminals most readily stimulated by the TMS pulse? So many questions, so few answers.

Studying the latencies of the descending CS volleys (section 0.2.3), it has been suggested that the pyramidal cells are - at least for intensities around threshold - activated indirectly by TMS via a transsynaptic process [69, 70, 71]. Yet, results between studies vary [61, 72, 73, 74] and it is impossible to draw definite conclusions on the neural origins of the TMS effect. In other words, it remains unclear which specific part of the brain and of the neuron is effectively stimulated when TMS targets the human M1 hand area [61, 73, 74, 75]. For instance, whilst some studies point M1 as the main site of stimulation, using morphologically-realistic neuronal models, Aberra and colleagues suggested the caudal dorsal premotor cortex (PMd) to be the favoured locus for TMS-induced axonal excitation of the motor representation of the hand area in M1. That is, this study implies that when TMS is applied over the precentral motor hand knob, it does not principally excite axonal structures located in M1. Rather, it stimulates M1 hand area indirectly via the PMd (i.e., at least for intensities around corticomotor threshold) [72]. Importantly, the heterogeneity of individual human brains makes it difficult the draw general conclusions as the gyral folding varies between persons [76, 77, 78, 79]. More studies are still needed to cast further light on these questions and to draw definite conclusions on the precise physiological and spatial extent of TMS.

BOX 1: The interest of measuring motor-evoked potentials (MEPs).

If "the eyes are the mirror of the soul" (Paulo Coelho), the MEPs are definitely the window to a better understanding of the tangled brain circuits making the human brain. As mentioned above (section 0.2.3), the term MEP stands for the action potential that is usually evoked by the direct and/or indirect stimulation of M1, commonly through using a non-invasive stimulation technique such as TMS or TES [22, 36, 80]. It represents the net effect of cortical, spinal and peripheral neuromuscular inputs. A MEP is typically portrayed by a short latency ($\sim$ 18 ms). It increases in size with voluntary contraction and/or when the intensity of stimulation raises. On the one hand, the onset (or latency) of the MEP indicates the time taken by descending impulses to reach the target muscle. The latency varies - quite logically - depending on the muscle in which the MEP is elicited (i.e., it increases with proximo-distal progression) or with the subject's height. Most of the time, this measure is used to assess the central motor conduction time. On the other hand, the MEP amplitude supplies with a measure of the portion of the spinal motoneurons triggered by TMS. Whilst recording MEPs with single-pulse TMS represents a reliable method to detect abnormalities of impulse propagation along the CS tract, the use of paired-pulse or repetitive TMS is of prime importance to investigate the excitability and role of different cortical areas targetting the CS tract (developed in section 0.2.5). As a result, MEPs represent key neurophysiological measures for examining both the *conductivity* and the *excitability* aspects of the CS tract in humans. At a clinical and research

level, MEPs render great services. Several abnormalities of standard MEP parameters have been documented in clinical populations. For instance, depending on the pathology, the MEP can be missing, the onset-latency can be retarded, and the amplitude can be diminished together with a enhanced threshold. Several mechanisms may explain such changes: failure of conduction due to damage to the CS tract, dispersion of multiple descending volleys causing de-synchronization of alpha-motoneurons discharges, hypo-cortico-motoneuronal excitability, etc. Changes of the MEP size can also highlight the efficiency of inhibitory and facilitatory systems within the human motor cortex that are thought to depend on the activation of inter- and intracortical circuits. Altogether, because MEPs represent the net effect of many inputs coming from several brain areas, they provide researcher with key information about the state of the CS tract as well as about the spinal, cortical and subcortical areas targetting this pathway.

0.2.5 Patterned protocols of transcranial magnetic stimulation

0.2.5.1 Context

Since the early studies with TMS, researchers have obsessed over developing and improving protocols of stimulation allowing them to better understand the activity of the human brain. At the beginning, spTMS has let them investigate the state of the motor output pathway. Through developing and using rTMS, researchers have later been able to induce excitatory or inhibitory lasting effects - a sort of reversible short-term damage. In addition, the dawn of paired-pulse TMS (ppTMS) has allowed scientists to explore intra- and

inter–regional physiological interactions. Theses TMS protocols are swiftly described below. For thorough reviews please refer to the substantial work made by Reis, Klomjai and colleagues [39, 56, 63, 81] - to name just a few.

0.2.5.2 Single-pulse transcranial magnetic stimulation

The delivery of multiple single pulses of TMS to the brain is very safe and does not appear to leave any lasting effect [35, 39]. During the last two decades, many studies have therefore applied spTMS over one M1 to track CSE changes at different moments in various contexts, including action preparation, action observation, motor imagery, inhibitory control, decision making, reward processing, reasoning, speech or sustained attention [49, 82, 83, 84]. M1 is a privileged area for neuroscientists as changes in activity of the motor output pathway can readily be measured through applying TMS over this region and recording the subsequent MEPs [22, 48, 51].

In clinic, spTMS has also played a key role. The measurement of the MEP amplitude, the central motor conduction time, the rMT, the cortical silent period or MEP recruitment curves have all been of central importance to provide evidence of the changes associated with a disease. Since M1 works in association with other motor-related brain areas, using spTMS has provided researchers with a unique opportunity to analyse the changes occurring in a cortical node which is part of different cortical networks.

Not only diseases, but drugs also, can alter measures obtained through using spTMS. The rMT, for instance, is modified by agents hindering voltage-gated sodium channels (i.e., channels that are critical for the tuning of axon excitability) and by agents operating on glutamate receptors (i.e., responsible for fast excitatory synaptic transmission in the cortex) [85, 86, 87]. Some other neurotransmitters and neuromodulator systems such as gamma aminobutyric

acid (GABA), dopamine (DA), norepinephrine, serotonin or acetylcholine have however no effect on the rMT [87].

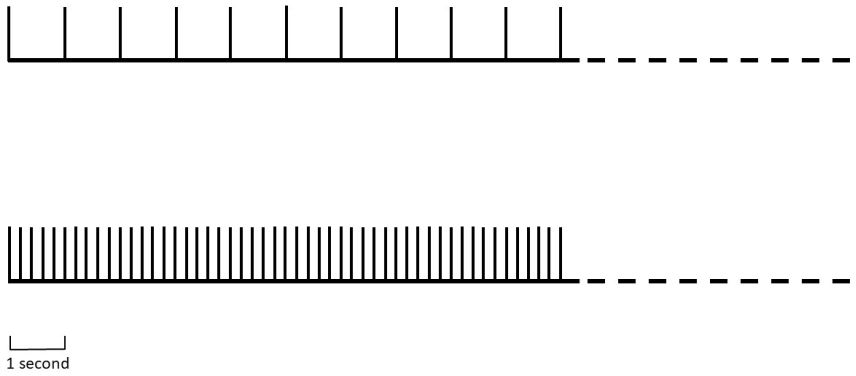
Similar to the rMT, the MEP is depressed by agents that inactivate sodium channels (e.g., volatile anaesthetics). It is, however, also altered by the application of modulators of inhibitory and excitatory transmission in neuronal networks such as those acting on $GABA_A$ receptors or DA and norepinephrine agonists [87]. Whilst the first group depresses MEP, the later ones increase it. Because changes in MEP amplitude can occur without any significant change in the rMT, it is supposed that these two measures rely on important physiological differences.

In addition to illnesses and drugs, cortical activity can also be modified by rTMS protocols and this, beyond the stimulation period. For many years, these protocols have been widely used for the treatment of neurological and psychiatric disorders. They are the subject of the following section.

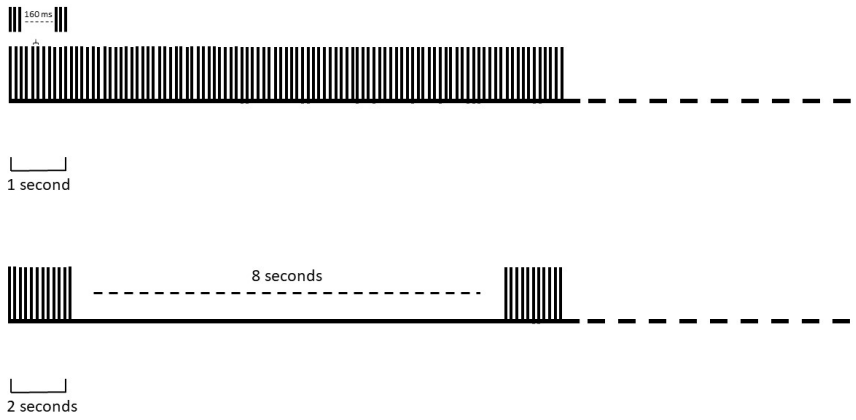
0.2.5.3 Repetitive transcranial magnetic stimulation

Repeated stimulation of neural circuits in the brain can alter the efficiency of synaptic transmission and lead to either synaptic long-term potentiation or long-term depression [88, 89]. These processes are thought to be closely linked to processes of learning, memory and functional cortical reorganisation after injury. Over the past 20 years, rTMS have emerged as a potential method for causing changes that last after the stimulation period in the cerebral cortex of conscious healthy humans [90]. rTMS studies have mainly focused on stimulating M1 as CSE can readily be measured through applying TMS over this region.

Conventional protocols of rTMS are of two types and differ by the fre-



(i) Conventional rTMS procedure.



(ii) Patterned rTMS procedure.

Figure 0.8: (i) Conventional repetitive transcranial magnetic stimulation (rTMS) and (ii) patterned rTMS procedures. Whilst conventional rTMS procedures mainly focus on the frequency of stimulation, patterned rTMS procedures can produce a long-term potentiation or depression like effect through using bursts having the same frequency (three pulses at 50 Hz, repeated five times per second). In this case, the direction of the after-effect depends on whether the theta bursts are delivered continuously or intermittently without experimentally changing other factors such as the frequency and intensity [88].

quency of stimulation. Low-frequency (< 1 Hz) stimulation tends to reduce CSE whereas higher frequencies (> 1 Hz) tend to increase CSE (Figure 0.8(i)) [35]. Beside these conventional protocols, sequenced rTMS protocol have recently been developed. Here, the effect is not induced by the stimulus rate but rather depends on whether the bursts are delivered continuously (producing long-term depression like effects) or intermittently (producing long term potentiation like effects) (Figure 0.8(ii)). Thus the after-effects depends more on the length of the train of bursts and of the pause between the trains than of the frequency itself [88].

Since energy expenditure is lower when using biphasic pulse waveform, a great majority of studies have opted for this approach when using rTMS. However, as the repeated use of monophasic pulses activates a homogeneous population of neurons (i.e., unlike biphasic pulses which gives rise to a more compound pattern of neural activation), it has been suggested that monophasic pulses rTMS could be more effective that biphasic one in producing steady after effects [91]. In a couple of studies, indeed, MEP size reduction - following 1 Hz rTMS delivered over M1 [92] - and enhancement - following 10 Hz rTMS delivered over M1 [93] - was more striking and prolonged when monophasic pulses were used. It is thought to be due to the fact that biphasic pulses may activate different populations of neurons that are both facilitatory and inhibitory. As such, the summation of the effect is not so clear with biphasic stimulation as it is when using monophasic pulses [93].

0.2.5.4 Paired-pulse transcranial magnetic stimulation

ppTMS protocols are stimulation procedures in which the MEP amplitude elicited by a TMS pulse can be modulated by a preceding conditioning pulse delivered either to the same cortical area (for real-time intra-regional interac-

tions) or elsewhere (for real time inter-regional interactions). These methods have been widely used to study inhibitory and excitatory microcircuits of the brain [56].

0.2.5.4.1 Intrahemispheric interactions within the primary motor cortex

Facilitation within the primary motor cortex Facilitatory interactions occurring locally within M1 can be measured by delivering two TMS pulses through the same TMS coil over the same cortical area. Using this approach, two types of local facilitation have been revealed.

Intracortical facilitation of a test MEP can be elicited at inter-stimulus intervals (ISIs) ranging from 6 to 25 ms using a sub-threshold conditioning stimulus to influence the response to a subsequent supra-threshold test stimulus. The facilitation becomes stronger with increasing conditioning stimulus intensity. When the intensity of the test stimulus increases, it tends to be weaker. Interestingly, direct recordings of the corticospinal discharge in the spinal cord show that intracortical facilitation (ICF) causes little or no change in the amplitude or number of I-waves even though facilitation occurs (i.e., the MEP is larger) [94, 95]. This suggests that the low intensity, first stimulus activates excitatory inputs to CS neurons that result in additional descending activity that is not synchronized to the I-waves and not evident in epidural recording. Alternatively, the effect of ICF may also be explained by a spinal origin of facilitation instead of a cortical one. For instance, the effect of glutamate on ICF [96] could both occur in the spinal or cortical CNS. Recently however, a study investigating the origin of ICF through recording the cortical electroencephalography (EEG) response to TMS using the ICF paradigm

demonstrated a clear cortical origin [97]. In this study, there was a close correlation between changes in TMS-evoked EEG responses and MEP amplitude, suggesting that spinal contribution may be small.

Another sort of facilitatory interaction can also be exposed within M1 using shorter ISIs. It occurs when a supra-threshold stimulus - deemed here as the test stimulus - is followed by a sub-threshold stimulus - deemed here as the conditioning stimulus -, or alternatively when two stimuli near motor threshold are given consecutively. Using this approach, facilitation can be demonstrated at three distinct ISIs after the first stimulus: 1.1 – 1.5, 2.3 – 2.9 and 4.1 – 4.4 ms [98].

Inhibition within the primary motor cortex Two main types of local intracortical inhibition can be studied through using ppTMS, viz., short interval intracortical inhibition (SICI) and long interval intracortical inhibition (LICI).

SICI can be elicited with a sub-threshold conditioning stimulus followed 1 to 6 ms later by a supra-threshold test stimulus. It is conceived that the first, sub-threshold pulse activates low threshold inhibitory neurons that hinder the excitatory inputs activated by the second pulse [43, 99]. Interestingly, suppression through SICI only occurs in late I-waves (i.e., I_3, I_4 and to a smaller extend I_2) when induced by PA TMS suggesting that only these waves are targeted by inhibitory projections. It is coherent with the idea that the excitatory input accountable for the initial I-wave and those accountable for the late I-waves are located in distinct sites of the CS neuron, that is, the soma or basal dendrites for I_1 and apical dendrites for the later I-waves [43]. Interestingly, the inhibition of the late I-waves through using the SICI protocol is very steady and cannot be subdue by an increase of the intensity of the

test stimulus; if the test stimulus is strengthened, an earlier wave is evoked (D-wave) but later I-waves are still suppressed [100]. Pharmacological experiments have investigated the different types of receptors likely to be involved in SICI. Since SICI is enhanced by pretreatment with non-selective $GABA_A$ alpha agonists (e.g., diazepam and lorazepam) but not affected by zolpidem (i.e., a selectively $GABA_A$-$\alpha 1$ receptor agonist at low concentration), it has been suggested that SICI is probably mediated by alpha 2-3 type of $GABA_A$ receptor mechanism [43].

The second type of intracortical inhibition, that is, LICI is elicited by a supra-threshold conditioning stimulus followed by a supra-threshold test stimulus triggered 50 to 200 ms later [101]. Corticospinal volleys elicited by this paired-pulse paradigm showed that late I-waves evoked by the second stimulus are reduced while the I_1-wave remains unaffected. Because of its duration (i.e., lasting more than 100 ms) and because baclofen - a specific $GABA_B$ receptor agonist - increases the magnitude of LICI, it is believed that LICI is mediated by slow inhibitory postsynaptic potential mediated by the $GABA_B$ receptor.

0.2.5.4.2 Interhemispheric interactions between primary motor cortices

Using a ppTMS technique with one coil over each M1, one can investigate interhemispheric interactions between the two primary motor cortices.

Interhemispheric facilitation between primary motor cortices In 1992, Ferbert et al. investigated whether a conditioning TMS pulse delivered over M1 of one hemisphere had any impact on the size of an MEP elicited by a TMS pulse over M1 of the opposite hemisphere. [102]. One of their findings

was a facilitation of the test response at conditioning-test intervals of between 3 ans 5 ms. This effect was however described as *[...] capricious and would often disappear if the block of trials was repeated, only to reappear again in the same subject on another day.* [102] They conclude their paper saying that they *[...] failed to find any convincing evidence for a period of transcallosal facilitation.*

9 years later, Hanajima et al. (2001) decided to re-explore interhemispheric facilitation (IHF) [103]. They discovered that under specific conditions, it was possible to obtain dependable IHF, that is, IHF was observed only at short ISIs (i.e., $\sim$ 4-5 ms; alike what was found by Ferbert et al. (1992)) if a conditioning stimulus 5 – 10 % above active motor threshold was used to induce medially directed currents in the brain. In addition, the test stimulus needed to (i) elicit I_3-waves and (ii) induced current in an AP direction. If the test responses resulted in I_1-waves or D-waves, MEPs were indeed never facilitated. Similar, not IHF occurred if PA directed induced current were used for the conditioning stimulus.

Divergent results were found by Baumer et al (2006) who demonstrated reliable IHF following a conditioning stimulus at two subthreshold intensities: at 60% and 80% of active motor threshold [104]. At 60 % of active motor threshold, IHF occurred at an ISI of 6 ms, with the test stimulus (i.e., the intensity of the test stimulus was defined to evoke, when given alone, an EMG response of approximately 1 mV peak-to-peak amplitude in the FDI muscle) current in a PA direction. At ISIs of 6 and 8 ms, IHF was observed with a conditioning TMS intensity at 80 % of active motor threshold and a test stimulus current in an AP direction [104].

Further experiments are still needed for a better understanding of IHF

and to disentangle the sometimes contradictory results between the studies presented above.

Interhemispheric inhibition between primary motor cortices In contrast to IHF, interhemispheric inhibition is robust and occurs over a variety of ISIs ranging from 6 to 50 ms. This form of inhibition is probably mediated by the corpus callosum as patients with ischaemic lesions to this structure do not show it [105, 106]. Interhemispheric inhibition requires a supra-threshold conditioning and test stimulus intensity adequate to elicit an MEP of 0.5 - 1.5 mV in amplitude.

BOX 2: Brain circuits influencing corticospinal excitability.

Studying the CS tract through applying TMS over one's M1 provides researchers with a unique opportunity to investigate a neural route targetted by multiple brain regions that exert control over bodily actions. To date, the understanding of which brain areas influence and determine the activity of the motor output pathway - and how they do so - is still slender [107]. Some circuits have however been highlighted through using patterned protocols of TMS (section 0.2.5). The intrahemispheric circuits are the ones probed with ppTMS using single-coil setups (section 0.2.5.4.1). They encompass ICF (mediated by glutamatergic neurotransmission), SICI (mediated by subtype of $GABA_A$ receptors) and LICI (mediated by $GABA_B$ receptors). The interhemispheric circuits are the one usually probed with ppTMS using double-coil setups (section 0.2.5.4.2). Using such protocols, several regions of interest have already been investigated. These regions are mainly located in frontal-parietal areas. They encompass non-primary motor areas (i.e., the premotor cortex [108] and SMAs [109]), the anterior intraparietal sulcus [110], the superior parietal lobule [111], the supramarginal gyrus [112], the superior parieto-occipital cortex [110, 113] and the lateral prefrontal cortex [114] that have all been linked to changes in the amplitude of MEPs. Beside these fronto-parietal regions, other areas such as the basal ganglia [115], the CB [116] and even secondary visual areas [117] also play key roles in the modulation of the activity of the CS tract. Of note, further studies remain needed to comprehend how each area influences CSE; whether they target motor representations in a generic or in a rather specific way [107].

KEY POINTS

* Through using transcranial magnetic stimulation, one can stimulate the human brain in a non-invasive and non-painful manner.
* A supra-threshold transcranial magnetic stimulation pulse over the primary motor cortex evokes a motor-evoked potential which is the result of a series of distinct descending corticospinal volleys.
* The first volley is termed the direct-wave whilst subsequent ones are named indirect-waves. Indirect-waves are numbered in order of their appearance.
* These volleys are elicited due to the stimulation of a range of neurons located under the coil, including corticospinal cells but also projecting axons from other sites.
* Hence, a motor-evoked potential represents the net effect of intracortical, transcortical, subcortical and spinal inputs.

In the current work

Over the years, paired-pulse transcranial magnetic stimulation (ppTMS) paradigms have allowed researchers to investigate real time interactions occurring in the human brain. These experiments had one main purpose: to explore how the motor evoked potential (MEP) elicited by a supra-threshold TMS pulse can be modulated by a preceding conditioning pulse. Thanks to these studies, we have now reached a better understanding of the circuits being behind both inter- and intra- cortical inhibition and facilitation. In the present work, we have used ppTMS with a strongly distinct objective in view. In Chapter 1, I describe a study where we utilised ppTMS to assess whether a method where the two primary motor cortices are stimulated at rest with an inter-pulse interval as short as 1 ms (double-coil$_{1ms}$) yields equivalent MEP results as the ones obtained with single-pulse TMS (spTMS). This experiment was performed because, in many situations, it would be useful to obtain MEPs in both hands simultaneously, to track corticospinal excitability (CSE) bilaterally. Our results suggest that double-coil$_{1ms}$ yields equivalent MEPs at rest as does spTMS and this, for intensities of stimulation ranging from 100 to 160 % of the resting motor threshold. This technique can be useful in many ways. For example, it allows researchers to double the amount of data they can acquire in a single experiment within a fixed amount of time. It is critical because it gives them the opportunity to test more conditions than could be done with a regular spTMS method. In addition, measuring MEPs in both hands within the same trial allows them to investigate the distinct impacts of a task on CSE of the dominant and non-dominant side in the exact same settings. This dramatically increases the signal to noise ratio. In summary, double-coil$_{1ms}$ permits to obtain new CSE dependent measures and may pave the way towards new research horizons.

0.3 Motor-related inhibition in action preparation

0.3.1 Context

> "We have a brain for one reason and one reason only - and that's to produce adaptable and complex movements."
>
> Daniel Wolpert

Movement is possibly one of the most important function of the nervous system [118]. It allows one to interact with the physical world and is essential for survival [119]. Movement is needed to hunt, to escape a danger and to reproduce. Whether is it to write a paper, make a speech or complete an Ironman, movement is mandatory and ubiquitous. It is more than just "exercise" as it does not necessarily require effort.

Beside the *trivial* ability of moving, what really allows humans to act in a goal-directed manner is their capacity not to respond in an automatic, stimulus-driven way [120]. One must refrain from drinking large amount of alcohol, however tempting it might be, if a job interview or exam is planned later in the day. Long-term goals must prevail. This ability, called inhibitory control is a critical aspect of everyday life. When it is deficient, behaviours become maladaptive [121, 122, 123]. Importantly, in addition to being capable of inhibiting prepotent responses, being able to cancel and reprogram already planned actions is critical. When driving a car, you must be prepared to quickly release the accelerator and switch to the brake if a child unexpectedly crosses the road.

Several studies have explored the neural correlates of behavioural inhibi-

tion through using laboratory tasks that require stopping an already prepared action. The stop-signal task, for instance, has been widely used to study response initiation and inhibition [124, 125]. In this paradigm, the subject takes part in a reaction time (RT) task with the stress on fast responses. In a subset of trials - usually 33% -, a stop signal stimulus appears shortly after the go-signal. Subjects are told to try to cancel the already initiated responses as soon as the stop signal appeared. Under such conditions, a rapid suppression of activity can be observed at various levels of the motor pathway (i.e., MEP amplitudes are smaller when a stop signal appears that under baseline conditions), likely reflecting a pause in motor output [115, 126].

Interestingly, recent studies have revealed that the motor output pathway also shows profound inhibitory changes during action preparation and this, even during the planning of simple finger movements [127, 128, 129]. Consequently, the motor system is inhibited not only when a movement needs to be suppressed, but also when it is in the process of establishing upcoming actions, a process referred to as *preparatory inhibition* [22, 130, 131]. The function(s) served by such inhibition as part of action preparation, and the extent to which it may support behavioural inhibition, have been the focus of considerable research over the past decade ranging from EEG, to TMS and single-neuron studies [22, 48, 127, 130, 132, 133, 134, 135, 136].

In the next sections, I review recent work that has investigated physiological markers of motor inhibition in situations requiring the preparation of an action. I mainly focus on studies that have used TMS in humans to monitor changes in the excitability of the CS pathway.

BOX 3: Inhibition in psychology and neurosciences.

The term *inhibition* has been and is still widely used in neuroscience [22, 137, 138]. In synaptic and neural circuits, its effect is obvious and there is little doubt about its meaning. In psychology also however, this term is omnipresent [137, 139, 140]. There though, the notion of inhibition is less tangible with subjects supposed to *inhibit* unwanted stimuli or actions, painful memories, etc. In folk psychology [141, 142], for instance, one readily says "He was drunk and lost his inhibition " or " I must suppress my urge to *Netflix* today as I have an exam tomorrow ". In the context of psychology, inhibition is therefore suggested to help the generation of goal-directed behaviours: it is a key component of cognitive control that is defined as "the active maintenance of patterns of activity in the prefrontal cortex (PFC) that represent goals and the means to achieve them" [143]. Since proper inhibitory abilities must help the generation of appropriate endeavours, in neuropsychiatry, impaired inhibition has been widely used as an explanation for attention deficit disorder, obsessions, impulsivity, poor decision making, etc. The source of the control is usually linked to PFC [123] whilst the targets are thought to be located in the posterior cortical and subcortical regions. The importance of the PFC for supporting appropriate actions was first made by the observation of the changes of one's behaviour following prefrontal damage. The case of Phineas Gage is a famous example. This railroad worker suffered an extensive prefrontal damage when blasting powder drove a tamping iron though his head. From that moment, his personality changed radically, forever [144].

0.3.2 Experimental paradigms for preparatory inhibition

The time course of CSE during action preparation has been investigated in several types of RT experiments in which humans are told to react as fast as possible following the appearance of a go-signal also called an imperative signal. In such studies, TMS is usually applied over M1 at several time points between the beginning of the trial and the movement onset. Changes in MEP amplitude - usually expressed with respect to baseline measurements obtained during the inter-trial interval - provide a temporally precise measure of the recruitment of the motor system preceding the emergence of the movement [22].

The simplest version of a RT task is one in which the go-signal always specifies the same action within a given block of trials (simple RT task; Figure 0.9). In such a task, the participant makes one specific response (e.g., pressing a specific key of the keyboard) whenever a stimulus (e.g., a shape) appears on the screen. This paradigm - in which the main behavioural dependent measure is the speed of responding - is straightforward as it only engages certain basic processes such as perception and response execution without requiring more complicated computations such as working memory, attentional focusing, decision making or action selection. In simple RT tasks, there is normally a progressive increase in the amplitude of MEPs recorded from the selected muscle originating around 100 ms prior the onset of the volitional EMG [145, 146]. This pre-movement increase in the amplitude of MEPs is thought to reflect the excitation of the corresponding motor representation in M1 through a joint modulation of facilitatory and inhibitory influences.

In more compound versions of the RT task, viz., choice RT tasks, the go-signal requires choosing between alternatives that are predefined within a

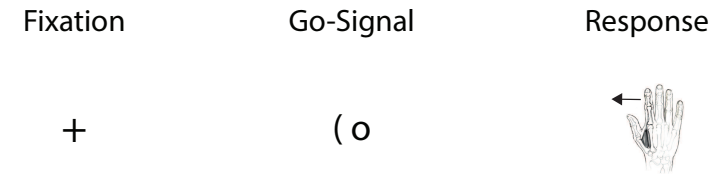


Figure 0.9: Example of a simple reaction time (RT) task. Example of a simple RT task requiring a right index finger movement response. Figure adapted from Figure 1 in Greenhouse et al. (2015) [128].

block of trials (Figure 0.10). In such paradigms, the option is often between a finger movement of the left or of the right hand allowing the investigation of the physiological correlates of action selection. Here, the TMS is usually applied at different moments during the RT period and MEPs can be measured and compared for conditions in which the muscle is either selected (e.g., left index finger MEP in a trial requiring a left index finger response), not-selected (e.g., right index finger MEP in a trial requiring a left index finger response) or irrelevant for the forthcoming response. Irrelevant muscles are effectors that are not part of the response set. They can either have the same innervation as the response set (e.g., abductor digiti minimi [ADM] muscle in a trial requiring an index finger response) or a different one (e.g., abductor pollicis brevis [APB] in a trial requiring an index finger response).

As one may have assumed, MEPs evoked in the selected effector exhibit a rise in amplitude throughout the pre-movement period, alike the one observed in simple RT tasks [147]. Before the activity commences to boost, however, there is an initial reduction in the amplitude of the MEPs [148, 149], indicating inhibition of the CS path connected to the selected movement. This decrease in MEP amplitude is also measured in the not selected effector and the irrelevant ones [148, 150, 151]. Here, however, the MEPs display an additional decline in amplitude along the pre-movement period. These effects are in agreement with the assumption that action selection entails not only excitatory processes

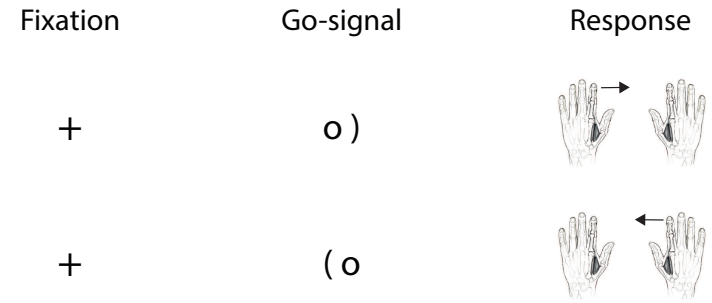


Figure 0.10: Example of a choice reaction time (RT) task. Example of a choice RT task requiring either a left (upper side) or right index (lower side) finger movement response. Figure adapted from Figure 1 in Greenhouse et al. (2015) [128].

shaping the selected effector, but inhibitory ones as well. Such processes are initially marked in selected, not-selected and irrelevant representations. Through the course of the trial - when movement execution is near - however, they tend to disappear for the selected effector whilst they strengthen for the not-selected and irrelevant ones [135].

Another standard type of RT tasks are called instructed-delay RT tasks. They encompass paradigms in which a preparatory cue gives either uninformative, partially informative or fully informative details about the movement that will have to be performed next. (Figure 0.11) [114, 127, 149, 153]. The fully informative instructed-delay choice RT task is the one I have been working with for the biggest part of my PhD. In such a paradigm, a cue supplies the subjects with complete information (e.g., the specific hand and muscle that should be used) about the forthcoming response (Figure 0.11C). For instance, if the cue is on the left side of the screen, participants know they must prepare a left index finger response and if the cue is on the right side, they know they must prepare a right index finger response. Subjects are explicitly told, however, to withhold their response until the onset of a go-signal even if they are aware of the type of movement they will have to perform next. When

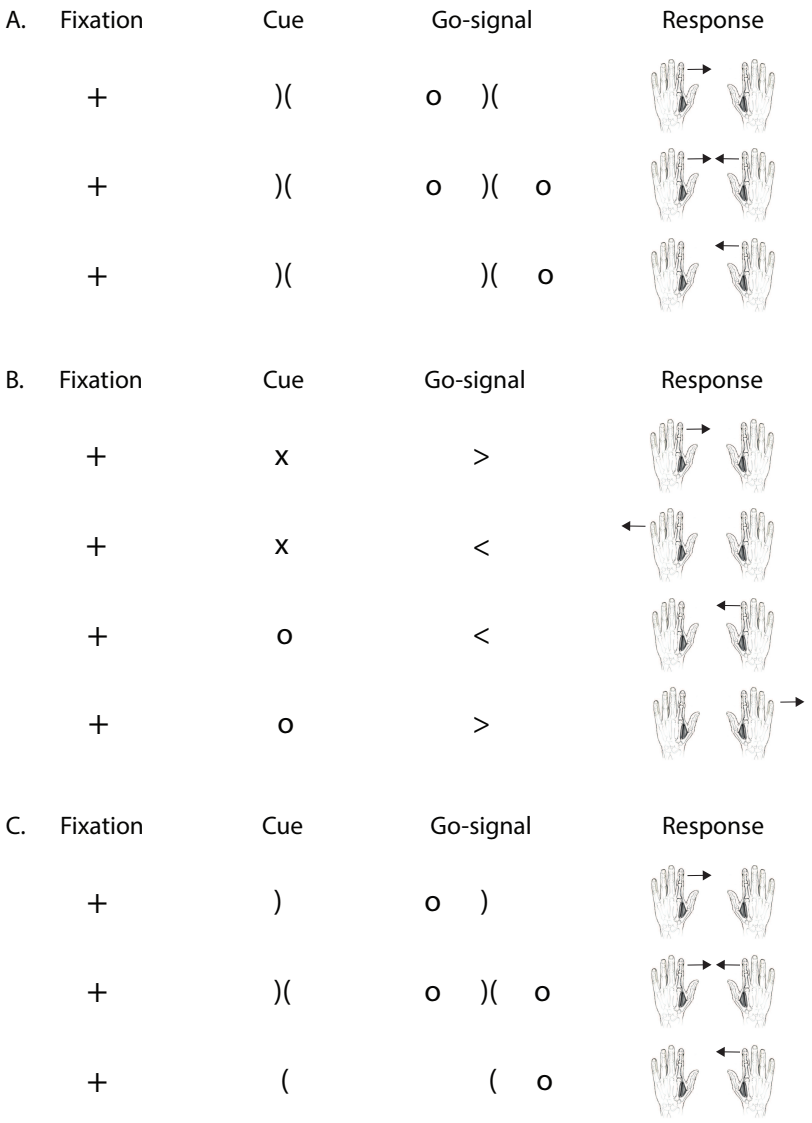


Figure 0.11: Examples of an (A.) uninformative, (B.) partially informative and (C.) fully informative instructed-delay choice reaction time (RT) task. (A.) Instructed-delay choice RT task in which the cue is uninformative. Here, subjects are required to response with either the right, the left or the right and the left index fingers depending on a go-signal. Figure adapted from Fig. 1 in [127]. (B.) Instructed-delay choice RT task in which the cue is partially informative. In this example, the cue gives information about the hand that will have to respond next but not about the muscle that should be used. This information is only available when the go-signal appears. Figure adapted from Fig. 1 and Fig. 2 in [152, 153], respectively. (C.) Instructed-delay choice RT task in which the cue is fully informative. In this paradigm, the cue gives all the information needed about the movement that will have to be performed next. Figure adapted from Fig. 1 in [128].

the go-signal appears, participants must release the prepared response as fast as possible.

As one may notice, the interest of this paradigm is its capability to investigate delay-related processes that are specifically involved in action preparation without being confused by functions related to movement execution. Of note, it has recently been proposed that such a delay period could also involve additional processes that are specific to the delay setting rather than being inherent to the preparation of an action. Further experiments are necessary to disentangle this point.

When assessing CSE at the end of the delay period in a muscle that is not-selected or irrelevant for the forthcoming movement in a instructed-delay RT task, results are alike those measured in choice RT task: CSE is suppressed both for not-selected and irrelevant representations [49, 128, 154, 155]. Intriguingly, so it is also for a selected representation with MEPs being strongly inhibited in the selected muscle during the delay period [153, 154, 156]. Additionally, this inhibition is sometimes even greater than the one in the not-selected representation at the end of the delay period [127, 157]. The existence of this broad phenomenon acting on selected, not-selected and irrelevant representations, and even more its functional role has been puzzling researchers for many years. Indeed, why should a muscle be suppressed compared to baseline prior to its activation; would you engage the brakes before pressing the gas pedal? In the following sections, I review both the neural sources and the ongoing hypotheses regarding the functional role of motor inhibition during action preparation.

In the current work

For more than 30 years now, studies investigating corticospinal excitability (CSE) changes underlying action preparation have been using single-coil transcranial magnetic stimulation (TMS) to elicit motor evoked potentials (MEPs) in a hand contralateral of the site of stimulation. In many situations, however, it would be useful to obtain MEPs in both hands at once, to track CSE bilaterally. For instance, in simple, choice and instructed-delay reaction time (RT) tasks, this would permit to obtain markers of CSE changes associated with selected, non-selected and irrelevant muscles within each trial in both hands. Such a method requires to use a double-coil TMS approach where both primary motor cortices are stimulated concurrently whilst avoiding electromagnetic interference between the two stimulating coils. In the present work - as mentioned above - we first evaluated the reliability of such a TMS method where both primary motor cortices are stimulated with a 1ms inter-pulse interval (i.e., double-coil$_{1ms}$) at rest (Chapter 1). MEPs obtained using this technique were found equivalent as those acquired with single-pulse (spTMS) and this, for intensities of stimulation ranging from 100 to 160 % of the resting motor threshold (rMT). To further investigate the reliability of this approach, in a second experiment (Chapter 2), we compared MEPs elicited at 115% of the rMT during an instructed-delay choice RT task using single- or double-coil$_{1ms}$ TMS. It was done to test whether double-coil$_{1ms}$ still provide researchers with dependable MEPs when they are elicited in a functional state requiring motor preparation. Alike was what found in the first experiment, MEPs were equivalent whether single-coil or double-coil$_{1ms}$ was used. This suggests that double-coil$_{1ms}$ is a reliable tool to

assess CSE and this, not only when subjects are at rest, but also when they are involved in a task, opening new research horizons for scientists interested in the corticospinal correlates of human behaviour.

0.3.3 Functional role of preparatory inhibition

The function - or functions - served by preparatory inhibition remains fundamentally unclear. A couple of theories have however been suggested.

First, preparatory inhibition could contribute to behavioural inhibition and thus ensure the generation of goal-oriented behaviours [48]. There are variants of this idea in the literature. Some postulate that inhibitory influences are specifically directed towards not-selected representations. The motor suppression observed during the preparation of a movement could assist the selection of an action through suppressing not-selected ones [114, 157]. Other suggest that preparatory inhibition could be essential for retaining selected muscles from becoming active before required: a sort of impulse control [127, 158]. It would help the peripheral motor system to stand still while cortical activity progresses across the cortex.

Beside the assumption that CS suppression is critical for successful behavioural inhibition, a second hypothesis suggests that the CSE suppression occurring during movement preparation is present to increase the gain of the motor system [128]. As such, it would enhance the signal-to-noise ratio to help the selected action to better stand out against a sluggish background [22, 128, 130]. This hypothesis puts forward that preparatory inhibition might facilitate the release of chosen responses promoting fast reactions [134]: the greater the amount of preparatory inhibition, the faster the RTs.

These hypotheses are developed in the subsequent sections. Of note, the

existence of one phenomenon does not exclude the actuality of the others; that is, they could coexist and work in parallel.

0.3.3.1 Preparatory inhibition for action selection and impulse control

The idea that preparatory inhibition is involved in action selection has first been brought into light by early TMS studies showing dependable MEP suppression in not-selected effectors during choice RT tasks [159]. When the hand is selected, MEP amplitudes typically increase over time whilst it decrease - CSE suppression - when it is not-selected. Such a phenomenon has been ascribed to a process in which the not-selected action representation is suppressed to help the selection of the intended response [159]. This duality between alternatives is often referred to as *competition resolution* and suggests that motor suppression should only be observed in muscles that are competing which each other - i.e., in muscles that are relevant with the task - either through an independent race between alternatives or through mutual inhibitory interactions between representations of potential actions [22, 153, 156]. The action that wins is ultimately executed whilst the other one is suppressed.

Dependable inhibition can however be observed in muscles that are irrelevant to the task during either a delay [49, 154] or pre-movement period [148] in choice delay and choice not-delay RT paradigms, respectively. The existence of response alternatives is not even required to observe this effect. For instance, a significant MEP suppression can be observed in the left first dorsal interosseous (FDI) muscle when subjects have to respond with the right hand only [128]. This has been observed both in an instructed-delay and in a no-delay simple RT task. Hence preparatory inhibition seems not to be only

restricted to not-selected effectors, but appears to extend to task-irrelevant motor representations as well.

Contradictory also with the competition resolution assumption is the fact that preparatory inhibition is dependably found in the winner of the competition, that is, in the muscle that will be used for the upcoming response. As such, substantial motor suppression is recorded in the selected effector during the delay period in instructed-delay simple and choice RT tasks [22, 48, 128, 153, 154, 157] as well as just after the onset of the go signal in tasks without a delay period [148, 149]. In the first two paradigms, MEP suppression is sometimes even stronger in a selected effector than in a not-selected one when measured at the end of delay period, moment at which preparation inhibition is most pronounced [153, 156, 157]. Taken together, these findings suggest a broadly tuned phenomenon entailing a generic suppression of the motor output pathway rather than one bringing attention to response *deselection* only.

The global influence of preparatory inhibition upon the motor output pathway is however likely to be somehow restricted. For instance, its effect are usually stronger in selected finger muscles than in not-selected ones [127, 157] and, notwithstanding the fact that leg muscles display some degree of suppression during the preparation of finger responses, this suppression is less dependable and of smaller importance when compared to the suppression observed in finger effectors (an conversely). Ergo, preparatory inhibition is generic but its strength seems to be function of the cortical distance to the selected effector: it declines as the distance increases [129].

It is not because preparatory inhibition is global (contrary to the prediction of a strict competition resolution process) that it does not assist action

selection as part of its impulse control function. Several lines of evidence suggest that in fact it may well contribute to shape our choices. For instance, the danger of selecting inappropriate responses (either because of conflicting information or because a not-selected response is biased) enhances the strength of preparatory inhibition [149, 160]. The amount of motor suppression is also increased by the intricacies of a task with subjects usually expressing more preparatory inhibition when preparing a complex movement requiring the coordination of multiple effectors than when drawing up a single effector response movement [161]. Additionally, the anatomical relations between possible competing effectors also seems to affect the size of preparatory inhibition: MEP suppression is usually higher when the response set consists of two hand movements compared to when it includes a hand versus a foot response. Last, alcoholic patients, a population characterised by a deficit of impulse control abilities, express surprising weak preparatory inhibition when compared to healthy matched controls [132].

At this point, the reader might wonder which regions are at the origin of the generic suppression of the motor output pathway. In reality, there is very little knowledge regarding that matter. Several areas are however supposed to play a role. One of these are the basal ganglia and more specifically the STN. This nucleus has indeed been shown to back the halt of the motor system when a stop or incongruent signal occurs [115, 162, 163]. The STN projects excitatory drives to the internal globus pallidus that result in an inhibition of the thalamus and subsequently a decrease of activity of excitatory thalamocortical neurons targetting the cerebral cortex [4, 5, 7]. Interestingly, substantial evidence also implicates the STN in a threshold-setting process [164, 165]. Alike the STN, the pre-SMA and the lateral PFC (LPFC) are also likely to mediate preparatory inhibition. Whilst altering the pre-SMA

with rTMS was linked to altered preparatory inhibition in conflict choice RT tasks [166], disruption of the LPFC with rTMS has been shown to reduce motor suppression in both the selected and the not-selected effectors [114]. Moreover, a correlation between LPFC cortical thickness and the amount of motor suppression was found in alcoholic patients: the thinner the LPFC, the weaker preparatory inhibition [167, 168].

In the current work

Whilst many transcranial magnetic stimulation (TMS) studies have evidenced a profound suppression of activity in the corticospinal (CS) pathway in situations requiring the preparation of a movement, others have shown that a loud (e.g., 124dB) sound, called a startling acoustic stimulus (SAS), can directly trigger the release of a prepared action when presented slightly before (- 25 ms), simultaneously or after (+25 ms) the onset of a go-signal in simple and choice reaction time (RT) tasks. That is, the action is initiated much faster in trials including a SAS than in control ones. In the current work (Chapter 3), we have intended to characterize the impact of a SAS occurring before the go-signal in an instructed-delay choice RT task, when the subject is actively withholding a prepared action. More critically, we have investigated whether anticipating the occurrence of a SAS can reduce its shortening impact on RTs (to avoid a penalty), presumably due to the recruitment of impulse control processes (producing preparatory inhibition) in order to help prevent premature startle responses. Of note, subjects were clearly told about the fact that the SAS could produce the premature release of their response and that they had to try to refrain that from happening. To ensure that they would retain their action, all premature response were penalised by a negative feedback (impacting the final monetary gain). In addition, subjects were told whether the block they had to perform next would involve a small amount or a large amount of SAS. Hence, based on the impulse control hypothesis, we predicted that in order to comply with the instruction requiring them to avoid responding prematurely, subjects would recruit more preparatory inhibition when they expected a SAS to occur compared to when a SAS was less likely.

0.3.3.2 Preparatory inhibition to reduce background activity and facilitate the release of a movement

Recently, a new hypothesis regarding the role of preparatory inhibition has emerged. It proposes that preparatory inhibition helps the release of an action and speed up motor responses [134]. The reasons for this theory are threefold. First, recent models suggest that inhibition is not a necessary step to prevent the premature release of movements [169, 170, 171, 172]. Second, preparatory inhibition has been observed in simple RT tasks that do not require any choice; it cannot therefore account for action selection/deselection only [128]. Third, a relationship between motor suppression and RTs has recently been shown: the stronger the inhibition, the faster the RTs [134]

To react appropriately to millions of inputs, the nervous system must sort out signals of various amplitudes. Some must be suppressed, others selected. To carry out this chore, structures are assumed to use gain control which seems now to be a fundamental principle of the brain [173]. Models have proposed several computational approaches to control the gain of a system. One of them consists in the modulation of background activity [174]. It suggests that the motor inhibition observed during the preparation of a movement decreases the background activity and therefore enhances the sensitivity of the selected response towards excitatory projections [128, 175]. A powerful analogy of this principle is the picture of a lecturer in a noisy auditorium in which an attendee would like to ask a question. If the lecturer quiets the entire audience, then the attendee will be more easily heard when he or she asks the question. Such a signal-to-noise mechanism has been well described in the leech motor system [176]; it is possible that a similar process was preserved in humans. The role of preparatory inhibition could therefore be to enhance the signal-to-noise ratio in the motor system through globally suppressing motor representations

(and particularly the surrounding ones): this would raise the sensitivity of the selected effector by allowing excitatory inputs to better stand out against a quiet background [128].

On one's behaviour, critically, the gain modulation model brings diametrically opposite predictions than the one described in the previous section. It suggests that both response selection and initiation are facilitated by an increase of preparatory inhibition. When preparatory inhibition becomes greater, so does the signal-to-noise ratio. As a result, the selected action can better stand out and be promptly released if necessary. This prediction contrasts with the assumption of motor suppression for *action selection and impulse control* which implies longer RTs when inhibition increases (i.e., to further avoid the release of the prepared response).

Up until now, a correlation between motor suppression and RTs has only been reported in an experiment where participants performed a simple RT task: the stronger the MEPs were suppressed, the faster the subjects responded [134]. This correlation is, however, not dependably observed: studies have demonstrated different RTs between conditions but similar MEP amplitudes [128].

Two main brain regions are supposed to underlie inhibition for gain control and movement release, viz. PMd and the CB. Whilst the first one is strongly implicated in movement control [169, 177, 178] and has been shown to participate in preparatory inhibition [114], the second one starts to consistently appear in recent models of movement disorders including the neurobiology of Parkinson's disease, dystonia, tics and even addictions [179, 180, 181, 182]. *Have we been ignoring the elephant in the room?* wondered Miquel et al. (2016) in their paper when pondering the role of the CB [179]. This

assumption is highly relevant as the CB is closely related to multiple brain regions that encompass the motor cortex. For instance, ppTMS studies with a conditioning pulse over the CB have shown cerebellar inhibition on M1; an effect known as cerebellar inhibition [116]. This sort of inhibition seems to be relevant to several motor functions including adaptive motor learning and muscle control [183]. Beside being implemented at the cortical level, studies also suggest a spinal contribution for preparatory inhibition. For instance, the Hoffmann- (H-) reflex, a response used as a probe of spinal cord excitability was showed suppressed for the selected effector only in choice RT tasks [153]. A similar effect was found in primates [184] and a spinal component for gain control has already been suggested in other non-human species [185, 186, 187].

0.3.3.3 Conclusion for the role of preparatory inhibition

For the last decades, the role of preparatory inhibition has been puzzling researchers and different models with sometimes divergent predictions have been suggested [22, 127, 128, 134, 160]. One of them suggests that preparatory inhibition helps the generation of goal-oriented behaviours (section 0.3.3.1) whilst the other one proposes that preparation inhibition is needed for the fast release of actions (section 0.3.3.2). In both models, it seems now accepted that the extend of preparatory inhibition is global despite some levels of restriction. Less evident is its source which remains fundamentally unknown despite evidences of cortical, subcortical and spinal influences. Of note, the relevance of a model does not eliminate the pertinence of another one. In the brain, cortical and sub-cortical structures are tightly interconnected and it seems possible that preparatory inhibitory may both help the premature release of an action and fasten RTs.

At this point, I must shed light on the fact that during the 4 years of

my PhD, I *only* focused on the role of preparatory inhibition for behavioural inhibition. The chapters in this thesis investigate this matter and none of them focuses on preparatory inhibition for movement release. However, since *alone we can do so little; together we can do so much*[4], during my time in research, I also contributed to other experiments led by colleagues. In some of these, we made observations that are consistent with inhibition for gain control and movement release. If the reader is interested in this topic, I invite him to refer to our work that target this specific field [188, 189].

[4]Helen Keller.

KEY POINTS

* Corticospinal suppression occurs when one needs to abruptly stop an already planned action but also during the preparation of a movement, a phenomenon referred to as preparatory inhibition.
* The extend of preparatory inhibition seems to be global as it is dependably measured in selected, not-selected and irrelevant effectors during reaction time tasks.
* The neural sources underlying preparatory inhibition are largely unknown but structures at the cortical, subcortical and spinal level are likely to play a role. These are - this is not an exhaustive list - the lateral prefrontal cortex, the dorsal premotor cortex, the pre-supplementary motor area, the basal ganglia and the cerebellum.
* Two main hypotheses regarding the role of preparation inhibition have been proposed, viz. inhibition for behavioural inhibition and inhibition for movement release.
* Whilst these two theories predict opposite results, there is strong evidence for both of them and they might in fact coexist.

0.4 Motor-related inhibition and cognitive control in addiction

0.4.1 Context

Humans - and mammals in general - tend to seek rewards and avoid unpleasant feelings. Natural reinforcers (e.g., food, water, sexual stimuli, etc.) have the property of eliciting approach responses. Unpleasant stimuli (e.g., electroconvulsive shocks), by contrast, evoke avoidance responses [190, 191, 192]. Through time, this innate formula has developed to optimise adaptive fitness and better the chances of survival [193]; the neural connexions have been modified as the way one faces these stimuli depends on multiple interactions that are all coordinated by the nervous system.

More than 3 millions years ago, a striking expansion in volume of the human brain began [194]. It gave rise to a general increase of intelligence. *Australopithecus* have been able to develop stone tools; *Homo erectus* to control fire. For medical purposes first, for recreational ones later, humans have mastered the art of extracting, processing and purifying reinforcing stimuli against which natural reinforcers cannot compete [195]. Examples of these include alcohol beverages and cigarettes but also synthetic opioids, cannabinoids and other mighty stimulants [193, 195]. When access to these drugs is combined with a promotive environment and personal vulnerabilities, the mixture is explosive and individuals may become *addicted*, that is, much of their time is aiming at accessing the substance of abuse despite the negative consequences that may follow. Adaptive fitness is at risk and the constant research of pleasant feelings may become hazardous.

Nowadays, the problematic of drug addiction is more relevant than ever.

In 2017, around 19.7 million people aged 12 or older in the United-States were believed to have a substance-use disorder (SUD) when regarded to their use of alcohol or illicit drugs in the past year [196]. This estimation included 14.5 million people with an alcohol use disorder (AUD) and 7.5 million people with an illicit drug use disorder. The most encountered illicit drug use disorder was for marijuana ($\sim$ 4.1 million people). It was followed by opioid use disorder ($\sim$ 2.1 million people). With regard to legal drugs (where alcohol stands), an estimated 48.7 million people aged 12 or older were current cigarette smokers. This number includes 27.8 million people who were daily cigarette smokers and 11.4 million people who smoked approximately a pack or more of cigarettes per day [196]. Globally, these numbers are appealing as they represent negative consequences on the health, economy, productivity, and social aspects of communities [197].

Interestingly, not only substances of abuse, but some behaviours also, can activate the reward systems [198]. For most individuals, these endeavours represent an enjoyable and harmless activity. Many people enjoy shopping, gaming on internet, having sexual intercourse, doing some exercise, gambling, etc. For a small minority however, similar to what happens with drugs, these activities can become addictive and severe negative consequences at personal, societal and professional levels can arise. In other words, the long for the feeling of a *high* from the behaviour becomes so powerful that *addicted* subjects continue to engage in the activity despite the negative consequences. For these people, alike for those suffering from a SUD, a discontinuation of the behaviour can lead to withdrawal[5]. Excessive behavioural patterns include *gambling addictions* (which prevalence varies between 0.1% and 6% across the

[5]The term withdrawal refers to: "a constellation of affective and physical symptoms that occur during periods of abstinence" [199]. Example of these are sleep problems, headache, anxiety, etc. [198]

world [200]) but also *sex addiction*, *gaming addiction* or *exercise addiction*, to name but a few [198].

In the next section, I present the reader with the terminology that I shall use to talk about the concept of addiction. Then, I swiftly develop the neurobiological underpinnings of drug reinforcement (section 0.4.3) and I address the relevance of studying the activity of the motor output pathway in substance-related and non-substance-related disorders[6] (sections 0.4.4).

0.4.2 Terminology for addiction

Figure 0.12: Terminology for addiction. Similar to what Humpty Dumpty said to Alice in the novel "Through the Looking-Glass, and What Alice Found There" [201], there is currently little agreement between scientists regarding the meaning of addiction. Illustration of Humpty Dumpty from Through the Looking Glass, by John Tenniel, 1871.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the guidebook used by health care professionals in most of the world to diagnose

[6]Reminder: SRDs and NSRDs, respectively.

mental disorders. It contains the nomenclature that must be used and includes descriptions, symptoms, and other criteria for recognising a disorder. In its fifth edition (i.e., DSM-V; the last one) the authors stated that: "*the categories of substance abuse and substance dependence have been eliminated and replaced with an overarching new category of substance use disorders—with the specific substance used defining the specific disorders. "Dependence" has been easily confused with the term "addiction" when, in fact, the tolerance and withdrawal that previously defined dependence are actually very normal responses to prescribed medications that affect the central nervous system and do not necessarily indicate the presence of an addiction. By revising and clarifying these criteria in DSM-5, we hope to alleviate some of the widespread misunderstanding about these issues" [198].*

Over the years, indeed, there has been little agreement between organisations according to the terminology that should be employed to define addictions [202, 203, 204]. As Wise and Koob stated in their paper: *"In truth, in our use of the word addiction, we share the sorry condition articulated by Humpty Dumpty: When I use a word it means just what I choose it to mean—neither more nor less"* [201, 205] (Figure 0.12).

In the present thesis, to dispel any doubts for the reader, the words addictions and SRDs/NRSDs will be used as synonyms whilst the word dependence will be avoided. The reader might, however, still encounter this term in a few phrases or chapters (e.g., Chapter 4). It will be the case when mentioning people suffering from an AUD. These subjects are indeed often described in the literature as alcohol-dependent individuals (ADIs) [132, 206, 207]. In other cases, however, this term will not appear.

0.4.3 The neurobiology of addiction

The neuroscience of drug reward and addiction is a complex matter that crosses different areas ranging from the molecular to the system level. It includes an immense amount of neurotransmitters, cortical and subcortical structures that are not the core of the present thesis. The reader could still, however, be interested in having a quick overview of the neurobiology of addiction. So is the goal of the current section. For thorough reviews of the principles underlying addiction, I invite the reader to refer to the outstanding work completed by Koob, Volkow et al. [193, 205, 208, 209, 210, 211, 212, 213, 214] - to name just of few of them.

Dopamine Every drug of abuse activates the reward system [215]. This is due - at least in part - to an either direct or indirect stimulation of the DA neurons which are located in the ventral tegmental area (VTA) [216]. Interestingly, the amount of DA release depends on the type of drug: ethanol and nicotine, for instance, can only induce a modest 100 % increase in extracellular levels of DA [217] whilst responses to intravenous cocaine are much higher ranging from 200 % to 800 % [218].

At rest, the tonic (1 - 8 Hz) firing of DA neurons sets the background dopaminergic tone and is sufficient to stimulate the high-affinity DA D2 receptors [219]. It cannot, however, affect the low-affinity DA D1 receptors which are necessary for the rewarding effects of drugs [208, 210]. These receptors are solely stimulated when a fast and steep increase of DA (i.e., phasic release; $<$ 500 ms; $>$ 15 Hz) occurs [219]. Interestingly, it has been shown that the boost of DA release observed during phasic firing is associated with the subjective sensation of the so called *high* [220, 221, 222, 223].

Incentive salience Initially, midbrain DA cells fire in response to a novel or unexpected reward, may it be natural or drug-related [193, 219, 224]. As a consequence, DA is phasically released in the nucleus accumbens[7] (NAc), a ventral forebrain region that has traditionally been associated with motivation and reinforcement learning [225, 226]. Because DA is released when a new or unpredictable reward occurs, it was first suggested that DA neurons encode for reward [216, 227]. Recent findings have, however, showed that DA release encodes for a reward prediction signal: DA neurons boost their firing rates if outcomes are better than expected and lessen their firing rates if outcomes are worse than assumed [210, 228, 229]. For instance, an halt in DA neuron firing is observed when an expected reward does not occur [224, 230, 231].

With repetition, DA neurons stop firing during reward delivery. Rather, they fire when they are exposed to stimuli that were predictive of the reward [208, 224]. This happens as a consequence of the stimulation of DA D1 receptors that strengthen the memory traces of reward reception and the events that immediately preceded it [219]. Hence, the release of DA does not only reflect the single reward value but also additional dimensions of the expected outcome such as places and individuals associated with the drug intake but also mental states that prevailed at the time the drug was being consumed [193, 232]. There is an association between the reinforcer and the predictive stimuli and the motivation to seek the drug is generated by the cues to which the reinforcer is associated. The release of DA that is triggered by these conditioned stimuli is often supposed to reflect the expectation of receiving the reward [228].

[7]The nucleus accumbens - also referred to as the ventral striatum - accounts for the most anterior parts of the caudate nucleus and putamen that are joined beneath the anterior limb of the internal capsule. Together, the putamen and caudate nucleus form the striatum. Of note, the striatum is different from the corpus striatum which is made of the caudate and lentiform nuclei [7].

The passage from recreational/controlled to chronic/compulsive drug consumption has been linked to a shift from the NAc to the dorsal striatum with as an effect, the emergence of habits [233]. The role of the dorsal striatum - which is stimulated by DA neurons that are located in the substantia nigra - is to translate recurrent reward signals into habitual actions that become increasingly insensitive to actual or updated goal values [234, 235, 236]. Instead, actions are selected based on prior experiences. This phenomenon allows former neutral stimuli to become provided with incentive salience[8]. With repeated exposure, it increases the learned association to the cues and results in a strong motivation to pursue a reward [211, 229].

Homeostasis or the formation of an allostatic state The chronic consumption of drug induces long-lasting neural changes in systems that are implicated in reward and stress. Accordingly, when people decide to stop or cut back on their consumption, the alterations induced trigger withdrawal symptoms that are characterised by many motivational elements such as chronic irritability, emotional pain, elevation of the reward threshold and increase stress and anxiety-like responses [208, 238, 239, 240]. These outcomes are coherent with the opponent-process theory of motivation developed by Solomon [241].

In 1974, Solomon & Corbit suggested that emotional states, once started, are automatically balanced by the CNS with processes that depress the intensity of these feelings [242]. In their paper, the authors suggested that two brain processes are at play to suppress or reduce all departures from emotional

[8]Incentive salience refers to a cognitive process that confers motivation towards a certain stimulus or reward. The incentive-sensitization theory suggests the nature of drug addiction to be due to a "wanting" process that evolves in obsessive craving as manifest behaviourally by compulsive drug seeking and drug taking. Importantly, this "wanting" process is not necessarily linked to a "liking" process. That is, subjects may well research the drug without seeking pleasure [212, 234, 237].

neutrality - may they be pleasant or aversive. They called them the a- and the b-process. The a-process is made up of either positive or negative emotional responses. It occurs briefly after the presentation of a stimulus, is linked with the stimulus intensity, quality, and duration and express tolerance. By contrast, the b-process occurs after the a-process has terminated. It is slow in onset, sluggish to build up, slow to decline, and gets bigger with multiple exposure.

In the context of SRDs, it was suggested that the first few self intakes of a drug lead to a pattern of motivational alterations alike to these of the a-process (or euphoria). Then, after the drug fades, an diametrically opposed, aversive negative emotional state arises: the b-process. Addiction was therefore conceptualized as a cycle of recurrent alteration of brain reward/antireward systems where tolerance and dependence are inseparably linked. With time, counter adaptive processes fail to return within the normal homeostatic range and form an allostatic[9] state in which within- and between-system neuroadaptations intervened.

Within-system neuroadaptations are the one in which "*the primary cellular response element to the drug ... adapt[s] to neutralize the drug's effects; persistence of the opposing effects after the drug disappears ... produce[s] the withdrawal response*" [244]. Such changes include a long-standing decrease in dopaminergic, serotonergic and GABAergic transmission but also an increased in N-methyl-D-aspartate (NMDA) glutamatergic release in the NAc [245]. These decreases in reward system function are thought to contribute to the condition of acute withdrawal and protracted abstinence and could explain the loss of interest in normal, non drug-related rewards.

[9] Allostasis is the fact of achieving stability through change. More specifically, it reflects the fact that organisms must be able to change the levels of one or more parameters to adjust to changing environments [243].

Importantly, not only within-system neuroadaptations, but also between-system ones are at play. These modulations occur outside the systems involved in the positive hedonic effects of substances of abuse. For instance, chronic drug exposure has been shown to recruit and/or alter both the hypothalamic-pituitary-adrenal axis and the brain stress system. As a result, there is an increase of norepinephrine, dynorphin, corticosterone, adrenocorticotropic hormone and amygdala CRF that induces a negative emotional states in addicted subjects. The consequence of this boost of stress like responses coupled with a decrease of reward sensitivity and an increase of the incentive salience of drug related cues often result into falling back into bad habits and to experience relapse.

Relapse The moment at which an individual restarts his/her drug-seeking behaviour after a period of abstinence is a critical stage. Indeed, this *step-back period* characterises addiction as a chronic relapsing disorder [208, 213]. A precise understanding of its neurobiological correlates helps the establishment of preventing policies and the development of medication for treatment.

The low levels of striatal D2 receptors observed in individual with addiction seems to be of particular importance as it has been associated with decreases in baseline glucose metabolism in the prefrontal cortex. Of note, prefrontal regions are known to play a key role in inhibitory control, conflict resolution and salience attribution [123]. A decrease of their activity is often behaviourally linked to impairments in the maintenance of spatial information, disruption of decision making, and impairments in behavioural inhibition [246, 247]. As a result, addicted individuals exhibit a loss of interest in normal, non-drug rewards and their behavioural repertoire is narrowed toward drugs and drug-related stimuli parallel with an inability to suppress

their maladaptive behaviour [221, 248]. Recently, the critical role of DA D2 receptor was highlighted in a study where methamphetamine addicted individuals with striatal D2 receptor availability within the normal range had better treatment outcomes, potentially reflecting a greater ability to acquire new reward-related behaviours and to pursuit healthy goals [249].

Of note, not only DA receptors are meaningful. Cravings for food, cocaine, and nicotine have also been linked to middle insular function for instance. Tobacco smokers with damage to the insula (but not control smokers with extra non-insular lesions) were indeed able to stop smoking easily and without experiencing cravings or relapse [250].

BOX 4: Using TMS and transcranial direct electrical stimulation (tDCS) for the treatment of addictions.

Although it is still too early to have a definite opinion about the effectiveness of TMS in the treatment of addictions, first results are promising [251]. With respect to cocaine for instance, studies that used repetitive TMS on the dorsolateral prefrontal cortex or continuous theta-burst TMS stimulations over the medial prefrontal cortex have showed a significant drop of cocaine intake and craving after TMS treatment [252, 253, 254, 255] (reviewed in [256]). The use of TMS for the treatment of methamphetamine addiction has given equivalent results even though less dependable [257, 258, 259]. With regard to cigarette smoking, using deep rTMS over the dorsolateral prefrontal cortex and insula [260] has been shown to significantly reduce cigarette consumption and nicotine dependence scores whilst rTMS over the superior medial frontal cortex yields to a significant decrease of smoking craving [261]. Parallel to TMS, tDCS seems to be an alternative non invasive brain modulation technique with therapeutic potential. For instance, tDCS studies found significant reductions in alcohol-related, nicotine, heroin and cocaine craving or consumption after tDCs treatments [262, 263, 264, 265, 266]. Of note, the effects induced by TMS and tDCS are thought to result from the modulation of DA in brain areas where DA disruption has led to altered executive function and reward processes [267, 268]. More research is still needed to assess the optimal sites and parameters of stimulation and disentangle the sometimes conflicting results [269]. TMS and tDCS remain, however, promising tools for the treatment of substance-related disorders. It is worth mentioning that, in the present thesis, TMS was not used as a therapeutic tool, but rather, as a technique allowing us to study the excitability of the CS tract.

Genetic In 1972, it was reported that persons of Asian descent were more sensitive to alcohol consumption and intoxication than Caucasians [270]. This heterogeneity of responses was caused by genetic differences in metabolizing enzymes between races. Since then, many studies have followed and investigated the role genetic factors can play in the process of addiction. These experiments - encompassing family, twin, and adoption studies - have demonstrated that both specific and generic genetic factors substantially contribute to the development of an addiction [271, 272]. For instance, the alteration of nicotine metabolizing genes influences one's smoking behaviour but has no effect on alcoholism or other SUDs. Besides, it has been shown that some generic genetic factors influence the co-existence of different SUDs [273, 274]. The role of genetic in the process from recreational use to addiction is not measly [275]. With regard to alcohol, nicotine and SUDs, the heritability of addiction ranges between 50 % to 60 % [273, 276, 277, 278]. Of note, it seems that genetic factors play their most important role in the transition from a recreational usage to a compulsive one whilst environmental factors have more influence on drug initiation [279].

KEY POINTS

* Addiction is described as a relapsing disorder that leads individuals to seek a drug of abuse or repeat a deleterious endeavour without regard to the negative consequences that might follow.
* Addiction arises from biological, environmental and personal factors.
* Whilst some vulnerability factors are specific to some disorders, generic factors have also been shown to account for the development of addictions in general.
* The chronic intake of a drug results in an alteration of the reward (hedonic aspect of addiction) and stress (*dark-side* of addiction) systems.
* The allostatic state that follow leads individuals to exhibit a loss of interest in normal, non-drug rewards coupled with an inability to suppress their maladaptive behaviour.

0.4.4 The role of cognitive control and preparatory inhibition in addiction

> "I'd go to a party and promise Michael I wouldn't drink too much. He'd plead: "Just take it easy, okay? Watch yourself," and I'd swear: "I won't. I don't want to get too drunk." I'd mean that, of course, and I'd start out by measuring myself: one glass of wine the first half hour, one glass the second, and so on. But then something would snap, some uncontrollable process would kick in, and all of a sudden it would be two or three hours later and I'd be on my sixth or tenth or God knows what glass of wine, and I'd be plastered. I couldn't account for it, couldn't explain it, couldn't even rationalize it, although I struggled mightily to. I seemed to get drunk, blind drunk, against my will."
>
> Caroline Knapp,
> Drinking: A Love Story [280].

As can seem obvious when looking at the paragraph above, what applies to AUD is similar to what applies to many addictions: *addicted* people can be aware of the deleterious effects and stigma of their excessive demeanour without being able to stop it. There is a real lack of control over their behaviour that may result from some of the within- and between- system neuroadaptations described above (i.e., section 0.4.3). As a consequence, the loss of

willpower observed in addictions is not merely the result of an individual moral failing but rather the outcome of the brain adaptations that are triggered by the chronic intake of a drug (i.e., for SRDs) or by the repetition of a behaviour (i.e., for NSRDs/behavioural addictions). It must be noted however, that to date, it is still difficult to know whether these neural shifts in norm only account for the consequence of the excessive intake of the substance of abuse (or of the repetition of the problematic endeavour in the case of NSRDs) or whether they represent – at least in part - a factor of vulnerability. As such, brain alterations could be present beforehand and rather promote, with the help of environmental and personal variables [198], the generation of an addiction. Coherent with this idea is the fact that adolescents with family history of AUD show frontal and parietal structural alterations that may underlie cognitive and behavioural features associated with the risks of developing an AUD [281, 282]. In addition, whilst the prevalence of AUD is increased in cultures that encourage adults to drink to intoxication [283, 284, 285], high levels of impulsivity are associated with an earlier onset and more severe AUD [198]. The same observations apply for many other substance-related and non-substance-related disorders such as cannabis use disorder, opiate use disorder or gambling disorder (GD) [198].

Amongst the various facets that characterise individuals suffering from a substance-related or a non-substance-related disorder, one has to do with cognitive control which is often reported as being impaired in the addicted population. Cognitive control (sometimes also referred to as *executive functions*) is defined as "*the active maintenance of patterns of activity in PFC that represents goals and the means the achieve them*" [143]. It sustains adaptable responses and complex goal-directed thoughts. Cognitive control is an umbrella term used to describe a repertoire of mental skills that include, working

memory, cognitive flexibility and inhibitory control [286], to name but a few. In the topic of addiction, one of these skills is supposed to be essential to support goal-directed behaviours, namely, inhibitory control.

Inhibitory control (also referred to as *inhibition*[10]) is a term that describes the voluntary control, or inhibition, of one's attention, endeavours, thoughts and emotions in order to disregard strong internal or external temptations [286, 287, 288, 289]. It is usually regarded as regulating visual, sensory, and auditory perturbators as well as unwanted memories, painful emotions and incompatible manual, vocal, and ocular responses [137, 286, 287, 288]. Inhibitory control makes it feasible for us to adapt, change and choose how we respond and how we behave rather than being unthinking creatures of habit [286]. Although its effects are difficult to notice in daily life for healthy individuals - as the suppressed endeavour never happens -, its valuable aspect becomes evident in the field of movement (e.g. Parkinson's disease) and psychiatric disorders (e.g. AUD, Tourette syndrome, hyperactivity disorder, etc.; BOX 3) [198, 290, 291, 292].

Experimentally, the psychological processes and neural mechanisms underlying inhibitory control have been substantially studied with versions of the stop-signal task [124, 125, 162, 293]. Employing functional/diffusion magnetic resonance imaging techniques, the neural substrates underlying inhibitory control in the context of action stopping have begun to be established. Studies have revealed a fronto-basal ganglia network for stopping in which the PFC-generated process seems to play a major role that is manifest at the level of the motor output pathway (i.e., global suppression of CSE) [115, 137, 162,

[10]Inhibitory control (or inhibition in general) encompasses two different types of control, namely, self-control (also called behavioural inhibition) and interference control. Whilst the former one expresses the ability to resist temptations and the tendency to act impulsively, the latter one stands for the capability to focus on a particular subject (i.e., selective attention) and to suppress powerful mental representations (i.e., cognitive inhibition) [286, 287].

294, 295, 296]. More specifically, two PFC areas have been suggested to be critical for inhibitory control in action stopping, viz., the right inferior frontal cortex (IFC) and the pre-SMA. While their specific contribution is still uncertain, it is supposed that when one of them - or both - is recruited during the stopping process, it triggers the STN via a hyperdirect pathway. As a consequence, the STN sends excitatory signals to the internal globus pallidus that result in an inhibition of the thalamus and subsequently in a decrease of the activity of excitatory thalamocortical neurons that target the cerebral cortex which, ultimately, results in a global decrease of the excitability of the CS tract [22, 115, 297]. This effect is noticeable when TMS is applied after the stop-signal with MEPs being suppressed in selected, not-selected and irrelevant muscles, reflecting widespread motor inhibition [155, 298]. The role of the PFC and the pre-SMA for inhibitory control is further borne out by neuropsychological experiments that have reported impairments of inhibitory control abilities in subjects with IFC damage [299, 300]. In addition, patients suffering from SUDs display abnormal IFC functioning associated with deficits in inhibitory control [221, 289, 301, 302, 303].

At this stage, it is worth to mention that action stopping stands for only one situation requiring inhibitory control. In many other circumstances, such as action selection, preparation and initiation, proper inhibitory control aptitudes are also necessary for the generation of appropriate behaviours [22]. A lack of inhibitory control in these contexts is often associated with inappropriate endeavours (e.g., talking aggressively or driving under the influence of alcohol) [286].

For the reasons mentioned above, and because proper inhibitory abilities are critical for the generation of goal-oriented behaviours, Goldstein and Volkow (2002) have suggested that addictions represent a *"syndrome of im-*

paired response inhibition and salience attribution" in which abnormal PFC functioning results in a lack of inhibitory control that coupled with an increased salience for addiction-related cues contribute to the inability to inhibit inappropriate behaviours and/or to control the consumption of the substance of abuse [304]. Critically, besides focusing on the role of the PFC when studying addictions, previous work implies that it is also crucial to focus on the integrity of the motor system as the PFC-generated inhibitory control process is implemented through a global suppression of motor activity [22, 115, 155, 298]. As a consequence, not only the PFC, but the motor system as well - which is interconnected to many prefrontal areas - must be considered for proper inhibitory control abilities. This is coherent with the role of the motor cortex for the production of adequate behaviours [22, 132, 305].

Several studies provide evidence for this idea (please refer to section 0.3.3.1 of this thesis for more details). First, it has been shown that CSE reflects the impact of various parameters that guide motor decisions [306, 307, 308, 309]. Second, the successful inhibition of actions following stop signals relies on a decrease in the excitability of the CS tract [22, 115]. Third, the mere preparation of motor acts is also associated with a strong CS suppression and this effect is commonly regarded as supporting behavioural inhibition [114, 153]. Last, neural motor inhibition is lacking in patients suffering from AUD, a population that typically displays a deficit of inhibitory control abilities which is linked to the risk of relapse [132] (Figure 0.13).

Even if the stop-signal paradigm is the neuropsychological task that is most frequently used to assess inhibitory control, interesting measures of motor inhibition can also be obtained with TMS when the pulse is applied during the delay period in instructed-delay choice RT tasks (Section 0.3.2). Studying preparatory inhibition for inhibitory control with instructed-delay choice

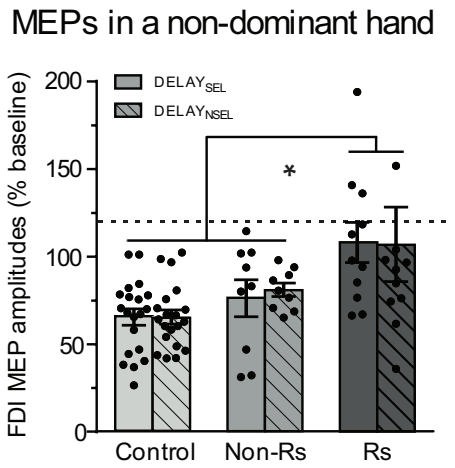


Figure 0.13: Preparatory inhibition is control subjects and patients suffering from alcohol use disorder (AUD) that did or did not relapse during the year following the experiment. Motor-evoked potentials (MEPs; expressed in percentage of baseline) elicited in a non-dominant hand that was selected (DELAY$_{SEL}$; open bars) or non-selected (DELAY$_{NSEL}$; dashed bars) for the forthcoming response in control subjects and in patients suffering from AUD who did not or did relapse (Non-Rs and Rs, respectively) during the year following the experiment. Modified with permission from Quoilin et al. (2018) [132].

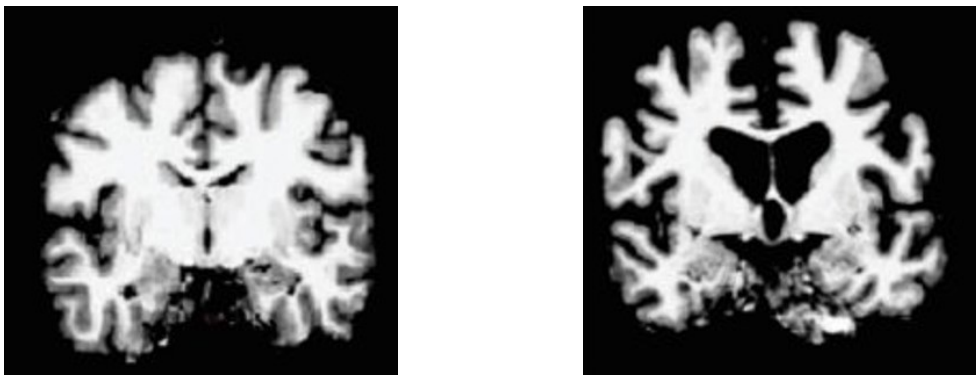
RT tasks is really appealing as it provides researchers with the advantage of obtaining a measure in a context that is quite representative of everyday life. Throughout the day indeed, we continuously need to prepare suitable actions and avoid to select inappropriate ones. This profit is almost non-existent with action stopping tasks that are more *artificial*. In most situations indeed, inhibitory control must be generated internally, in the absence of explicit signals: you usually decide to wake up early to have a productive day at work without the need for your boss to come to your house and knock at your door.

Despite the ecological validity[11] and consequently advantage of assessing preparatory inhibition for inhibitory control, to the author's knowledge, to date, only one study [132] has investigated the role the motor cortex plays in

[11]The ecological validity is a concept that refers to the fact that one can generalize an *"observed behaviour in the laboratory to a natural behaviour in the world"* [310].

subjects suffering from an addiction. In this particular experiment that targetted patients suffering from an AUD, the authors found an abnormally weak preparatory activity in ADIs that was related to the risk of relapse: the weaker the amount of preparatory inhibition, the more subjects were likely to backslide the year following the experiment (Figure 0.13). Obviously, chronic alcohol consumption has considerable neurotoxic effects on the human brain, and the most pronounced damage are often reported in regions underpinning inhibitory control, such as the frontal lobes and the basal ganglia [311, 312, 313] with the underlined cognitive functions (e.g., attention, memory, problem solving, decision making, response inhibition, etc) impaired [302, 314, 315, 316]. In addition, the degree of brain atrophy is related to the amount of alcohol previously consumed [317]. Hence, the deficit in preparatory inhibition could represent a consequence of the brain damage induced by chronic alcohol exposure (Figure 0.14). Alternatively, a lack of inhibitory control might have been present before the pathology, predisposing individuals to early recreational experiences with alcohol, ultimately facilitating their transition towards AUD. This assumption is coherent with the fact that some of the structural and cognitive alterations reported above in ADIs are sometimes observed even before the start of excessive alcohol consumption. For instance, functional magnetic resonance imaging studies have shown reduced fronto-parietal activations in young adolescents prior to any alcohol consumption that may represent predictors of subsequent excessive drinking [318, 319]. Similarly, offspring of ADIs with limited or no past alcohol use display frontal and parietal structural alterations that might underlie cognitive and behavioural traits associated with a risk of AUD [281].

Unhealthy drinking habits are common characteristics not only of ADIs but of binge drinkers (BDs) as well. BDs are people that display a pattern of



(i) Healthy subject (ii) Alcohol-dependent individual

Figure 0.14: Brain damage associated with excessive alcohol consumption (i) Magnetic resonance imaging (MRI) scanner picture of the human brain of a healthy individual. (ii) MRI scanner picture of the human brain of an individual suffering from an alcohol use disorder. Please note the dramatic decrease of cortical matter for the picture at the right.

consumption characterised by the repeated alternation between massive alcohol intakes and abstinence periods (i.e., binge drinking pattern [320, 321, 322, 323]). In young adults, a population in which binge drinking has become increasingly prominent [324, 325], regular heavy alcohol consumption is linked to poorer academic results, less adequate social integration, car accidents, sexual assaults, violence, health issues, etc. [322, 326]. At the neural level, similar to ADIs, BDs display a thinner cortex in prefrontal and cerebellar regions [327, 328, 329, 330] and an overall decrease in white matter integrity [327, 331]. Behaviourally speaking, BDs show impairments in sustained attention, a lack of inhibitory control and an abnormally short post-error slowing indicating attenuated response monitoring [327, 332, 333].

The similarities between the structural and functional alterations observed in ADIs and BDs [314, 316, 334] have led researchers to suggest that binge drinking and AUD represent two different stages of the same phe-

nomenon rather than independent conditions [332, 335, 336, 337]. Based on this idea, called the *continuum hypothesis*, binge drinking would represent a first step towards AUD and excessive drinking could lead individuals down the slippery slope of compulsive intake. The continuum hypothesis is further borne out by studies showing that binge drinking patterns started during late adolescence frequently remain into early adulthood [324] and that initiating heavy drinking at an early age significantly enhances the risk for subsequent AUD [338].

What could be do next for a better understanding and to better reach the problematic of addiction? In my opinion, future research should aim at finding biological markers to detect subjects that are likely to suffer from an addiction. Particular emphasis should be made on inhibitory control capabilities and particularly on the role the state of the motor cortex plays for inhibition and consequently, for the generation of goal-directed and appropriate behaviours. In the field of AUD, one option is to test preparatory inhibition in a population of BDs to assess whether the deficit of motor inhibitory capabilities observed in ADIs is already present *upstream*. If it is the case, measures of preparatory inhibition could permit to detect subjects that are likely to develop an AUD but which, however have not yet passed the necessary and sufficient conditions for the state of addiction. Importantly however, early brain alterations might be precocious in the transition from recreational to problematic alcohol consumption and therefore, through testing BDs only, we could miss a part of the story and only partially answer the question as to whether damaged preparatory inhibitory mechanisms represents a vulnerability marker for AUD - and potentially for addictions in general. Hence, to shed further light on the problematic of addiction - and of the role of preparatory inhibition in addiction -, studies should also test individuals that suffer from

an addiction in the absence of any substance-induced brain damage (e.g., subjects suffering from GD[12], shopping addiction or internet gaming disorder, to name but a few). Doing so could cast light on whether a preparatory inhibition deficit also concerns behavioural, substance-free, addictions, and thus whether it might represent a vulnerability factor common to both substance and behavioural addictive disorders.

KEY POINTS

* People suffering from an addiction usually display impaired inhibitory control capabilities that seems to arise from many biological, environmental and personal factors.
* The prefrontal cortex plays a major role for cognitive control in the generation of goal-oriented behaviours.
* Proper cognitive control abilities seem also to rely on the motor cortex.
* Using transcranial magnetic stimulation over the primary motor cortex, preparatory inhibition was reported altered in alcohol-dependent individuals and linked to the risk of relapse.
* It remains unclear whether altered preparatory inhibition represents a biomarker for future AUD - and/or for addictions in general - or rather arises from the neurotic effects of alcohol.

[12]Reminder: GD accounts for Gambling Disorder.

In the current work

Binge drinking consists in a pattern of consumption characterised by the repeated alternation between massive alcohol intakes and abstinence periods. It is a widespread phenomenon as over 40 % of adolescents and young adults in Western countries report at least one binge drinking episode per month. Interestingly, a continuum hypothesis suggests that binge drinking represents an early stage of alcohol-dependence rather than a separate phenomenon. In Chapter 4, based on the continuum hypothesis, we investigated whether the deficit of preparatory inhibition observed in alcohol-dependent individuals (ADIs) is already present *upstream*, among a population of binge drinkers (BDs). To do so, we asked 20 BDs and 20 healthy control subjects to perform the instructed-delay choice reaction task used in Quoilin et al. (2018) [132]. Transcranial magnetic stimulation (TMS) pulses were applied bilaterally on the primary motor cortex using the double-coil$_{1ms}$ TMS method developed in Chapters 1 and 2. Our data suggest abnormal preparatory activity in BDs, similar to ADIs, though some of the current results also raise new questions regarding the significance of these observations.

> "I wanted to gamble all the time [...] I loved it - I loved that high I felt."
>
> Shirley, former pathological gambler.

Gambling is the act of betting money in the hope of obtaining something of greater value [198]. It is widespread in our society with 50 to 80 % of the general population buying a lottery ticket more that once a year [339]. For many individuals, gambling is a recreational activity like running, *chilling* with friends or having a drink. For a few tough, it becomes problematic.

GD is a psychiatric condition that involves periodic, dysfunctional gambling behaviours that lead to considerable troubles or distress [198, 340]. In 2013, the DSM-V included GD in the *Substance-Related and Addictive Disorders* chapter under the *non-substance-related disorders* section [198, 341]. In the former edition, it was classified as an impulse control disorder under the section *Impulse Control Disorders Not Elsewhere Classified* along with Trichotillomania, Intermittent Explosive Disorder, Kleptomania and Pyromania [291].

The switch from one category to another is not bland. It reflects evidence that gambling behaviours activate reward systems similar to those activated by drugs of abuse and produce some behavioural symptoms in much the same way as those produced by SRDs [342, 343]. For instance, gamblers can crave gambling the way someone craves alcohol whilst compulsive gambling can lead to problems with finances, relationships, work, etc. The diagnostic criteria are also very alike for some point as illustrated in Table 0.1.

In this context, extensive work is being dedicated to a better understanding of the similarities between SRDs (e.g., AUD) and NSRDs (e.g., GD). Identifying physiological and vulnerability markers that might be common to all addictive disorders is of first importance with one particularly promising candidate being a lack of inhibitory control. The possibility to study individuals that suffer from GD presents therefore researchers with a great opportunity

as it makes it possible to investigate inhibitory control and more specifically preparatory inhibition in a group of subjects presenting a behavioural, but substance-free addiction. Doing so could unveil the mask as to whether the deficient preparatory inhibitory mechanisms reported in ADIs are mainly the results of the neurotoxic effects of alcohol or whether they more likely represent a common characteristic of both substance and substance-free (i.e., behavioural) addictions.

In the current work

In Chapter 5, we assessed whether a lack of preparatory inhibition is observed in a population suffering from gambling disorder (GD). The goal of the present study was to determine whether subjects who suffer from an addictive disorder, namely GD, but are preserved from the neurotoxic influence of drugs of abuse, display a lack of preparatory inhibition in the motor system, similar to the findings made in alcohol-dependent individuals. To test this idea, 20 pathological gamblers and 20 control subjects were asked to perform the choice instructed delay reaction time task used by Quoilin et al. (2018) [132] and transcranial magnetic stimulation (TMS) pulses were applied bilaterally on the primary motor cortex using the double-coil$_{1ms}$ TMS method developed in Chapters 1 and 2. Based on the hypothesis that a lack of preparatory inhibition may represent a common feature to both substance-use and non-substance-use disorders, we expected preparatory inhibition to be less pronounced in subject suffering from GD than in healthy control subjects. Together our results suggest that pathological gamblers display significantly higher choice impulsivity than control subjects, but there was no difference at the level of the motor system where preparatory inhibition was found similar between groups.

DSM-V Diagnostic Criteria	
Alcohol Use Disorder (AUD)	**Gambling Disorder (GD)**
Alcohol is often taken in larger amounts or over a longer period than was intended.	Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.	Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.	Is restless or irritable when attempting to cut down or stop gambling.
Craving, or a strong desire or urge to use alcohol.	Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
Recurrent alcohol use in situations in which it is physically hazardous.	Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.	After losing money gambling, often returns another day to get even ("chasing" one's losses).
Important social, occupational, or recreational activities are given up or reduced because of alcohol use.	Lies to conceal the extent of involvement with gambling.
Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.	Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.	Relies on others to provide money to relieve desperate financial situations caused by gambling.
Tolerance.	–
Withdrawal.	–

Table 0.1: Diagnostic criteria for alcohol use disorder (AUD; left column) and gambling disorder (GD; right column). As evident in the table, AUD and GD share similar symptoms such as: a lack of control over the problematic behaviour, craving, compulsivity, etc. Note: for AUD, at least two of the following criteria must have occurred within a 12-month period. Concerning GD, the individual must have exhibited four (or more) of the following criteria in a 12-months period. Adapted from [198]

0.5 Aims and hypotheses of the thesis

> "Mange bække små gør en stor å"
>
> Danish proverb.

This thesis is divided in three main parts regrouping five different chapters.

The first part is made of Chapters 1 & 2 and results from the thought that much could be done if it were possible to record MEPs in both hands simultaneously. To do so, it requires the use of a double-coil TMS approach where the two M1 are stimulated concurrently whilst (1) avoiding electromagnetic interference between the two stimulating coils and (2) making sure that the two descending volleys do not influence each other. In the first part of this thesis, we hypothesised that a double-coil TMS method with an interlude of 1 ms between the two TMS pulses would represent the best of two worlds to overcome the requirements raised above. Chapter 1 assessed the reliability of such a double-coil TMS method a rest and Chapter 2 during the preparation of an action.

The second part encompasses Chapter 3 in which we used the double-coil TMS method we developed in Chapters 1 & 2 to test the hypothesis that preparatory inhibition contributes to inhibitory control and more specifically to behavioural inhibition. To do so, we made the use of SAS (i.e., a SAS is a loud and narrow sound that can trigger the release of prepared responses in RT tasks) to vary the difficulty of the task and the risk of premature action release. Based on the impulse control hypothesis, we predicted that, in order to avoid responding prematurely, subjects would recruit more preparatory

inhibition in conditions in which they expected SAS to occur compared to when SAS were less likely.

The goal of Chapters 4 & 5 was to test preparatory inhibition in BDs (Chapter 4) and pathological gamblers (Chapter 5), respectively. In Chapter 4, we based our research on the continuum hypothesis that suggests that binge drinking and AUD represent two stages of the same phenomenon rather than independent conditions. Our assumption was that if there is a concrete continuum between BDs and ADIs, BDs should already display some alterations in neurophysiological correlates of action preparation (alike ADIs), potentially representing biomarkers of the risk of later AUD. In Chapter 5, we aimed at something different. In that chapter indeed, we made the assumption that if the deficit of preparatory inhibition observed in Quoilin et al. (2018) [132] represents a common feature to both substance-related and non-substance-related disorders, it should also appear in subjects suffering from GD *only* as this population shares strong similarities with ADIs but are preserved from the neurotoxic influence of drugs of abuse. If by contrast it represents the consequence of compulsive drinking, a shortage of inhibition should be absent in this population.

In summary, our desire was to implement a novel TMS method (Chapter 1 & 2) that could help the investigation of the CS tract more efficiently and to use this method for assessing the role of preparatory inhibition for behavioural inhibition (Chapter 3), and its potential alteration in addictions (Chapters 4 & 5). More generally, I aimed to contribute - even just a little - to the field of neuroscience.

0.6 Thread of the manuscript

(A) Developing an innovative double-coil TMS method

- In Chapter 1, we investigated the reliability of a ppTMS method where the two M1 are stimulated with a 1 ms inter-pulse interval (double-coil$_{1ms}$). To do so, we examined MEPs obtained at rest using double-coil$_{1ms}$ and MEPs acquired using single-coil TMS. MEPs were compared between conditions at five different intensities of stimulation: 100, 115, 130, 145 or 160% of the rMT.

- In Chapter 2, we investigated if double-coil$_{1ms}$ is reliable when MEPs are elicited not only at rest but also in another functional state demanding motor preparation. To do so, we asked participants to perform an instructed-delay choice RT task. Then we compared the amplitude as well as the coefficient of variation of MEPs produced through using double-coil$_{1ms}$ or single-coil TMS.

(B) Preparatory inhibition for behavioural inhibition

- In Chapter 3, we tested the hypothesis that preparatory inhibition contributes to impulse control abilities. To do so, we asked subjects to perform two experiments. The first one was a behavioural one while the second one consisted in a TMS study. In both experiments, we used an instructed-delay choice RT task that required participants to choose a response based on a preparatory cue but to only release it after the appearance of the go-signal. SAS and double-coil$_{1ms}$ TMS pulses (for the TMS experiment only) were elicited at the end of the delay period and subjects were asked to do their best to only release their response after the go-signal, even in the presence of SAS. Differences of behaviour

and motor suppression were analysed between the blocks in which the SAS were either rare or frequent.

(C) Preparatory inhibition in addictions

- In Chapter 4, we investigated whether BDs already present a lack of preparatory inhibition, alike ADIs. To do so, BDs (n=20) were matched with healthy control subjects (n=20) and the amount of preparatory inhibition between both groups was compared in a choice instructed-delay RT task during which double-coil$_{1ms}$ TMS was applied.

- In Chapter 5, pathological gamblers were tested to investigate if a lack of preparatory inhibition is present in a population suffering from a NSRD. Pathological gamblers (n=20) as well as matched healthy control subjects (n=20) performed the same experiment as the one in Quoilin et al. (2018) [132] where a shortage of preparatory inhibition in ADIs was disclosed. Double-coil$_{1ms}$ TMS was applied and the amount of preparatory inhibition between groups was compared.

Chapter 1 Towards assessing corticospinal excitability bilaterally: validation of a double-coil TMS method

"The creative adult is the child who survived."

Ursula Leguin

Towards assessing corticospinal excitability bilaterally: validation of a double-coil TMS method

Chapter 1: reminder of the aim and hypotheses

TMS applied over M1 elicits MEPs which provide a temporally precise and muscle-specific readout of state-changes in the motor output system. Many studies have used TMS over M1 to investigate corticospinal excitability changes occurring when choosing which hand to use for an action. So far, these studies have used single-pulse TMS eliciting MEPs in one hand when this hand is either selected or non-selected for the forthcoming action. However, an important limitation of this "single-coil" method is that MEPs are measured in selected and non-selected conditions during separate trials and even more importantly, they are computed in relation to the movement of different hands. The purpose of the present study was to evaluate a "double-coil" TMS method by which MEPs are elicited in both hands at once. That is, we assessed whether double-coil TMS applied at rest (at 100, 115, 130, 145 or 160 % of the resting motor threshold, rMT) yields comparable MEPs as single-coil TMS.

Towards assessing corticospinal excitability bilaterally: validation of a double-coil TMS method

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Keywords

Transcranial magnetic stimulation; motor-evoked potentials; paired-pulse; primary motor cortex; bimanual; transcallosal interactions; electromyography.

1.1 Abstract

Background: For several decades, Transcranial magnetic stimulation (TMS) has been used to monitor corticospinal excitability (CSE) changes in various contexts. Habitually, single-coil TMS is applied over one primary motor cortex (M1), eliciting motor-evoked potentials (MEPs) in a contralateral limb muscle, usually a hand effector. However, in many situations, it would be useful to obtain MEPs in both hands simultaneously, to track CSE bilaterally. Such an approach requires stimulating both M1 concurrently while avoiding interference between the two descending stimuli.

Towards assessing corticospinal excitability bilaterally: validation of a double-coil TMS method

New method: We examined MEPs obtained at rest using a double-coil TMS approach where the two M1 are stimulated with a 1 ms inter-pulse interval (double-coil$_{1ms}$). MEPs were acquired using double-coil$_{1ms}$ (MEP$_{double}$) or single-coil (MEP$_{single}$) TMS, at five different intensities of stimulation (100, 115, 130, 145 or 160% of the resting motor threshold, rMT). Given the 1 ms inter-pulse interval in double-coil$_{1ms}$ trials, MEP$_{double}$ were either evoked by a 1^{st} (MEP$_{double-1}$) or a 2^{nd} (MEP$_{double-2}$) TMS pulse.

Results: All MEP$_{TYPE}$ (MEP$_{TYPE}$ = MEP$_{single}$, MEP$_{double-1}$ and MEP $_{double-2}$) were equivalent, regardless of the hand within which they were elicited, the intensity of stimulation or the pulse order.

Comparison with existing method: This method allows one to observe state-related CSE changes for the two hands simultaneously on a trial-by-trial basis.

Conclusion: These results infer the absence of any neural interactions between the two corticospinal volleys with double-coil$_{1ms}$ TMS. Hence, this technique can be reliably used to assess CSE bilaterally, opening new research perspectives for scientists interested in physiological markers of activity in the motor output system.

1.2 Introduction

During the two last decades, many studies have applied single-coil Transcranial Magnetic Stimulation (TMS) over one primary motor cortex (M1), eliciting motor-evoked potentials (MEPs) in a contralateral hand or limb muscle to track corticospinal excitability (CSE) changes in various contexts, including action preparation, action observation, motor imagery, inhibitory control, decision making, reward processing, reasoning, speech, sustained attention, or

motor recovery after stroke [83, 84, 344, 345, 346, 347]. MEPs represent a valuable indicator of the CSE at the time of stimulation [48] and their amplitude can be compared at different moments within a given condition and between different states [51]. For example, in studies of action preparation, MEPs have been elicited at different times during the reaction time period preceding left and right hand responses in varying tasks [154, 306]. This work has led to considerable advances in the understanding of neural processes underlying action preparation, including the identification of various excitatory and inhibitory influences modulating CSE distinctively depending on the role of the probed muscle in the forthcoming response [348] and on the task-setting (reviewed in Bestmann and Duque (2016) [48] and in Duque et al. (2017) [22]).

However, a substantial caveat in the previously mentioned literature (including our own work) is that MEPs are usually only recorded from muscles of a single hand following the application of TMS over one M1 only. This occurs because applying TMS over both M1 in separate blocks doubles the duration of the experiment, making it impossible to fit all the conditions in a single session. Hence, in most experiments, the MEP data have only provided researchers with half of the story, increasing the risk of shortcuts in data interpretations. For example, in action preparation studies, it has been typically assumed that differences in MEP amplitudes between conditions in which a muscle (e.g. right index agonist) is either selected (e.g. right index response) or non-selected (e.g. left index response) for the forthcoming movement are due to the distinct function of the probed muscle in these two situations [148, 153, 156]. Yet, there is a substantial confound here because besides the function (selected vs. non-selected), conditions also differ in regard to the hand being cued for the response (right or left). Hence, MEP differences may be due to the use of the dominant vs non-dominant hand, a

possibility that has rarely been considered in the past [349]. For the reasons outlined above, it would be useful to obtain MEPs in both hands at once, to track CSE bilaterally. For instance, in the hand choice example above, this would allow researchers to obtain markers of CSE changes associated with selected and non-selected hands within each trial, whether the dominant or non-dominant hand is chosen for the response.

Obtaining MEPs in both hands requires using a double-coil TMS approach where the two M1 are stimulated concurrently. In this context, a critical issue is to avoid electromagnetic interference between the two stimulating coils. That is, if triggered exactly at the same time, the two magnetic fields (duration $\sim$200 μs) interact, exerting a force on the TMS coils; the resulting MEPs are smaller compared to when a single-coil TMS method is used (unpublished observations). Fortunately, this problem can be overcome by adding a short interval between the two M1 pulses. Another critical point is to make sure that the two descending volleys do not influence each other. Notably, cortical interactions through the corpus callosum can occur with intervals as short as 4 ms [102, 103]; reviewed in Reis et al. (2008) [63]). Hence, the inter-pulse interval should be kept shorter than that to avoid transcallosal interactions; yet, neural connections may still occur subcortically.

Here, we tested a double-coil TMS method where the two M1 are stimulated with a 1ms inter-pulse interval (double-coil$_{1ms}$). MEPs elicited using this new approach (MEP$_{double}$) were compared to those elicited using a standard single-coil TMS method (MEP$_{single}$). These MEPs were recorded for five different intensities of stimulation while participants were completely relaxed, at rest (n=32). The goal of the present study was to assess whether double-coil$_{1ms}$ TMS yields comparable MEPs as single-coil TMS.

1.3 Materials and methods

1.3.1 Participants

A total of 32 subjects were tested (16 women; 23.3 ± 1.9 years old). All were right-handed according to the Edinburgh Questionnaire [350]. Participants were naïve to the purpose of the study and financially compensated. None of them suffered from any neurological disorder or had a history of psychiatric illness, alcohol or drug abuse; they were not undergoing any drug treatment that could influence their performance or their neural activity. The protocol was approved by the institutional review board of the Université catholique de Louvain (Belgium) and required written informed consent.

1.3.2 Transcranial magnetic stimulation

TMS was delivered through one (single-coil TMS) or two (double-coil TMS) small figure-of-eight coils (wing internal diameter, 35 mm). Small coils were used because, in most subjects, it is not possible to place two large coils over the two M1s at the same time. The coil stimulating right M1 was connected to a Magstim 200^2 magnetic stimulator (Magstim, Whitland, Dyffed, UK) while the one stimulating left M1 was plugged into a Magstim Bistim^2 magnetic stimulator. Both stimulators delivered monophasic pulses. The coils were placed tangentially on the scalp with the handle oriented toward the back of the head and laterally at a 45° angle away from the midline. For each M1, the optimal scalp position (called hotspot) for eliciting a contralateral MEP in the first dorsal interosseous (FDI) muscle was identified and marked on a cap placed on the subjects' head to provide a reference mark throughout the experiment. It was important to check that both coils could be positioned simultaneously on the head without touching each other. It was sometimes

necessary to adjust the orientation of one TMS coil by increasing the angle of its handle up to a maximum of 60° from the midline (instead of 45°). Importantly, these adjustments did not preclude us from keeping the same hotspot and thus from obtaining optimum MEP amplitudes, except for two subjects who were excluded from the study on this basis (34 subjects were originally recruited but 32 did the experiment). The resting motor threshold (rMT) corresponded to the minimal TMS intensity required to evoke MEPs of ∼50 μV peak-to-peak in the contralateral FDI in at least 5 out of 10 consecutive stimulations. Across participants, the rMTs corresponded to 40.4 ± 5 % and 39.5 ± 4.4 % of the maximum stimulator output for the left and right M1, respectively.

1.3.3 Experimental design

The goal of the present experiment was to compare the amplitude of MEPs elicited at rest using single-coil or double-coil TMS. Subjects sat on a chair with their arms semi-flexed and both hands resting palm-down on a table. Participants were explicitly asked to stay still and to keep their eyes open during the whole experiment. TMS pulses were applied during 10 blocks of 48 trials. In half of the trials, single-coil TMS was used, eliciting MEPs in a single hand (MEP_{single}); pulses were delivered through the coil positioned on the left or right M1, eliciting right or left hand MEP_{single} in a balanced proportion. In the other half, MEPs were elicited in both hands at once using a double-coil method (MEP_{double}) where the two M1 are stimulated with a 1 ms inter-pulse interval ($double\text{-}coil_{1ms}$). Hence, MEP_{double} could either result from a first ($MEP_{double-1}$) or a second ($MEP_{double-2}$) pulse (see Figure 1.1 for more details). The MEPs were obtained at 5 intensities of stimulation ($TMS_{INTENSITY}$ = 100%, 115%, 130%, 145% or 160% of rMT) in separate

blocks (2 blocks per $TMS_{INTENSITY}$ in a counterbalanced order). Given this design, 24 MEPs were obtained for each TMS condition. Blocks lasted approximately 4 minutes and were run successively. Short breaks were made between the blocks.

1.3.4 EMG recording

MEPs were recorded from surface electrodes (Neuroline, Medicotest, Oelstykke, Denmark) placed over the left and right FDI muscles. The raw electromyography (EMG) signals were amplified (x1000), bandpass filtered online (10-500 Hz; NeuroLog; Digitimer), and digitized at 2000 Hz for off-line analysis. EMG data were collected for 1000 ms on each trial, starting 300 ms before the TMS pulse. Trials with background EMG activity (root mean square computed from - 250 to - 50 ms before the TMS pulse) exceeding 3 standard deviations (SD) around the mean were discarded from the following analysis. The remaining MEPs were classified according to the experimental condition within which they were elicited; for each condition, we excluded trials with peak-to-peak MEP amplitudes exceeding 3 SD around the mean. After having excluded these outliers, a total of 22.3 ± 3.4 trials remained in each condition. Left and right FDI data were pooled together as MEP amplitudes were comparable in both hands (all $p > .05$). Hence, analyses considered three main types of MEPs (MEP_{TYPE} = MEP_{single}, $MEP_{double-1}$ and $MEP_{double-2}$) elicited at five different intensities ($TMS_{INTENSITY}$ = 100%, 115%, 130%, 145% or 160% of rMT).

1.3.5 Statistical analyses

MEP amplitudes were analysed using non-parametric tests because data samples were not normally distributed for each of the above-mentioned experi-

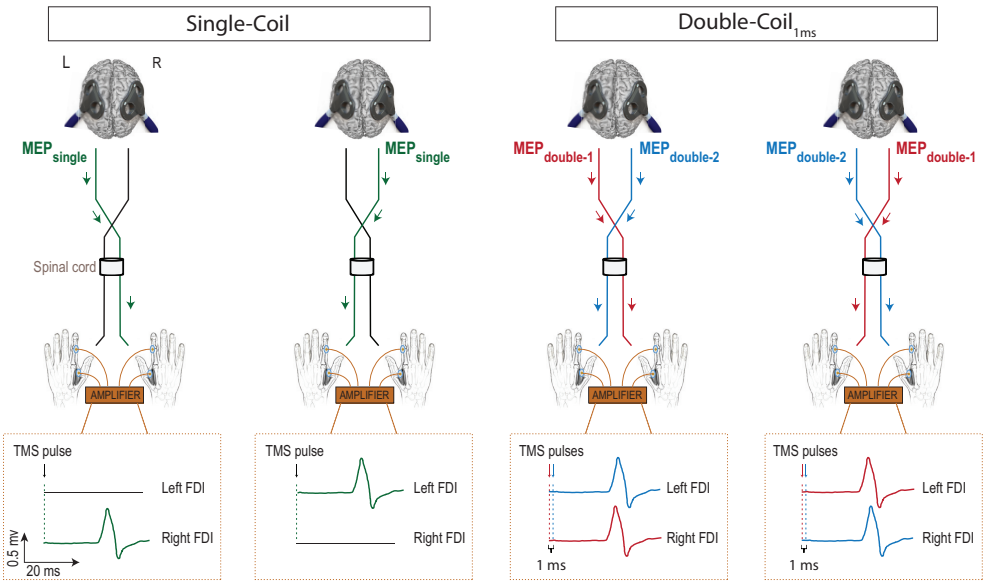

Figure 1.1: Single- and double-coil procedures. Illustration of the single-coil (left panel) and double-coil$_{1ms}$ (right panel) procedures. Single-coil TMS elicited MEP$_{single}$ in the left (L) or right (R) first dorsal interosseous (FDI) muscle (green traces) in separate trials. Double-coil$_{1ms}$ TMS elicited MEP$_{double}$ in the L and R FDI muscles at once. Given the 1 ms interval between the two pulses, MEPs were either elicited by a first (MEP$_{double-1}$, red traces) or second TMS pulse (MEP$_{double-2}$, blue traces). The pulse order was counterbalanced such that MEP$_{double-1}$ and MEP$_{double-2}$ were obtained in equal proportions for the L and R hands. Consequently, there were four TMS conditions in each block, including single-coil TMS over the L or R M1 (eliciting R or L MEP$_{single}$, respectively) and double-coil TMS with the first pulse applied over L or R M1 (eliciting L and R MEP$_{double-1}$ and MEP$_{double-2}$). Notably, TMS coils were positioned over both M1 during the whole experiment, even in single-coil trials, as all conditions were intermingled within each block. While identifying the hotspot for each M1, we always verified that the two coils could be positioned simultaneously on the head without touching each other. Minor adjustments were sometimes necessary without precluding the acquisition of optimum FDI MEPs. Subjects were asked to remain still and to keep their eyes open during the 10 experimental blocks. MEP trials were separated by a delay ranging from 5000 to 5500 ms. Blocks lasted approximately 4 minutes and were run successively.

mental conditions.

First, the effect of $\text{TMS}_{INTENSITY}$ was assessed by means of three Friedman ANOVAs run separately for each MEP_{TYPE}. Post hoc comparisons were conducted using Wilcoxon signed-rank tests. Alpha p-levels were Bonferroni-corrected to .017 (.05/3) and to .013 (.05/4) for the Friedman and the Wilcoxon tests, respectively.

Second, the effect of MEP_{TYPE} was evaluated by using five Friedman ANOVAs conducted separately for each $\text{TMS}_{INTENSITY}$. Alpha p-levels were Bonferroni-corrected to .01 (.05/5) for these Friedman ANOVAs.

Finally, we assessed the statistical equivalence of each MEP_{TYPE} by testing "average bioequivalence hypotheses" [351, 352, 353]. Specifically, the procedure consists of testing two sets of one-sided hypotheses:

$$\text{H}_{01} : \mu\text{T}/\mu\text{R} \leq \text{-}\theta, \text{H}_{11} : \mu\text{T}/\mu\text{R} > \text{-}\theta$$

$$\text{H}_{02} : \mu\text{T}/\mu\text{R} \geq \theta, \text{H}_{12} : \mu\text{T}/\mu\text{R} < \theta$$

where μT stands for the average double-coil_{1ms} MEPs (e.g. $\text{MEP}_{double-1}$), μR for the average single-coil MEPs (MEP_{single}) and where -θ and θ represent the boundaries of the equivalence margin, i.e. the values between which the ratio $\mu\text{T}/\mu\text{R}$ must be enclosed for μT and μR to be considered equivalent [352, 354]. Briefly, this procedure consists of concluding equivalence of μT and μR if and only if both H_{01} and H_{02} are rejected, the logic being that if it can be concluded that -$\theta < \mu\text{T}/\mu\text{R}$ and that $\mu\text{T}/\mu\text{R} < \theta$, then it can be concluded that -$\theta < \mu\text{T}/\mu\text{R} < \theta$. Equivalence is established if a 90% confidence interval for $\mu\text{T}/\mu\text{R}$ is significantly different from [-θ, θ] based on the use of two one sided tests at a 5% significance level [352, 353, 354]. Note that, consistent with the recommendation of the FDA, here we tested average bioequivalence

hypotheses and not individual bioequivalence hypotheses. Following this procedure, H_{01} and H_{02} may be rejected even if some individual values stand outside the equivalence margin, provided that the mean value is significantly different from $\pm\ \theta$.

To run the bioequivalence tests, the amplitudes of $MEP_{double-1}$ and $MEP_{double-2}$ were expressed in percentage of MEP_{single} for each $TMS_{INTENSITY}$. To be considered as equivalent to MEP_{single}, these normalized data needed to be significantly different from the boundaries of a $\pm$ 20% window centred around 100% [351, 353]. This was tested for each $TMS_{INTENSITY}$ using one-tailed Wilcoxon signed-rank tests with alpha p-levels Bonferroni-corrected to .005 (.05/10). In a second step, we also determined the smallest significant boundaries at each $TMS_{INTENSITY}$. To do so, Wilcoxon signed-rank tests starting at $\pm$ 20% around 100% and decreasing by $\pm$ 1% were performed until we found the narrowest windows between which $MEP_{double-1}$ and $MEP_{double-2}$ significantly fitted ($p < .005$). These windows are represented in 1.2B.

1.4 Results

Figure 1.2A illustrates the mean amplitude of MEP_{single}, $MEP_{double-1}$ and $MEP_{double-2}$ for each $TMS_{INTENSITY}$. As expected, all MEP_{TYPE} amplitudes depended on the $TMS_{INTENSITY}$ (all Friedman $\chi^2 > 123$, all $p < 0.01$, n=32). On average, MEPs equalled 0.14 $\pm$ 0.07 mV, 0.91 $\pm$ 0.5 mV, 1.95 $\pm$ 0.99 mV, 2.68 $\pm$ 1.25 mV and 3.15 $\pm$ 1.35 mV when elicited at 100%, 115%, 130%, 145% and 160% of rMT, respectively. Post hoc tests confirmed that increasing the $TMS_{INTENSITY}$ by 15% always resulted in significantly larger MEP amplitudes (all $W < 13$, all $p < 0.001$, n=32).

Importantly, we did not observe any other effect on MEPs. As such,

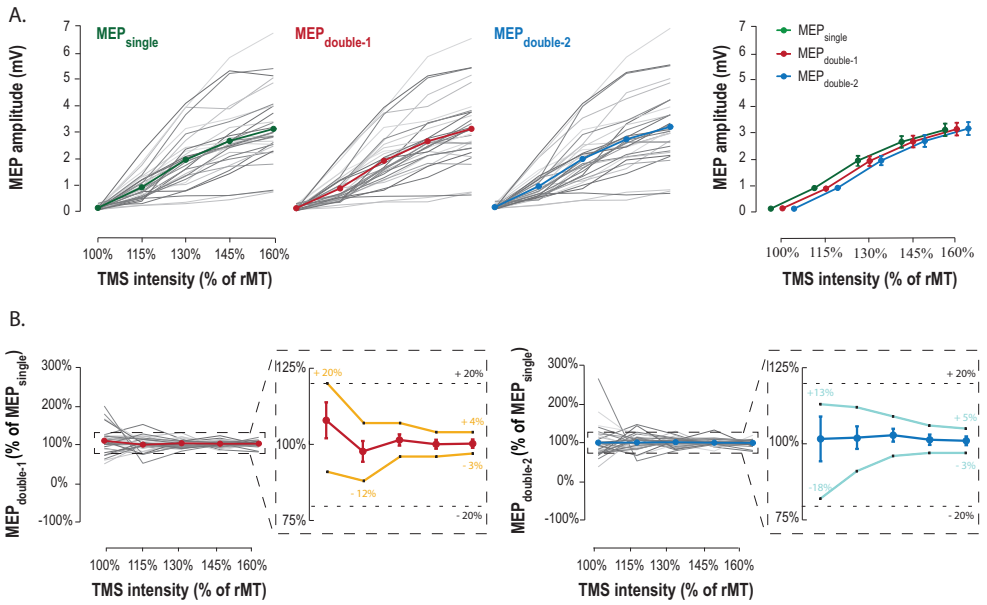

Figure 1.2: MEP amplitudes in single- and double-coil trials. (A) Illustration of MEP_{single} (green trace), $\text{MEP}_{double-1}$ (red trace) and $\text{MEP}_{double-2}$ (blue trace) amplitudes (mV) as a function of $\text{TMS}_{INTENSITY}$ (expressed in percentage of resting motor threshold, rMT). The grey lines represent single-subject data (n=32) for each MEP_{TYPE}; the thicker coloured lines represent the mean values. The right-side panel gathers all mean values on a single figure, highlighting the similarity of MEP_{TYPE} amplitudes at each $\text{TMS}_{INTENSITY}$. Data are expressed as mean ± standard error (SE). (B) Illustration of $\text{MEP}_{double-1}$ (left panel) and $\text{MEP}_{double-2}$ (right panel) amplitudes (expressed in percentage of MEP_{single}) as a function of $\text{TMS}_{INTENSITY}$ (ranging from 100% to 160% of resting motor threshold, rMT). The grey lines represent single-subject data (n=32) whereas the thicker coloured lines stand for the mean values. As shown on the right side of the figure, $\text{MEP}_{double-1}$ and $\text{MEP}_{double-2}$ amplitudes (mean values ranging from 97.8 % to 108 % and from 101 % to 102.8%, respectively) significantly fitted into a ± 20% window around the MEP_{single} mean ($p < 0.005$) indicating comparable MEP amplitudes for all MEP_{TYPE}. For each $\text{TMS}_{INTENSITY}$, the narrowest windows within which the $\text{MEP}_{double-1}$ and $\text{MEP}_{double-2}$ data significantly fitted are also represented by orange and blue lines, respectively. Data are expressed as mean ± standard error (SE).

Friedman ANOVAs revealed that amplitudes were not statistically different in the three MEP_{TYPE} conditions, whatever the $TMS_{INTENSITY}$ (all $\chi^2 < 3.9$, all $p > 0.14$, n=32; see Fig. 2A, right side). Furthermore, the equivalence tests run on the normalized MEP_{double} data (expressed in percentage of MEP_{single}) revealed that $MEP_{double-1}$ and $MEP_{double-2}$ amplitudes (mean values ranging from 98 % to 108 % and from 101 % to 103 % of MEP_{single}, respectively) significantly fitted into a ± 20% window around the MEP_{single} mean (all $W < 127$, $p < 0.005$, $n = 32$). In fact, for the higher $TMS_{INTENSITY}$ conditions, the MEP_{double} data even fitted in smaller windows, as evident on Figure 1.2B. For instance, when TMS was applied at 160% of rMT, the normalized $MEP_{double-1}$ mean was equal to 100 ± 7.7 % and fitted in a ± 4% window ($p < .005$); similar observations can be made for $MEP_{double-2}$ at this $TMS_{INTENSITY}$ (mean = 101 ± 8.1 %, ± 5% window, $p < .005$).

Altogether, these results indicate that double-$coil_{1ms}$ and single-coil TMS elicit comparable MEPs, at least when applied at rest. These results are further supported by linear regression models characterising the relationship between MEP_{double} and MEP_{single} for each $TMS_{INTENSITY}$. As evident on Figure 1.3, this relationship was extremely strong for most intensities of stimulation (all but 100% $r \geq .91$); the use of a 100 % $TMS_{INTENSITY}$ was associated with a slightly weaker link ($r = .80$). Moreover, examination of the linear regression equations [$\acute{Y} = a + bX$] revealed low intercept values (all $a \leq .12$) and a slope close to one (all but 100% b between [.90, 1.02], confirming that $Y \simeq X$; the use of a 100 % $TMS_{INTENSITY}$ was associated with smaller slopes ($b \simeq .55$).

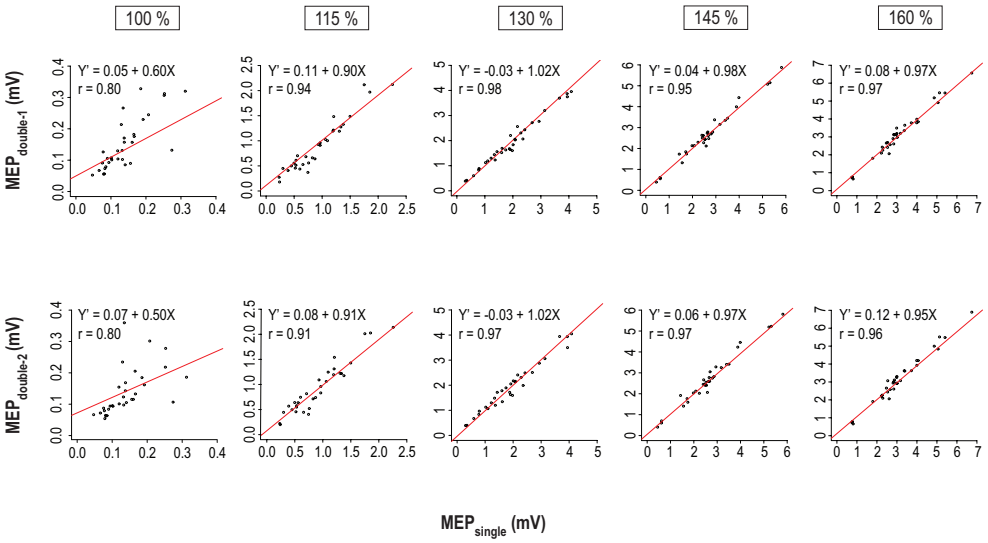

Figure 1.3: Regression analyses. Illustration of the relationship between $\text{MEP}_{double-1}$ (upper part) or $\text{MEP}_{double-2}$ (lower part) and MEP_{single} for each $\text{TMS}_{INTENSITY}$ (on x-axis). Each dot represents a single subject (n=32). Note the strong r values (all r $\geq$ .80) and the equations of the regression lines plotted in red (all intercepts between [-.03, .12] and all slopes between [.90, 1.02] for all conditions but 100%.

1.5 Discussion

1.5.1 Summary

TMS is a non-invasive technique, usually painless, which has been used in many experiments in the past to investigate CSE in a safe manner. In these studies, TMS is usually applied through a single-coil positioned over one M1, eliciting MEPs in a targeted muscle of the contralateral hemibody. However, many studies would benefit from a double-coil TMS technique eliciting MEPs in homologous effectors simultaneously. The goal of the present study was to examine whether double-coil_{1ms} TMS elicits MEPs that are comparable to those obtained using single-coil TMS, a prerequisite to use this method in future studies of CSE. Assessments were made whilst at rest for different in-

tensities of stimulation ranging from 100% to 160% of rMT. Our data indicate that MEP_{single}, $\text{MEP}_{double-1}$ and $\text{MEP}_{double-2}$ are all comparable, whatever the intensity of stimulation.

1.5.2 Impact of TMS intensity on MEP amplitude

As expected, MEPs increased with the intensity of stimulation, reaching the highest peak-to-peak amplitude at 160% of rMT. This is consistent with the fact that higher intensities of stimulation result in stronger magnetic fields, stimulating a larger proportion of CS neurons some of which are in deeper cortical layers [36, 55, 355]. Neurons activated with higher intensities of stimulation are thought to be at a greater distance from the centre of activation induced by the magnetic stimulus and/or to have an intrinsically lower excitability [36]. Such a pattern of response can easily be observed when building up recruitment curves, plotting the influence of the stimulation intensity on MEP amplitudes [356, 357].

1.5.3 Comparing MEP_{double} to MEP_{single}

Overall, all MEP_{TYPE} were equivalent. That is, whatever the intensity or type of stimulation, the amplitude of MEP_{double} was always equivalent to MEP_{single}. As such, the normalized MEP_{double} (expressed in percentage of MEP_{single}) always fitted in a $\pm$ 20% window around the MEP_{single} mean (i.e. around 100%). In addition, we did not observe any order effect on the amplitude of MEP_{double}: the size of $\text{MEP}_{double-2}$ was comparable to that of $\text{MEP}_{double-1}$. These findings contrast with observations made in other studies having used double-coil TMS over M1 [102, 358]. However, a major difference in these latter studies stands in the longer duration of the inter-pulse interval, purposely set to probe transcallosal interactions [102, 103]; for a review see

Reis et al. (2008) [63]. In these experiments, the inter-pulse interval typically ranges from 4 to 50 ms: short delays (∼4 ms) are used to assess facilitatory interactions whereas longer intervals (> 7-8 ms) are used to probe inhibitory influences. As such, the amplitude of $\text{MEP}_{double-2}$ is usually increased with respect to MEP_{single} with a ∼4 ms delay whereas it is strongly reduced with longer intervals. These protocols have proved useful to characterize changes in interhemispheric interactions in various settings including movement preparation in healthy and pathological populations [151, 359, 360, 361]. Obviously, the goal of the double-coil TMS_{1ms} procedure under consideration in the current study is very different. In fact, here we used the shortest possible interval (1 ms) to avoid these transcallosal interactions to take place, in order to obtain non-biased MEPs in both body sides, similar to those elicited in single-coil situations. As mentioned earlier, a small delay is nevertheless mandatory to avoid electromagnetic interferences between the two stimulating coils. Our results indicate that a 1 ms delay is short enough to avoid interactions through the corpus callosum. In addition, the equivalence of MEP_{double} and MEP_{single} amplitudes suggests that interactions neither occurred at a subcortical or spinal site.

Notably, the normalized MEP_{double} data (expressed in percentage of MEP_{single}) showed the largest variability at the lowest intensities of stimulation. For instance, whereas MEP_{double} values were close to 100% (i.e. equal to MEP_{single}) at 160% of rMT for most subjects, data were more variable at 100% of rMT, with participants displaying MEP_{double} values that were either slightly larger or lower than 100%. Consistently, the equations of the regression lines show an extremely strong relationship between MEP_{double} and MEP_{single} for all the intensities of stimulation except for when 100 % is used (Figure 1.3). This is likely due to the fact that MEPs fluctuate a lot when elicited at a

low TMS intensity; decreasing the signal to noise ratio [362]. Consistently, previous works have shown that the variability of MEPs is inversely related to the MEP amplitude [356, 363, 364]. Altogether, these observations support the use of intensities of stimulation above the rMT; 115-130% seems quite optimal as it also keeps discomfort to a minimum [35].

1.5.4 Staying away from a confounding block or sample effect

In the current work, all the different conditions of stimulation were intermingled within each block, precluding any block effect. As such, it was not possible for the subjects to know which kind of stimulation (single or double pulses) they would receive next. This means that they were in the same state of attentiveness when MEP_{double} and MEP_{single} were elicited. This is crucial as the level of alertness is known to impact MEP amplitudes [345, 365] and could differ when expecting double- compared to single-coil TMS. In fact, this methodological aspect is likely to be responsible for the fact that MEP_{double} were found to be larger than MEP_{single} in a recent study using the same double-coil_{1ms} TMS method in the context of action preparation [349]. A critical difference between the two experiments is the fact that contrary to the current work, Wilhelm et al. (2016) [349] tested the single-coil and double-coil approaches in separate blocks, thus eliciting MEP_{single} and MEP_{double} in different contexts. Hence, we believe that the larger MEP_{double} in that study is likely due to a biasing block effect.

Another important feature of the present study is that all the experimental conditions were tested with the same subjects, precluding any sample effect. Again, this differs from what was done in [349]. As such, because of the large number of conditions in that study, we had decided to test the two orders of stimulation ("left M1 > right M1" or "right M1 > Left M1") in dif-

ferent subjects. Yet, this is likely to have biased our results. In fact, the larger MEP_{double} reported above was only found in one of the groups (the one receiving a pulse over left M1 first). From there, it is difficult to know whether this effect is due to the use of different orders of stimulation or to the inclusion of different samples of healthy volunteers. The absence of difference between all MEP_{TYPE} in the current study supports the second scenario. Future studies are required to assess the double-$coil_{1ms}$ method during action preparation in the absence of confounding block and sample effects.

1.5.5 Spatial constraints

The double-$coil_{1ms}$ method requires using two small figure of eight coils, ideally with a wing internal diameter of maximum 35 mm [151, 349, 366]. Minor adjustments are sometimes still necessary when using these coils but they should never preclude the acquisition of optimum MEPs. Because of this constraint, this technique can hardly be used to evaluate CSE of more proximal arm muscles which are represented more medially in M1. It may also be difficult, if not impossible, to apply this procedure in children, a population characterized by smaller heads.

1.5.6 Future directions

Double-$coil_{1ms}$ can be very useful in many ways. First, it allows acquiring double the data in the same amount of time. That is really a critical aspect because it gives the opportunity to test more conditions than could be done with a regular single-coil method, while maintaining a reasonable length of experiment. Second, obtaining MEPs in both hands within the same trial allows to investigate the distinct impact of a task on CSE of the dominant and non-dominant sides in the exact same setting. This increases the signal

to noise ratio in a significant way. Third, with this design, one can also make direct comparisons between MEPs elicited in the two hands on a single-trial basis. New dependent measures can be obtained, such as for example, indexes reflecting the difference (or ratio) between CSE of the two hands; correlations can also be computed between individual MEPs on both sides. Note that because a single TMS pulse can elicit MEPs in several muscles of the contralateral hand [348], these indexes/correlations can be evaluated for several muscles at the same time. The relationship between bilateral MEPs may change according to the instruction, the level of perceptual evidence, the speed-accuracy trade-off, the presence of reward biases, etc.

1.6 Conclusion

The present results suggest that double-coil$_{1ms}$ TMS is a reliable method to assess CSE bilaterally. Further studies are required to verify whether this assumption holds when MEPs are elicited in other functional states such as during motor preparation. This method has many advantages, including the possibility to acquire twice the amount of data in a single trial and to observe state-related CSE changes for the two hands simultaneously on a trial-by-trial basis. Double-coil$_{1ms}$ may therefore reveal the second half of the story and pave the way towards new research horizons.

1.7 Funding

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Chapter 2 Using a double-coil TMS protocol to assess preparatory inhibition bilaterally

"Creativity involves breaking out of expected patterns in order to look at things in a different way."

Edward de Bono

Chapter 2: reminder of the aim and hypotheses

During the last two decades, studies have used TMS to monitor CSE changes in various contexts. Habitually, single-coil TMS is applied over one M1, eliciting MEPs in the contralateral hand or limb muscle. However, in many studies, such as those focusing on CSE changes during action preparation, it would be useful to obtain MEPs in both hands at once. Such an approach requires stimulating both M1 concurrently while avoiding any interference between the two electromagnetic fields and the two descending volleys induced by the TMS pulses. In Chapter 1, we tested the reliability of double-coil$_{1ms}$ at rest. Our data inferred the absence of any neural interactions between the two CS volleys with double-coil$_{1ms}$. In the present chapter (Chapter 2), we investigated whether these results hold in another functional state, namely during motor preparation.

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Keywords

Transcranial magnetic stimulation, motor-evoked potentials, primary motor cortex, corticospinal excitability, coefficient of variation, action preparation, inhibition.

2.1 Abstract

Transcranial magnetic stimulation (TMS) applied over the primary motor cortex (M1), elicits motor-evoked potentials (MEPs) in contralateral limb muscles which are valuable indicators of corticospinal excitability (CSE) at the time of stimulation. So far, most studies have used single-coil TMS over one M1, yielding MEPs in muscles of a single limb - usually the hand. However, tracking CSE in the two hands simultaneously would be useful in many contexts. We recently showed that, in the resting state, double-coil stimulation of the two M1 with a 1 ms inter-pulse interval (double-coil$_{1ms}$ TMS) elicits MEPs

in both hands that are comparable to MEPs obtained using single-coil TMS. To further evaluate this new technique, we considered the MEPs elicited by double-coil$_{1ms}$ TMS in an instructed-delay choice reaction time task where a prepared response has to be withheld until an imperative signal is displayed. Single-coil TMS studies have repetitively shown that in this type of task, the motor system is transiently inhibited during the delay period, as evident from the broad suppression of MEP amplitudes. Here, we aimed at investigating whether a comparable inhibitory effect can be observed with MEPs elicited using double-coil$_{1ms}$ TMS. To do so, we compared the amplitude as well as the coefficient of variation (CV) of MEPs produced by double-coil$_{1ms}$ or single-coil TMS during action preparation. We observed that MEPs were suppressed (smaller amplitude) and often less variable (smaller CV) during the delay period compared to baseline. Importantly, these effects were equivalent whether single-coil or double-coil$_{1ms}$ TMS was used. This suggests that double-coil$_{1ms}$ TMS is a reliable tool to assess CSE, not only when subjects are at rest, but also when they are involved in a task, opening new research horizons for scientists interested in the corticospinal correlates of human behaviour.

2.2 Introduction

Transcranial magnetic stimulation (TMS), a technique used to assess corticospinal excitability (CSE), has gained substantial attention since it was first described about 30 years ago [367]. The amplitude of motor-evoked potentials (MEPs) elicited in muscles of the contralateral limb (often the hand) by TMS over the primary motor cortex (M1) is a precious indicator of CSE at the time of stimulation [22, 48, 51]. Comparing MEP amplitudes in different conditions have helped to characterize the corticospinal correlates of various neural processes including those underlying action preparation and stopping

[84, 114, 126, 153, 166, 298, 368], decision making and reward processing [82, 306, 307, 308, 346, 369], sustained attention [345], speech [83, 370], and motor imagery [371]. TMS has also proved useful in characterizing the corticospinal correlates of behavioural deficits in several neurologic disorders [344] including stroke [372, 373, 374, 375], Parkinson's disease [376, 377, 378, 379], or Alzheimer's disease [380].

To date, almost all TMS-based CSE studies have recorded MEPs from muscles of a single hand following the application of TMS over one M1 only. Hence, in most experiments, the MEP data have only provided researchers with half of the story, increasing the probability of seeing data being misinterpreted. This occurs because applying TMS over both M1 in separate blocks doubles the duration of the experiment, making it impossible to fit all the conditions in a single session. For example, studies investigating inhibitory processes during action preparation have typically recorded MEPs from left hand muscles (following right M1 TMS) in instructed-delay choice RT tasks where subjects have to withhold cued left or right hand responses (e.g., left or right index finger key-presses) until an imperative signal is displayed [127, 128, 153, 154, 157]: left MEPs are deeply suppressed in this context (compared to a baseline), a phenomenon often referred to as preparatory inhibition [22]. Critically, many studies have reported a stronger left MEP suppression in conditions where the target muscle is selected for the forthcoming movement (i.e., left response) compared to when it is non-selected (i.e., right response) and it has been commonly accepted that this difference results from the distinct function (selected vs. non- selected) of the left hand muscle in these two situations [148, 153, 156]. That is, preparatory inhibition is thought to be more prominent for selected than non-selected effector representations. Yet, there is a substantial confound here because besides the

function (selected vs. non-selected), conditions also differ in regard to the hand being cued for the response (left vs. right). Hence, the stronger left MEP suppression with left than right hand responses may be due to the use of the non-dominant vs. dominant hand rather than to the distinct function of the targeted muscle in these trials.

Recently, we have proposed the use of double-coil TMS over both M1, to obtain MEPs from bilateral muscles at once [349, 381]. In these previous studies, we tested a double-coil TMS method where the two M1 are stimulated with a 1 ms inter-pulse interval (double-coil$_{1ms}$ TMS). An interval between the two TMS pulses is necessary to avoid direct electromagnetic interference between the two stimulating coils. Yet, the latter must be kept short enough to avoid cortical interactions through the corpus callosum occurring with delays as small as 4 ms [102, 103]; reviewed in Reis et al. (2008) [63]. In Grandjean et al. (2018) [381], MEPs elicited using this new double-coil$_{1ms}$ approach (MEP$_{double}$) were recorded for five different intensities of stimulation while participants were completely relaxed, at rest, and were compared to those elicited in the same conditions using single-coil TMS (MEP$_{single}$) applied successively over the two M1. Note that given the 1 ms inter-pulse interval in double-coil$_{1ms}$ trials, MEP$_{double}$ were either evoked by a 1^{st} (MEP$_{double-1}$) or a 2^{nd} (MEP$_{double-2}$) TMS pulse. Importantly, the study revealed that MEP$_{double-1}$ and MEP$_{double-2}$ are comparable to MEP$_{single}$ when elicited at rest, regardless of the TMS intensity, suggesting that this method may be used to assess CSE bilaterally. However, it still remains to be determined whether double-coil$_{1ms}$ TMS produces comparable MEPs as single-coil TMS in the context of a task.

In the present study, we compared MEP$_{double-1/2}$ and MEP$_{single}$ during action preparation, applying double-coil$_{1ms}$ or single-coil TMS in an instructed-

delay choice RT task where subjects have to withhold a cued response until an imperative signal is displayed [22, 48, 154]. We compared the strength of preparatory inhibition when probed using double-coil$_{1ms}$ or single-coil TMS. Some of these results have already been reported in abstract form [357, 382].

2.3 Materials and methods

2.3.1 Participants

A total of 15 right-handed healthy subjects participated in the present study (n = 15; 10 women; 22.4 ± 1.63 years old). Handedness was determined via a shortened version of the Edinburgh Handedness inventory [350] and all subjects filled out a TMS safety questionnaire. None of the participants suffered from any neurological disorder or had a history of psychiatric illness, drug or alcohol abuse; neither was anybody undergoing a drug treatment that could influence their performance or their neural activity. All subjects were financially compensated for their participation and provided written informed consent. The protocol was approved by the Ethics Committee of the Université catholique de Louvain.

2.3.2 The "Rolling Ball" Task

Participants sat in front of a 21-inch monitor screen positioned about 60 cm in front of them with their arms semi-flexed and both hands resting palm-down on a response device developed in our laboratory [154]. They performed an instructed-delay choice reaction time (RT) task, which required them to choose between abduction movements of the left or right index finger. The task was implemented with Matlab 7.5 (the Mathworks, Natick, Massachusetts, USA) using the Psychophysics Toolbox extensions [383, 384]. The refresh rate of

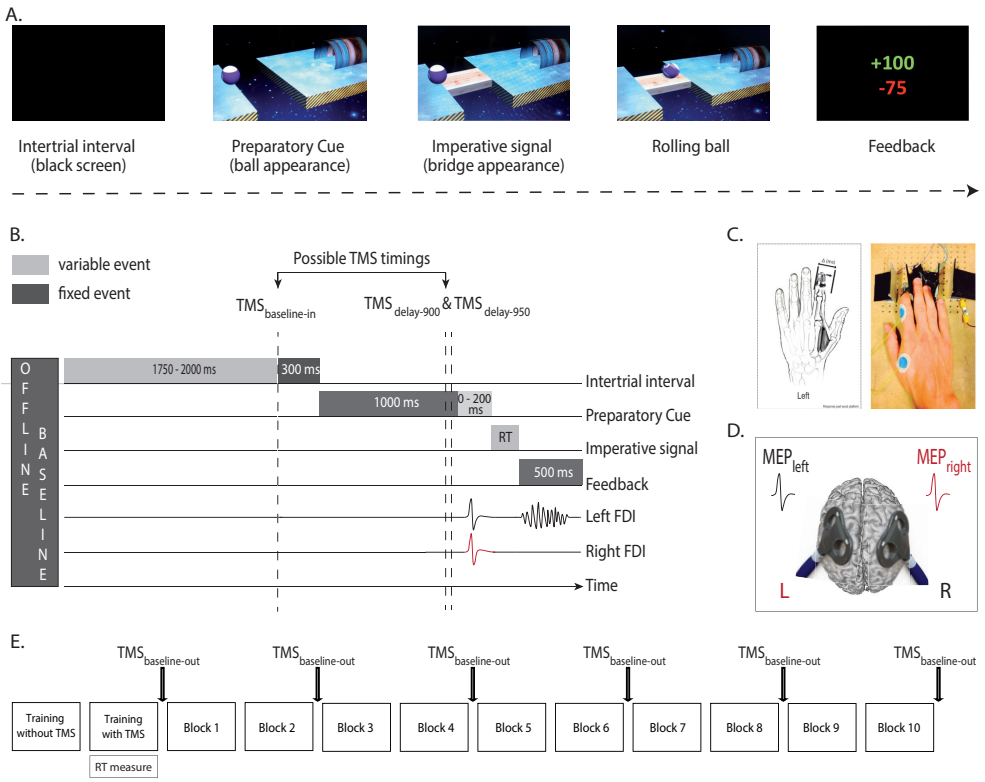

Figure 2.1: (Continued on the following page.)

the monitor was set at 100 Hz.

The task consisted in a virtual "Rolling Ball" game previously used in another study [154] (Figure 2.1A). In this game, participants were informed that the position of a preparatory cue (i.e., a ball separated from a goal by a gap) indicated the movement side for the forthcoming response: if the ball was on the left side of the screen, subjects had to prepare a left index finger response (to get ready to "shoot the ball into the goal") and if the ball was on the right side, subjects had to prepare a right index finger response. Subjects were explicitly told to withhold their response until the onset of an imperative signal (i.e., a bridge). The latter appeared 1,000 - 1,200 ms after the ball and remained on the screen until a finger movement was detected or for a

Figure 2.1: (A) "Rolling Ball" task. Subjects were asked to choose between responding with the left or right index finger according to the position of a ball (Preparatory cue) appearing on the left or right part of the screen (left in the current example). They had to wait until the onset of a bridge (Imperative signal) to release their response. The ball then rolled on the bridge (when the subjects answered correctly) to reach a goal located on the other side of the gap. A feedback reflecting how fast and accurate the subjects had been concluded each trial. **(B) Time course of a trial.** Each trial started with a blank screen (intertrial interval; 2,050 - 2,300 ms). Then, the preparatory cue appeared for a variable delay period (1,000 - 1,200 ms), followed by the imperative signal until the reaction time (RT). The feedback was presented at the end of each trial for 500 ms. TMS pulses occurred either during the intertrial interval (1,750 - 2,000 ms after the blank screen onset; $\text{TMS}_{baseline-in}$), or during the delay period (900 or 950 ms after the preparatory cue onset; $\text{TMS}_{delay-900}$ and $\text{TMS}_{delay-950}$). In double-coil_{1ms} trials, motor-evoked potentials (MEPs) were elicited in the first dorsal interosseous (FDI) of both hands at a near simultaneous time (1 ms delay); in single-coil trials, MEPs were elicited in the left or right hand. The figure displays a left hand trial with double-coil_{1ms} at $\text{TMS}_{delay-950}$. **(C) The response device.** Index finger responses were recorded using a home-made device positioned under the left (graphic representation) and right (photographic representation) hands. **(D) TMS protocol.** Two figure-eight-shaped coils were placed over the subject's primary motor cortex (M1), eliciting MEPs in the left and/or right FDI. **(E) Time-course of the experiment.** After two training blocks (see section Materials and Methods), subjects executed 10 blocks of 40 trials during which MEPs were elicited at $\text{TMS}_{baseline-in}$ or TMS_{delay} ; MEPs were also elicited outside the blocks ($\text{TMS}_{baseline-out}$), before block 1 and after blocks 2, 4, 6, 8, and 10.

maximum duration of 500 ms. When the bridge was on the screen, subjects had to respond as fast as possible to allow the ball to roll on it and to quickly reach the goal. Subjects knew that they would get a score after each trial reflecting how fast and accurate they had been on the previous trial. Note that in each block, some catch trials (trials in which the bridge did not appear; 5% of all trials) were included. Subjects were required not to respond on these trials and were penalized if they did so. Hence, they had to avoid initiating their response prematurely, before the bridge onset. Trials were separated by the presentation of a blank screen lasting for a duration that varied between 2,050 and 2,300 ms (Figure 2.1B).

The home-made response device (Figure 2.1C) was composed of two pairs

of metal edges fixed on a wooden platform (one for each hand) and each trial of the Rolling Ball game required participants to move one index finger from the outer to the inner metal edge (i.e., abduction of the index finger). The contact between the finger and the metal parts of the device was continuously monitored using a Makey Makey printed circuit board with an ATMega32u4 microcontroller running the Arduino Leonardo firmware, based on the principle of high resistance switching between two electrical contacts. This device provided us with a very precise measure of the RTs (precision = 1 ms) and allowed us to control for any anticipated movement. That is, the device permanently checked the initial position of each index finger (which had to be in contact with the outer metal edge) and any contact release before the onset of the imperative signal led to the cancellation of the trial and to a penalty.

Subjects received a feedback of their performance at the end of each trial. On correct trials, the feedback score (displayed in green) was inversely proportional to the reaction time (RT): the faster the subjects, the higher the score. The RT was defined as the time interval between the onset of the bridge and the time when the index finger left the outer metal edge of the response device. The score was determined based on the following equation, with α = 0,8 median RT measured at the end of the training session just before the main experiment:

$$x = \frac{(100.(\alpha))}{(\alpha+(\frac{RT-\alpha}{10})^{2,4})}$$

Using this equation, scores on correct trials ranged from 1 to 100. Incorrect responses were penalized with negative scores displayed in red. They involved responses occurring too early, referred to as "anticipation errors" (penalized by 75 points), responses occurring too late, referred to as "time-out errors" (penalized by 50 points), responses provided with the incorrect hand

(penalized by 20 points), referred to as "choice errors" and responses provided on catch trials (penalized by 12 points), referred as "catch errors." Anticipation errors consisted in responses provided either before the bridge onset or after its onset but with a RT smaller than 100 ms. Time-out errors consisted in responses provided in more than 500 ms (after the bridge offset). Note that when subjects succeeded not to respond on a catch trial, they were rewarded by +12 points. The total score was always displayed at the end of each block.

2.3.3 TMS Protocol

TMS was delivered through one or two small figure-of-eight shaped coils (wing internal diameter 35 mm), each connected either to a Magstim 200^2 magnetic stimulator (Magstim, Whitland, Dyfed, UK) or a Magstim Bistim^2 magnetic stimulator. Both stimulators delivered monophasic pulses and their relationship to a specific hemisphere was counterbalanced between subjects. Each coil was placed tangentially over one primary motor cortex (M1) with the handle pointing backward and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus (Figure 2.1D). Small coils were chosen because in most subjects, it is not possible to place two large coils over the two M1s at the same time. For each M1, the optimal scalp position to elicit a contralateral MEP in the first dorsal interosseous muscle (FDI) was identified and marked on a head cap placed on the subject's scalp to provide a reference mark throughout the experiment [148, 160, 385]. Importantly, this was done by always checking for the fact that the two coils could be positioned simultaneously on the head without touching each other; to reduce electromagnetic interference it was sometimes necessary to adjust the orientation of the coils a little but these adaptations remained marginal and did not preclude us from obtaining the best MEP amplitudes.

The resting Motor Threshold (rMT) was determined at the hotspot for each M1 as the minimal TMS intensity required to evoke MEPs of about 50 μV peak-to-peak in the relaxed FDI muscle in at least 5 out of 10 consecutive trials. Across participants, the rMTs corresponded to 41.7 $\pm$ 5.05 and 40.8 $\pm$ 6.39% of the maximum stimulator output for the left and the right FDI, respectively. The intensity of TMS used throughout the experiment was always set at 115% of the individual rMT for each hemisphere.

2.3.4 Experimental procedure

The experiment started with two training blocks. The first one (20 trials) was conducted without TMS whereas the second one (40 trials) involved TMS, exactly as in the main experiment. Thereby, the subjects could first practice the task without being disturbed by the TMS pulse and then get used to the stimulations while performing the task in the second training block. The latter block also served to obtain the median RTs, used to individualize the scores on correct trials (see below). Then, during the main phase of the experiment, subjects performed 10 blocks of 40 trials (Figure 2.1E). Using these numbers, we obtained 20 MEPs in each condition.

The goal of the present experiment was to compare the amplitude of MEPs elicited during motor preparation using either single-coil or double-coil$_{1ms}$ TMS. In half of the trials, single-coil TMS was used, eliciting MEPs in a single hand (MEP$_{single}$), either in the left or the right FDI in a balanced proportion. In the other half, MEPs were elicited in both hands at once (MEP$_{double}$) using a double-coil$_{1ms}$ method where the two M1 are stimulated with a 1 ms inter-pulse interval (double-coil$_{1ms}$; [381]). In all subjects, half of the double-coil$_{1ms}$ trials involved a pulse over left M1 first whereas the other half of the trials involved a pulse over the right M1 first. Therefore, for each

hand, MEPs double could either result from a first ($MEP_{double-1}$) or a second pulse ($MEP_{double-2}$). Importantly, the single- and double-$coil_{1ms}$ trials were always randomized within a block so that the subject could not anticipate the type of pulse (single or double) they would have next, an aspect that could bias MEPs, as suggested in a previous study [349].

Single- and double-$coil_{1ms}$ TMS pulses were applied at three different timings during the Rolling Ball task (only one pulse per trial; Figure 2.1B). First, some TMS pulses occurred during the intertrial interval, at a random time falling 1,750 - 2,000 ms after the blank screen onset; these trials were used to compare MEP_{single} and MEP_{double} at baseline (rest) within the blocks ($TMS_{baseline-in}$, 20% of all trials). In the remaining trials, the TMS was delivered during the delay period either 900 ms ($TMS_{delay-900}$, 40% of all trials) or 950 ms ($TMS_{delay-950}$, 40% of all trials) after the occurrence of the preparatory cue. Based on previous studies (reviewed in [47]), we assumed that at these TMS_{delay} timings, inhibitory changes would be substantial whether MEPs are elicited in a selected condition (e.g., left MEPs elicited in a left hand trial) or a non-selected condition (e.g., left MEPs elicited in a right hand trial). Finally, we also recorded baseline MEPs outside the blocks ($TMS_{baseline-out}$), at six different times (before block 1 and after blocks 2, 4, 6, 8, and 10; 20 MEPs each). These MEPs provided us with a measure of CSE outside the context of the task, at complete rest. Moreover, the comparison of MEP_{single} and MEP_{double} at $TMS_{baseline-out}$ allowed us to check whether we could replicate our previous observations [381].

2.3.5 Electromyography (EMG) recording

EMG activity was recorded from surface electrodes (Neuroline, Medicotest, Oelstykke, Denmark) placed over the left and right FDI. MEPs recorded from

these homonymous muscles offered a measure of CSE changes occurring in muscles that are involved in the task (whether selected or non-selected). Note that for all participants, stimulating the hotspot for the FDI also elicited reliable MEPs in the abductor digiti minimi (ADM), a pinkie abductor muscle which is irrelevant for the task. These MEPs were also considered in the present study. EMG data were collected for 1,000 ms on each trial, starting 300 ms before the TMS pulse. The EMG signals were amplified (x1,000), bandpass filtered online (10 - 500 Hz; NeuroLog; Digitimer), and digitalized at 2,000 Hz for offline analysis.

Trials with background EMG activity (root mean square computed from -250 to -50 ms before the TMS pulse) exceeding 3 standard deviations (SD) around the mean were discarded for the following analyses. This was done to prevent contamination of the MEP measurements by significant fluctuations in background EMG [148, 160, 385]. The remaining MEPs were classified according to the experimental condition within which they had been elicited. Trials in which subjects made an error were also removed from the data set; the task was easy so these trials remained rare and errors were not analysed

For each condition, we excluded trials with a peak-to peak MEP amplitude exceeding 3 SD around the mean. After screening the data for errors, background EMG activity and outliers, a total of 15.9 ± 2.7 trials per condition were left to evaluate CSE changes during action preparation. One subject had to be taken off the MEP analyses because we encountered a technical problem during the experiment (remaining $n = 14$ subjects).

2.3.6 Statistical analyses

Analyses were carried out with the RStudio software (version 1.0.153., RStudio, Inc., Boston, MA). The assumptions of normality and homogeneity of

variance were tested before analyses. All data were systematically tested for the sphericity assumption using Maunchley's tests. The Greenhouse - Geisser correction was used for sphericity when necessary.

2.3.6.1 Reaction time

The RT data were classified according to whether subjects performed a movement with the left or right index finger (Mvt_{SIDE} : Mvt_{left} or Mvt_{right}). In addition, trials were divided depending on the time of the TMS pulse (TMS_{TIMING} : $\text{TMS}_{baseline-in}$ or TMS_{delay} ; trials with $\text{TMS}_{delay-900}$ and $\text{TMS}_{delay-950}$ pooled together for the RT analysis). Finally, RTs were considered separately for trials in which double-coil_{1ms} or single-coil_{1ms} TMS was used and for the latter condition we also distinguished trials according to whether the responding hand corresponded to the one in which the MEP was elicited or not ($\text{MEP}_{CONDITION}$: MEP_{double}, $\text{MEP}_{single-Resp}$, $\text{MEP}_{single-NonResp}$). These data were analysed using a two-way analysis of variance for repeated measures (ANOVA RM) with the factors Mvt_{SIDE}, TMS_{TIMING}, and $\text{MEP}_{CONDITION}$.

2.3.6.2 MEP amplitude

Analyses considered three main types of MEPs (MEP_{TYPE} = MEP_{single}, $\text{MEP}_{double-1}$, and $\text{MEP}_{double-2}$) elicited in the left or right hand (MEP_{SIDE} = MEP_{left}, MEP_{right}), at one of four different timings (TMS_{TIMING} = $\text{TMS}_{baseline-out}$, $\text{TMS}_{baseline-in}$, $\text{TMS}_{delay-900}$, and $\text{TMS}_{delay-950}$), during preparation of a left or right side movement (Mvt_{SIDE} = Mvt_{left} or Mvt_{right}).

In a first analysis, we focused on MEPs elicited at rest, when subjects were not preparing a response, considering both MEPs obtained outside the blocks ($\text{TMS}_{baseline-out}$) and those acquired within the blocks ($\text{TMS}_{baseline-in}$). These

MEPs were log-transformed in order to normalize the data distribution. A three-way ANOVA RM was then conducted on the normalized MEP data, with TMS_{TIMING} ($TMS_{baseline-out}$ or $TMS_{baseline-in}$), MEP_{TYPE} (MEP_{single}, $MEP_{double-1}$, or $MEP_{double-2}$), and MEP_{SIDE} (MEP_{left} or MEP_{right}) as within-subject factors.

Second, we aimed at comparing the strength of MEP suppression during the delay period according to whether a single- or double-$coil_{1ms}$ procedure was used. To do so, MEPs elicited at $TMS_{delay-900}$ and $TMS_{delay-950}$ were expressed in percentage of MEPs acquired at $TMS_{baseline-in}$ for each condition. These data were log-transformed and multiple one-sided t-tests were performed to compare the MEPs elicited at $TMS_{delay-900}$ and $TMS_{delay-950}$ to a constant value of 2 [standing for the $TMS_{baseline-in}$ MEPs because log(100) = 2]. In a second step, we analysed these data using a four-way ANOVA RM with TMS_{TIMING} ($TMS_{delay-900}$ or $TMS_{delay-950}$), MEP_{TYPE} (MEP_{single}, $MEP_{double-1}$, or $MEP_{double-2}$), MEP_{SIDE} (MEP_{left} or MEP_{right}), and Mvt_{SIDE} (Mvt_{left} or Mvt_{right}) as within-subject factors.

In a further analysis, we assessed the statistical equivalence of MEP amplitudes elicited using a single-coil or double-$coil_{1ms}$ procedure. We did so by testing "average bioequivalence hypotheses" [351, 352, 353]; a procedure detailed in our previous study [381]. Briefly, $MEP_{double-1}$ and $MEP_{double-2}$ elicited at TMS baseline ($TMS_{baseline-in}$ and $TMS_{baseline-out}$) and TMS_{delay} ($TMS_{delay-900}$ and $TMS_{delay-950}$) were expressed as a percentage of MEP_{single} elicited at the same TMS_{TIMING} . We then computed the log of the percentage obtained to further normalize the distribution of the data in each experimental condition. To be considered as equivalent to MEP_{single}, the normalized data needed to be significantly different from the boundaries of a ± 0.4 window centred around 2 (corresponding to a MEP_{double} data fitting

within a ±20% window centred on 100% of MEP_{single} in log) [351, 353, 381]. This was tested for each experimental condition, using two one-sided t-tests (one for each boundary) given our a priori hypotheses [381]. In a second step, we also determined the smallest significant boundary for each condition. To do so, one-sided t-tests starting at ±0.4 around 2 (i.e., ±20% around 100% in log) and decreasing by ±0.02 (i.e., 1% of 2) were performed until we found the narrowest windows between which $MEP_{double-1}$ and $MEP_{double-2}$ significantly fitted ($p < 0.05$).

2.3.6.3 MEP coefficient of variation (CV)

The variability of MEP amplitudes was assessed by computing a coefficient of variation (CV = [SD/mean MEP amplitude] x 100) in each experimental condition [364]. Similar to the procedure followed for the analysis of MEP amplitudes, we first focused on CVs at rest (at $TMS_{baseline-out}$ and $TMS_{baseline-in}$; three-way ANOVA RM, same factors as for MEP amplitudes). Then, after having expressed the CVs at $TMS_{delay-900}$ and $TMS_{delay-950}$ as a percentage of CVs at $TMS_{baseline-in}$, we considered changes during the delay period (four-way ANOVA RM, same factors as for MEP amplitudes). The CVs were also log-transformed for these analyses as the data were not normally distributed. Finally, bioequivalence of CVs obtained in the context of $double\text{-}coil_{1ms}$ and single-coil TMS was also estimated for the TMS baseline and TMS_{delay} timings, using the exact same procedure as for the MEP amplitudes.

Post-hocs comparisons were always conducted using the Fisher's Least Significant Difference (LSD) procedure. All of the data are expressed as mean ± SE and the significance level was set at $p \leq 0.05$.

2.4 Results

2.4.1 Reaction time (RT)

The RTs are shown on Figure 2.2 separately for the left and right hand trials. The ANOVA RM revealed a significant influence of TMS_{TIMING} [$F_{(1,14)}$ = 124.015 and $p \leq 0.001$]: RTs were generally faster with TMS_{delay} (272.6 ± 36.4 ms) than with $TMS_{baseline-in}$ (309.4 ± 38.8 ms), consistent with many previous reports showing that a TMS pulse applied close to the imperative signal can speed up the release of a motor response [114, 128, 156]. Furthermore, the $MEP_{CONDITION}$ also influenced the RTs [$F_{(2,28)}$ = 6.007, p = 0.007]: Fisher LSD post-hoc tests revealed that RTs were significantly longer in the $MEP_{single-Resp}$ condition than in the $MEP_{single-NonResp}$ and MEP_{double} conditions (both $p \leq 0.004$); the two latter were not different (p = 0.597). These results indicate that the RTs were slower in the presence of a single pulse eliciting a MEP in the responding hand compared to when the MEP was elicited in the non-responding hand or in both hands at once. Finally, the Mvt_{SIDE} x TMS_{TIMING} x $MEP_{CONDITION}$ interaction was significant [$F_{(2,28)}$ = 5.125, p = 0.013]. As such, the slowing effect of $MEP_{single-Resp}$ reported above was systematically observed with TMS_{delay} in both hands (all $p \leq 0.038$). Yet, in trials with $TMS_{baseline-in}$, it was only present for right hand (both $p \leq 0.023$) but not for left hand trials (both $p \geq 0.198$).

2.4.2 MEP amplitude

2.4.2.1 FDI MEPs recorded at $TMS_{baseline}$

First, we considered FDI MEPs acquired at rest, either during the blocks ($TMS_{baseline-in}$) or outside them ($TMS_{baseline-out}$). As evident on Figure 2.3A, MEPs were generally larger at $TMS_{baseline-in}$ (1.8 ± 0.79 mV) than at

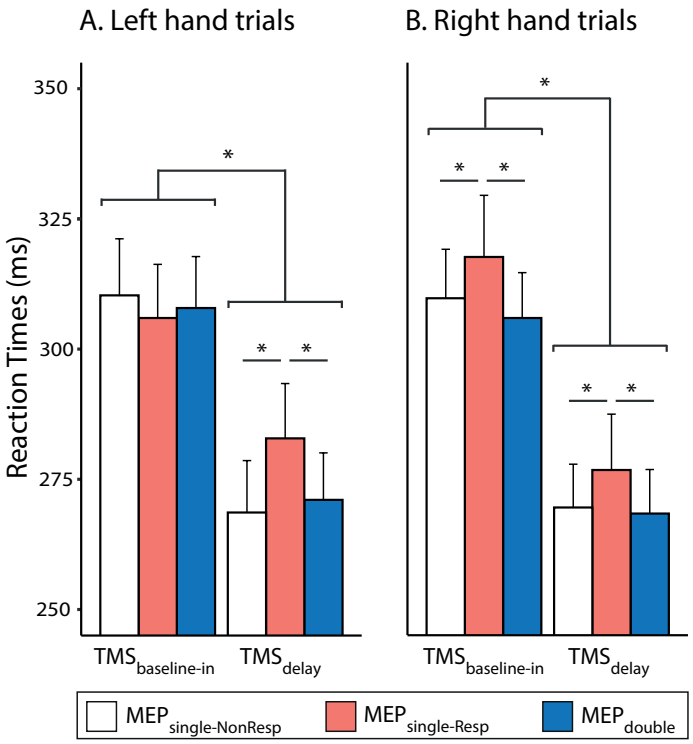

Figure 2.2: Left (A) and Right (B) hand reaction times (RTs, in ms) recorded in trials with $TMS_{baseline-in}$ or TMS_{delay} ($TMS_{delay-900}$ and $TMS_{delay-950}$ pooled together), eliciting a MEP_{single} in the responding or non-responding hand ($MEP_{single-Resp}$ or $MEP_{single-NonResp}$, respectively) or MEP_{double} in both hands. *Significantly different ($p \leq 0.05$).

$TMS_{baseline-out}$ (1.3 ± 0.70 mV; $p \leq 0.001$). Hence, MEP amplitudes were increased when elicited in the context of the task, as shown in previous reports [160, 365, 385]. Importantly this increase was equivalent in all conditions and occurred in the same proportion whether MEPs were elicited using single-coil (MEP_{single}) or double-$coil_{1ms}$ TMS ($MEP_{double-1}$ and $MEP_{double-2}$); the different MEP_{TYPE} never differed from one another, whether elicited at TMS $_{baseline-out}$ or $TMS_{baseline-in}$ [$F_{(2,26)} = 0.405$, $p = 0.671$].

Second, we aimed to further assess the bioequivalence of the FDI MEP $_{TYPE}$ at TMS baseline. To do so, similar to the procedure used in a pre-

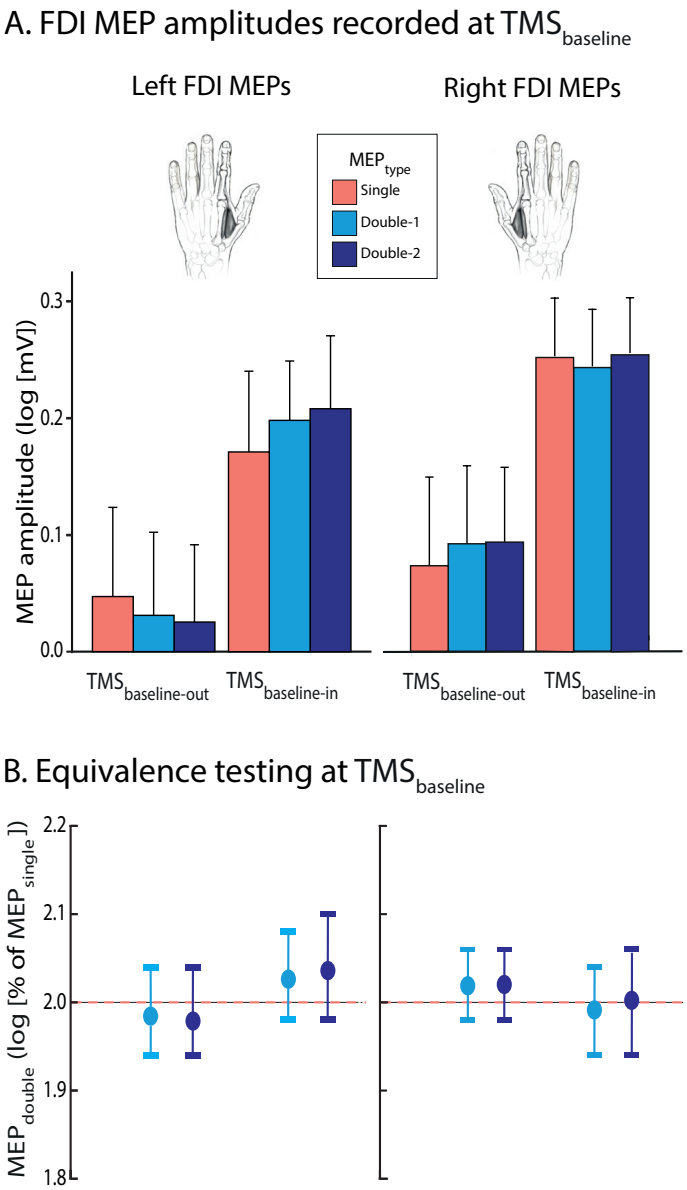

Figure 2.3: (A) Log-transformed MEP$_{single}$ (red bars), MEP$_{double-1}$ (light blue bars), and MEP$_{double-2}$ (navy blue bars) at TMS$_{baseline-out}$ and TMS$_{baseline-in}$, elicited in the left or right first dorsal interosseous (FDI) muscle. Note that MEP amplitudes at TMS$_{baseline-in}$ were significantly larger than at TMS$_{baseline-out}$; $p \leq 0.001$. (B) MEP$_{double-1}$ and MEP$_{double-2}$ amplitudes (expressed as log-transformed percentages of MEP$_{single}$) significantly fitted in windows ranging between 1.94 and 2.10 l.u. [log(100) = 2], indicating comparable amplitudes for all MEP$_{TYPE}$. The vertical bars represent the smallest significant boundaries around the mean for each condition. Each plot refers to the above colour-coded condition on the x-axis.)

vious study [381], we expressed the $MEP_{double-1}$ and $MEP_{double-2}$ data as a percentage of MEP_{single}. We compared these percentages with boundaries set at ± 20% around 100% (corresponding to MEP_{single}), through multiple one-sided t-tests [351]. Notably, because the percentages were log-transformed for the analyses, this involved comparing them with boundaries set at ± 0.4 around 2 log units (l.u) [because log(100) = 2]. At $TMS_{baseline-out}$ as well as at $TMS_{baseline-in}$, the log-transformed normalized $MEP_{double-1}$ and $MEP_{double-2}$ amplitudes significantly fitted into the ± 0.4 window. As we can see on Figure 2.3B, the $MEP_{double-1}$ and $MEP_{double-2}$ even fitted in smaller windows (all $MEP_{double-1}$ between 1.94 and 2.08 l.u.; i.e., between 97 and 104% of MEP_{single} and all $MEP_{double-2}$ between 1.94 and 2.10 l.u. [97 - 105%], all $p \leq 0.05$).

2.4.2.2 FDI MEPs recorded at TMS_{delay}

Then, we evaluated FDI MEP amplitudes during action preparation. To do so, MEPs elicited at $TMS_{delay-900}$ and $TMS_{delay-950}$ were expressed as a percentage of MEPs elicited at $TMS_{baseline-in}$. On average, MEPs equalled 69.7 ± 18.85 and 70.0 ± 21.13% of baseline when elicited at $TMS_{delay-900}$ and $TMS_{delay-950}$, respectively. These data were log-transformed for the analyses (Figure 2.4A); all normalized MEPs were smaller than 2 [i.e., log(100); all $t \leq -3.442$, $p \leq 0.003$], reflecting a consistent suppression of MEPs during the delay period, both at $TMS_{delay-900}$ and $TMS_{delay-950}$. Importantly, the ANOVA RM did not reveal any significant effect of the factor MEP_{TYPE} [$F_{(2,26)} = 0.513$, $p = 0.685$]: the MEPs acquired with double-$coil_{1ms}$ TMS, either by a first ($MEP_{double-1}$) or second pulse ($MEP_{double-2}$), were comparable to MEP_{single}. Besides, MEP amplitudes were the same at both TMS_{TIMING} [$F_{(1,13)} = 0.115$ and $p \geq 0.45$] and did not depend on whether they were

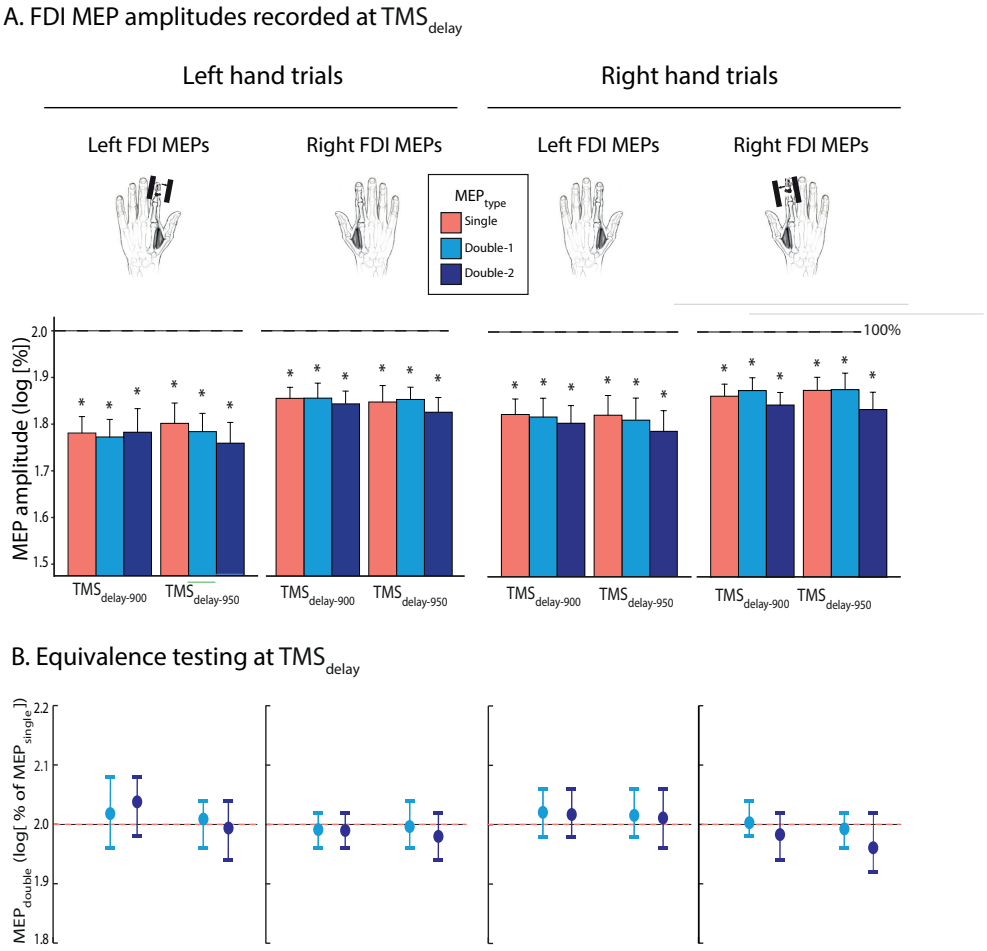

Figure 2.4: (A) Log-transformed MEP$_{single}$ (red bars), MEP$_{double-1}$ (light blue bars), and MEP$_{double-2}$ (navy blue bars) at TMS$_{delay-900}$ and TMS$_{delay-950}$ (initially expressed as a percentage of TMS$_{baseline-in}$), elicited in the left or right first dorsal interosseous (FDI). Data are shown separately for left (left panel) and right hand (right panel) trials. (B) Log-transformed MEP$_{double-1}$ and MEP$_{double-2}$ amplitudes at TMS$_{delay}$ (initially expressed in percentage of MEP$_{single}$). These data significantly fitted in windows ranging from 1.92 to 2.08 l.u. [i.e., between 96 and 104% of MEP$_{single}$ in log], indicating comparable amplitudes for MEP$_{double}$ and MEP$_{single}$ during action preparation. The vertical bars represent the smallest significant boundaries around the mean for each condition. Each plot refers to the above colour-coded condition on the x-axis. *p $\leq$ 0.005.

elicited in the left or right FDI [MEP_{SIDE} : $F_{(1,13)}$ = 3.241, p = 0.095], or on whether they occurred during a left or right hand trial [Mvt_{SIDE} : $F_{(1,13)}$ = 4.182, p = 0.062], although there was a small non-significant trend for the MEP suppression to be more pronounced preceding left hand trials, especially when probed in the left hand. None of the interactions were significant (all F $\leq$ 1.159, all p $\geq$ 0.330).

Concerning the bioequivalence testing at $TMS_{delay-900}$ and $TMS_{delay-950}$, the log-transformed $MEP_{double-1}$ and $MEP_{double-2}$ data (initially expressed in percentage of MEP_{single}) significantly fitted into the $\pm$ 0.4 window around 2. These data even fitted in smaller windows as shown on Figure 2.4B (all $MEP_{double-1}$ between 1.96 and 2.08 l.u. [i.e., between 98 and 104% of MEP_{single}] and all $MEP_{double-2}$ between 1.92 and 2.08 l.u. [96 - 104%]; all p $\leq$ 0.05).

2.4.2.3 Additional analyses on FDI MEP Amplitudes

We performed a three-way ANOVA RM focusing on the normalized MEP_{single} data, with TMS_{TIMING} ($TMS_{delay-900}$, $TMS_{delay-950}$), MEP_{SIDE} (MEP_{left} or MEP_{right}), and Mvt_{SIDE} (Mvt_{left} or Mvt_{right}) as within-subject factors to ensure that the absence of effect between conditions in which the muscle was selected or not selected for the forthcoming response was not related to the inclusion of additional MEP_{TYPES} ($MEP_{double-1}$ and $MEP_{double-2}$). This ANOVA RM did not reveal any significant MEP_{SIDE} x Mvt_{SIDE} interaction [$F_{(1,13)}$ = 0.457, p = 0.511], neither did this interaction interact with the factor TMS_{TIMING} [TMS_{TIMING} x MEP_{SIDE} x Mvt_{SIDE} : $F_{(1,13)}$ = 1.99, p = 0.182]. Hence, the level of inhibition was comparable in selected and non-selected conditions in the present study, regardless of whether a single- or double-coil procedure was used.

2.4.2.4 Additional analyses on ADM MEP amplitudes

As mentioned above, stimulation of the hotspot for the FDI, also elicited MEPs in the ADM, a pinkie abductor. Although this muscle is irrelevant in the "Rolling Ball" game, its MEPs basically showed the same changes as those observed in the FDI, although in an attenuated manner. At rest, ADM MEPs were globally larger at $TMS_{baseline-in}$ than $TMS_{baseline-out}$ [$F_{(1,13)}$ = 24.791, p $\leq$ 0.001]. Most importantly, ANOVA RM revealed that single-coil and double-$coil_{1ms}$ TMS elicited comparable ADM MEPs at rest [MEP_{TYPE} $F_{(2,26)}$ = 0.148, p = 0.863]. Consistently, the bioequivalence tests showed that all log-transformed $MEP_{double-1}$ and $MEP_{double-2}$ amplitudes (initially expressed in percentage of MEP_{single}) significantly fitted into smaller windows than $\pm$ 0.4 around 2: all $MEP_{double-1}$ and $MEP_{double-2}$ amplitudes fitted in a 1.92 - 2.08 window, i.e., 96 - 104%, all p $\leq$ 0.05).

In addition, ADM MEPs were also suppressed during the delay period (all t $\leq$ -2.042, all p $\leq$ 0.031), regardless of the TMS_{TIMING} [$F_{(1,13)}$ = 0.036, p = 0.853] or the MEP_{SIDE} [$F_{(1,13)}$ = 0.149, p = 0.705]. Note that the MEP suppression was significantly less pronounced preceding right than left hand movements [$F_{(1,13)}$ = 5.165, p = 0.041]. Importantly, the factor MEP_{TYPE} was non-significant [$F_{(2,26)}$ = 0.157, p = 0.855]. At both delay timings, all $MEP_{double-1}$ and $MEP_{double-2}$ amplitudes fitted in 1.94 - 2.08 [97 - 104%] and 1.92 - 2.06 [96 - 103%] windows, respectively. Thus the double-$coil_{1ms}$ protocol seemed to induce comparable MEPs as single-coil TMS in an irrelevant muscle as well.

2.4.3 Coefficient of variation (CV) of MEPs

2.4.3.1 CV of FDI MEPs recorded at $TMS_{baseline}$

First, we focused on the CV of FDI MEPs elicited at $TMS_{baseline-out}$ and $TMS_{baseline-in}$ (Figure 2.5A). Overall, they equalled 54.8 ± 18.91% and 47.1 ± 17.88% at these two TMS timings, respectively. The ANOVA RM revealed a significant effect of TMS_{TIMING} on the log-transformed data [$F_{(1,13)}$ = 5.14, p = 0.041], with smaller CVs at $TMS_{baseline-in}$ than at $TMS_{baseline-out}$. Hence, MEPs were generally larger and less variable when elicited at rest but in the context of a task, than when elicited outside the blocks. This effect tended to be stronger for MEPs elicited in the right than in the left FDI, but the TMS_{TIMING} x MEP_{SIDE} interaction did not reach significance [$F_{(1,13)}$ = 4.092, p = 0.064]. Though, the factor MEP_{SIDE} was significant [F = 7.67; p = 0.02]: CVs were smaller for MEPs elicited in the right FDI compared to when they were evoked in the left FDI, indicating an overall smaller variability of MEPs in the dominant hand. Importantly, all these effects occurred regardless of whether the MEPs were elicited using a single-coil or a double-$coil_{1ms}$ procedure. That is, neither the factor MEP_{TYPE} [$F_{(2,26)}$ = 0.049, p = 0.952], nor its interaction with the other factors (all F ≤ 1.431, all p ≥ 0.257) were significant. Similar to the MEP amplitudes, in order to assess the statistical bioequivalence of the double-$coil_{1ms}$ and single-coil CVs, we expressed the CVs of $MEP_{double-1}$ and $MEP_{double-2}$ as log-transformed percentages of MEP_{single} and tested whether these normalized data were significantly different from boundaries set at ± 0.4 around 2. As we can see on Figure 2.5B, the $MEP_{double-1}$ and $MEP_{double-2}$ even fitted in smaller windows (all $MEP_{double-1}$ between 1.88 and 2.14 l.u. [i.e., between 94 and 107% of MEP_{single}] and all $MEP_{double-2}$ between 1.90 and 2.14 l.u. [95 - 107%]; all p ≤ 0.05).

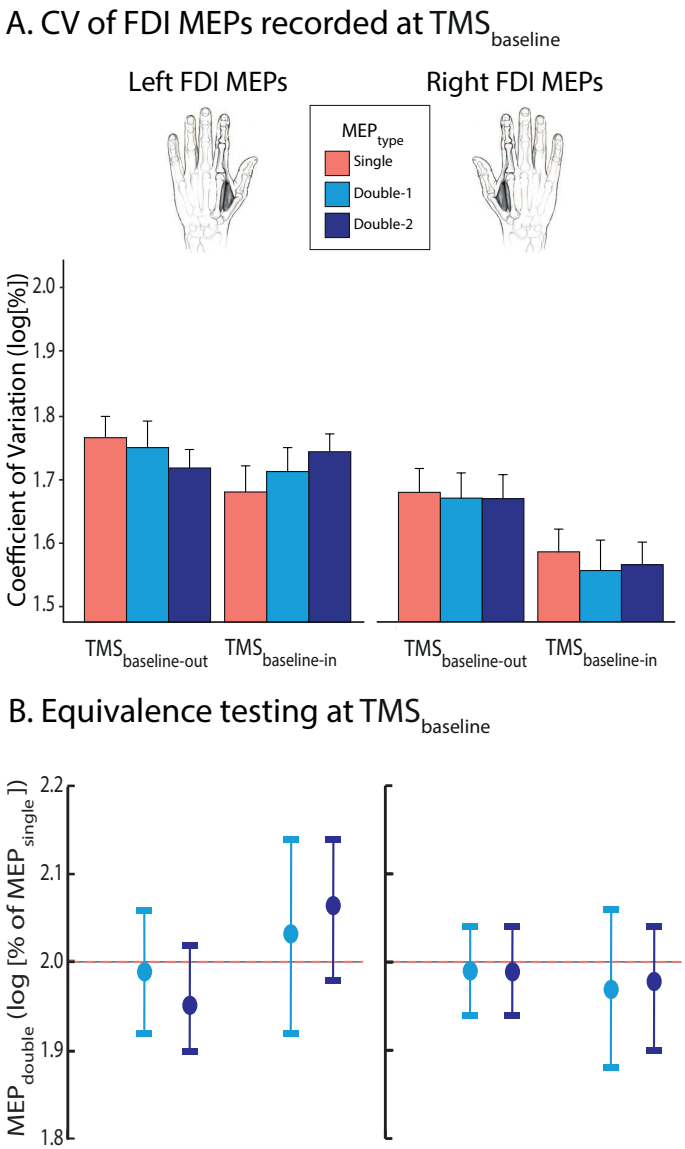

Figure 2.5: (A) Log-transformed coefficients of variation (CV) of MEP_{single} (red bars), $\text{MEP}_{double-1}$ (light blue bars), and $\text{MEP}_{double-2}$ (navy blue bars) at $\text{TMS}_{baseline-out}$ and $\text{TMS}_{baseline-in}$, elicited in the left or right first dorsal interosseous (FDI) muscle. Note that CVs were significantly reduced at $\text{TMS}_{baseline-in}$ compared to $\text{TMS}_{baseline-out}$. Also, MEPs were generally less variable in the right than in the left FDI; $p \leq 0.05$ for both effects. (B) $\text{MEP}_{double-1}$ and $\text{MEP}_{double-2}$ CVs significantly fitted in windows ranging between 1.88 and 2.14 l.u. [log(100) = 2] indicating comparable CVs for all left and right FDI MEP_{TYPE}. The vertical bars represent the smallest significant boundaries around the mean for each condition. Each plot refers to the above colour-coded condition on the x-axis.

2.4.3.2 CV of FDI MEPs recorded at TMS_{delay}

Then, we turned to the CV of MEPs elicited during the delay period (Figure 2.6A). On average, they reached 90.2 ± 28.63 and 92.8 ± 36.12% of baseline values at $TMS_{delay-900}$ and $TMS_{delay-950}$, respectively. The t-tests performed on the log-transformed data revealed that CVs tended to show a further decrease at both TMS_{delay} timings compared to $TMS_{baseline-in}$, although this effect was only significant for 37.5% of conditions; it was close to significance in 46.7% of the remaining conditions ($0.05 \leq p \leq 0.10$). The four-way ANOVA RM did not reveal any further difference. None of the interactions or factors, including the MEP_{TYPE} [$F_{(2,26)} = 0.692$, $p = 0.509$], were significant.

Again, at both delay timings, the log-transformed $MEP_{double-1}$ and $MEP_{double-2}$ data (initially expressed in percentage of MEP_{single}) significantly fitted into a ± 0.4 window around 2. As evident on Figure 2.6B, the $MEP_{double-1}$ and $MEP_{double-2}$ CVs even fitted in smaller windows (all $MEP_{double-1}$ between 1.90 and 2.12 l.u. [i.e., between 95 and 106% of MEP_{single}] and all $MEP_{double-2}$ between 1.88 and 2.12 l.u. [94 - 106 %]; all $p \leq 0.05$).

Hence, altogether, these data show that the double-$coil_{1ms}$ protocol is associated with comparable MEP amplitudes and CVs as the single-coil TMS procedure, whether these MEP parameters are assessed at rest or during action preparation.

2.4.3.3 Additional analyses on CV of ADM MEPs

The CVs were also computed for the ADM MEPs. Globally, we observed the same changes as those observed for the FDI. At rest, the CVs of ADM MEPs were globally smaller at $TMS_{baseline-in}$ than $TMS_{baseline-out}$ [$F_{(1,13)} = 18.314$, $p = 0.001$] but comparable for the different MEP_{TYPE} [$F_{(2,26)} = 1.011$, $p =$

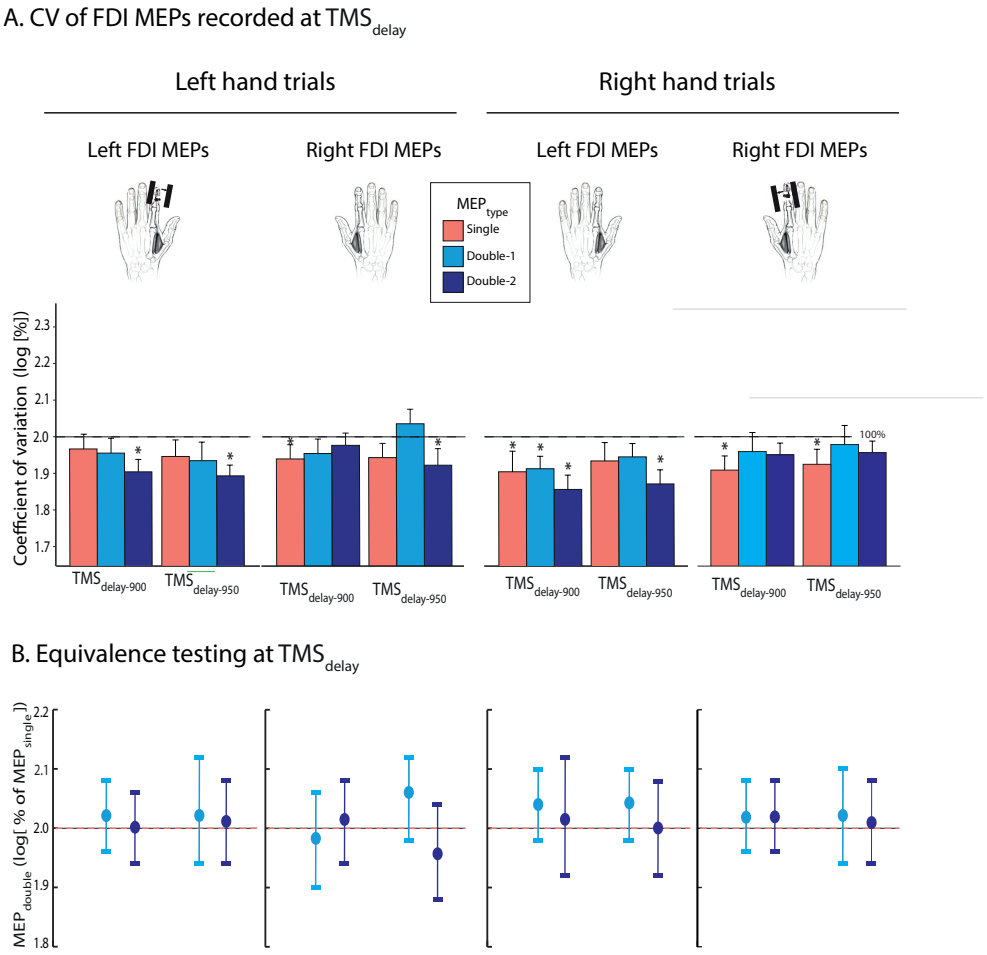

Figure 2.6: (A) Log-transformed coefficient of variation (CV) of MEP_{single} (red bars), $\text{MEP}_{double-1}$ (light blue bars), and $\text{MEP}_{double-2}$ (navy blue bars) at $\text{TMS}_{delay-900}$ and $\text{TMS}_{delay-950}$ (initially expressed as a percentage of $\text{TMS}_{baseline-in}$), for the left or right first dorsal interosseous (FDI) muscles. Data are shown separately for MEPs acquired during left (left panel) and right hand (right panel) trials. Note that the factor MEP_{TYPE} was never significant. (B) Log-transformed CV of $\text{MEP}_{double-1}$ and $\text{MEP}_{double-2}$ at TMS_{delay} (initially expressed in percentage of MEP_{single}). These data significantly fitted in windows ranging from 1.88 to 2.12 l.u. [i.e., between 94 and 106% of MEP_{single} in log], indicating comparable CVs for MEP_{double} and MEP_{single} during action preparation. The vertical bars represent the smallest significant boundaries around the mean for each condition. Each plot refers to the above colour-coded condition on the x-axis. *p $\leq$ 0.05.

0.378]. Consistently, the bioequivalence tests showed that all $MEP_{double-1}$ and $MEP_{double-2}$ amplitudes significantly fitted into smaller windows than ± 0.4 (all $MEP_{double-1}$ between 1.94 and 2.14 l.u. [97 - 107%] and all $MEP_{double-2}$ between 1.92 and 2.20 l.u. [96 - 110%]; all $p \leq 0.05$).

There was also a small trend for ADM CVs to decrease during the delay period with respect to $TMS_{baseline-in}$ (but reaching significance in only 20.8% of TMS_{delay} conditions). Similarly to FDI CVs, the ANOVA RM showed that CVs across the MEP_{single}, $MEP_{double-1}$, and $MEP_{double-2}$ conditions were similar [$F_{(2,26)} = 1.284$, $p = 0.294$]. No other interaction was found (all $F \leq 3.036$, all $p \geq 0.105$]. At both delay timings, all $MEP_{double-1}$ and $MEP_{double-2}$ CVs fitted in 1.94 - 2.12 [97 - 106 %] and 1.90 - 2.10 [95 - 105%] windows, respectively. Thus, MEPs elicited in an irrelevant muscle also displayed a CV that was comparable for the single-coil and double-$coil_{1ms}$ protocols.

2.5 Discussion

2.5.1 Summary of study goals

The goal of the present study was to assess whether the MEPs acquired using double-$coil_{1ms}$ are equivalent to those obtained by means of a classical single-coil TMS method. To do so, we compared MEPs elicited by a first ($MEP_{double-1}$) or second ($MEP_{double-2}$) double-$coil_{1ms}$ TMS pulse to MEPs obtained using single-coil TMS (MEP_{single}). Both the amplitude and coefficient of variation (CV) of MEPs were considered. We compared these MEP variables in the context of a motor task requiring subjects to prepare and delay left or right index finger responses until the onset of an imperative signal. MEP_{single} are typically suppressed during the delay period [48, 385]. Here, we show that comparable inhibitory changes can be observed with $MEP_{double-1}$

and $MEP_{double-2}$. The MEPs exhibited comparable amplitudes and CVs, regardless of whether they had been elicited using a single-or double-$coil_{1ms}$ TMS approach.

2.5.2 Comparing the amplitude of MEP_{single} and MEP_{double} during action preparation

The amplitude of MEPs was much smaller at TMS_{delay} compared to $TMS_{baseline-in}$, consistent with many previous reports [127, 128, 154, 157, 349]. This effect was observed regardless of whether the MEPs were recorded from a muscle that was selected or non-selected for the forthcoming response. This result may seem inconsistent with previous work [128, 149, 161]. However, several recent studies have failed to observe a difference of inhibition between selected and non-selected conditions, suggesting that this effect is not consistent and does not systematically show up [154, 349, 386]. As suggested in Quoilin et al. (2016) [154], it is likely to depend on the task details, including the use (or not) of response devices, the presence (or not) of catch trials, the time at which TMS is delivered and eventually, the presentation of a feedback (or not). Inhibition at TMS_{delay} was also observed for a muscle that was irrelevant in the task, corroborating the idea that withholding a prepared action is associated with widespread inhibitory influences suppressing CSE until the movement can be initiated (reviewed in Duque et al. (2017) [22]). The suppression of MEPs tended to be deeper in the left compared to the right hand, consistent with the view that inhibitory changes are often more pronounced on the non-dominant compared to the dominant side [147, 154, 349, 387]. Note that this tendency was not observed in a previous work [149]. Yet, an important difference there is that Klein et al. (2016) [149] registered MEP_{left} and MEP_{right} in separate blocks, reducing the signal to noise ratio when com-

paring these conditions. Furthermore, we found that MEPs were similarly decreased at $\text{TMS}_{delay-900}$ and $\text{TMS}_{delay-950}$, probably because preparatory inhibition had reached a plateau by the time TMS was applied, in accordance with recent observations [157].

Most importantly, the strength of the inhibitory effect at TMS_{delay} was comparable across all MEP_{TYPE}. As such,bioequivalent analyses revealed that MEP_{single}, $\text{MEP}_{double-1}$, and $\text{MEP}_{double-2}$ displayed the exact same level of suppression during action preparation. This result may stand at odds with another study in which we observed differences between MEP_{single} and MEP_{double} at TMS_{delay} [349]. However, an important weakness in that work is that the single and double-coil_{1ms} protocols were tested in separate blocks. Hence, the difference between MEP_{single} and MEP_{double} was likely due to the fact that subjects were more vigilant or alert when they expected two pulses to occur (increasing MEP amplitudes) compared to when only one pulse was anticipated [160, 308, 365]. By intermingling all conditions within each block, the present study allowed to control for this bias: our data show that in its absence, all MEP_{TYPE} display a comparable degree of suppression during action preparation. Note however that, because MEPs are rather global readouts of CSE, these results do not allow to rule out completely the occurrence of some bilateral interactions following double-coil_{1ms} TMS. Yet, even if present, these interactions do not alter MEP amplitudes in a systematic way and do not preclude from obtaining measures of preparatory inhibition that are comparable to those acquired with single-coil TMS.

2.5.3 Comparing the CV of MEP$_{single}$ and MEP$_{double}$ during action preparation

In order to evaluate changes in the variability of CSE during action preparation, we measured the CV of MEPs elicited using single-coil or double-coil$_{1ms}$ TMS. Overall, we observed a decrease in the CV of MEPs at TMS$_{delay}$ compared to TMS$_{baseline-in}$, even if this effect was not present in all conditions. Therefore, CSE tended to be less variable during action preparation compared to rest, consistent with a previous report [364]. Such a decrease in the variability of CSE during action preparation may reflect an optimization process of neuronal firing rates in the motor cortex [177]. Following this view, firing rates progressively become more consistent during action preparation, reaching a specific state to produce the desired movement [388]. Interestingly, this small decrease in the CV of MEPs at TMS$_{delay}$ was not only observed for the FDI but also for the ADM. Hence, the variability of CSE decreased for both task-relevant and irrelevant muscles; the tuning of motor activity during action preparation may thus not be completely specific to the agonist effectors [364, 389]. Most importantly, changes in the CV from TMS$_{baseline-in}$ to TMS$_{delay}$ were equivalent for MEP$_{single}$, MEP$_{double-1}$ and MEP$_{double-2}$, suggesting that double-coil$_{1ms}$ TMS is as effective as single-coil TMS to capture changes in the variability of CSE during action preparation.

2.5.4 Comparing the amplitude and CV of MEP$_{single}$ and MEP$_{double}$ at rest

In the present study, we acquired two baseline measures of MEPs at rest. That is, MEPs were elicited during the intertrial interval (TMS$_{baseline-in}$) within the blocks, but also outside the blocks (TMS$_{baseline-out}$). At both timings, MEP amplitudes were generally comparable when elicited in the left

or right hand, confirming that measures of CSE are highly comparable for both hemispheres at rest [390]. Yet, the CV of FDI MEPs was smaller in the right than in the left hand. Hence, neuronal firing rate may be steadier on the dominant side. Interestingly, MEP amplitudes were larger when acquired within the blocks compared to outside them and this effect was associated with a decrease in the CV of MEPs. Hence, CSE was larger and less variable when probed within the context of the motor task compared to when the subjects were at complete rest, outside the blocks. Such an effect on MEP amplitudes has been reported in a previous study comparing different baseline conditions [365]. That is, Labruna et al. (2011) [365] showed that MEPs were larger when elicited in the context of a task requiring subjects to passively view hand or landscape pictures than when elicited outside the task, suggesting that the level of vigilance has a significant influence on CSE.

Importantly, our bioequivalence analyses revealed that MEP_{single}, $\text{MEP}_{double-1}$, and $\text{MEP}_{double-2}$ were comparable in all baseline conditions. The bioequivalence of MEPs at complete rest ($\text{TMS}_{baseline-out}$) had already been reported in a previous study [381]. Here, we show that this equivalence persists when baseline MEPs are elicited in the context of a motor task ($\text{TMS}_{baseline-in}$).

2.5.5 Comparing the impact of MEP_{single} and MEP_{double} on reaction times (RTs)

First of all, RTs were generally faster with TMS_{delay} than with $\text{TMS}_{baseline-in}$, consistent with many previous reports showing that a TMS pulse applied close to the imperative signal can prime subjects to respond faster [114, 128, 154, 156] probably because the TMS sound triggers the release of the movement that is being prepared [391, 392]. Interestingly, we also found that RTs were

longer in trials where a MEP_{single} occurred in the responding hand compared to when the MEP_{single} fell in the non-responding hand, or in both hands at once (MEP_{double}). This effect was present in all conditions at TMS_{delay}, indicating that the boosting effect of the TMS sound was slightly attenuated when the MEP fell specifically in the responding hand, compared to when it fell in the other hand or in both hands, consistent with other works [166, 349]. Surprisingly this effect of the $\text{MEP}_{CONDITION}$ was also observed with $\text{TMS}_{baseline-in}$ in right hand trials but not left hand trials. This result was unexpected given that here, MEPs were elicited during the intertrial interval and should thus not affect behaviour, an issue for future investigation.

2.5.6 Advantages of Double-coil$_{1ms}$ TMS and future directions

The double-coil$_{1ms}$ protocol shows many advantages over the regular single-coil technique. First, the number of MEPs that can be collected in a given amount of time is doubled. This is a crucial aspect as it gives the opportunity to test more conditions within the same duration than could be done with a regular single-coil method. Second, CSE is probed bilaterally on the same trial meaning that both hands can be probed simultaneously. Hence, dominant and non-dominant hand MEPs are elicited in the exact same conditions during the task [166]. This obviously increases the signal to noise ratio in a significant way. Third, the acquisition of MEPs in both hands allows researchers to make direct comparisons between bilateral MEPs on a single-trial basis and to develop new measures such as indexes reflecting the ratio between the CSE of the two hands. In fact, one may be interested in studying the impact of various task parameters (e.g., instruction, presence of reward, sensory evidence, level of urgency, effort required etc.) on the relationship between bilateral MEP

amplitudes and CVs. Hence, the present technique opens new horizons in the study of how both hemispheres interact in various task settings [149, 393].

2.6 Conclusion

The present study suggests that the double-coil$_{1ms}$ TMS can be used to probe CSE within the context of a motor task. As such, we show that MEPs elicited using a double-coil$_{1ms}$ technique are equivalent to those obtained by means of single-coil TMS, both at rest and during action preparation. This new method is promising since it allows to record MEPs from both hands simultaneously, doubling the amount of data that can be acquired in a given period of time. The development of double-coil$_{1ms}$ TMS might participate in the actual expansion of TMS in a broad range of neurophysiological as well as neurological studies.

Author contributions

PV and JG: contributed equally; PV, JG, GD, and JD: designed research; PV, JG, YdW, and LQ: performed research; PV, JG, GD, YdW, LQ, and JD: analysed data; PV and JD: wrote the article.

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Chapter 3 Investigating the effect of anticipating a startling acoustic stimulus on preparatory inhibition

"Life is full of surprises."

John Major

Chapter 3: reminder of the aim and hypotheses

Whilst many TMS studies have evidenced a profound suppression of activity in the CS pathway in situations requiring the preparation of a movement, others have shown that a loud sound, called a SAS, can directly trigger the release of a prepared action when presented slightly before, simultaneously or after the onset of a go-signal in simple and choice RT tasks. In the current Chapter, we have intended to characterize the impact of a SAS occurring before the go-signal in an instructed-delay choice RT task, when the subject is actively withholding a prepared action. More critically, we have investigated whether anticipating the occurrence of a SAS can reduce its shortening impact on RTs (to avoid a penalty), presumably due to the recruitment of impulse control processes in order to help prevent premature startle responses. Based on the impulse control hypothesis, we predicted that in order to comply with the instruction requiring them to avoid responding prematurely, subjects would recruit more preparatory inhibition when they expected SAS to occur compared to when SAS were less likely.

Investigating the effect of anticipating a startling acoustic stimulus on preparatory inhibition

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Keywords

Action preparation, corticospinal excitability, double-coil, impulse control, motor-evoked potential, transcranial magnetic stimulation.

3.1 Abstract

Objectives: Motor-evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) show a profound suppression when elicited during the instructed-delay of reaction time (RT) tasks. One predominant hypothesis is that this phenomenon, called "preparatory inhibition", reflects the operation of processes that suppress motor activity to withhold prepared (but delayed) responses, a form of impulse control. In addition, a startling acoustic stimulus (SAS) - a loud and narrow sound - can trigger the release of prepared responses in RT tasks. We predicted that, if such premature release is clearly forbidden, then anticipating a SAS during delay periods may be associated with increased preparatory inhibition for greater impulse control.

Investigating the effect of anticipating a startling acoustic stimulus on preparatory inhibition

Methods: Subjects performed a behavioural (n=16) and TMS (n=11) experiment. Both used a choice RT task that required subjects to choose a response based on a preparatory cue but to only release it after an imperative signal. SAS and TMS pulses were elicited at the end of the delay period and subjects were asked to do their best to only release their response after the imperative signal, even in the presence of SAS. SAS could be either rare or frequent, in separate blocks.

Results: Consistent with the literature, SAS shortened RTs, especially when they occurred frequently. Moreover, MEPs were suppressed when subjects delayed prepared responses but this preparatory inhibition did not depend on whether SAS were frequent or rare.

Discussion: The stronger RT shortening with frequent rather than rare SAS may be due to increased attention and/or reduced reactive inhibition to SAS, leaving preparatory inhibition unaffected.

3.2 Introduction

Acting adequately in everyday life often requires the ability to inhibit prevailing tendencies that are not consistent with our internal goals or to suppress actions that are no longer appropriate [297, 394]. When deficient, this capacity called response inhibition, can lead to improper behaviours, such as those seen in addiction and attention deficit hyperactivity disorders [132, 198, 395].

Response inhibition is commonly conceptualized as an executive function relying largely on the structural and functional integrity of the prefrontal cortex [123]. However, recent work using transcranial magnetic stimulation (TMS) has also implicated the motor system [126, 298]. When applied over the primary motor cortex (M1), this non-invasive technique can elicit motor-

evoked potentials (MEPs) in targeted contralateral hand or limb muscles; MEPs represent a valuable indicator of the excitability of the corticospinal (CS) motor output pathway at the time of stimulation, and their amplitude can be compared at various moments within a given condition and between different states [36, 48, 90].

Many TMS studies have evidenced a profound suppression of activity in the CS pathway in situations requiring abortion of a movement after a stop signal [126, 294, 298]. However, motor suppression is not solely present when one needs to abruptly stop an action but also during the preparation of a movement, a phenomenon referred to as preparatory inhibition [22, 48, 131, 156, 161]. Preparatory inhibition is particularly strong during instructed-delay reaction time (RT) tasks that require postponing a pre-cued response until a delayed imperative signal. In such conditions, one prominent hypothesis is that the motor suppression observed during the delay period assists impulse control, preventing the premature release of the prepared response [127, 385].

Previous studies have shown that a loud (e.g., 124dB) sound, called startling acoustic stimulus (SAS), can directly trigger the release of a prepared action when presented slightly before (- 25 ms), simultaneously or after (+25 ms) the onset of an imperative signal in simple and choice RT tasks [396, 397, 398, 399]. That is, the action is initiated much faster in trials including a SAS than in control trials; the RT shortening typically ranges from 46 to 62 ms [400] and can occur in parallel with a typical sequence of other events, including eye blink, neck flexion and facial grimacing, which together are referred to as a startle response [391, 401].

In line with these observations, here we intended to characterize the impact of a SAS occurring before the imperative signal in an instructed-delay

choice RT task, when the subject is actively withholding a prepared action. More critically, we aimed to assess whether anticipating the occurrence of a SAS can reduce its shortening impact on RTs (to avoid a penalty, see below), presumably due to the recruitment of impulse control processes that increase preparatory inhibition, in order to help prevent premature startle responses. To answer these questions, we performed both a behavioural (n=16) and a TMS (n=11) experiment. In both experiments, participants performed an instructed-delay choice RT task in two different block settings. In one type of block, the SAS were rare (referred to as "Rare SAS"; RSAS context) whereas in the other block type they were frequent ("Frequent SAS"; FSAS context). The task was the same in both contexts and required the participants to perform a left or right index finger abduction movement according to a preparatory cue but to withhold their response until a delayed imperative signal. After that, they had to respond as fast as possible. The SAS was always elicited close to the end of the delay period and subjects were asked to do their best to only release their response after the imperative signal, even in the presence of a SAS. Critically, subjects were clearly told about the fact that the SAS may produce the release of their response prematurely and that they had to try to refrain from doing so (premature responses provided in less than 90 ms were penalized). Moreover, they knew whether the ongoing block would either involve a small amount (RSAS context) or a large amount of SAS (FSAS context), as this information was explicitly provided before the beginning of each block. Hence, based on the impulse control hypothesis, we predicted that in order to comply with the instruction to avoid responding prematurely, subjects would recruit more preparatory inhibition when they expected SAS to occur (FSAS) compared to when SAS were less likely (RSAS).

3.3 Materials and Methods

3.3.1 Participants

A total of 27 subjects participated either in a behavioural (n= 16; 9 women; 21.9 ± 0.37 years old) or in a TMS experiment (n= 11; 7 women; 22 ± 0.75 years old). All were right-handed according to the Edinburgh Questionnaire [350]. None of them suffered from any neurological disorder or had a history of psychiatric illness, alcohol or drug abuse; none was taking drug treatment that could influence performance or neural activity. Participants were naive to the purpose of the study and were financially compensated. The protocol was approved by the institutional review board of the Université catholique de Louvain (Belgium) and required written informed consent.

3.3.2 Task

In both experiments, participants performed an instructed-delay choice RT task, which was implemented with Matlab 7.5 (Mathworks, Natick, Massachusetts, USA) using the Psychophysics Toolbox extensions [383, 384]. The task consisted in a virtual rolling ball game previously used in other studies [132, 154] (Figure 3.1A). In this game, a ball and a goal appear on a computer screen and participants must "shoot the ball into the goal", by performing a movement with the left or right index finger. On each trial, the required response is indicated by the position of the ball, which serves as a preparatory cue: participants were instructed to prepare an abduction of the left index finger when the ball was presented on the left side of the screen, and an abduction of the right index finger when it appeared on the right. Subjects were told to release their prepared movement once a bridge was presented (imperative signal), allowing the ball to reach the goal. A score reflecting the subjects'

performance was provided at the end of each trial. All objects were displayed on the computer screen with 3D perspective.

3.3.3 Experimental procedure

Experiments were conducted in a quiet and dimly-lit room. Participants sat in front of a 21-inch monitor screen positioned about 60 cm in front of them. Their arms were semi-flexed with both hands resting palm-down on a response device developed in our laboratory to detect any horizontal movement of the index fingers (Figure 3.1B). This setup has the advantage of delivering a very precise measure of the RT (precision = 1ms) and to control the initial index finger position at the beginning of the trial. Moreover, as the metal parts are mobile, they can be placed according to the morphology of each participant (for more details regarding this device, please refer to Quoilin et al. (2016) [154]).

Each trial was composed of several events (Figure 3.1C). It first started with a blank screen lasting for 2800 ms. Then, the preparatory cue appeared, which consisted of the ball and the goal separated by a gap. Subjects were explicitly told to prepare their response based on the position of the ball but to withhold it until the onset of the imperative signal (i.e. the bridge) which appeared 550 to 700 ms later. We purposely varied the duration of the delay period to decrease the subjects' tendency to respond prematurely (i.e. before the imperative signal). For the same reason, each block involved a few trials in which the bridge did not appear (i.e. catch trials - 4 per block). In these trials, subjects were required not to respond and were penalized if they did so. Once the bridge was on the screen, subjects had to respond as fast as possible to allow the ball to roll on it and to quickly reach the goal. Each trial ended with a feedback displaying a score for 500 ms. Subjects knew that this score would

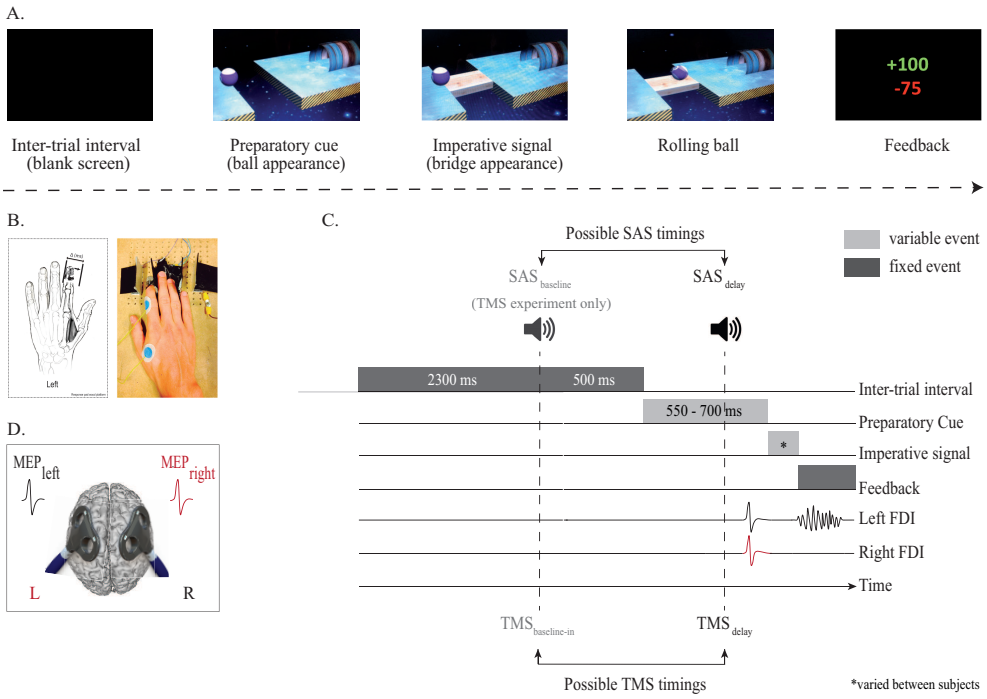

Figure 3.1: (A.) Rolling Ball task. Participants were asked "to shoot a ball in a goal" on each trial. To do so, they had to provide a response with the left or right index finger according to the position of the ball (preparatory cue) which could appear either on the left or on the right side of the screen (on the left side in the current example). Participants had to prepare their response as soon as the ball was presented but had to wait until the appearance of a bridge (imperative signal) to release their response. When the response was correct, the ball rolled on the bridge and reached the goal. A feedback reflecting how fast and accurate the subjects had been concluded each trial. (B.) The response device. Index finger responses were recorded using a home-made device positioned under the left (graphic representation) and right (photographic representation) hands. (C.) Time course of a trial. Each trial started with a blank screen (inter-trial interval) lasting for 2800ms. Then, the preparatory cue appeared for a variable delay period (550 - 700ms), followed by the imperative signal (duration determined on an individual basis based on the participant's RT, see below). The feedback was presented at the end of each trial for 500ms. In the TMS experiment, pulses either fell during the inter-trial interval (2300 ms after the blank screen onset; $\text{TMS}_{baseline-in}$), or during the delay period (500 ms after the preparatory cue onset; TMS_{delay}). Motor-evoked potentials (MEPs) were elicited in the first dorsal interosseous (FDI) of both hands using a double-coil TMS procedure. In SAS trials, the sound always occurred concurrently with the TMS pulse, either at $\text{SAS}_{baseline}$ (TMS experiment only) or SAS_{delay}. The figure displays a left hand trial with a SAS and a TMS pulse during the delay period. (D.) Double-coil_{1ms} TMS protocol. Two small figure-of-eight shaped coils were placed over the left and right primary motor cortex (M1), eliciting MEPs in the left and right FDIs on each trial, at a near simultaneous time (1ms delay).

depend on how fast and accurate they had been on the previous trial. That is, on correct trials, scores were inversely proportional to the RT (i.e., the faster the subjects, the higher the score); they were displayed in green and ranged from 1 to 100 [402]. The RT was defined as the time interval between the bridge appearance and the time at which the responding index finger left the outer metal edge of the response device. Incorrect responses were penalized, as indicated by negative scores displayed in red. They involved (1) responses occurring too early, referred to as anticipation errors (penalized by - 75 points), (2) responses occurring too late, referred to as time-out errors (penalized by - 50 points), (3) responses provided with the incorrect hand, referred to as choice errors (penalized by - 80 points) and (4) responses provided on catch trials, referred to as catch errors (penalized by - 75 points). Anticipation errors consisted in responses provided either before the bridge onset or after its onset but with a RT smaller than 90 ms: below this time, we consider that the response was released prematurely (i.e. before detection of the bridge) given the fixed time required for visuo-motor conversion to occur [401]. Time-out errors consisted in responses provided after the bridge offset (determined on an individual basis, see below). Note that when subjects succeeded not to respond on a catch trial, they were rewarded by + 12 points. The total score was displayed at the end of each block. In some trials, a SAS occurred. This consisted of a narrow band noise pulse (1 kHz, 40 ms, 118 decibel) produced and presented via headphones (Harman International [Stamford, USA] Model AKG K430). The sound was calibrated by a Digital Sound Level Meter (SECOMP International [Bassersdorf, Switzerland] Model Roline RO1350) using the standard A-weighted decibel scale and measured 2 cm from the headphone speaker. Importantly, when applied during action preparation in RT tasks, a SAS can accelerate the initiation of the prepared movement

[391, 398, 401, 403]. As such, RTs are usually reduced on trials in which a SAS is presented at the imperative signal, and the extent of the shortening effect has led researchers to propose that such a loud sound prompts the release of preliminary motor plans that have already reached subcortical aspects of the motor output pathway [392, 399, 404], but see also Marinovic et al. (2016) [405] for opposing views.

Interestingly, the influence of SAS applied when subjects are actively withholding a movement following a fully informative preparatory cue, postponing its initiation until an imperative signal, is unknown. In fact, inhibitory influences are largely deployed during such delay periods [22] and these processes may reduce the impact of a SAS occurring at that time (SAS_{delay}), compared to when it is applied in regular RT tasks that do not explicitly require postponing a fully prepared response. Here, we aimed at testing the influence of a SAS_{delay} by applying it always 500 ms after the preparatory cue onset (i.e. falling - 150 to - 50 ms before the imperative signal) in the Rolling Ball task. Moreover, we were interested in investigating whether the impact of a SAS_{delay} can be reduced when it is anticipated, possibly through the strengthening of inhibitory influences serving to withhold prepared responses. To address this point, the probability of a SAS_{delay} was varied in two different types of blocks. In a first block type, SAS_{delay} were rare (R) occurring only in very few trials (6.6% and 3.3% trials for the behavioural and TMS experiment, respectively - RSAS blocks) whereas in the other block type, SAS_{delay} were more frequent (F), occurring in 26.6% and 18.8% of trials for the behavioural and TMS experiment, respectively (FSAS blocks). Subjects were always told about the type of block they would start performing next. Consequently, the degree to which subjects anticipated a SAS_{delay} clearly varied in these two contexts; it was smaller in the RSAS blocks than in the FSAS blocks. The

order of the blocks was pseudo-randomized such that some subjects performed the RSAS blocks first and others the FSAS blocks first. Within each block, the order of trials was also pseudo-randomized in order to avoid having two trials with a SAS in a row [403, 406]. In the RSAS context, an additional undisclosed rule was introduced: the SAS trials were separated by at least 7 trials without any sound. Each block consisted in an equal proportion of left and right hand trials. They lasted approximately 5 min and were run successively. Short breaks were made between the blocks.

3.3.4 Behavioural experiment

The behavioural experiment (n=16) served to characterize the influence of a SAS_{delay} in the RSAS and FSAS blocks on the subjects' behaviour (RTs, anticipation and time-out errors): we hypothesized that the occurrence of frequent SAS would generally increase cautiousness and prolong RTs in the FSAS blocks. Each experimental session involved 2 preliminary blocks of 60 trials followed by 8 testing blocks. The first block served to familiarize the subjects with the task. It consisted of 20 trials without any SAS, followed by 40 trials in which some SAS_{delay} were elicited (15% of the trials) to familiarize the subjects with the sound. Then, the second block was run to compute the individual's median RT. This block involved 60 trials in the absence of SAS. We used this RT measure to adapt the duration of the bridge presentation in the subsequent 8 testing blocks on an individual basis. As such, the duration of the bridge was set to correspond to the subject's median RT + 2 standard deviations (SD). Subjects were required to elicit a response within this time window. If subjects responded later, they were provided with a negative feedback. Based on pilot experiments, this procedure seemed optimal to force the subjects to prepare their movement in advance. After that, the actual

experiment began with the 8 testing blocks. There were 4 RSAS blocks and 4 FSAS blocks, each involving 60 and 64 trials, respectively (same amount of left and right hand trials). The RSAS blocks consisted of 56 trials without SAS (including 4 catch trials) and 4 SAS_{delay} trials (6.6%); the FSAS blocks were composed of 44 trials without SAS (including 4 catch trials) and 16 SAS_{delay} trials (26.6%). For the behavioural data analysis, trials were separated according to whether responses were provided with the left or right hand, in the presence of a SAS_{delay} or not, in RSAS or FSAS blocks.

3.3.5 TMS experiment

The TMS experiment (n=11) served to compare preparatory inhibition during the delay period in the RSAS and FSAS blocks. Similar to the behavioural experiment, each session started with 2 preliminary blocks that served to familiarize the participants with the task and to set the bridge duration. Then, the main phase of the experiment began, with 4 testing blocks, half of which were performed in a RSAS context (60 trials/block) and the other half in a FSAS context (64 trials/block). A TMS pulse was applied in each trial at one of two possible timings (Figure 3.1C). To obtain a baseline measure of CS excitability, some trials involved a TMS pulse falling 2300 ms after the blank screen onset (22 trials per block [RSAS blocks] or 20 trials per block [FSAS blocks]), eliciting MEPs in the context of the task but during the inter-trial interval ($TMS_{baseline-in}$). In the remaining trials (38 trials [RSAS blocks] or 44 trials [FSAS block]), the TMS pulse was delivered 500 ms after the preparatory cue onset (TMS_{delay}) (Figure 3.1C). MEPs elicited at TMS_{delay} were always sorted according to whether they fell in a hand that was selected for the forthcoming response ($TMS_{delay-selected}$) or non-selected ($TMS_{delay-nonselected}$). Based on previous studies, we assumed that, at this

time, MEPs would be strongly suppressed, reflecting preparatory inhibition when subjects are withholding a motor response [22, 149, 154, 402]. In addition to these probes of CS excitability within the blocks, MEPs were also elicited between the blocks to obtain a baseline measure of CS excitability outside the context of the task ($TMS_{baseline-out}$, 20 pulses between each block, each separated by a delay ranging from 3200 to 4000 ms).

Critically, in trials involving a sound, the SAS always occurred concurrently with the TMS pulse (Figure 3.1C). That is, the SAS_{delay} always occurred at the same time as the TMS_{delay} pulse (500 ms after the preparatory cue onset, as in the behavioural experiment). Moreover, the TMS experiment also involved trials in which a SAS occurred during the inter-trial interval, at the time of $TMS_{baseline-in}$. We did not expect such $SAS_{baseline}$ to elicit a startle response as it has been shown that such a response only occurs when a movement is already planned [391, 404]. However, we included some $SAS_{baseline}$ to make sure that a potential difference between MEPs elicited during the delay period or at baseline could not be explained by a different level of SAS expectancy at these two times. The RSAS blocks consisted of 56 trials without SAS (including 4 catch trials), 2 SAS_{delay} trials (3.3%) and 2 trials with $SAS_{baseline-in}$; the FSAS blocks were composed of 48 trials without SAS (including 4 catch trials), 12 SAS_{delay} trials (18.8%) and 4 trials with $SAS_{baseline-in}$.

Importantly, TMS was always delivered using a double-$coil_{1ms}$ TMS method recently developed in our laboratory [349, 381, 402]. Briefly, this method consists in a near-simultaneous stimulation of the two M1 (1ms inter-pulse interval), allowing to obtain MEPs in both hands at once (Figure 3.1D). The short inter-pulse interval allows to avoid direct electromagnetic interference between the two coils, while preventing transcallosal interactions to occur be-

tween motor areas [102, 103]; the MEPs obtained using this approach are comparable to those elicited using single-coil TMS, regardless of the pulse order [381, 402]. In the present study, the first TMS pulse was always applied over the right M1, eliciting a first MEP in the left hand, followed shortly (1 ms later) by a MEP in the right hand.

The two TMS pulses were delivered through small figure-of-eight coils (wing internal diameter, 35 mm); the coil stimulating right M1 was connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK) and the coil stimulating left M1 to a Magstim Super Rapid magnetic stimulator. The coils were placed tangentially on the scalp and the handle was oriented toward the back of the head and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus. For each M1, the optimal scalp position for eliciting a contralateral MEP in the first dorsal interosseous (FDI) muscle was identified and marked on a cap placed on the subject's head to provide a reference mark throughout the experiment [381]. It was important to check that both coils could be positioned simultaneously on the head without touching each other. Minor adjustments were sometimes necessary without precluding the acquisition of optimum FDI MEPs [349, 381, 402]. The resting motor threshold (rMT) was determined as the minimal TMS intensity required to evoke MEPs of about 50 μV peak-to-peak in the relaxed FDI muscle in at least 5 out of 10 consecutive trials. Across participants, the rMTs corresponded to 36.9 $\pm$ 1.71% and 53.8 $\pm$ 2.98% of the maximum stimulator output for the right and the left M1, respectively. The higher rMT value for the left M1 is due to the use of a Super Rapid Magstim on that side [114]. For each hand, the intensity of TMS throughout the experiment was always set at 115% of the individual rMT.

3.3.6 Electromyography recording

Electromyography (EMG) data were collected for 3200 ms on each trial, starting always 200 ms before the SAS/TMS pulse (or at the corresponding time in the absence of SAS in the behavioural experiment). Raw EMG signals were amplified (gain, 1K), bandpass filtered online (10-500 Hz; NeuroLog; Digitimer) and digitized at 2000 Hz for offline analysis.

The presence of EMG activity in the sternocleidomastoid (SCM) in a time window from 30 ms to 90 ms after the occurrence of a SAS has been considered to be a sensitive indicator reflecting the occurrence of a startle response [391, 392]. For this reason, we placed surface electrodes (Neuroline, Medicotest, Oelstykke, Denmark) on the left and right SCM and similar to previous investigations, we recorded the number of SAS trials in which the SCM EMG activity exceeded more than two standard deviations above the baseline level. This number was then expressed in percentage of the total number of SAS trials [391]. Surprisingly, only 31% of our participants displayed some SCM EMG activity following SAS. Moreover, in all these responsive subjects, SCM activity was only present in the first testing block but disappeared afterwards. Because such responses were rare, we did not further analyse them. Critically, previous studies have failed to observe dependable SCM activity following SAS [407]. Then, the fastening effect of SAS on RTs is still present but typically attenuated compared to when SCM activity is elicited. In this case, RTs are typically about 46 ms shorter than in control trials [400].

In the TMS experiment, additional electrodes were placed on the left and right FDI to measure MEP amplitudes. For the MEP analysis, trials with any background EMG activity (root mean square computed in the 200 ms windows preceding the TMS artefact) exceeding 3 standard deviations (SD)

around the mean were discarded for the following analyses. This was done to prevent contamination of the MEP measurements by significant fluctuations in background EMG [345]. The remaining MEPs were classified according to the experimental condition within which they were elicited. For each condition, trials in which the subjects made an error were discarded. Finally, we excluded trials with peak-to peak MEP amplitudes exceeding 3 SD around the mean. After having trimmed the MEP data, a minimum of 24.0 ($\pm$ 5.8) trials remained in each condition.

3.3.7 Statistical analysis

3.3.7.1 Behavioural experiment

Behaviour was assessed by considering RTs as well as the percentage of anticipation and time-out errors for each subject; choice errors were rare and thus not analysed. RTs were analysed using a three-way repeated measure (RM) analysis of variance (ANOVA) with CONTEXT (RSAS, FSAS), RESPONDING HAND (left, right) and SOUND (No SAS, SAS_{delay}) as within-subject factors. For the analysis of anticipation and time-out errors, we used separate two-way RM ANOVAs, with CONTEXT and SOUND as within-subject factors (left and right hand trials were pooled together to increase the number of observations in each condition). Statistical significance was set at $p < 0.05$.

3.3.7.2 TMS experiment

For the analysis of CS excitability, we first considered MEPs (mV) at baseline. These data were analysed using a two-way RM ANOVA, including MEP-SIDE (left or right) and BASELINE-TYPE ($TMS_{baseline-out}$, RSAS $TMS_{baseline-in}$, FSAS $TMS_{baseline-in}$) as within-subject factors. Then, to compare the strength of preparatory inhibition in the two block types, MEP

amplitudes at $TMS_{baseline-in}$ and at TMS_{delay} were analysed with a three-way RM ANOVA, with CONTEXT (RSAS or FSAS), MEP-SIDE (left or right) and TMS-CONDITION ($TMS_{baseline-in}$, $TMS_{delay-selected}$, $TMS_{delay-nonselected}$) as within-subject factors. When appropriate, ANOVAs were followed by post-hoc tests, using the Fishers Least Significant Difference (LSD) procedure. All data are expressed as mean ± standard error (SE). Statistical significance was set at $p < 0.05$.

3.4 Results

3.4.1 Behavioural experiment

3.4.1.1 Reaction times

Two participants were excluded from this analysis as they failed on too many trials in the RSAS context. More precisely, these subjects made a lot of anticipation and time-out errors when a SAS occurred, precluding us from analysing their RT data. In the remaining subjects (n = 14), the average RTs were 200 ms (SE = 7.4) and 204 ms (SE = 7.2) in trials without SAS, in the RSAS and FSAS contexts, respectively. In the presence of a sound, RTs equalled 186.7 ms (SE = 10.4, n = 14) and 174 ms (SE = 7.6, n = 14) in the corresponding contexts. The three-way RM ANOVA performed on these data revealed a significant main effect of the factor SOUND ($F = 11.73$, $p < 0.01$): RTs were significantly reduced in trials including a SAS (Figure 3.2A), consistent with previous studies showing that a loud sound can shorten RTs if triggered when a movement is being prepared in simple and choice RT tasks [396, 397, 408, 409]. Our analyses also revealed a significant CONTEXT X SOUND interaction ($F = 5.25$, $p < 0.05$). As such, although the presence of a SAS reduced RTs in both contexts (all $p < 0.05$), this shortening effect was

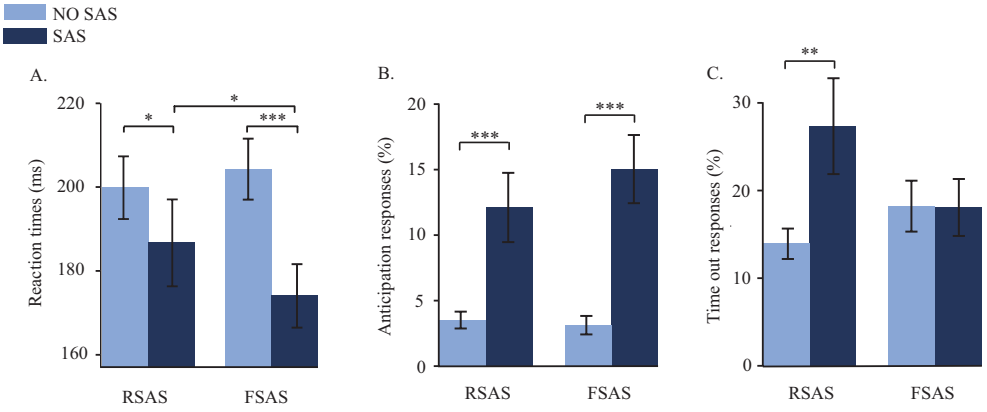

Figure 3.2: (A.) Reactions times (RTs). Reaction times (ms) measured in both contexts (that is, rare (R) startling acoustic stimulus (SAS) resulting in RSAS context and frequent (F) SAS resulting in FSAS context) in trials with (light blue bars) or without (dark blue bars) SAS. Note that RTs were systematically shortened when a sound was elicited. In addition, RTs were significantly shorter in the FSAS context relative to the RSAS one in trials including a SAS. (B.) Percentage of anticipation responses. Percentage of anticipation responses in both contexts in the presence or absence of a SAS. The presence of a SAS increased the percentage of anticipation responses, which confirmed its ability to induce a startle response. (C.) Percentage of time-out responses. Time-out responses shown for trials in both contexts with or without a sound. Note the CONTEXT X SOUND interaction, due to a significant increase in the percentage of time-out responses when a sound was produced in the FSAS context only. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Error bars represent (SE).

more pronounced in the FSAS than in the RSAS blocks. Hence, the SAS led to faster responses when the sound had been anticipated ($p < 0.001$) compared to when it was unlikely ($p < 0.05$). In the absence of SAS, RTs were comparable in the RSAS and FSAS contexts ($p = 0.41$). Hence, contrary to our prediction, a high probability of SAS did not increase RTs (i.e. cautiousness) in FSAS blocks. Finally, we did not observe any effect of the RESPONDING HAND on RTs (all $F < 2.10$ and $p > 0.17$).

3.4.1.2 Percentage of errors

3.4.1.2.1 Anticipation errors.

The two-way RM ANOVA revealed a significant main effect of SOUND ($F = 25.79$, $p < 0.001$). By contrast, we did not observe a significant effect of CONTEXT ($F = 0.78$, $p = 0.39$) or a SOUND X CONTEXT interaction ($F = 1.80$, $p = 0.20$). As evident on Figure 3.2B, subjects made more anticipation errors when a SAS_{delay} occurred compared to when it was absent, regardless of the context.

3.4.1.2.2 Time-out errors.

The two-way RM ANOVA revealed a significant CONTEXT X SOUND interaction ($F = 7.28$, $p < 0.05$), in the absence of any main effect. As evident on Figure 3.2C, the presence of a SAS_{delay} increased the percentage of timeout errors in the RSAS context ($p < 0.01$) but not in the FSAS context ($p = 0.96$), possibly because the sound was more disturbing when it was less expected.

3.4.2 TMS experiment

The TMS experiment was carried out on 11 participants but only 10 were included in the analyses because MEPs were abnormally high in one subject, exceeding 3 SD above the mean of the other participants, due to an error while establishing the rMT. When this subject was excluded, the mean MEP amplitude at $TMS_{baseline-out}$ was 1.65 mV ($SE = 0.29$, $n = 10$). Then, when elicited within the blocks, MEPs at $TMS_{baseline-in}$, equalled 2.60 mV ($SE = 0.41$, $n = 10$), and 2.27 mV ($SE = 0.38$, $n = 10$) in the RSAS and FSAS contexts, respectively. The two-way RM ANOVA performed on those data revealed a main effect of BASELINE ($F = 7.40$, $p < 0.01$). As evident in Figure 3.3, MEPs were smaller when elicited at $TMS_{baseline-out}$ compared to

$TMS_{baseline-in}$ in the FSAS ($p < 0.05$) and RSAS ($p < 0.001$) contexts, respectively. Importantly, MEP amplitudes at $TMS_{baseline-in}$ were comparable in the two contexts ($p = 0.13$). Finally, we did not observe any significant main effect of MEP-SIDE ($F = 0.57$, $p = 0.47$) or a significant interaction between the two factors ($F = 0.33$, $p = 0.72$). In order to assess the strength of preparatory inhibition in both contexts, a three-way RM ANOVA was performed on left and right FDI MEPs obtained at $TMS_{baseline-in}$ and TMS_{delay} preceding left and right hand responses (Figure 3.4). Our analysis revealed a significant main effect of the factor TMS-CONDITION ($F = 23.78$, $p < 0.001$), due to systematically smaller MEPs at TMS_{delay} compared to $TMS_{baseline-in}$ (all $p < 0.001$). No other main effect or interaction between the different factors was found (all $F < 2.16$, $p > 0.14$). These results indicate that varying the probability of a SAS in the two contexts (RSAS or FSAS) did not significantly impact the strength of preparatory inhibition in the present study.

3.5 Discussion

Behaving in a goal-directed manner to fulfil short, middle and long-term goals requires the ability to refrain from automatic, stimulus-driven tendencies [394]. It is often assumed that the motor system plays a central role in this function, with its activity being shaped by overlapping control processes to favour goal-directed behaviours over premature or inappropriate responses [120, 160]. Several control processes seem to involve inhibition of the motor system. Yet, the exact role of motor inhibitory changes is still largely debated [22, 131, 134]. One predominant hypothesis is that motor inhibition assists impulse control.

In the present experiments, we combined the TMS and SAS methodology in an instructed-delay choice RT task to deepen our understanding of the

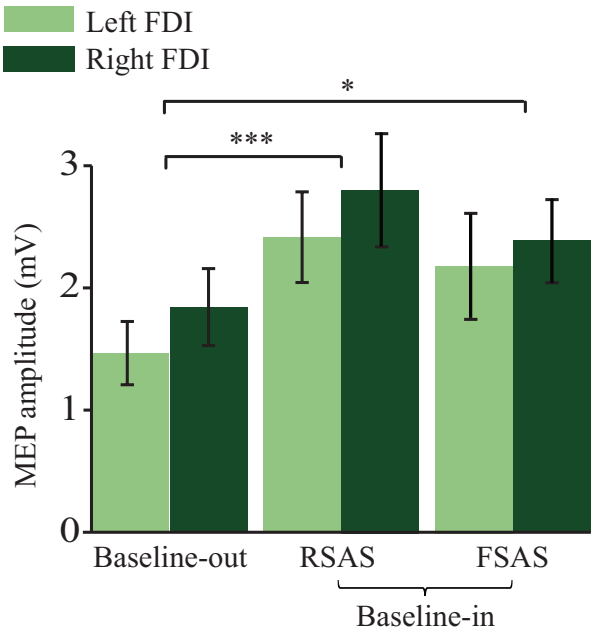

Figure 3.3: Change in motor-evoked potentials (MEPs) from baseline-out to baseline-in. Amplitude of first dorsal interosseous (FDI) MEPs (in mV) recorded in both hands between ($TMS_{baseline-out}$) or during ($TMS_{baseline-in}$) the blocks in the rare (R) startling acoustic stimulus (SAS) resulting in RSAS context and frequent (F) SAS resulting in FSAS context. MEPs were smaller at $TMS_{baseline-out}$ compared to $TMS_{baseline-in}$ in both contexts. *$p < 0.05$, ***$p < 0.001$. Error bars represent (SE).

functional role of motor inhibition during action preparation. Importantly, we varied the rate of SAS in separate blocks, assuming that subjects would engage more impulse control to withhold their response during the delay period when SAS are expected (FSAS context) compared to when they are rare (RSAS context). More critically, we expected that enhanced impulse control in FSAS blocks would be associated with deeper preparatory inhibition. Results turned out to be very different from these predictions.

First, in the TMS experiment, MEPs showed a profound suppression during the delay period, consistent with previous studies [128, 132, 154, 161, 402]. However, this effect was comparable in both contexts. Hence, varying the

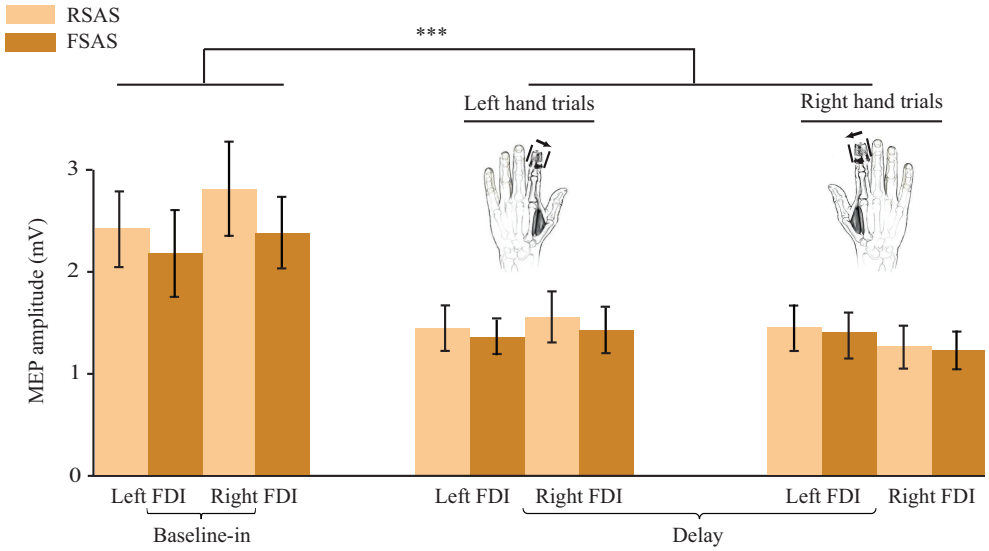

Figure 3.4: Change in motor-evoked potentials (MEPs) from baseline-in to delay. Amplitudes of MEPs recorded at $TMS_{baseline-in}$ and at TMS_{delay} in a selected or non-selected hand in the left and right first dorsal interossei (FDIs) in both block types (rare (R) startling acoustic stimulus (SAS) resulting in RSAS context - light orange bars - and frequent (F) SAS resulting in FSAS context – dark orange bars). Note the consistent suppression of MEPs at TMS_{delay} compared to $TMS_{baseline-in}$, reflecting comparable preparatory inhibition in the two contexts. ***$p < 0.001$. Error bars represent (SE).

probability of SAS did not influence the extent of preparatory inhibition implemented at the time of its potential occurrence. Second, in the behavioural experiment, SAS elicited during the delay period reduced RTs, similar to when applied at the imperative signal in previous studies [401, 408]. Yet, contrary to our predictions, this shortening effect on RTs was stronger in FSAS blocks than in the RSAS blocks, suggesting that increasing the frequency of SAS did not push subjects to recruit further impulse control. Consistently, in the absence of SAS, RTs were comparable in both block types, as were the anticipation errors. Interestingly, time-out errors occurring following the presentation of a SAS were less common in FSAS than in RSAS blocks. Altogether, these results indicate that rather than augmenting impulse control

resources, increasing the frequency of SAS might have increased the attention payed to the acoustic stimulus. Another non-exclusive possibility is that, on top of their startling effect, SAS induced some reactive inhibition, depending on the frequency (surprising effect) of SAS.

3.5.1 Impact of SAS expectation on subjects' behaviour and preparatory inhibition

Several previous studies have shown that manipulating the probability of events or trial types in a given block can vary the strength of control processes engaged in the task. For instance, it has been shown that increasing the proportion of incongruent trials in the Flanker task increases the amount of impulse control resources engaged in the task [385, 410]. Contrary to our predictions, increasing the probability of SAS in the present study did not produce such an effect, although subjects were explicitly required to withhold their response even in the presence of SAS. As such, we did not observe any evidence for increased impulse control in FSAS compared to RSAS blocks: subjects did not slow down in the former context and the boosting effect of the sound was not attenuated. Such a negative effect in the present study may be due to the fact that subjects did not need to rely on such control process to succeed in the task, even in FSAS blocks. As such, the presence of preparatory inhibition during the delay period might be sufficient to handle the occurrence of SAS at that time and avoid premature responding, while complying with the instruction to respond fast. One interesting finding here is that increasing the probability of SAS enhanced their shortening effect on RTs and reduced the amount of trials in which they produced time-out errors. This finding may be due to the fact that subjects payed more attention to the sound in the FSAS than in the RSAS context, consistent with a recent study

[411]. In that study, the authors performed two experiments showing that the level of attention participants pay to a specific sensorial modality (either a tone or a figure) can strongly affect the release of motor responses when SAS are presented. Hence, in the present experiment, it is possible that participants shifted more their focus on the sound in the FSAS than in the RSAS context. Another, non-exclusive, possibility is that, on top of their startling effect, SAS induced some inhibition of motor activity and that this effect depended on the frequency (surprising effect) of SAS. This idea is consistent with a recent line of research showing that surprising events can produce inhibition of the motor system in a way that resembles reactive inhibition following stop signals [22, 294, 297]. In fact, it is likely that increasing the probability of SAS reduced their surprising effect and thus the strength of the associated reactive inhibition that might have occurred on top of preparatory inhibition. Unfortunately, here we focused on preparatory inhibition occurring at the time of the SAS but did not apply TMS at later time points to measure reactive inhibition after the SAS occurrence, which would have allowed us to address this point directly. Yet, we propose that reactive inhibition is likely to have been stronger in the RSAS context, reducing the boosting effect of the SAS on RTs and increasing time-out errors, an interesting hypothesis for future investigations.

3.5.2 Limitations of the present studies

Some limitations in the design of the present study should be considered before drawing conclusion about the effect of SAS expectancy on preparation inhibition. First, we think it would have been useful to include a block type with no SAS at all in the present study. As such, although the SAS were rare in the RSAS blocks, their presence might have already changed preparatory

inhibition, with no further modulation in FSAS blocks. Second, due to technical constraints, we were forced to present SAS through headphones and their use is known to be less efficient in producing startle responses compared to loud speakers. As such, in a recent study using headphones, Maslovat et al. (2015) [399] only observed SCM activity in 28% of trials, in contrast to the 80% (or more) usually observed when using a loud-speaker [404, 408]. Here too, SAS only rarely induced SCM activity. Finally, the literature shows that at least 10 - 15% of people are non-responsive to SAS. That is, a SAS never (or only very rarely) induces a startle response in this population [412, 413]. Here, we did not have enough subjects to cluster them into two categories (SAS responders vs SAS non-responders), yet this would be interesting in future studies.

3.6 Conclusion

These experiments support and extend previous work, which has revealed that preparatory inhibition is at play during motor preparation [48, 153, 402]. They are also in keeping with the studies of Carlsen et al. (2004) [408] and Valls-Solé et al.(1999) [401] who showed a significant decrease of RTs when a SAS is elicited. Additional studies are required to investigate whether the lack of difference of preparatory inhibition between the two contexts is due to limitations in the task design and whether variations in preparatory inhibition can be evidenced with the use of loudspeakers, the inclusion of blocks without any SAS and the segregation of subjects according to their SAS sensitivity. These studies should also include TMS pulses after the SAS to measure the potential occurrence of reactive inhibition due to their surprising effect

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be a potential conflict of interest.

Chapter 4 A TMS study of preparatory inhibition in binge drinkers

"Here's to alcohol, the rose
colored glasses of life."

F. Scott Fitzgerald

Chapter 4: reminder of the aim and hypotheses

Binge drinking (i.e., the repeated alternation between excessive alcohol intakes and abstinence periods) has become widespread in our western societies, especially in young adults. Many studies have already shown the deleterious consequences of repetitive alcohol consumption on brain regions and/or systems such as the prefrontal cortex and the mesolimbic dopamine system. Moreover, functional deficits have been largely described for cognitive functions such as attention, memory, decision making and response inhibition, in people suffering from an AUD but also in BDs. Yet, few studies have assessed the functional integrity of the motor system in these pathological conditions, despite the predominant role of this region in guiding our behaviour. Recently, we found that patients suffering from an AUD show deficient neural inhibition in the motor system during action preparation. Critically, this effect was related to the risk of relapse. Here, based on the continuum hypothesis that suggests that binge-drinking could be a first step towards alcohol use disorder, we investigated whether such a deficit of motor inhibition is already present in BDs.

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Keywords

Binge drinking; heavy drinking; alcohol-use disorder; transcranial magnetic stimulation; motor-evoked potentials; corticospinal excitability.

Highlights

- Normally, action preparation involves a global suppression of motor activity
- Such preparatory suppression is deficient in alcohol-dependent patients
- Binge drinking may represent a first step toward alcohol-use disorder
- Here, we tested whether binge drinkers also display altered preparatory suppression
- Our results indicate abnormally high motor preparatory activity in binge drinkers

4.1 Abstract

Binge drinking consists in a pattern of consumption characterised by the repeated alternation between massive alcohol intakes and abstinence periods. A continuum hypothesis suggests that this drinking endeavour represents an early stage of alcohol dependence rather than a separate phenomenon. Among the variety of alterations in alcohol-dependent individuals (ADIs), one has to do with the motor system, which does not show a normal pattern of activity during action preparation. In healthy controls (HCs), motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) over primary motor cortex (M1) show both facilitation and suppression effects, depending on the time and setting of TMS during action preparation. A recent study focusing on the suppression component revealed that this aspect of preparatory activity is abnormally weak in ADIs and that this defect scales with the risk of relapse. In the present study, we tested whether binge drinkers (BDs) present a similar deficit. To do so, we recorded MEPs in a set of hand muscles applying TMS in 20 BDs and in 20 matched HCs while they were preparing index finger responses in an instructed-delay choice reaction time task. Consistent with past research, the MEP data in HCs revealed a strong MEP suppression in this task. This effect was evident in all hand muscles, regardless of whether they were relevant or irrelevant in the task. BDs also showed some preparatory suppression, yet this effect was less consistent, especially in the prime mover of the responding hand. These findings suggest abnormal preparatory activity in BDs, similar to alcohol-dependent patients, though some of the current results also raise new questions regarding the significance of these observations.

4.2 Introduction

Concision in style, precision in thought, decision in life (Victor Hugo); when meticulously selected, actions, just like words, are powerful and can lead to great accomplishments. By contrast, the inability to suppress prevailing tendencies that are not consistent with our internal goals - or to inhibit actions that are no longer appropriate - leads to improper and hazardous behaviours [292, 395, 414, 415]. So it is in the field of addictions where excessive and/or chronic alcohol consumption stands.

Ingesting alcohol occasionally - may it be through drinking a beer, a glass of wine or a cocktail - is widespread in the western society and occurs in many everyday life situations [197]. Indeed, people usually have a drink when they get a job, get married, celebrate their birthday, or watch football. For most of them, drinking alcohol is a recreational activity, and the amount consumed is controlled. For others, however, alcohol problems arise from drinking too much, too fast, or too often.

Unhealthy drinking habits are common characteristics of both binge-drinkers (BDs) and alcohol-dependent individuals (ADIs). BDs are people that display a pattern of consumption characterised by the repeated alternation between massive alcohol intakes and abstinence periods (i.e., binge drinking; [320, 321, 322, 323]) whilst ADIs are individuals suffering from an alcohol use disorder [198]. In these two populations, the results of excessive alcohol consumption are frequently appalling (alcohol is directly involved in $\sim$ 4% of deaths worldwide [416, 417]). For instance, in young adults, a population in which binge-drinking has become increasingly prominent [324, 325], regular heavy alcohol consumption is linked to poorer academic results, less adequate social integration, car accidents, sexual assaults, violence, health is-

sues, etc. [322, 326]. For ADIs, the consequences are usually the same but exacerbated with many problems at personal (e.g., quarrels with partner), societal (e.g., bar brawls) and professional (e.g., being unfit to accomplish professional demands) levels [197, 198].

From a neural perspective also, excessive alcohol consumption has harmful consequences. For instance, several studies have revealed grey and white matter atrophy in ADIs in structures that are responsible for cognitive functions, such as attention, memory, problem solving, decision making, response inhibition, etc. with the underlined cognitive functions impaired [302, 314, 315, 316]. Consequently, ADIs typically display a reduced ability to successfully regulate thoughts and behaviours, resulting in a tendency to make risky or thoughtless decisions through favouring immediate rewards without consideration for the delayed - potentially deleterious - consequences [418]. Critically, these cognitive deficits persist long after drinking cessation and are strongly involved in relapse [334]. In BDs also, the damages are substantial. For instance, BDs display a thinner cortex in prefrontal and cerebellar regions [327, 328, 329, 330] and an overall decrease in white matter integrity [327, 331]. Behaviourally speaking, BDs show impairments in sustained attention, a lack of inhibitory control and an abnormally short post-error slowing indicating attenuated response monitoring [327, 332, 333]. Importantly, to date, it is still difficult to know whether these shifts in norm arise from the neurotoxic effects of alcohol [419] or whether they represent - at least in part - a factor of vulnerability [420] as some of the structural and cognitive alterations reported above in BDs and ADIs are sometimes observed even before the engagement of excessive alcohol consumption. For instance, functional magnetic resonance imaging studies have shown reduced fronto-parietal activations in young adolescents prior to any alcohol consumption that may represent predictors of

subsequent excessive drinking [318, 319]. Similarly, offspring of ADIs with limited or no past alcohol use display frontal and parietal structural alterations that might underlie cognitive and behavioural traits associated with a risk of alcohol use disorder [281].

The similarities between the structural and functional alterations observed in ADIs and BDs [314, 316, 334] has led researchers to suggest that binge-drinking and alcohol use disorder represent two different stages of the same phenomenon rather than independent conditions [332, 335, 336, 337]. Based on this idea, called the continuum hypothesis, binge-drinking could be a first step towards alcohol use disorder and excessive drinking could lead individuals down the slippery slope of compulsive intake. The continuum hypothesis is further borne out by studies showing that binge-drinking patterns started during late adolescence frequently remain into early adulthood [324] and that initiating heavy drinking at an early age significantly enhances the risk for subsequent alcohol use disorder [421].

As a core cognitive function, inhibitory control is tightly related to the prefrontal cortex and its alteration seems to play a crucial role in the development and maintenance of addictions [422, 423, 424]. Moreover, findings of recent work using transcranial magnetic stimulation (TMS) suggest that not only the prefrontal cortex, but the motor system as well, which is interconnected to prefrontal areas, may be involved in inhibitory control [22, 306, 309, 346]. When applied over the primary motor cortex (M1), TMS elicits motor-evoked potentials (MEPs) in targeted contralateral hand or limb muscles. Their amplitude provides a temporally precise and muscle-specific measure of the net impact of facilitatory and inhibitory inputs to corticospinal (CS) cells [20, 48, 51, 107]. Inhibitory control is particularly strong in stop-signal tasks where the successful suppression of actions following stop signals

relies on a decrease in the excitability of the CS tract [22, 115, 155]. Interestingly, not only stopping but also preparing motor acts is associated with a robust CS suppression [22, 114, 153], a phenomenon referred to as preparatory suppression (or inhibition) [22, 49, 128, 129, 130, 131, 386, 402]. An advantage of the latter measure of inhibitory control is that it is obtained in a context that is quite representative of everyday life (we continuously need to prepare actions and avoid selecting inappropriate ones) while stop-signal tasks are more artificial: most situations require inhibitory control to be internally generated, in the absence of explicit stop-signals.

Preparatory suppression is most pronounced in instructed-delay reaction time (RT) tasks that require postponing a pre-cued response until a delayed imperative signal [22, 48, 154, 157, 161, 425]. In such circumstances, one prominent hypothesis is that the motor suppression observed during the delay period prevents the premature release of the prepared response [22, 127]. Hence, preparatory suppression in this context may reflect the operation of processes ensuring some sort of impulse control [305, 425]. Consistent with this view, a recent study revealed that preparatory suppression is impaired in alcohol-dependent patients, a population typically lacking inhibitory control, and that this deficiency is linked to the risk of relapse [132].

In the present study, we assessed motor suppression during action preparation in 20 BDs and 20 healthy controls (HCs) who were asked to perform the same instructed-delay RT task as the ADIs in Quoilin et al. (2018) [132]. The goal here was to address the question of whether BDs share similar alterations as ADIs at the level of the motor system - i.e., the continuum hypothesis. Such an approach also allows extending the observations made in ADIs to another population associated with abnormal inhibitory control. Finally, it sheds new light on the neurophysiological correlates of a behaviour that remains ubiqui-

tous in youths despite its deleterious consequences.

Overall, our data suggest abnormal preparatory activity in BDs, though some of the current results also raise new questions regarding the significance of these observations. Are inhibitory processes genuinely deficient in these patients during action preparation - as hypothesized here - or do these individuals (and maybe ADIs too) rather suffer from an excessive facilitation of prepotent motor representations? Perhaps they suffer from both, an issue for future investigations.

4.3 Materials and Methods

4.3.1 Participants

Participants were recruited through a preliminary anonymous online survey posted on social media that assessed sociodemographic, psychological and medical variables as well as the pattern of alcohol consumption of the individuals. 192 answers were collected. To be selected for the study, participants needed to fulfil the following conditions : they had to be native or fluent French speakers, between 18 and 30 years old and right handed (according to the Edinburgh Questionnaire; subjects showing crossed laterality were not recruited [350]). Selection criteria also included an absence of psychological or neurological disorders, no current medication (i.e., except for oral contraception), no major medical problems, no history of concussion, normal or corrected-to-normal visual abilities, a total absence of past or current drug consumption (except for alcohol), no family history of alcohol use disorder, no more than 4 drinking occasions per week (to avoid any subject with chronic alcohol consumption) and no teetotalism (i.e., the practice of complete abstinence from alcoholic drinks [426]). Based on this survey, some responders satisfying the

aforementioned criteria were included. These individuals were then allocated to one of two groups (Table 4.1) based on the number of drinks they consumed in one occasion (i.e., alcohol consumption per se) and the specific pattern of alcohol consumption they exhibited (i.e., binge drinking score).

To be classified as binge drinker (BD; n=20: 9 women, 21.8 ± 1.8 years old), subjects needed to drink hebdomadally a minimum of 6 (for women) or 7 (for men) alcohol drinks overs a period of 2 hours (i.e., BAC level = 0.08gr /dl) within the last 6 months [320, 427]. We adapted the usual cutoff of 4/5 doses because the quantity of alcohol contained in one drink varies from one country to another (e.g., an alcohol drink contains 10 grams of pure ethanol in Belgium whereas it only contains 8 grams in the United Kingdom and 14 grams in the United States). In addition, subjects needed to exhibit a binge drinking score higher than or equal to 16 [426, 428, 429]. This score is crucial because - as mentioned above - it describes the drinking pattern exhibited in drinking occasions rather than alcohol consumption per se. It was measured as follows [323]:

[(4 x consumption speed) + number of drunkenness episodes in the last six months + (0.2 x percentage of drunkenness episodes in the last six months)]

The consumption speed was defined as the number of alcohol drinks usually consumed per hour; drunkenness was defined as an inability to speak clearly, a loss of coordination and nausea. The percentage of drunkenness episodes was the ratio between the number of drunkenness episodes and the total number of drinking episodes.

Other subjects were categorised as healthy controls (HCs; n = 20: 10 women, 22.5 ± 1.9 years old) if their binge drinking score was lower than

or equal to 12 but higher than 0 [426]. They were matched to BDs for age, gender and education level (i.e., the number of education years completed since starting primary school [132, 335]). Some of the subjects who filled in the survey did not fall in neither group and were therefore not included in the study. Participants were naive to the purpose of the study and financially compensated. The protocol was approved by the institutional review board of Université catholique de Louvain (UCLouvain, Belgium) and required written informed consent.

4.3.2 Questionnaires

To be selected for the study, participants had to first fill in an online survey created specifically for this study. The online questionnaire assessed the specific pattern of alcohol consumption of the participants and was composed of the Alcohol Use Disorders Identification Test (AUDIT) and of other questions evaluating their drinking habits (e.g., consumption speed, number of drunkenness episodes in the last six months, etc.). It also ensured that every participant fitted with the conditions reported above. Some of the responders satisfying the aforementioned criteria were then invited to come to our laboratory where we ensured, once again, the total absence of exclusion criteria (e.g., history of concussion, history of epilepsy, etc.). Then, subjects performed the task. Once the task was finished, subjects filled in the Beck Depression Inventory (BDI; [430, 431]), the State Trait Anxiety Inventory (STAI; A = state anxiety; B = trait anxiety; [432]), the UPPS impulsive behaviour scale [433] and the Monetary Choice Questionnaire (MCQ; [434]). The two first questionnaires were used to ensure that participants did not differ with regard to depression or anxiety. The UPPS and MCQ questionnaires were administrated to assess impulsivity and reward discounting, respectively.

	BDs (N = 20)		**HCs (N = 20)**	
	mean (± SD)	**min - max**	**mean (± SD)**	**min - max**
Age^{NS}	21.8 (± 1.8)	18 - 26	22.5 (± 1.9)	19 - 26
Gender (Female/Male)^{NA}	9 / 11	NA	10 / 10	NA
Educational Level^{NS}	15.8 (± 2.1)	12 - 19	15.9 (± 1.6)	12 - 19
Smoker	0 / 20	NA	1 / 20	NA
BDI^{NS}	2 (± 2.7)	0 - 9	2.8 (± 2.8)	0 - 10
STAI-A^{NS}	31.5 (± 6.8)	20 - 44	32.2 (± 7.7)	20 - 46
STAI-B^{NS}	35.9 (± 5.9)	23 - 51	40.6 (± 9.7)	24 - 57
UPPS^{NS}	105.5 (± 12.5)	82 - 137	101.5 (± 14.1)	76 - 122
MCQ overall K^{NS}	8.10^{-3} (± 0.01)	10^{-4} - 0.04	0.016 (± 0.03)	10^{-4} - 0.11
AUDIT***	15.2 (± 5.1)	7 - 25	6.0 (± 2.8)	1 - 10
Binge drinking score***	37.4 (± 23.2)	16.4 - 110	7.2 (± 3.2)	2 - 12
Age at first alcohol consumption*	14.6 (± 1.1)	12 - 17	15.3 (± 1.2)	13 - 17
Years of regular alcohol consumption^{NS}	4.8 (± 1.8)	1 - 8	4.2 (± 2.3)	0.7
Consumption speed^{ab***}	3 (± 0.9)	2 - 5	1.4 (± 0.6)	0.5 - 2
Number of alcohol drink consumed within 2 hours^{b***}	5.9 (± 1.8)	4 - 10	2.8 (± 1.3)	1 - 4
rMT left hemisphere^{NS}	41.7 (± 5.1)	34 - 52	41.5 (± 5.8)	33 - 57
rMT right hemisphere^{NS}	42.9 (±4.5)	36 - 53	42.1(± 6.0)	35 - 55

Table 4.1: Results for demographic, psychological and alcohol consumption measures for binge-drinkers (BDs) and healthy controls (HCs). BDI = Beck Depression Inventory [430, 431]; STAI = State Trait Anxiety Inventory (A = state anxiety; B = trait anxiety; [432]); UPPS = UPPS impulsive behaviour scale [433]; MCQ = Monetary Choice Questionnaire [434]; AUDIT = Alcohol Use Disorders Identification Test [435]; rMT = resting motor threshold; SD = standard deviation. ^{a}In doses per hour. ^{b} During the last six months. ^{NA} = not-applicable; ^{NS} = not-significant; * $p < .05$; *** $p < .001$.

4.3.3 Task

Participants performed an instructed-delay choice RT task, which was implemented with Matlab 7.5 (Mathworks, Natick, Massachusetts, USA) using the Psychophysics Toolbox extensions [383, 384]. It consisted in a virtual rolling ball game previously used in other studies [49, 132, 154, 386, 425, 436] (Figure 4.1A). In this task, a ball and a goal appear on a computer screen and participants must virtually "shoot the ball into the goal", by performing an abduction movement with the left or right index finger which requires the activation of the left or right first dorsal interosseous (FDI) muscle, respectively.

Each trial started with the presentation of a preparatory cue, consisting of a ball and a goal separated by a gap. Participants had to prepare an abduction of the left index finger when the ball was presented on the left side of the screen, and an abduction of the right index finger when it appeared on the right side. Subjects were explicitly told to withhold their prepared response until the onset of the imperative signal (i.e., the bridge) which appeared 1000 to 1200 ms later (Figure 4.1 B). We purposely varied the duration of the delay period to decrease the subjects' tendency to respond prematurely (i.e., before the imperative signal). For the same reason, each block involved a few trials in which the bridge did not appear (i.e., catch trials - 2 per block). In these trials, subjects were required not to respond and were penalised if they did so. Once the bridge was on the screen, subjects had to respond as fast as possible to allow the ball to roll on it and to quickly reach the goal. Each trial ended with a feedback displaying a score for 500 ms, followed by a blank screen lasting between 3100 and 4000 ms (inter-trial interval).

The feedback score depended on how fast and accurate subjects had been on the previous trial. That is, on correct trials, scores were inversely propor-

tional to the RT (i.e., the faster the subjects, the higher the score); they were displayed in green and ranged from 1 to 100. The score was individualised based on the following equation [402, 436], with α = 0.8 x median RT measured at the end of the training session (please refer to the 4.3.5 experimental procedure section for more information):

$$x = \frac{(100.(\alpha))}{(\alpha+(\frac{RT-\alpha}{10})^{2,4})}$$

Incorrect responses were penalised by a negative score (-75 points) displayed in red. They involved (1) responses occurring too early, referred to as anticipated responses, (2) responses occurring too late, referred to as time-out responses, (3) responses provided with the incorrect hand, referred as the choice errors and (4) responses provided on catch trials, referred to as catch errors. Anticipated responses consisted in responses provided either before the bridge onset or after its onset but with a RT $<$ 100 ms [349, 402, 425]: below this time, we consider that the response was released prematurely (i.e., before detection of the bridge) given the fixed time required for visuo-motor conversion to occur [401]. Time-out responses consisted in responses that were longer than 500 ms (i.e., provided after the bridge offset) or that were never provided [49, 349, 425, 436]. Note that when subjects succeeded not to respond on a catch trial, they received + 75 points.

4.3.4 TMS protocol

TMS was always delivered using a double-coil TMS method recently developed in our laboratory [349, 357, 381, 436, 437]. This method consists in a near-simultaneous stimulation of the two M1 (1ms inter-pulse interval), eliciting MEPs in both hands at once (Figure 4.1C). The short interval allows

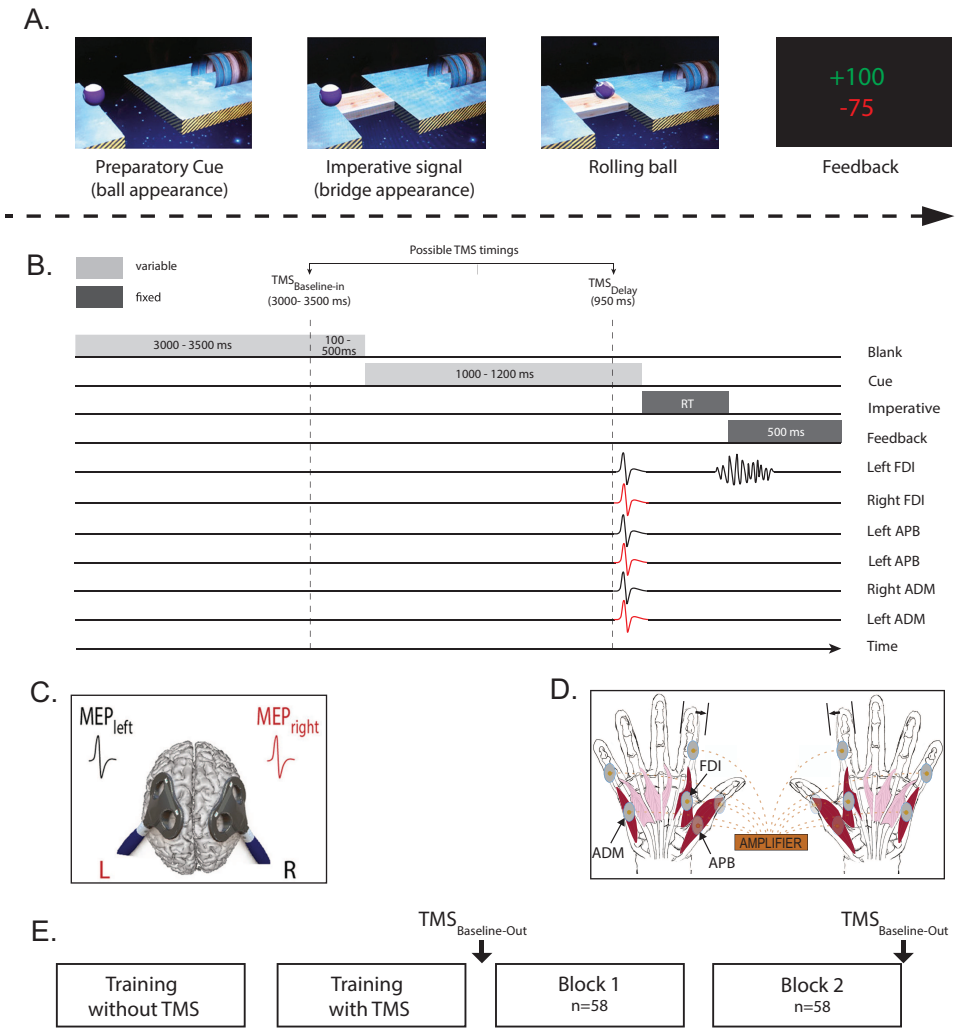

Figure 4.1: (Continued on the following page).

Figure 4.1: A. Rolling ball task. Subjects performed an instructed-delay choice reaction time (RT) task, which required them to choose between an abduction movement of the left or right index finger (left in the current example) depending of the position of a preparatory cue (i.e., the ball). They had to withhold their response until the onset of an imperative signal (i.e., the bridge). Once the bridge appeared, they were required to release their prepared response as fast as possible. If they answered correctly, the ball then rolled on the bridge and reached the goal located on the other side of the gap. A feedback reflecting how fast and accurate subjects had been concluded each trial. **B. Time course of a trial.** Each trial started with the preparatory cue (random duration; 1000 - 1200 ms) followed by the imperative signal which remained visible until the subject responded (maximum duration of 500 ms). The feedback was presented at the end of each trial for 500 ms. A blank screen (inter-trial interval; between 3100 and 4000 ms) separated each trial. When TMS was applied, motor-evoked potentials (MEPs) were elicited in the first dorsal interosseous (FDI), in the abductor digiti minimi (ADM) and in the abductor pollicis brevis (APB) muscles of both hands at a near simultaneous time (1ms delay interval between hands, see C). TMS pulses could occur during the inter-trial interval (between 3000 - 3500 ms after the blank screen onset; $\text{TMS}_{Baseline-in}$), or during the delay period (950 ms after the preparatory cue onset; TMS_{Delay}). This figure displays a left-hand trial with MEPs elicited at TMS_{Delay}. **C. TMS protocol.** Two figure-of-eight coils were placed over the subject's primary motor cortex (M1), eliciting near simultaneous MEPs (1ms delay) in the left and right hands. **D. Response device and EMG recording.** Index finger responses were recorded using a home-made response device positioned under the left and right hands (graphic representation). The response device was composed of two pairs of metal edges fixed on a plastic support. Each response required to move one index finger from the outer to the inner metal edge. EMG activity was recorded from surface electrodes placed on the FDI, the ADM and the APB muscles of both hands. **E. Time course of the experiment.** After 2 training blocks, subjects performed 2 blocks of 58 trials during which MEPs were elicited either at $\text{TMS}_{Baseline-in}$ or TMS_{Delay}, in a random order; MEPs were also elicited outside the context of the task ($\text{TMS}_{Baseline-out}$, that is, before block 1 and after block 2.

to avoid direct electromagnetic interference between the two coils, while preventing transcallosal interactions to occur between motor areas [63, 103]. The MEPs obtained using this double-coil_{1ms} approach are comparable to those elicited using single-coil TMS, regardless of the pulse order or the intensity of stimulation [107, 381, 436]. In the present study the order of stimulation was pseudo-randomised. That is, 50 % of the participants (50% of the HCs and 50% of the BDs) received the first TMS pulse over the right M1, eliciting the

first MEP in the left hand whilst the other 50% received the first TMS pulse over the left M1 (i.e., first MEP in the right hand).

We applied TMS pulses through small figure-of-eight coils (wing internal diameter, 35 mm), each connected to a stimulator delivering monophasic pulses. The coils were placed tangentially on the scalp of the participant with the handle oriented toward the back of the head and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus (Figure 4.1C) [49, 127, 149]. For each M1, we identified the optimal scalp position for eliciting consistent MEPs in 3 different muscles of the contralateral hand, including the FDI, the abductor digiti minimi (ADM) and the abductor pollicis brevis (APB). This multi-muscle hotspot was marked on a cap placed on the subject's head to provide a reference mark throughout the experiment [349, 381, 402, 425, 438]. Such a procedure allowed us to obtain MEPs from several effectors (bilaterally), including a muscle that was involved in the task (i.e., FDI), another muscle that was irrelevant to the task but with the same innervation as the FDI (i.e., ADM, ulnar nerve) and finally, an irrelevant muscle with a different innervation compared to the FDI (i.e., APB, median nerve) (Figure 4.1D). Obtaining MEPs in all these finger muscles was critical as recent studies suggest that preparatory suppression can be underestimated in task relevant effectors, due to concurrent facilitatory influences producing an opposite boost in MEP amplitudes, especially in the prime mover [154, 349]. In contrast, because preparatory suppression is a rather global effect surpassing the relevant muscles [22, 128], MEPs in surrounding effectors, which are irrelevant in the task, provide a particularly pure measure of preparatory suppression (preserved from any facilitatory input), probably even more dependable when the innervation diverges. Notably, when finding the hotspots on both M1, we always checked that both coils could be positioned simul-

taneously on the head without touching each other [349, 381, 436]. Minor adjustments were sometimes necessary without precluding the acquisition of reliable MEPs in these 3 muscles.

The resting motor threshold (rMT) was determined as the minimal TMS intensity required to evoke MEPs of at least 50 μV peak-to-peak in all 3 muscles for at least 5 out of 10 consecutive trials [107, 129, 188, 385, 439]. In practice, most of the time it consisted in finding the rMT for the ADM, which was usually a bit higher than the rMT of the 2 other muscles. Across participants, the rMT corresponded to 41.6 $\pm$ 5.4% and 42.5 $\pm$ 5.2% of the maximum stimulator output for the left and the right M1, respectively (Table 4.1). For each hand, the TMS intensity was set at 120% of the individual rMT. Such an intensity allowed us to elicit reliable MEPs in the 3 different hand muscles on both sides.

TMS pulses were delivered during the blocks at one of 2 possible timings (Figure 4.1B). To obtain a baseline measure of CS excitability, TMS pulses fell during the inter-trial interval, between 3000 and 3500 ms after the blank screen onset (20 trials per block), eliciting MEPs at rest but in the context of the task ($TMS_{Baseline-In}$). In other trials (32 trials per block - including catch trials), TMS pulses were delivered 950 ms after the preparatory cue onset (TMS_{Delay}) (Figure 4.1B). Based on previous studies, we assumed that at TMS_{Delay}, MEPs would be strongly suppressed - at least for HCs -, reflecting preparatory suppression when subjects are withholding a motor response [22, 48, 157, 402]. The remaining trials (6 per block), did not include any TMS pulse, preventing participants from anticipating TMS pulses at TMS_{Delay} when it had not occurred at $TMS_{Baseline-In}$. As a result, each block was composed of 58 trials. In addition to these probes of CS excitability within the blocks, MEPs were also elicited out of the blocks to obtain a

baseline measure of the CS excitability at rest and outside the context of the task ($TMS_{Baseline-Out}$). This involved applying 20 TMS pulses (every 5100 to 6200 ms) at both the beginning and the end of the experiment (Figure 4.1E).

4.3.5 Experimental procedure

All participants were asked to abstain from any alcohol consumption for at least 3 days before the session [335]. Experiments were conducted in a quiet and dimly lit room. Participants sat in front of a 21-inch monitor screen positioned about 60 cm in front of them. Their arms were semi-flexed with both hands resting palm-down on a home-made response device developed in our laboratory to detect any horizontal movement of the index fingers (Figure 4.1 D). This setup provides us with a very precise measure of the RT (precision = 1 ms) and allows us to control the initial index finger position at the beginning of each trial (for more details regarding this device, please refer to Quoilin et al. 2016 [154]). Before starting the experiment, participants were presented with some slides containing all the instructions required to understand and perform the task properly. This was done to standardise the information we gave. After presentation of the slides, subjects were asked if they had any questions regarding the task.

The experiment always started with 2 training blocks (Figure 4.1E). The first one was composed of 20 trials without TMS and served to familiarize the subjects with the task. The second one involved TMS pulses and was composed of 58 trials, as in the main experiment. Thereby, the subjects could first practice the task without being disturbed by the TMS pulses and then get used to the stimulations while performing the task in the second training block. The latter block also served to obtain the median RT for each individual. As mentioned above, this RT was used to individualise the

feedback score (cf. section 4.3.3 Task). Then, during the main phase of the experiment, subjects performed 2 blocks of 58 trials that were preceded and followed by 20 MEP measurements at $\text{TMS}_{Baseline-Out}$. Using these numbers, for each FDI, ADM and APB muscles, we obtained in each hand, a total of 40 MEPs at $\text{TMS}_{Baseline-Out}$, 40 MEPs at $\text{TMS}_{Baseline-In}$ and 64 MEPs at TMS_{Delay} (with half elicited in left hand trials and the other half in right hand trials). Each block lasted approximately 5 minutes; 2-minute breaks were made between them. After completion of the experiment, participants were asked to fill in psychopathological questionnaires such as the STAI [432], the BDI [430, 431], the AUDIT [435], etc. Results of these surveys are reported in Table 4.1.

4.3.6 Electromyography (EMG) recording

EMG activity was recorded from surface electrodes (Neuroline, Medicotest, Oelstykke, Denmark) disposed on the FDI, ADM and APB muscles of both hands (Figure 4.1D). The electrodes (Ambu Blue Sensor NF-50-K/EU/12) have a skin contact size of 28 x 20 mm. The raw EMG signals were amplified (gain, 1K), bandpass filtered online (10-500 Hz; NeuroLog; Digitimer) and digitised at 2000 Hz for offline analysis. EMG data were collected for 3000 ms on each trial, starting always 200 ms before the TMS pulse. Trials with any background EMG activity (root mean square computed in the 200 ms windows preceding the TMS artefact) exceeding 3 standard deviations (SD) above the mean were removed; this was made for each muscle to prevent contamination of the MEP measurements by significant fluctuations in background EMG [402, 425]. The remaining MEPs were then classified according to the muscle and the experimental condition within which they were elicited. For the analysis of MEPs at TMS_{Delay}, trials in which the subjects made an error were

also discarded [49, 349, 425, 436]. For each condition, we excluded trials with peak-to-peak MEP amplitudes exceeding 3 SD above the mean [189]. Following data cleaning, a minimum of 13 trials remained in each condition for each subject. The means of the remaining MEPs in TMS_{Delay} and $\text{TMS}_{Baseline-In}$ trials were 27.5 ± 3.1 SD and 38.6 ± 1.6 SD respectively. Importantly, data processing led to the same rate of trial rejection in the two groups.

4.4 Statistical analysis

4.4.1 Demographic and psychopathological measures

Comparisons between groups were performed on demographic, psychological and alcohol consumption characteristics using independent-samples two-sided t-tests (for all variables but gender and smoker). Statistical significance was set at $p < 0.05$.

4.4.2 Behaviour

Behaviour was assessed by considering RTs as well as the percentage of anticipated and time-out errors for each subject; choice errors and catch errors were rare and thus not analysed. RTs were analysed using a mixed-design analysis of variance (ANOVA) with TMS TIMING ($\text{TMS}_{Baseline-In}$, TMS_{Delay}) and RESPONDING-HAND (left, right) as within-subject factors and GROUP (BDs, HCs) as between-subject factor. Trials without TMS were not analysed because of their limited number (i.e., 12 trials in total; all conditions together). For the analysis of the anticipated and time-out errors, 2 two-sided t-tests were used to compare the percentage values between either group (BDs, HCs). For this analysis, all trials were pooled together, regardless of the responding hand and the TMS setting, to increase the number of observations in each condi-

tion. When appropriate, ANOVAs were followed by post-hoc tests using the Fishers least significant difference (LSD) procedure. This procedure was the same as that used in Quoilin et al. 2018 [132]. Statistical significance was always set at $p < 0.05$ for all the analyses. All data are expressed as mean ± standard error (SE).

4.4.3 MEP amplitudes

First, we considered MEPs elicited at baseline. The raw amplitudes of FDI, ADM and APB MEPs (mV) were analysed using three separate mixed-design ANOVAs (one for each muscle) with MEP-SIDE (left, right) and TMS TIMING ($TMS_{Baseline-Out}$, $TMS_{Baseline-In}$) as within-subject factors and GROUP (BDs, HCs) as between-subject factor. The three muscles were analysed separately consistent with past research on preparatory suppression, as the multi-muscle hotspot procedure provides MEP amplitudes that vary a lot from one muscle to the other, which makes comparisons between them meaningless. Second, MEPs elicited at TMS_{Delay} were expressed as percentage of MEPs at $TMS_{Baseline-In}$. To assess the presence of preparatory suppression in each condition, multiple one-sided t-tests (the critical area of the distribution that represents preparatory suppression is one-sided) were carried out to compare these values to 100 (i.e., standing for MEPs elicited at $TMS_{Baseline-In}$) [49, 161, 402, 425]. Then, to contrast the amount of preparatory suppression between conditions and groups, we used three mixed-design ANOVAs (one for each muscle) with MEP-SIDE (left, right) and RESPONDING-HAND (left, right) as within-subject factors and GROUP (BDs, HCs) as between-subject factors. Finally, similar as for the behavioural data, we used the Fishers LSD procedure (consistent with the procedure in Quoilin et al. 2018 [132]) for post-hoc tests when appropriate. Statistical significance was set at $p < 0.05$ for all

the analyses except for the multiple one-side t-tests against 100 (i.e., t-tests assessing the presence of preparatory suppression at TMS_{Delay}) where we applied Bonferroni corrections to alpha p-levels by dividing the significance level by a factor of 4 (i.e., corresponding to the number of conditions ; significance level at $p < 0.0125$). MEP data are always expressed as mean ± SE.

4.5 Results and Discussion

4.5.1 Demographic and psychopathological measures

As illustrated in Table 4.1, BDs and HCs were fully matched for age (t_{38} = -1.20, p = 0.24) and education level (t_{38} = -0.17, p = 0.87). In addition, the independent-sample two-sided t-tests showed that BDs did not significantly differ from HCs for depression (BDI; t_{38} = - 0.99, p = .33), state of anxiety (STAI-A; t_{38}= - 0.30, p = 0.76), trait of anxiety (STAI-B; t_{38} = - 1.88, p = 0.07), impulsivity (UPPS; t_{38} = 0.95, p = 0.35), reward discounting (MCQ; t_{38} = - 1.20 , p = 0.24), years of regular alcohol consumption (t_{38}= -0.92, p= 0.36) as well as for the rMT of the left hemisphere (t_{37} = 0.13, p = .90), the rMT of the right hemisphere (t_{37} = 0.47, p = 0.64) and the age at first alcohol consumption (t_{38} = -1.87, p = 0.07). By contrast, the two groups significantly differed for the AUDIT score (t_{38} = 6.81, $p < 0.001$), the binge drinking score (t_{38} = 5.75, $p < 0.001$), the consumption speed (t_{38} = 6.34, $p < 0.001$) and the number of alcohol drinks taken within two hours (t_{38} = -6.34, $p < 0.001$).

Taken together, these results imply that BDs and HCs only differed with respect to the pattern of alcohol consumption exhibited in drinking occasions. At first sight, this might seem odd as scores of impulsivity and sensation seeking are often higher in BDs than HCs [440]. Note though that there is a high heterogeneity in the profile of BDs that could explain such seemingly

contradictory results found in the literature [441, 442]. For instance, Lannoy and colleagues showed with cluster analysis that the impulsivity traits, drinking motives, and alcohol consumption pattern strongly vary among BDs [442]; whilst BDs belonging to the cluster "emotional BDs" strongly differ from HCs for many subscales of impulsivity, BDs belonging to the "Hazardous BDs" cluster show similar impulsivity traits as HCs. To decrease heterogeneity, future studies could select subjects beforehand to investigate a specific subgroup of BDs or they could enlarge their sample size to perform cluster analyses later.

4.5.2 Behaviour

Even though the TMS experiment was carried out on 20 HCs, only 19 of them were included in the behavioural analyses because of a technical problem that occurred during the task for one subject (the computer did not save any data). The full data set of BDs was considered (n=20) for the behavioural analyses.

4.5.3 Reaction times

The mixed-design ANOVA showed no significant effect of the factor GROUP ($F_{1,37} = 0.34$, $p = .56$) but a significant main effect of the factor TMS TIMING ($F_{1,37} = 15.86$, $p < .001$): RTs at TMS_{Delay} were significantly shorter than RTs at $TMS_{Baseline-In}$ (264.65 $\pm$ 6.08 ms vs 282.54 $\pm$ 6.82 ms, respectively, see Figure 4.2), both in HCs and BDs (no GROUP x TMS TIMING interaction; $F_{1,37} = 2.46$, $p = 0.13$). This effect is consistent with many previous reports showing that a TMS pulse applied close to the imperative signal can speed up the release of a motor response [128, 135, 402] ; similar to the effect of a startling acoustic stimulus when triggered close to an imperative signal [391, 401, 425]. Besides, none of the interactions were significant (all $F < 2.92$ and all $p > 0.10$). Hence, BDs and HCs responded equally fast in the instructed-

delay RT task.

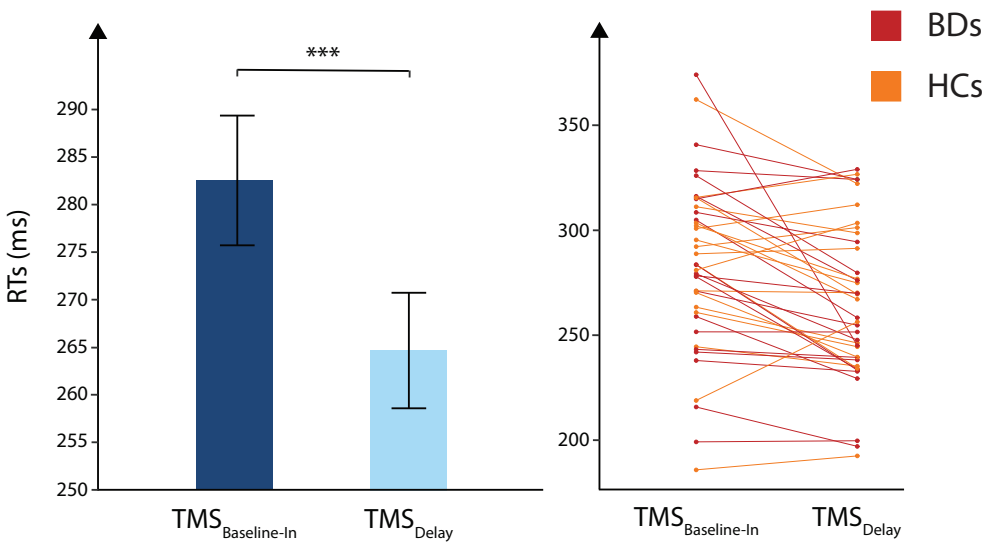

Figure 4.2: Reaction times. Mean reaction times (RTs, in ms) recorded in trials with $TMS_{Baseline-in}$ (dark blue bar) or TMS_{Delay} (light blue bar). Note that RTs were significantly shortened at TMS_{Delay} when compared to $TMS_{Baseline-in}$. Data from the two GROUPS (binge drinkers and healthy controls) were comparable and thus pooled together on the figure. *** = $p < 0.001$. Individual data for binge drinkers and healthy controls are also displayed.

4.5.4 Percentage of errors

On average, the percentage of anticipated responses corresponded to 3.72 ± 0.54 % and 3.75 ± 0.89 % for BDs and HCs respectively (Figure 4.3A) whilst the percentage of time-out responses equalled 1.96 ± 0.55 % and 2.46 ± 0.58% for BDs and HCs respectively (Figure 4.3B). The two-sided t-tests performed on the data did not reveal any difference between groups for either variable (t_{37} = - 0.03, p = 0.98 and t_{37} = - 0.64, p = 0.53 for anticipated and time-out responses, respectively). These results suggest that BDs and HCs committed a similar amount of errors, as expected in such a simple task [305].

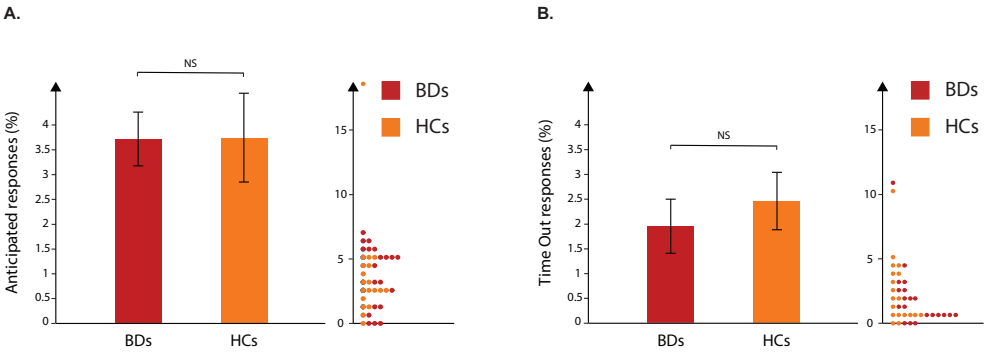

Figure 4.3: A. Anticipated responses. Percentage of anticipated responses (in %) obtained for binge drinkers (BDs; red bars) and healthy controls (HCs; orange bars). **B. Time-out responses.** Percentage of time-out responses (in %) obtained for BDs (red bars) and HCs (orange bars). Individual data for BDs and HCs are also displayed. NS = not-significant.

4.5.5 MEP amplitude

MEP analyses were carried out on the full data set of BDs (n=20) but on only 17 out of the 20 HCs who participated in the study. As such, 3 HCs were excluded due to several technical problems that occurred during the experiment (i.e., the cap moved for one subject, the hotspot turned out not being appropriate in another one and a last subject exhibited a history of concussion, precluding us from obtaining MEP measures in this subject).

4.5.5.1 MEPs elicited at TMS$_{Baseline-Out}$ and TMS $_{Baseline-In}$

With regard to the FDI, prime mover in the task, the ANOVA showed a main effect of the factor TMS TIMING ($F_{1,35} = 41.58$, $p < 0.001$) but no main effect of the factor GROUP ($F_{1,35} = 0.05$, $p = 0.83$) or TMS TIMING x GROUP interaction ($F_{1,35} = 0.38$, $p = 0.54$). As such, both in HCs and BDs, the amplitude of FDI MEPs elicited at TMS$_{Baseline-In}$ (2.52 $\pm$ 0.30 mV) was greater than the amplitude of MEPs at TMS$_{Baseline-Out}$ (1.45 $\pm$ 0.20 mV, Figure 4.4), consistent with several past reports on HCs [49, 402, 425].

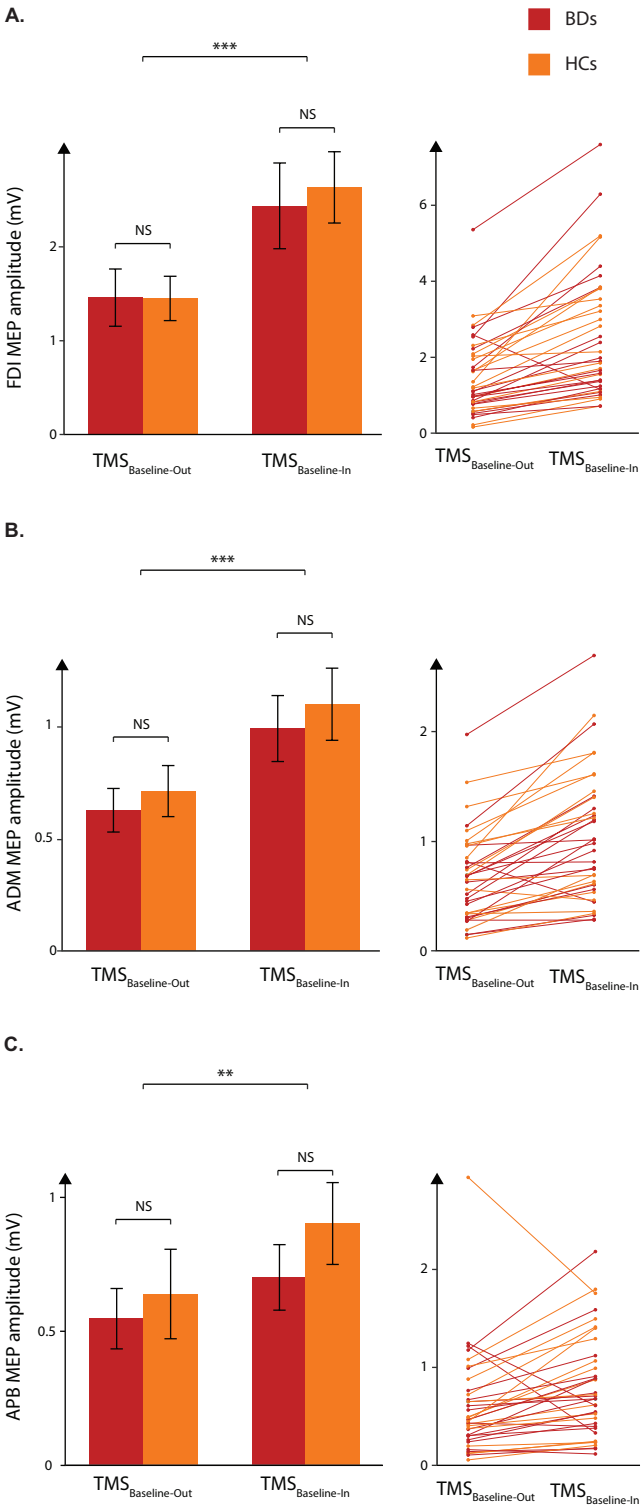

Figure 4.4: MEPs at baseline. Amplitude of motor-evoked potentials (MEPs) recorded at baseline (in mV) in the first dorsal interosseous (FDI, A), the abductor digiti minimi (ADM, B) and the abductor pollicis brevis (APB, C). MEPs were always greater when elicited at $\text{TMS}_{Baseline-in}$ that when elicited at $\text{TMS}_{Baseline-out}$ both for binge drinkers (BDs; red bars) and healthy controls (HCs; orange bars), regardless of muscle within which MEPs were recorded. Individual data for BDs and HCs are also displayed. NS = not significant; ** = p < . 01*** = p < .001.

Besides, there was no effect of the factor MEP-SIDE ($F_{1,35} = 0.03$, p= 0.85) and none of the interactions were significant (all $F_{1,35} < 2.95$, all $p > 0.09$).

MEPs elicited in the task-irrelevant muscles (ADM and APB) showed a similar pattern as those reported above for the FDI. Indeed, the ANOVAs revealed a main effect of the factor TMS-TIMING for the ADM ($F_{1,35} = 45.20$, $p < 0.001$) and APB ($F_{1,35} = 8.56$, $p < 0.01$): MEPs were significantly greater when elicited at $TMS_{Baseline-In}$ (1.04 ± 0.11 mV and 0.79 ± 0.1 mV, respectively) than at $TMS_{Baseline-Out}$ (0.67 ± 0.07 mV and 0.59 ± 0.1 mV, respectively) in these task-irrelevant muscles. No other main effect or interaction was significant (ADM: all $F_{1,35} < 0.14$, all $p > 0.71$; APB: all $F_{1,35} < 0.58$, all $p > .45$). Hence, resting CS excitability was higher during the blocks compared to when subjects were not involved in the task and this effect was present in both groups of subjects and in all hand muscles, regardless of their contribution to the task. This is likely due to differences in the subjects' state of arousal between the two conditions. Indeed, a previous study [365] reported that MEPs are larger when elicited in the context of a task requiring subjects to passively view hand or landscape images than when MEPs are elicited outside the context of the task, suggesting that the level of vigilance has a significant influence on CS excitability.

4.5.5.2 MEPs elicited at TMS_{Delay}

In the FDI of HCs, the t-tests against 100 (i.e., standing for MEPs elicited at $TMS_{Baseline-In}$) revealed that percentage MEPs were consistently suppressed at TMS_{Delay}. This effect occurred regardless of the hand within which MEPs were elicited and the side of the response (all $t > 2.57$ and all $p < 0.0125$), consistent with previous studies [22, 48, 128, 402, 425] (Figure 4.5). BDs also displayed some preparatory suppression in the FDI, yet contrary to HCs, they

did not as consistently: MEPs were suppressed in most of the conditions but not when they fell in a right (i.e., dominant) hand that was selected to respond shortly ($t = 0.59$ and $p = .28$). The mixed-design ANOVA did not reveal any main effect of the factors GROUP, MEP-SIDE or RESPONDING HAND but a significant GROUP x RESPONDING HAND x MEP-SIDE interaction ($F_{1,35} = 5.18$, $p < 0.05$). For BDs, FDI MEPs were significantly less suppressed in a responding hand, either left or right, than in a nonresponding hand (LSD all $p < 0.05$), contrasting with MEPs in HCs, which were evenly suppressed across all conditions in this task-relevant muscle.

Surprisingly, preparatory suppression turned out to be quite normal in the task-irrelevant muscles of BDs. In the ADM, MEPs did not show the usual suppression when they fell in the right responding hand of BDs ($t = 1.16$, $p = 0.13$) but despite that, the ANOVA did not reveal any GROUP x RESPONDING HAND x MEP-SIDE interaction ($F_{1,35} = 0.39$ and $p = 0.54$). For the APB, the MEPs were suppressed in all conditions (all values smaller than 100%) in BDs as in HCs (all $t > 3.52$ and all $p < 0.01$) and no main effect or interaction were found (all $F < 1.16$ and all $p > 0.29$).

In summary, our results are consistent with the view that withholding responses during action preparation involves a global suppression of motor activity [22, 107, 443]. This phenomenon was clear in HCs who systematically displayed smaller MEP amplitudes at TMS_{Delay} in both relevant (FDI) and task-irrelevant (ADM, APB) effectors compared to MEPs probed at $TMS_{Baseline-In}$. Contrary to our predictions, the MEP suppression was also quite strong in BDs, although CS excitability were not quite normal at TMS_{Delay} either. In fact, preparatory suppression was absent in a very specific condition, when MEPs were elicited in the right FDI (and to some extent in the right ADM too) in right hand trials (i.e. when MEPs were elicited in the

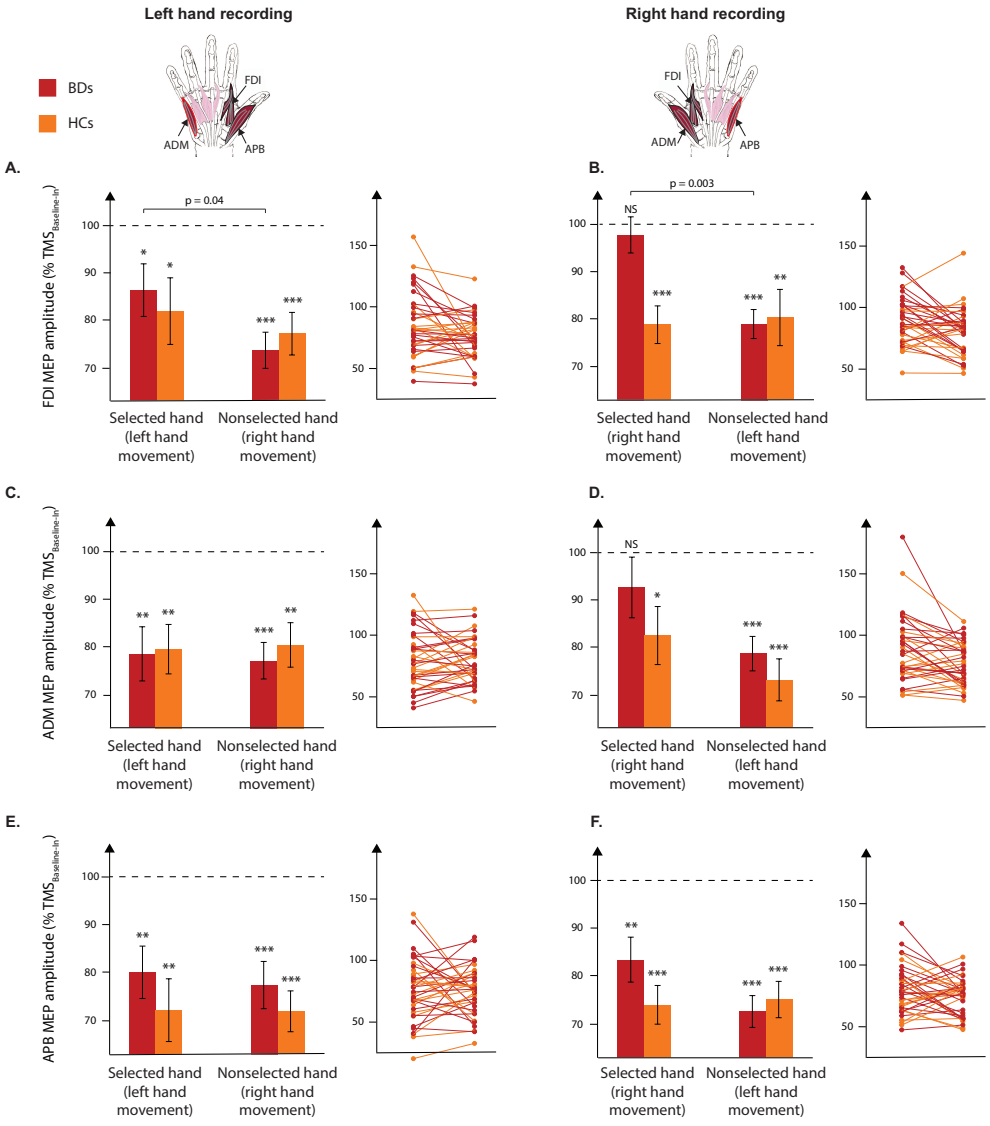

Figure 4.5: (Continued on the following page).

Figure 4.5: MEPs at delay. A/B. Amplitude of motor-evoked potentials (MEPs) elicited at TMS_{Delay} (expressed in percentage of MEPs elicited at $TMS_{Baseline-in}$) in the first dorsal interosseous (FDI) muscles of the left (left panel) or right (right panel) hand for binge drinkers (BDs, red bars) and healthy controls (HCs, orange bars). Note the absence of preparatory suppression for BDs in the right FDI in a condition in which this muscle was selected for the forthcoming response. Of importance also is the fact that FDI MEPs were significantly less suppressed for BDs when they were elicited in a hand that was selected for the forthcoming response than when recorded in a hand that was nonselected. C/D. Amplitude of MEPs elicited at TMS_{Delay} (expressed in percentage of MEPs elicited at $TMS_{Baseline-in}$) in the abductor digiti minimi (ADM) muscles of the left (left panel) or right (right panel) hand for BDs and HCs. Note the absence of preparatory suppression for BDs in the right ADM in a condition in which the right (i.e., dominant) hand was selected for the forthcoming response. E/F. Amplitude of MEPs elicited at TMS_{Delay} (expressed in percentage of MEPs elicited at $TMS_{Baseline-in}$) in the abductor pollicis brevis (APB) muscles of the left (left panel) or right (right panel) hand for BDs and HCs. Note that APB MEPs were significantly suppressed at TMS_{Delay} in all conditions for both groups. Individual data for BDs and HCs are also displayed. NS = not-significant; * = $p < 0.0125$; ** = $p < 0.0025$; *** = $p < 0.00025$. Horizontal bars represent the GROUP x RESPONDING HAND x MEP-SIDE interaction.

right selected hand). Consistently, right FDI MEPs were systematically larger when the right hand was selected for the forthcoming movement compared to when it was nonselected (i.e. in left hand trials) and a comparable effect was also found for left FDI MEPs : they were larger preceding left hand responses (selected condition) than right hand responses (nonselected condition). Importantly, preparatory suppression was perfectly normal in the APB, a muscle innervated separately from the FDI, on top of being irrelevant. Altogether, these findings suggest that generic inhibition operated quite normally in the group of BDs recruited for the current study. If anything, it seems that motor activity associated with the prime mover was larger in BDs than in HCs. This is quite clear from the fact that MEPs were larger (they did not show as much - or any - suppression) in the responding muscle.

It is well accepted that preparatory suppression reflects an initial neural state made of the balance of excitatory and inhibitory influences that foster

the preparation of the movement but eventually cancel it out until a go-signal appears [134, 135, 169, 170]. Hence, in BDs, the weaker preparatory suppression observed in the FDI when this muscle was selected for the forthcoming action could reflect a stronger activity of facilitatory inputs to this particular muscle rather than a real lack of inhibition, which again seems normal when considering the other muscles (irrelevant in the task). Interestingly, the strongest effect was observed when movements were performed with the right hand. Even if this was not the case in HCs here, some past studies have reported less preparatory suppression in the responding hand, especially on the dominant side [154, 349]. Direct comparisons between studies remain however tricky as these experiments substantially differ with regard to the device used to record the response (i.e., standard keyboard vs. response device vs. response provided "in the air") [154] and/or with regard to the task parameters (i.e., TMS timings, number of catch trials, individualized score, etc.) [157, 365, 386]. Noteworthy, it has been proposed that the larger right hand MEPs preceding responses on that side reflect a greater amount of excitatory influences supporting a strong prepotency or readiness for moving with that hand [48, 349]. Hence, action readiness (and related excitatory influences) may be particularly strong in BDs, resulting in an apparent lack of preparatory suppression, even in a task where inhibitory influences usually take over the changes due to facilitatory inputs at the time of the TMS pulse.

In our prior work on ADIs [132], we proposed a deficit of preparatory suppression based on observations that were limited to the prime mover (i.e. FDI), as this was the standard in most past studies where task-irrelevant muscles were only rarely considered [48, 157, 402]. Our findings in BDs clearly question this first reading of our data and emphasize the importance of considering task-irrelevant effectors to assess preparatory suppression. As such,

the suppression effect is known to expand to various muscles within the moving limb, even if they are not involved in the task [129], as also supported by the current study. Moreover, irrelevant effectors are not (or little) influenced by facilitatory inputs that are mainly centred on the prime mover. Hence, these muscles are likely to provide even cleaner probes of preparatory suppression than the prime movers, where excitatory and inhibitory changes mix up. Given this, at this stage, we do not know whether preparatory suppression is really lacking in ADIs [444] as the weak preparatory suppression may also be due to an abnormally strong facilitation of the prime mover in ADIs. Chronic alcohol exposure has indeed been shown to trigger changes in the functions of both inhibitory and excitatory systems leading to decreased GABAergic and increased glutamatergic functions [445, 446, 447, 448]. As a result, the motor cortex of ADIs is often reported to be hyper excitable at rest [444, 449], though not systematically [132].

Importantly, it is unclear whether the altered preparatory activity evidenced in BDs arose from heavy alcohol consumption or whether it was present beforehand and rather caused heavy drinking. Indeed, the question of what comes first and what follows [205] is prominent in the addiction literature and, depending on the proposal, the reading of the data strongly differs. According to the first view, drinking is what altered preparatory activity, while with the second view, this abnormality may have led BDs to drink, thus representing a vulnerability marker of heavy alcohol consumption [322]. Importantly, both hypotheses are not exclusive and whilst it is possible that altered preparatory activity represents a biomarker for excessive drinking, it is now clearly recognised that heavy alcohol consumption has deleterious consequence on the human brain [290]. Ideally, longitudinal studies should be performed to shed light on this important question.

In conclusion, future studies are required to identify the cause of abnormal preparatory activity, both in BDs and in ADIs. A clear understanding of preparatory suppression in ADIs should involve measures in task-irrelevant muscles. Only then, will we be able to conclude whether BDs and ADIs share similar alterations at the motor level as implied by the continuum hypothesis [322, 450]. Moreover, the use of paired-pulse or directional TMS approaches [39, 43, 63, 66, 90, 107, 134, 443] or the combination of TMS with functional/diffusion magnetic resonance imaging techniques represent interesting lines of future investigation to evaluate the involvement of specific cortical circuits to preparatory suppression (including facilitatory and inhibitory inputs).

4.6 Conclusion

This study provides first evidence that BDs present abnormal preparatory activity at the level of the motor output system, alike ADIs. It remains however unclear whether the underlying causes of these alterations are shared amongst BDs and ADIs. Ultimately, for both populations, the question remains wide open as to whether peculiar preparatory activity accounts for a deficit of inhibition, from an excess of facilitation, or from both.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Chapter 5 Considering Motor Excitability During Action Preparation in Gambling Disorder: A Transcranial Magnetic Stimulation Study

"Conventional wisdom nor scientific, mathematical prove of randomness in life could do nothing to deter human's curiosity for the unknown, however small the chance of a positive outcome maybe."

Vann Chow, The White Man and the Pachinko Girl

Chapter 5: reminder of the aim and hypotheses

A lack of inhibitory control appears to contribute to the development and maintenance of addictive disorders. Among the mechanisms thought to assist inhibitory control, an increasing focus has been drawn on preparatory inhibition, which refers to the drastic inhibition observed in the motor system during action preparation. Interestingly, deficient preparatory inhibition has been reported in ADIs. When we started the study, it was still unknown whether this deficit also concerns behavioural, substance-free, addictions, and thus whether it might represent a physiological marker common to both SRDs and NSRDs. The goal of the present study was to determine whether GD subjects, who suffer from an addictive disorder but are preserved from the neurotoxic influence of drugs of abuse, display a lack of preparatory inhibition in the motor system, similar to the findings in patients suffering from an AUD. Based on the hypothesis that a lack of preparatory inhibition represents a common feature to both substance and behavioural addictions, we expected preparatory inhibition to be less pronounced in GD patients than in healthy control subjects.

Considering Motor Excitability During Action Preparation in Gambling Disorder: A Transcranial Magnetic Stimulation Study

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Keywords

Gambling disorder, addiction, inhibitory control, impulsivity, transcranial magnetic stimulation, motor system, action preparation.

5.1 Abstract

A lack of inhibitory control appears to contribute to the development and maintenance of addictive disorders. Among the mechanisms thought to assist inhibitory control, an increasing focus has been drawn on the so-called preparatory suppression, which refers to the drastic suppression observed in the motor system during action preparation. Interestingly, deficient preparatory suppression has been reported in alcohol use disorders. However, it is currently unknown whether this deficit also concerns behavioural, substance-free, addictions, and thus whether it might represent a vulnerability factor common to both substance and behavioural addictive disorders. To address this question, neural measures of preparatory suppression were obtained in gambling disorder patients (GDPs) and matched healthy control subjects. To

do so, single-pulse transcranial magnetic stimulation was applied over the left and the right motor cortex to elicit motor-evoked potentials (MEPs) in both hands when participants were performing a choice reaction time task. In addition, choice and rapid response impulsivity were evaluated in all participants, using self-report measures and neuropsychological tasks. Consistent with a large body of literature, the MEP data revealed that the activity of the motor system was drastically reduced during action preparation in healthy subjects. Surprisingly, though, a similar MEP suppression was observed in GDPs, indicating that those subjects do not globally suffer from a deficit in preparatory suppression. By contrast, choice impulsivity was higher in GDPs than healthy subjects, and a higher rapid response impulsivity was found in the more severe forms of GD. Altogether, those results demonstrated that although some aspects of inhibitory control are impaired in GDPs, these alterations do not seem to concern preparatory suppression. Yet, the profile of individuals suffering of a GD is very heterogeneous, with only part of them presenting an impulsive disposition, such as in patients with alcohol use disorders. Hence, a lack of preparatory suppression may be only shared by this sub-type of addicts, an interesting issue for future investigation.

5.2 Introduction

Self-regulation is essential to behave in a goal-directed manner. In particular, the ability to suppress prepotent but inappropriate responses is a key component, preventing one to respond to stimulus-driven impulses [48, 123]. Without the efficient operation of this inhibitory control, behaviour becomes maladaptive, as evidenced in a range of psychiatric disorders, including addictive disorders [207, 415]. As such, a core element of addiction is a loss of control over either the use of a substance or the engagement in a recurrent

activity, despite awareness of negative consequences, which clearly interfere with long-term goals.

Among the different processes assisting inhibitory control, an increasing focus has been drawn on mechanisms allowing to downregulate the excitability of the motor system [22]. Accordingly, a drastic suppression of motor activity has been reported when subjects are in the process of stopping an action [298, 451], but also during the preparation of motor acts [132, 425]. In particular, by measuring motor-evoked potentials (MEPs) elicited by single-pulse transcranial magnetic stimulation (TMS) over the primary motor cortex (M1), studies have monitored changes in the excitability of the corticospinal pathway during instructed-delay choice reaction time (RT) tasks [114, 129, 153, 157, 452]. Such tasks typically require participants to choose between responding with the left of the right hand according to an informative preparatory cue, and to withhold their response until the onset of an imperative signal. When TMS pulses are applied between the cue and the imperative, the amplitude of MEPs probed in both hands are strongly reduced relative to resting conditions [149, 161, 402]. This phenomenon, referred to as preparatory suppression (or inhibition), is thought to help prevent premature or inappropriate motor responses and, more generally, to ensure some sort of impulse control [127, 160, 385, 425].

Consistent with this view, preparatory suppression appears to be deficient in individuals lacking inhibitory control, such as in addictive disorders. We have recently shown that alcohol-dependent patients (ADPs) display a reduced MEP suppression during action preparation relative to matched healthy participants [132], suggesting that a shortage of preparatory suppression might represent a newly identified feature of addictive disorders. Moreover, it might serve as an objective indicator of addiction severity, as the magnitude of this

defect was linked to the subsequent propensity to relapse.

Chronic alcohol consumption has considerable neurotoxic effects, with the most pronounced damage reported in regions underpinning response inhibition, such as the frontal lobes and basal ganglia [311, 312, 313]. In addition, the degree of brain atrophy is related to the amount of alcohol previously consumed [317]. Hence, the deficit in preparatory suppression could be a consequence of brain damage induced by chronic alcohol exposure. Alternatively, a lack of inhibitory control might have been present before the pathology, predisposing individuals to early recreational experiences with alcohol, or facilitating their transition towards alcohol use disorder. For example, offspring of ADPs, known to be at higher risk of developing alcohol use disorders [453], display deficient inhibitory control [454, 455]. In addition, impulsivity assessed during childhood or adolescence predicts substance use disorders later in life [456, 457].

Inhibitory control is also impaired in behavioural, substance-free, addictions, implying that it might act as a vulnerability factor common to both substance and behavioural addictive disorders [207, 458]. This matter has been especially addressed in gambling disorder (GD), which shares considerable phenomenological parallels with substance addiction, including difficulties to control the urge to gamble despite awareness of its negative impact, unsuccessful attempts to cut back, or the emergence of craving in front of gambling-related cues [459]. In particular, an increasing body of literature has highlighted that patients suffering from GD (GDPs) have higher levels of impulsivity and lower response inhibition abilities than control subjects [460, 461, 462]. Moreover, several studies have reported an interesting association between those alterations and gambling severity [463, 464, 465].

The goal of the present study was to determine whether GDPs, who suffer from an addictive disorder but are preserved from the neurotoxic influence of drugs of abuse, display a lack of preparatory suppression in the motor system, similar to our findings in ADPs. To test this idea, we applied single-pulse TMS over the left and the right M1 to elicit MEPs in GDPs and matched healthy control subjects performing an instructed-delay choice RT task. The study also involved the examination of other aspects of inhibitory control, including trait impulsivity, choice impulsivity, and response inhibition. Based on the hypothesis that a lack of preparatory suppression represents a common feature to both substance and behavioural addictions, we expected preparatory suppression to be less pronounced in GDPs than in healthy subjects.

5.3 Materials and Methods

5.3.1 Participants

Thirteen right-handed individuals with a diagnosis of GD were included in the study. All patients were recruited through advertisements in several gambling areas, such as in casinos and sports betting facilities, and through a collaboration with the psychiatry unit of the Saint-Luc Academic Hospital (Université catholique de Louvain, Brussels, Belgium). Gambling dependence severity was assessed before the experiment using the South Oaks Gambling Scale (SOGS); a score higher than 5 was required to participate, indicating probable pathological gambling [466]. Based on this criterion, we selected 16 participants. Moreover, on the day of the experiment, a face-to-face clinical interview was conducted by an experienced psychologist, and only patients who met DSM-5 criteria for GD [198] were kept in the final sample (n = 13). All patients gambled at least more than once a week; the mean duration of

gambling behaviour was 6.1 years (SD = 3.86). Their main gambling activity was either sports betting (n = 7) or online casino games (n = 6). GDPs were matched for age, gender, and education level with 13 right-handed healthy control subjects (HCs); all controls had a SOGS score of 0. Exclusion criteria for both groups included major neurological or psychiatric disorder, any drug treatment that could influence performance or neural activity (including benzodiazepine), and no history of substance use disorder (except nicotine). Nicotine dependence was more prevalent among GDPs (n = 4) than controls (n = 0). Finally, in order to avoid any confounding effects due to a problematic consumption of alcohol, subjects from both groups had to complete the Alcohol Use Disorder Test (AUDIT); a score higher than 10 was considered as an exclusion criterion [467]. All participants gave written informed consent, following a protocol approved by the Biomedical Ethic Committee of the Saint-Luc University Hospital, Université catholique de Louvain. All the experimental procedures occurred at the Institute of Neuroscience of the Université catholique de Louvain, and a 50-euro voucher was provided at the end of the experiment as a financial compensation.

5.3.2 Experimental procedure

5.3.2.1 Self-reported measures

Current clinical status was measured using French versions of the Spielberger State Trait Anxiety Inventory [STAI Trait and State; [432, 468]] and the Beck Depression Inventory [BDI; [430, 431]]. To evaluate trait impulsivity, both the Barratt Impulsiveness Scale Version 11 [BIS-11; [469, 470]] and the UPPS Impulsive Behavior Scale [471, 472] were used. While the former is composed of three subscales, namely attentional, motor, and non-planning impulsivity, the latter allows to assess four different dimensions of impulsivity, referred to

as urgency, lack of premeditation, lack of perseverance, and sensation seeking. Finally, choice impulsivity was measured using the Monetary Choice Questionnaire [MCQ; [434]]. This tool consists of 27 dichotomous choices between smaller immediate and larger-delayed monetary rewards to provide individual's delay discounting rate, i.e. the k-value. Three magnitudes are assessed, resulting in separate discounting rates for small, medium, and large reward; an overall discounting rate was also obtained. K-values can range from 0 (consistent selection of the delayed reward) to 0.25 (consistent selection of the immediate reward); hence, the higher the k is, the more the individual discounts delayed reward.

5.3.2.2 Behavioural measures of motor inhibition.

5.3.2.2.1 Stop-signal task

The STOP-IT software was used to assess action stopping [124]. Overall, the task consisted of 32 practice trials, followed by three experimental blocks of 96 trials. On each trial, participants were presented with an arrow (go signal); their task was to press the left arrow key of a keyboard with the left index finger when they saw a left arrow, and to press the right arrow key with the right index finger when they saw a right arrow. However, on 25% of the trials (stop trials), the arrow became blue after a variable delay (stop-signal delay; SSD), notifying participants to abort their response. The SSD was initially set at 250 ms, and was continuously adjusted via a standard adaptive tracking procedure (i.e. decrease of 50 ms after a successful stop and increase of 50 ms after an unsuccessful stop); this converges on a response rate to a stop trial of ± 50%. Importantly, participants were instructed to respond as accurately and as fast as possible (maximal reaction time [RT] set at 1,250 ms), and not to delay their response to wait for the potential onset of a stop-signal. The

stop-signal reaction time (SSRT), which corresponds to the latency of the stop process, was estimated with the integration method (with replacement of go omissions, i.e. 0.007% of the trials in the current study), such as recently recommended by Verbruggen et al. (2019) [125]. In addition to the SSRT, we measured the RTs on Go trials, RTs on unsuccessful stop trials, and the SSDs.

5.3.2.2.2 Anti-saccade task

In this task [adapted from Roberts et al. (1994) [473]], participants performed three different blocks, all of them involving a similar procedure. Each trial started with the presentation of a fixation cross in the middle of the screen for 1,500 to 3,500 ms, followed by the onset of a target stimulus. This stimulus was an arrow inside a square displayed for 150 ms on the left or the right side of the screen, before being masked by a gray cross-hatching square. The participant's task was to indicate the orientation of the arrow (towards the left, the right, or upwards) by pressing the corresponding key on a keyboard. The first two blocks corresponded to control conditions, whereas the third one was the experimental condition. In the first block (No cue [NC]; 40 trials), the sequence of events for each trial occurred as described above. In the second type of block (Congruent cue [CC]; 40 trials), a visual cue (a black square) was presented for 225 ms between the fixation cross and the target stimulus on the same side as the arrow. Finally, the last block involved trials in which the visual cue was systematically displayed on the side opposite to the target stimulus (Incongruent cue [IncC]; 80 trials). Given that the arrow appeared for only 150 ms, participants had to inhibit the automatic response triggered by the IncC in order to correctly identify the orientation of the arrow. The critical measure was the anti-saccade cost, which was computed for

both RTs and percentage of correct responses, by calculating the difference between the average scores obtained in the IncC block and the average scores recorded in the two other NC and CC blocks.

5.3.2.3 Neural measures of preparatory inhibition

5.3.2.3.1 The *rolling ball* task

Participants performed an instructed-delay choice RT task, which was implemented with Matlab 7.5 (Mathworks, Natick, Massachusetts, USA) using the Psychophysics Toolbox extensions [383, 384]. It consists in a virtual "rolling ball" game previously used in other studies [[49, 132, 402, 425]; see Figure 5.1A]. In this task, a ball and a goal appear on a computer screen and participants must virtually "shoot the ball into the goal" by performing an abduction movement with the left or right index finger, which requires the activation of the left or right first dorsal interosseous (FDI) muscle, respectively.

The sequence and timing of events are shown in Figure 5.1B. Each trial started with the presentation of a preparatory cue, consisting of a ball and a goal separated by a gap. Participants had to prepare an abduction of the left index finger when the ball was displayed on the left side of the screen, and an abduction of the right index finger when it appeared on the right. Subjects were explicitly told to withhold their prepared response until the onset of an imperative signal (i.e., the bridge), which appeared 1,000 to 1,200 ms later. We purposely varied the duration of the delay period to decrease the subjects' tendency to respond prematurely (i.e., before the imperative signal). For the same reason, each block involved a few trials in which the bridge did not appear (i.e., catch trials - 4 per block). In these trials, subjects were required not to respond and were penalized if they did so. Once the bridge was on the screen, subjects had to respond as fast as possible to make the

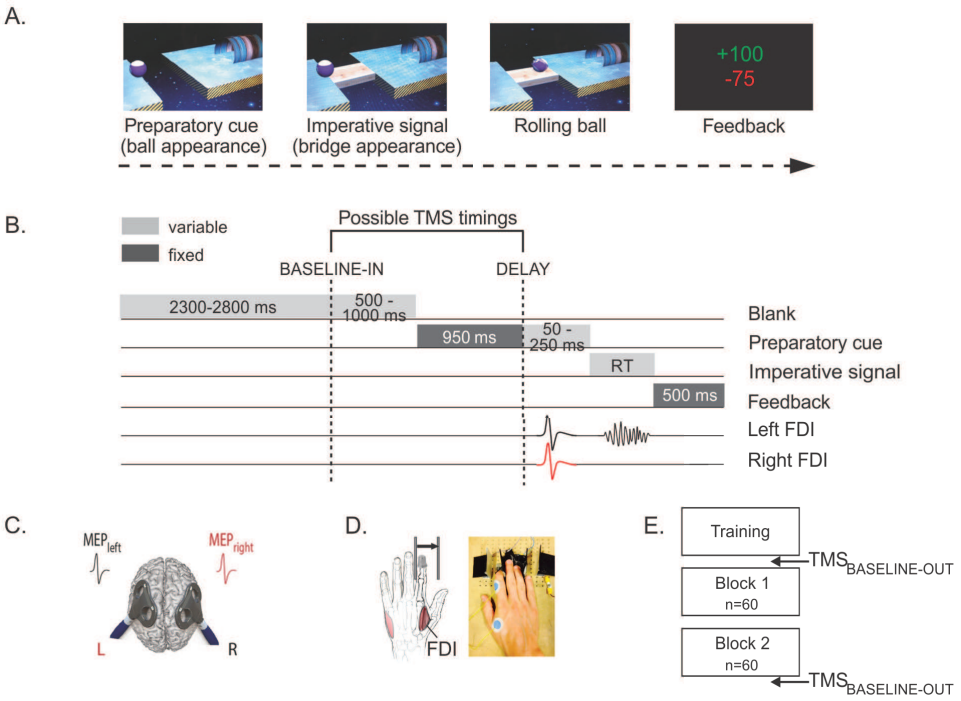

Figure 5.1: Experimental procedure to measure preparatory suppression. **(A)** Rolling ball task. Subjects performed an instructed-delay choice reaction time task, requiring them to choose between an abduction movement of the left or right index finger (left in the current example) depending of the position of a preparatory cue (i.e., the ball). They had to withhold their response until the onset of an imperative signal (i.e., the bridge). Once the bridge appeared, they were required to release their response as fast as possible. If they answered correctly, the ball then rolled over the bridge and reached the goal located on the other side. A feedback reflecting how fast and accurate subjects had been concluded each trial. **(B)** Time course of a trial. Each trial started with the preparatory cue (random duration; 1,000–1,200 ms) followed by the imperative signal, which remained visible until the subject responded (maximum duration of 700 ms). The feedback was presented at the end of each trial for 500 ms. Transcranial magnetic stimulation (TMS) was used to elicit motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) of both hands. TMS pulses could occur either during the inter-trial interval (between 2300 and 2800 ms after the blank screen onset; $\text{TMS}_{BASELINE-IN}$), or during the delay period (950 ms after the preparatory cue onset; TMS_{DELAY}). **(C)** TMS protocol. Two figure-of-eight coils were placed over the subject's primary motor cortex, eliciting near simultaneous MEPs (1ms delay) in the left and right FDIs. **(D)** Response device. Index finger responses were recorded using a home-made response device positioned under the left (graphic representation) and right (photographic representation) hands. **(E)** Time course of the experiment. After a training block, subjects performed two blocks of 60 trials. Moreover, MEPs were elicited before and after the two experimental blocks to obtain a measure of corticospinal excitability outside the context of the task ($\text{TMS}_{BASELINE-OUT}$).

ball roll over it, within a maximum time of 700 ms. The imperative screen disappeared once a response was detected (or after 700 ms) and a feedback was presented for 500 ms. Following a correct response, the feedback consisted of a positive score depicted in green, which ranged from 1 to 100 and was inversely proportional to the trial's RT (Score= $\frac{100*(0.8*250)}{(0.8*250)+(\frac{RT-(0.8*250)}{10})^{2,4}}$). By contrast, incorrect responses (i.e., responses provided prematurely, that is before the onset of the imperative, responses provided too late, that is more than 700 ms after the imperative onset, or responses that were provided with the incorrect finger) were penalized by a negative score (-75) displayed in red. Note that when subjects succeeded not to respond on a catch trial, they received +75 points. Finally, each trial ended up with a blank screen, lasting between 2,800 and 3,800 ms (inter-trial interval).

5.3.2.3.2 TMS protocol

TMS was always delivered using a double-coil TMS method recently developed in our laboratory [349, 381, 402, 443], where both M1 are stimulated with a 1 ms inter-pulse interval, eliciting MEPs in both hands at a near simultaneous time (Figure 5.1C). Adding an interval between both pulses allows to avoid direct electromagnetic interference between the two coils, while keeping it short prevents transcallosal interactions to occur between motor areas. The MEPs obtained using this double-coil approach are comparable to those elicited using single-coil TMS, regardless of the pulse order or the intensity of stimulation [381, 402]; here, the first pulse was systematically applied over right M1. Both pulses were delivered through small figure-of-eight coils (wing internal diameter 35mm), each connected to a stimulator delivering monophasic pulses. The coils were placed tangentially on the scalp with the handle pointing backward and laterally at 45° angle away from the midline, approx-

imatively perpendicular to the central sulcus. For each M1, the optimal coil position for eliciting MEPs in the contralateral FDI was identified and marked on a head cap placed on the participant's scalp to provide a reference mark throughout the experiment [127, 425, 438].

The resting motor threshold (rMT) was determined at the hotspot for each M1 as the minimal TMS intensity required to evoke MEPs of 50 μV peak-to-peak in the relaxed FDI muscle in 5 out of 10 consecutive stimulations. Across control subjects, the rMTs corresponded to 41.92 $\pm$ 2.56% and 41.46 $\pm$ 2.65% of the maximum stimulator output for the left and right M1, respectively. In GDPs, the rMTs equaled 41.77 $\pm$ 2.58% and 41.53 $\pm$ 2.79% in the corresponding conditions. The intensity of TMS used throughout the experiment was always set at 115% of the individual rMT for each hemisphere.

5.3.2.3.3 Experimental design

Participants sat in front of the computer screen with forearms resting in a semi-flexed position and hands placed palms down on a home-made response device developed in our laboratory to detect any horizontal movement of the index fingers (Figure 5.1D). This setup provides us with a very precise measure of the RT (precision = 1 ms) and allows us to control the initial index finger position at the beginning of each trial [for more details regarding this device, please refer to Quoilin et al. (2016) [154]].

As illustrated in Figure 5.1E, the testing always began with a training block in order to familiarize the subjects with the task, followed by two experimental blocks of 60 trials. During those blocks, TMS pulses were delivered at one of two possible timings (Figure 5.1B). To establish a baseline measure of corticospinal excitability (CSE), TMS pulses fell during the inter-trial interval, between 2,300 and 2,800 ms after the blank screen onset (i.e., 500 to

1,000 ms before the onset of the preparatory cue), eliciting MEPs at rest but in the context of the task ($TMS_{BASELINE-IN}$; 18 MEPs per block). In other trials, TMS pulses were delivered 950 ms after the onset of the preparatory cue, when subjects were withholding their response (TMS_{DELAY}; 18 MEPs per responding side and per block). The remaining trials (six per block) did not include any TMS pulse, preventing participants from anticipating TMS pulses at TMS_{DELAY} when it had not occurred at $TMS_{BASELINE-IN}$. Finally, 18 TMS pulses were applied before and after the two experimental blocks to obtain a baseline measure of CSE at rest outside the context of the task ($TMS_{BASELINE-OUT}$).

5.3.2.3.4 Electromyography (EMG) recording.

EMG activity was recorded from surface electrodes (Ambu Blue Sensor NF-50-K Neuroline, Medicotest, Oelstykke, Denmark) placed over the FDI muscle of the left and right hands. EMG data were collected for 3,200 ms on each trial, starting 200 ms before the TMS pulse. The raw EMG signals were amplified (gain, 1 K), bandpass filtered online (10–500 Hz, NeuroLog; Digitimer) and digitized at 2,000 Hz for offline analysis. The latter consisted in extracting the peak-to-peak amplitude of MEPs recorded in both FDIs. In order to prevent contamination of MEP measurements by significant fluctuations in background EMG, trials with EMG activity (root mean square computed in the 200 ms windows preceding the TMS pulse) exceeding 2.5 standard deviations (SD) around the mean were discarded from the following analyses [402, 425]. The remaining MEPs were classified according to the experimental condition within which they had been elicited. Trials in which subjects made an error were also removed from the data set; the task was so easy that these trials remained rare and errors were not analysed. For each

condition, we excluded trials with peak-to-peak MEP amplitudes exceeding 2.5 SD around the mean. Following data cleaning, a mean of 30.7 ± 3.5 trials per condition were left.

5.3.3 Statistical analyses

5.3.3.1 Self-reported measures

Demographic variables and current clinical status were compared in HCs and GDPs using independent sample t-tests. Trait impulsivity was analysed by conducting two separate multivariate analyses of variance (MANOVAs) on scores reported at the different subscales of the BIS-11 and the UPPS questionnaire, with GROUP (HCs, GDPs) as the between-subject factor. To analyse choice impulsivity, a two-way ANOVA was computed on k-values obtained at the MCQ, with MAGNITUDE (small, medium, large) as the within-subject factor and GROUP (HCs, GDPs) as the between-subject factor. Importantly, as several works reported that using the natural log (nlog) transformation allows to approximately normalize the distribution of k-values [474, 475], analyses were performed on nlog k-values.

5.3.3.2 Behavioural measures of motor inhibition.

To compare motor inhibition in both groups, independent sample t-tests were performed on the critical measures specific to each task, i.e. the SSRT and the anti-saccade cost. In addition, RTs on Go trials, RTs on unsuccessful stop trials and SSDs were compared using Welch's t-tests, because of unequal variances in HCs and GDPs.

5.3.3.3 Neural measures of preparatory inhibition.

First, we focused on CSE at rest, by considering MEPs probed outside the blocks ($TMS_{BASELINE-OUT}$) and those recorded within the blocks ($TMS_{BASELINE-IN}$). The raw amplitude of those MEPs (mV) was analysed using a three-way ANOVA, with MEP-SIDE (Left, Right) and TMS-TIMING ($TMS_{BASELINE-OUT}$, $TMS_{BASELINE-IN}$) as within-subject factors and GROUP (HCs, GDPs) as the between-subject factor. Then, we considered MEPs at TMS_{DELAY}; those MEPs were expressed in percentage of MEPs elicited at $TMS_{BASELINE-IN}$. To assess the presence of preparatory suppression in each sub-condition, one-sample t-tests (Bonferroni-corrected) were carried out to compare these values to 100 (i.e. to $TMS_{BASELINE-IN}$). Furthermore, the strength of preparatory suppression was compared between both groups by performing a three-way ANOVA, using MEP-SIDE (Left, Right) and CONDITION (Selected, Non-Selected) as the within-subject factors and GROUP (HCs, GDPs) as the between-subject factor. Finally, to analyse behaviour during the rolling ball task, a three-way ANOVA was computed on RTs, with RESPONDING-SIDE (Left, Right) and TMS-TIMING ($TMS_{BASELINE-IN}$, TMS_{DELAY}) as within-subject factors and GROUP (HCs, GDPs) as the between-subject factor.

5.3.3.4 Exploratory analyses on the relationships with gambling severity

In order to assess the potential link between the total number of DSM-V criteria and psychopathological variables as well as our different measures of inhibition in GDPs, partial Pearson's correlations were performed in these subjects, using the factor AGE as a covariate. The Fisher's Least Significant Difference (LSD) method was used to run post-hoc comparisons. All of the

data are expressed as mean ± SE and the statistical significance was set at $p < 0.05$. Analyses were carried out using Statistica 10 (StatSoft, Cracow, Poland).

5.4 Results

5.4.1 Demographics and current clinical status.

As illustrated in Table 5.1, analyses confirmed that both groups were matched for age ($t_{(24)}$ = - 0.21, p = 0.67) and education level ($t_{(24)}$ = 1.92; p = 0.07). In addition, they did not significantly differ for state anxiety ($t_{(24)}$ = - 1.29; p = 0.74), trait anxiety ($t_{(24)}$ = 0.97; p = 0.45), and depression (BDI, $t_{(24)}$ = - 1.67; p = 0.11). Finally, the AUDIT score was not significantly different between HCs and GPDs ($t_{(24)}$ = 1.71; p = 0.10).

	HCs (N = 13)	**GDPs (N = 13)**
Age^{NS}	27.8 (2.4)	28.6 (2.7)
Education level[1,NS]	15.5 (0.48)	14.1 (0.6)
Trait anxiety^{NS}	35.3 (2.9)	40.5 (2.7)
State anxiety^{NS}	43.3 (3.2)	43.5 (2.6)
BDI^{NS}	3.6 (1.0)	6.8 (1.6)
AUDIT^{NS}	6.1 (0.7)	4.2 (0.9)
Tobacco (n smokers)	0	4
SOGS	0	9.1 (0.6)
DSM-V criteria	0	5.8 (0.4)

Table 5.1: Demographic and psychopathological measures for healthy controls (HCs) and gambling disorder patients (GDPs) (Mean [SE]). [1]The education level reflects the number of years of education completed since starting primary school. BDI, Beck Depression Inventory; AUDIT, Alcohol Use Disorders Identification Test; SOGS, South Oaks Gambling Screen; DSM, Diagnostic and Statistical Manual; NS, non-significant.

5.4.2 Trait impulsivity

The MANOVA performed on scores at the BIS-11 questionnaire showed a significant main effect of the factor GROUP ($\lambda_{(3,22)} = 0.49$; $p < 0.01$). As shown in Table 5.2, univariate results obtained for each subscale reveal that the significant difference between both groups was due to higher scores on the non-planning impulsiveness subscale in GDPs relative to HCs ($F_{(1,24)} = 21.21$; $p < 0.001$). Moreover, scores on the motor subscale also tended to be higher in GDPs, even if it did not reach significance ($F_{(1,24)} = 3.31$; $p = 0.08$).

Surprisingly, the main effect of GROUP was not significant for the UPPS scale ($\lambda_{(3,22)} = 0.70$; $p = 0.10$). Nonetheless, it is interesting to note that univariate analyses still reveal a significant difference between both groups for the lack of premeditation subscale ($F_{(1,24)} = 6.79$; $p < 0.05$), consistent with the results regarding the BIS-11 questionnaire.

		HCs (N = 13)	**GDPs (N = 13)**
BIS-11**			
	Attentional	17.1 (1.2)	17.3 (0.9)
	Motor	20.5 (1.0)	23.3 (1.2)
	Non-planning***	21.2 (1.0)	27.2 (0.8)
UPPS Scale^{NS}			
	Urgency	26.6 (1.5)	29.7 (1.8)
	Lack of premeditation	20.1 (1.1)	23.9 (0.9)
	Lack of perseverance	19.1 (1.5)	21.4 (1.4)
	Sensation seeking	35.2 (1.8)	35.3 (2.5)

Table 5.2: Trait impulsivity measures for healthy controls (HCs) and gambling disorder patients (GDPs) (Mean [SE]). NS = non-significant. **p < 0.01 and ***p < 0.001.

5.4.3 Choice impulsivity

The ANOVA performed on the nlog k-values of HCs and GDPs revealed a significant main effect of GROUP ($F_{(1,24)} = 22.17$; $p < 0.001$). Hence, and as evident on Figure 5.2, GDPs discounted reward at a significantly higher rate than HCs did. Furthermore, the main effect of MAGNITUDE was significant ($F_{(2,48)} = 15.03$; $p < 0.001$), which reflected a decrease in discounting rates as the amount of the delayed reward increased. Interestingly, the interaction between both factors was not significant ($F_{(2,48)} = 0.13$; $p = 0.73$), indicating that GDPs had higher discounting rates relative to controls regardless of the reward amount. Accordingly, further analyses performed on the mean discounting rate estimated for the whole questionnaire (i.e. 0.006 ± 0.002 and 0.056 ± 0.018 for HCs and GDPS,respectively) revealed a significant difference between both groups ($t_{(24)} = -4.47$; $p < 0.001$).

5.4.4 Behavioural measures of motor inhibition

In the stop-signal task, two GDPs did not properly follow the instructions - i.e. probability of responding on a stop trial higher than 0.75 - and were consequently excluded from the subsequent analyses, as recommended [125]. In the remaining subjects, the mean response rate on stop trials equaled 49.17 and 47.76% in HCs and GDPs, respectively, indicating that the tracking procedure was successful, which should allow a valid interpretation of the SSRT. As shown on the left panel of Figure 5.3A, the t-test performed on this index revealed no significant difference between both groups ($t_{(22)} = 0.18$; $p = 0.86$), suggesting similar abilities to abort an ongoing action in HCs and GDPs. However, GDPs seemed to be slower than controls when performing the task, such as indicated by longer RTs on Go trials ($t_{(22)} = -2.23$; $p = 0.06$; see right panel of Figure 5.3A). This overall slowness was also reflected

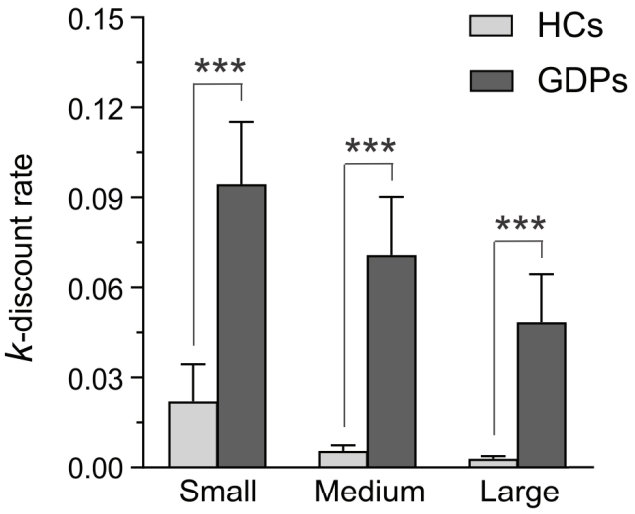

Figure 5.2: Self-reported measures for choice impulsivity. K-values estimated from the Monetary Choice Questionnaire (MCQ) are shown for HCs (light gray) and GDPs (dark gray) when the delayed reward was small, medium, or large. Higher k-values reflect higher discounting rates. Please note that statistical analyses were performed on nlog k-values, although this figure depicts the raw data. Those results highlight the higher discount rate in GDPs relative to HCs, regardless of the magnitude of the delayed reward. ***$p < 0.001$: significantly different.

in measures of the SSD (243.7 ± 23.9 and 396.3 ± 75.6 ms in HCs and GDPs, respectively; $t_{(22)}$ = - 1.92; p = 0.07) and of RTs on unsuccessful stop trials (393.9 ± 10.9 and 523.5 ± 60.1 ms in HCs and GDPs, respectively; $t_{(22)}$ = - 2.12; p = 0.06).

Regarding the anti-saccade task, even though the figures suggest a larger cost in GDPs than in controls, our analyses did not reveal any significant difference between both groups, neither for the percentage of correct responses ($t_{(24)}$ = - 1.71; p = 0.10; left panel of Figure 5.3B) nor for the RTs ($t_{(24)}$ = - 0.57; p = 0.57; right panel of Figure 5.3B). Hence, GDPs did not signifi-

cantly display more difficulties than HCs to inhibit the initial reflexive saccade towards the incongruent visual cue.

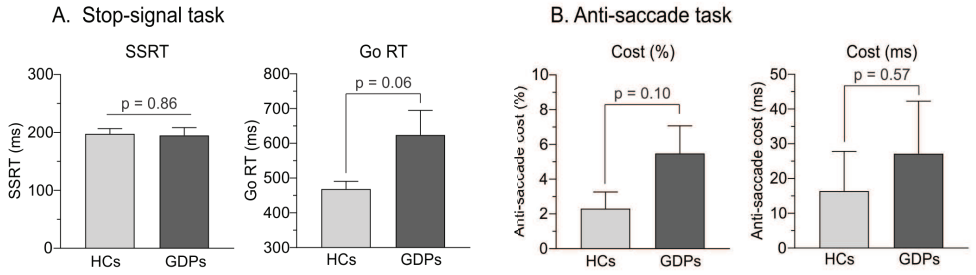

Figure 5.3: Behavioral measures of motor inhibition. **(A)** Stop-signal reaction time (SSRT) and reaction time (RT) on go trials during the stop-signal task in HCs (light gray) and GDPs (dark gray). **(B)** Anti-saccade cost, defined as the difference between the scores (% of errors and RTs) in incongruent and control trials, in HCs and GDPs (same color code).

5.4.5 Neural measures of preparatory inhibition

5.4.5.1 MEPs measurements

First, we considered MEPs acquired at rest, either outside or within the blocks ($TMS_{BASELINE-OUT}$ and $TMS_{BASELINE-IN}$). Overall, the amplitude of MEPs probed at $TMS_{BASELINE-OUT}$ was 1.06 ± 0.26 mV and 0.84 ± 0.16 mV in HCs and GDPs, respectively. When elicited at $TMS_{BASELINE-IN}$, MEPs equalled 1.64 ± 0.34 mV and 1.06 ± 0.21 mV in the corresponding groups. In line with previous studies [49, 402, 425], MEPs were globally larger at $TMS_{BASELINE-IN}$ relative to $TMS_{BASELINE-OUT}$ ($F_{(1,24)} = 39.14$; $p < 0.001$), reflecting an increase in the level of CSE in the context of the task. However, consistent with the significant GROUP X TMS-TIMING interaction ($F_{(1,24)} = 8.07$; $p < 0.01$) and as shown on Figure 5.4, this increase was more pronounced in controls ($p < 0.001$) than in GDPs ($p < 0.05$).

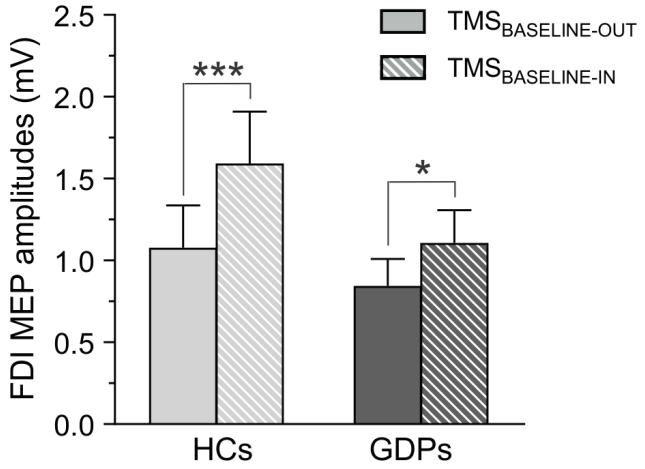

Figure 5.4: Measures of corticospinal excitability (CSE) at rest. Raw amplitude of motor-evoked potentials (MEPs, in mV) recorded in the FDI at rest, either outside ($TMS_{BASELINE-OUT}$; open bars) or within ($TMS_{BASELINE-IN}$; dashed bars) the blocks. MEPs are shown for HCs (light gray) and GDPs (dark gray). Such as revealed by the significant GROUP X TMS-TIMING interaction, the increase in CSE during the task was larger in HCs than in GDPs. *$p < 0.05$ and ***$p < 0.001$: significantly different.

Then, we evaluated the amplitude of MEPs elicited during action preparation (expressed in percentage of MEPs at $TMS_{BASELINE-IN}$). As evident on Figure 5.5A, MEPs probed in control subjects were drastically decreased at TMS_{DELAY} when compared to $TMS_{BASELINE-IN}$. This effect occurred for MEPs in both the left and the right FDIs, regardless of whether the muscle was selected or non-selected for the forthcoming response (all $t_{(12)} <$ - 4.92 and all $p < 0.0125$). Hence, HCs displayed a strong MEP suppression during action preparation, such as extensively shown in many other works [161, 365, 438]. Interestingly, MEPs at TMS_{DELAY} were also significantly suppressed in all

conditions in GDPs (all $t_{(12)} < -3.02$ and all $p < 0.0125$), indicating that those subjects displayed preparatory suppression as well (Figure 5.5B). Moreover, as revealed by the ANOVA computed on these data, the strength of this MEP suppression was comparable in both groups ($F_{(1,24)} = 1.58$; $p = 0.22$).

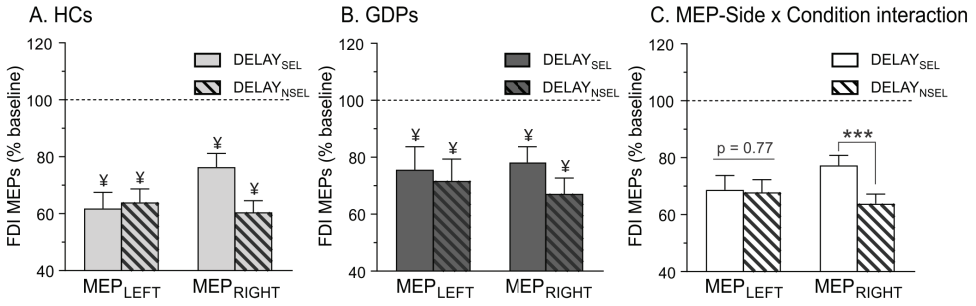

Figure 5.5: Neural measures of preparatory suppression. Amplitude of motor-evoked potentials (MEPs) recorded at TMS_{DELAY}, expressed in percentage of MEPs elicited at $TMS_{BASELINE-IN}$, shown for the left (MEP_{LEFT}) and the right (MEP_{RIGHT}) FDI, which was either selected ($DELAY_{SEL}$; open bars) or non-selected ($DELAY_{NSEL}$; dashed bars) for the forthcoming response in HCs **(A)** and GDPs **(B)**. ¥= significantly different from MEPs probed at $TMS_{BASELINE-IN}$. **(C)** MEP-Side x Condition interaction. MEPs were larger in the selected relative to the non-selected condition only in the right FDI, regardless of the group. ***$p < 0.001$: significantly different.

Besides, analyses showed a significant main effect of CONDITION ($F_{(1,24)} = 4.46$; $p < 0.05$), due to a weaker MEP suppression in an effector that was selected for the forthcoming response relative to when the effector was non-selected. However, and as shown on Figure 5.5C, this effect depended on the hand within which the MEPs were elicited (CONDITION x MEP-SIDE interaction $F_{(1,24)} = 7.64$; $p < 0.05$), as it concerned the right ($p < 0.001$) but not the left ($p = 0.78$) hand, regardless of the group (GROUP X MEP-SIDE X CONDITION interaction, $F_{(1,24)} = 1.44$; $p = 0.24$).

5.4.5.2 Behaviour

The RTs measured during the rolling ball task are shown in Figure 5.6. The ANOVA computed on these data revealed a main effect of TMS-TIMING ($F_{(1,24)} = 13.05$; $p < 0.01$): RTs were faster with TMS_{DELAY} than with $TMS_{BASELINE-IN}$, consistent with many previous reports showing that a TMS pulse applied close to the imperative signal can speed up the release of a motor response [114, 402, 438]. By contrast, RTs were comparable in both groups ($F_{(1,24)} = 0.71$; $p = 0.41$), regardless of the TMS timing (GROUP X TMS-TIMING interaction; $F_{(1,24)} = 1.38$; $p = 0.25$), indicating that HCs and GDPs performed equally in the task.

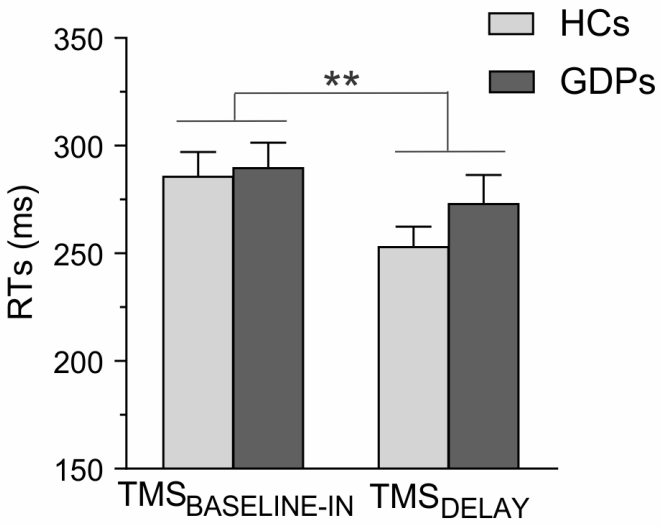

Figure 5.6: Reaction times (RTs) during the rolling ball task. The RTs are shown for trials in which the TMS pulses were applied either at baseline ($TMS_{BASELINE-IN}$) or during action preparation (TMS_{DELAY}) for HCs (light gray) and GDPs (dark gray). Data from responses performed with both hands are pooled together, as the main effect of RESPONDING-SIDE was not significant ($F_{(1,24)} = 0.02$; $p = 0.89$). Please note the shortening of RTs at TMS_{DELAY}. **$p < 0.01$: significantly different.

5.4.5.3 Exploratory analyses on the relationships with gambling severity

Regarding the psychopathological variables, the total number of DSM-V criteria significantly correlated with the scores for state anxiety ($r = 0.84$; $p < 0.001$) and BDI ($r = 0.62$; $p < 0.05$), which indicates that more severe GDs were associated with higher anxiety and depression. Moreover, we observed a significant positive correlation between the DSM-V criteria and the anti-saccade cost in terms of RTs ($r = 0.65$; $p < 0.05$; Figure 5.7), suggesting lower motor inhibition abilities in more severe GDs. Nonetheless, note that only the relationship between gambling severity and state anxiety remained after correction for multiple comparisons. None of the other correlations was significant (all - $0.37 < r < 0.55$ and $p > 0.06$).

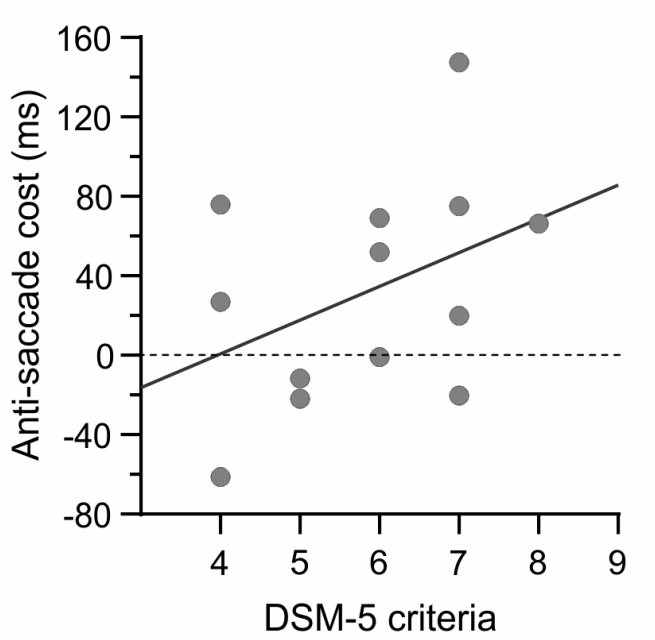

Figure 5.7: Relationship with gambling severity. A positive correlation ($r = 0.65$) was observed between the number of DSM-V criteria and the anti-saccade cost (in terms of RT), suggesting lower motor inhibition abilities in more severe GDs. However, note that the correlation did not survive Bonferroni correction.

5.5 Discussion

The fifth edition of the DSM recently reclassified pathological gambling from the "Impulse Control Disorder" category to the newly established "Substance-related and Addictive Disorders" section [198]. Such a decision implies that this substance-free gambling addiction shares many features with addictions to substances [476, 477, 478]. In this context, extensive work is being dedicated to understanding these similarities and to identifying vulnerability markers that may be common to all addictive disorders, with one particularly promising candidate being a lack of inhibitory control. In the present study, we addressed this question by assessing preparatory suppression, a specific facet of inhibitory control, in a group of GDPs and in matched HCs. Contrary to our hypothesis, GDPs did not lack any preparatory suppression, though they had some deficits in other aspects of inhibitory control, such as a steeper delay discounting rate and a higher trait impulsivity than HCs.

In control subjects, MEPs elicited during the rolling ball task were globally smaller at TMS_{DELAY} than at $\text{TMS}_{BASELINE-IN}$, consistent with the literature reporting a lower corticospinal excitability during action preparation [22]. Also, in line with some previous studies ([349, 438]; but see also [402]), this preparatory suppression was less prominent in the dominant hand, especially when it was selected for the subsequent movement, possibly reflecting a higher readiness of effectors from the dominant hand to initiate actions [349, 443]. Interestingly, the same pattern of results was found in GDPs, suggesting that those subjects did not suffer from a deficit in preparatory suppression. In fact, the only group difference that we found during the rolling ball task concerns MEPs elicited during the inter-trial interval, at $\text{TMS}_{BASELINE-IN}$. In both groups, these MEPs were larger than those

elicited outside the blocks, at $TMS_{BASELINE-OUT}$, in agreement with previous studies [49, 365, 402]. Yet, this increase was more pronounced in HCs than in GDPs. This difference might be the result of dissimilarities at the level of attention, vigilance, or arousal [48, 51]. As such, one possibility is that GDPs are less motivated by a task in which the sole reward consisted in a feedback score, leading to a blunted resting excitability during the blocks. Accordingly, fMRI studies have reported a diminished sensitivity towards small or non-monetary rewards in gamblers relative to control subjects [479, 480]. Nevertheless, this plausible reduced vigilance in GDPs did not impact the level of preparatory suppression or even the performance in the rolling ball task.

While we did not observe an alteration of preparatory suppression in GDPs, there were some differences between both groups regarding some aspects of impulsivity, substantiating the presence of a deficit as expected in these patients. Although multiple theoretical models have been put forward [481, 482, 483], impulsivity is commonly divided into two primary components, called choice impulsivity and rapid response impulsivity [484, 485]. In line with the relative independence of those two types of impulsivity, GDPs were affected differently depending on the assessed component. Our findings at the MCQ revealed that GDPs had significantly steeper discounting rates than HCs, highlighting a higher choice impulsivity in this group of patients, as shown previously [463, 486, 487]. This predisposition to prefer smaller sooner-rewards over larger-delayed ones was also supported by our measures of trait impulsivity. Indeed, GDPs obtained higher scores than controls on the "non-planning" and "lack of premeditation" subscales of the BIS-11 questionnaire and the UPPS Impulsive Behavior Scale, respectively, implying that those individuals are more oriented to the present rather than the future and tend to act without consideration of the consequences. In this line, an as-

sociation between scores on both subscales and discounting rates has been previously reported [474, 487, 488]. Altogether, this pattern of results is likely to contribute to the tendency of GDPs to favour immediate bets, despite the negative consequences of their gambling behaviour.

By contrast, GDPs and HCs did not seem to differ at the level of rapid response impulsivity. This lack of group effect concerned not only behavioural motor inhibition, such as assessed by the stop-signal and the anti-saccade tasks, but also impulsivity trait, as scores at the motor subscale of the BIS-11 questionnaire were not significantly different between both groups. This result contrasts with recent meta-analyses suggesting higher rapid response impulsivity in subjects suffering from pathological gambling [458, 489], although some studies failed to identify a deficit [490, 491]. Nonetheless, the present results need to be put into perspective in several ways. First, while the SSRT was similar in HCs and GDPs, it is noteworthy that other task variables estimated in the stop-signal task, such as the RTs on Go trials and unsuccessful stop trials, as well as the SSDs, indicated a general slowness to respond in GDPs. Hence, it might be that GDPs strategically slowed down in anticipation of the stop-signals to compensate for a potential inhibitory deficit, even though blocks without stop-signals would have been required to ascertain this hypothesis. Besides, the slowness reported in GDPs might have prevented us from highlighting a lack of response inhibition. Indeed, while the tracking procedure was efficient, the SSD had to drastically increase to adapt to the slower responses of GDPs. Consequently, the number of trials was probably insufficient in the present study to allow the SSD to reach a relatively steady value at which the SSRT can be computed reliably. Hence, future studies should use initially longer SSDs to observe a potential deficit in GDPs [463]. Moreover, despite the overall lack of group effect in the anti-saccade task, we

found an interesting positive correlation between the number of DSM-V criteria and the anti-saccade cost, which was quite variable in GDPs. In fact, and in line with previous works [463, 464, 492], this association indicates that a deficit in rapid response impulsivity only concerned the most severe forms of pathological gambling, contrary to choice impulsivity, which was higher regardless of gambling severity. Finally, it is worth noting that GDPs tended to score higher at the motor subscale of the BIS-11 questionnaire, and that the lack of significant difference is likely to result from our small sample size.

The current findings in GDPs contrast considerably with our prior observations in alcohol-dependent patients (ADPs), which revealed a major lack of preparatory suppression, especially in the patients who relapsed during the year following the testing [132]. As GDPs are preserved from the neurotoxic influence of drugs of abuse, one straightforward interpretation of the discrepancy between both studies is that the lack of preparatory suppression observed in ADPs arises as a consequence of chronic alcohol consumption. Accordingly, it has been shown that the lateral prefrontal cortex - i.e., the region of the alcoholic brain in which the decrease in gray matter volume is the most significant [493] - generates at least part of the preparatory suppression effect [107, 114]. Hence, it is plausible that this prefrontal source of preparatory suppression is specifically reduced in ADPs after years of alcohol abuse. Future studies, combing structural magnetic resonance imaging to quantify the brain damage and TMS to assess preparatory suppression in ADPs, are required to conclude on this point. Moreover, it would be interesting to investigate whether the lack of preparatory suppression extends to other substance-use disorders. Yet, it is noteworthy that structural and functional prefrontal alterations still exist in GDPs [494, 495, 496, 497, 498], even in the absence of any substance use disorder comorbidity [499]. In particular, an increasing literature has led

to consider the neuromodulation of the dorsolateral prefrontal cortex, using high-frequency repetitive TMS, as a potential treatment for GD [478], with encouraging results in terms of craving reduction [500, 501, 502], but not regarding inhibitory control [503]. That being said, the absence of deficit in preparatory suppression reported in GDPs makes it an unlikely common vulnerability marker of whether one is going to develop an addiction or not.

The present finding that preparatory suppression was comparable in GDPs and HCs should be interpreted with caution and requires further evidences as the current study suffer from several limitations. First, GDPs represent a highly heterogeneous group, characterized by different impairments depending on the form of gambling in which they engage [460, 504]. Although impulsivity is an important etiological factor for GD, the recognized pathway model of Blaszczynski and Nower [505] posits that it represents only one of the three routes than can lead to pathological gambling. Hence, it is likely that our results reflect the average of different GD profiles, and that our findings would have been more similar to those observed in ADPs if we had only included GDPs from the impulsivity pathway. Second, the power of our study is rather low given our small sample sizes. Yet, this is the best we could do in view of the real challenge of recruiting patients suffering of GD only. Indeed, many GDPs show high extent of comorbidity with alcohol and substance use disorders [506], preventing them from participating in experiments aiming at assessing the neuropsychological profile exclusively associated with GD. Finally, our sample was entirely male. Although this is consistent with gender biases in the GD population [458, 487, 504], this limits the generalizability of our findings to females.

In summary, although we found some alterations in several aspects of inhibitory control in the sample of GDPs tested in the current study, prepara-

tory suppression was not deficient in these patients. This finding contrasts with prior observations reported in subjects suffering from an alcohol use disorder, suggesting that a lack of preparatory suppression does not represent a common feature shared by behavioural and substance-related addictions. Critically, future studies would gain from taking into account the large heterogeneity in GDP profiles and possibly focus on patients that are part of the impulsivity pathway. Moreover, extending investigations of preparatory suppression to other "Substance-related and Addictive Disorders" should further our understanding of inhibitory control as a vulnerability marker underlying these conditions.

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

Ethics statement

This study was reviewed and approved by Biomedical Ethic Committee of the Saint-Luc University Hospital, Université catholique de Louvain. The patients/participants provided their written informed consent to participate in this study.

Author contribution

CQ, JG, and JD: designed the experiment. CQ and JG: performed the experiments. CQ and JG: analysed data. CQ and JD: wrote the article.

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General discussion

"Discussion is an exchange of knowledge; an argument an exchange of ignorance."

Robert Quillen

6.1 Reminder: objectives and research questions

The purpose of the present thesis was threefold:

1. In Chapters 1 & 2, we investigated whether a double-coil TMS method where the two primary motor cortices are stimulated with an inter-pulse interval as short as 1 ms (double-coil$_{1ms}$) yields equivalent MEPs as the ones obtained with single-coil TMS. In Chapter 1 we addressed this question at rest, in Chapter 2 during the preparation of an action.

2. In Chapter 3, through using the double-coil$_{1ms}$ TMS method developed in Chapters 1 & 2, we investigated the relevance of preparatory inhibition for behavioural inhibition. To do so, we asked subject to perform an instructed-delay choice RT task in conditions composed of either a small amount or a large amount of SAS. Based on the impulse control hypothesis, we predicted that, in order to avoid responding prematurely, subjects would recruit more preparatory inhibition in conditions in which they expected SAS to occur frequently compared to when SAS were less likely.

3. In Chapters 4 & 5, we assessed preparatory inhibition in BDs and GDPs respectively, to measure whether abnormal preparatory activity is at play in a population that is likely to suffer from an AUD (i.e., BDs) and in a population experiencing a behavioural addiction (i.e., GDPs). To do so, we applied TMS during the instructed delay choice RT task used in Quoilin et al. 2018 [132] using the double-coil$_{1ms}$ TMS method developed in Chapters 1 & 2. The level of preparatory inhibition observed in each population was compared with the one of matched HCs.

6.2 Main findings

6.2.1 Chapters 1 & 2: Double-Coil$_{1ms}$

In Chapters 1 & 2, we showed that double-coil$_{1ms}$ is a reliable TMS method that yields equivalent results as the one obtained through using a single-coil TMS method and this, both at rest (Chapter 1) and in the context of a motor task (Chapter 2). The notion of equivalence is of first importance here as it does not simply imply an absence of difference. That is, MEPs elicited through using double-coil$_{1ms}$ were always significantly inside the boundaries of an equivalence margin (Figure 1.2 & 2.4) and this, independently of the functional state (i.e., at rest or during the preparation of an action), of the order of stimulation (i.e., first TMS pulse applied on the left or right hemisphere) and of the intensity of stimulation (i.e., ranging from 100% to 160% of rMT).

Main message from Chapters 1 and 2

Double-Coil$_{1ms}$ is a reliable TMS method to assess CS excitability bilaterally and this, not only when subjects are at rest but also when they are involved in a task.

6.2.2 Chapter 3: Preparatory inhibition for behavioural inhibition

In Chapter 3, we supported and extended previous work that showed dependable motor inhibition during the preparation of an action. We also provided further evidence for the facilitatory effect of a SAS when it is released close to an imperative signal. Due to several limitations in our experiments, we were however not able to draw a definite conclusion about whether the presence or absence of SAS shapes preparatory inhibition and as a consequence, about whether the modulation of the activity of the motor output pathway observed during action preparation accounts for behavioural inhibitory capabilities.

Main message from Chapter 3

First, SAS can significantly shorten RTs when they are applied slightly before the imperative signal, especially when they occurred frequently.
Second, MEPs are strongly inhibited when subjects delay a prepared motor response. Third, varying the probability of SAS does not seem to influence the extent of preparatory inhibition. Rather, it may increase the level of attention participants pay to acoustic stimuli.

6.2.3 Chapters 4 & 5: Preparatory inhibition in addictions

In Chapter 4, we observed abnormal preparatory activity in BDs and this, specifically in the prime mover of the task in conditions in which it was likely to be targeted by strong facilitatory influences. In other conditions or effectors, preparatory inhibition was perfectly normal suggesting that generic inhibition operates quite normally in BDs. As a result, it seems that the unusual motor

activity associated with the prime mover of BDs arises from excessive facilitatory inputs to prepotent motor representations rather than from deficient motor inhibition. In Chapters 5, although we found a steeper delay discounting rate and a higher trait impulsivity in GDPs than in HCs, we did not find any evidence that preparatory inhibition is altered in a population suffering from a NSRD, namely GD: preparatory inhibition was equivalent between GDPs and controls subjects in both hands and in all conditions.

Main message from Chapters 4 & 5

BDs present abnormal preparatory activity at the level of the motor output system, alike ADIs. It remains however unclear whether the underlying causes of these alterations are shared amongst BDs and ADIs. As such, for both populations, the question remains wide open as to whether peculiar preparatory activity accounts for a deficit of inhibition, from an excess of facilitation, or from both. With regard to GDPs, although some aspects of inhibitory control are impaired, these alterations do not seem to concern preparatory inhibition, making it an unlikely common vulnerability marker of substance-related and non-substance-related disorders. In any case, regardless of the population studied, measures in task-irrelevant muscles are necessary for a proper understanding of preparatory inhibition.

6.3 Interpretation and theoretical implications

6.3.1 Double-Coil$_{1ms}$ (Chapters 1 & 2)

TMS, a painless and non-invasive technique used to assess CS excitability, has gained substantial attention since it was first described about 30 years ago [367]. When applied over one M1, TMS elicits MEPs in muscles that are controlateral of the site of stimulation. MEPs represent a valuable indicator of CS excitability at the time of stimulation [48] and their amplitude can be compared at different moments within a given condition and between different states [22, 51]. Over the years, the assessment of MEPs has helped to characterise the CS correlates of various neural processes including those underlying action preparation and stopping [114, 126, 298], decision making and reward processing [82, 307, 346], sustained attention [345], speech [83], and motor imagery [371].

When I started my PhD, almost all TMS-based CS excitability studies had recorded MEPs from muscles of a single hand following the application of TMS over one M1 only. In most experiments therefore, the MEP data had only provided researchers with one half of the story, increasing the probability of seeing data being misinterpreted. In the topic of action preparation, for instance, it was commonly assumed that differences in MEP amplitudes between conditions in which a muscle was either selected or non-selected for the upcoming movement were due to the distinct function of the probed muscle in these two situations [148]. Yet, there was an important confound here because besides the function (i.e., selected vs. non-selected), conditions also varied in regard to the hand being cued for the response (i.e., left or right hand; dominant or non-dominant hand). The shortcut of data interpretation often occurred because applying TMS over both M1 in separate blocks doubles

the duration of an experiment, making it impossible to fit all the conditions into a single session.

Since obtaining MEPs in both sides simultaneously appeared to be an interesting way to *reveal the second half of the story*, in Chapters 1, we assessed whether a double-coil TMS method where the two M1s are stimulated at rest with an inter-pulse interval as short as 1 ms (double-coil$_{1ms}$) yields equivalent MEPs as the ones obtained with single-coil TMS. Because double-coil$_{1ms}$ was reported reliable at rest, in Chapter 2 we addressed the same question during another functional state, namely the preparation of an action. Fortunately, results in Chapter 2 were similar to the ones obtained in Chapter 1: double-coil$_{1ms}$ yields equivalent results as the ones obtained with single-coil TMS.

At first sight, our findings can seem surprising. They contrast indeed with observations made in previous experiments that have used double-coil TMS protocols over M1 [102, 107, 344, 358, 449]. However, a major difference between our studies and the ones cited above stands in the duration of the inter-pulse interval. In previous studies, this interval was purposely set to probe transcallosal interactions. Short delays ($\sim$ 4 ms) are typically used to assess facilitatory interactions whereas longer intervals ($>$ 7 - 8 ms) are used to probe inhibitory influences [63]. The goal of the double-Coil$_{1ms}$ procedure is very different. It aims at using the shortest possible interval (1 ms) to avoid these transcallosal interactions to occur in order to obtain non-biased MEPs in both body sides, that is, MEPs similar to those elicited in single-coil situations. Of note, a small delay remains mandatory to avoid electromagnetic interferences between the two stimulating coils. Taken together, our results from Chapter 1 and 2 indicate that a 1 ms delay is short enough to avoid interactions through the corpus callosum and at a subcortical or spinal site.

The fact that double-Coil$_{1ms}$ TMS yields equivalent results as does a single-coil TMS method provides researchers with several advantages. First, double-Coil$_{1ms}$ allows to acquire double the data in the same amount of time. This is critical as it enhances the reliability of the measures obtained through decreasing their variability. It also allows to test more conditions than could be done with a regular single-coil TMS method, while maintaining a reasonable length of experiment. Second, obtaining MEPs in both hands within the same trial allows to investigate the distinct impact of a task on CSE of the dominant and non-dominant sides in the exact same settings. This increases the signal to noise ratio in a significant way. Third, with this design, one can also make direct comparisons between MEPs elicited in the two hands on a single-trial basis. New dependent measures can be obtained and computed. In Vassiliadis et al. (2020) for instance, through using double-coil$_{1ms}$, we were able to assess the relationship between the percentage of suppression measured both in a hand that was responding and in a hand that was nonresponding for the forthcoming response and the subsequent RTs [189]. Obviously, this is just one example and other indexes reflecting the differences (or ratios) between CSE measures of the two hands as well as correlations between individual MEPs on both sides can also be computed. In summary, double-coil$_{1ms}$ appears to be a very promising protocol, that researchers can use for their experiments, that might pave the way towards new research horizons.

Despite the common employment of TMS, the neural types and neural elements that it activates remain largely unknown (please refer to Section 0.2.4 for more information) [67, 74]. For instance, it was recently suggested that TMS applied over the precentral motor hand knob does not originally stimulate axonal structures in the M1 hand representation [72, 75]. Instead, it seems to excite the M1-HAND indirectly via the PMd, at least for intensities

of stimulation below or slightly above threshold with the neurons located in the crown and lips of the precentral gyrus being the one observed with the lowest threshold for stimulation. In addition, when the current direction was inverted from P-A to A-P, an anterior shift of threshold allocations was observed. These observations have important implications for studies using TMS - and therefore ours. Indeed, they suggest that changing the current direction does not only activate different populations of neurons within M1, they also account for the activation of specific neurons within the PMd. As a result, not only differences of M1 neuroanatomy or functioning but PMd inter-individual variabilities as well are likely to account for (1) the specific effect induced by rTMS and for (2) the amplitude of the MEPs obtained [75, 507, 508]; an interesting issue for future investigations. Ultimately, these observations, even if highly interesting, do not challenge our results. Neither have they an impact on our conclusion about the reliability of double-coil$_{1ms}$. Rather, they highlight the fact that MEPs represent the net effect of several cortical, subcortical and spinal inputs [22].

Behaviourally speaking, double-Coil$_{1ms}$ seems to yield equivalent RTs as does single-coil TMS. In brief, in Chapter 2, 4 & 5, RTs were reported faster when the TMS pulse was elicited at TMS$_{delay}$ than when it was elicited at TMS$_{baseline-in}$ (Figure 2.2). This pattern is similar to what is usually found in TMS studies when a TMS pulse is applied close to the imperative signal [114, 154, 156]. With regard to single-coil TMS, in Chapter 2, RTs were reported longer in trials where the MEP$_{single}$ pulse occurred in the responding hand compared to when the MEP$_{single}$ pulse fell in the non-responding hand or in both hands at once (i.e., when using double-Coil$_{1ms}$). This effect was present at TMS$_{delay}$ both in left and right hand trials, indicating that the boosting effect of the TMS pulse was slightly attenuated when the MEP fell

in the responding hand, compared to when it fell in the non-responding hand or in both hands. These results at TMS_{delay} are, even if singular, consistent with previous works [166, 349]. More surprising was the effect of the MEP_{single} condition that was observed at $TMS_{baseline-in}$ in right hand trials but not in left hand trials (Figure 2.2). This result was unexpected given that at $TMS_{baseline-in}$, MEPs are elicited during the intertrial interval and are not supposed to affect one's behaviour. An issue for future investigations. Of note, the behavioural differences observed for RTs in trials where the MEP_{single} pulse occurred in the responding hand did not transferred into differences in the amount of preparatory inhibition observed at TMS_{delay} as MEP amplitudes were equivalent whether single-coil or $double\text{-}coil_{1ms}$ TMS was used.

6.3.2 Preparatory inhibition for behavioural inhibition (Chapter 3)

Acting adequately in everyday life often requires the ability to inhibit prevailing tendencies that are not consistent with our internal goals or to suppress actions that are no longer appropriate [123, 394]. When this capacity called behavioural inhibition [286] is deficient, one's endeavour becomes maladaptive, as evidenced in a range of psychiatric disorders [198].

Amongst the various processes assisting behavioural inhibition, an increasing focus has been drawn on processes allowing to down-regulate the excitability of the motor system. One of them, namely preparatory inhibition seems to be of first importance for inhibitory control capabilities and, as a consequence, for the generation of goal-directed behaviours [22] (reviewed in Chapter 0.3.3.1). Different models have been proposed. A couple suggest that inhibitory influences are specifically directed towards not-selected representa-

tions to assist the selection of an action through suppressing not-selected ones [114, 157]. Others postulate that preparatory inhibition could be essential for retaining selected muscles from becoming active before required: a sort of impulse control [127, 158]. There is strong evidence in support of these two ideas. First, substantial MEP suppression is measured when a response must be retained until a go signal in instructed-delay choice RT tasks [22, 48, 128]. Second, the danger of selecting inappropriate responses (either because of conflicting information or because a not-selected response is biased) enhances the strength of preparatory inhibition [149, 160]. Third, subjects suffering from AUD, a population typically lacking inhibitory control abilities, display a deficit of preparatory inhibition [132].

The fact that preparatory inhibition may support impulse control abilities suggests that the inhibition observed in the motor output pathway during the preparation of an action helps preventing the premature expression of pre-movement activity: CS neurons are inhibited during the pre-movement period so that they cannot respond to a gradually increasing amount of excitation at the cortical level. Hence, motor suppression should correlate with one's behaviour: the stronger the need to retain an action, the higher the amount of preparatory inhibition should be.

In Chapter 3, we tested this hypothesis through using SAS. We hypothesised that anticipating a SAS during delay periods may be associated with increased preparatory inhibition for greater impulse control. In this chapter, however, we did not find any relationship between the difficulty of withholding an action and the amount of preparatory inhibition exerted by the subjects. We must however be cautious when interpreting these data as the absence of effect might result from the several limitations we discussed in section 3.5.2.

Beside the assumption that CS suppression is critical for successful behavioural inhibition, another hypothesis suggests that the CSE suppression that occurs during the preparation of a movement is present to increase the gain of the motor system [128] so that excitatory inputs can better stand out against the background. As such, through suppressing the background activity, preparatory inhibition may in fact facilitate the release of a movement [22]: the higher the level of motor suppression, the faster the RTs. A pattern only found in a couple of studies [134, 189].

As one may observe, these two hypotheses suggest quite distinct predictions. Whilst inhibition for behavioural inhibition predicts longer RTs with an higher level of preparatory inhibition, inhibition for motor release suggests the inverse. Because these two models are considered as mutually exclusive, much work is currently being done to discover which hypothesis is correct [128, 129, 134, 135]. It seems aberrant indeed that stronger MEP suppression may be related to faster RTs in some occasions and to slower RTs in others.

My view is different. In my opinion, it is very likely that the inhibition observed at the level of the motor output pathway during the preparation of an action does not reflect an unitary process. Rather, it may express the impacts of several proceedings that help the selection of an action and adjust the activity of the motor output pathway in order to perform a movement that is both precise and opportune. Because standard RT paradigms do not aim at distinguishing the motor and choice components leading to the release of an action, the link between MEP suppression and one's endeavour is based on very flimsy evidence - or totally absent as was the case in Chapter 3 - and probably reflects to combined influence of both processes. Hence, it appears now crucial for researchers to address the question of preparatory inhibition in a unified manner - by contrast to a segregated one - through studying the

collective influence of the motor and choice aspects of a task on the motor output pathway. To do so, it seems important for scientists to develop new paradigms in which it is possible to modify the choice and motor components independently. An appealing issue for scientists.

6.3.3 Preparatory inhibition in addictions (Chapters 4 & 5)

Coherent with the view that the motor cortex, and more specifically preparatory inhibition helps the generation of goal-directed behaviours is the fact that ADIs, a population typically lacking inhibitory control, display a shortage of neural motor inhibition during the preparation of an action [132]. Unfortunately, chronic alcohol consumption has considerable neurotoxic effects, with the most pronounced damage reported in regions underpinning response inhibition, such as the frontal lobes and basal ganglia [311, 312, 313]. In addition, the degree of brain atrophy is related to the amount of alcohol previously consumed [317]. As a consequence, when we started the experiments making Chapters 4 and 5, it was unclear whether or not the shortage of preparatory inhibition observed in ADIs represents a consequence of the brain damage induced by chronic alcohol exposure. Instead, it might have been present before the pathology, utlimately predisposing individuals to early recreational experiences with alcohol and/or facilitating their transition towards AUD. Another option is that it could account for a common vulnerability marker of whether one is going to develop an addiction or not. The goal of Chapters 4 and 5 was to shed new light on these questions.

With regard to Chapter 4, our results provide further evidence for the close link between BDs and ADIs as both populations display an abnormal level of preparatory activity. Such data goes in the direction of the continuum hypothesis that suggests that BDs display qualitatively similar but quantita-

tively attenuated impairments than ADIs [450].

However, we must be cautious before jumping to conclusions. The paucity of longitudinal studies as well as the lack of direct comparison between BDs and ADIs restrain to draw strong conclusions about the development of the successive stages of AUD. As a result, the existence of the continuum hypothesis is still widely debated and remains to be tested [322, 509]. This arises mainly because, similar to what happened 10 years ago [320], the field still lack cohesion in the conceptualisation, operationalization and quantification of what defines a binge drinking pattern [509]. The same apply - to a smaller extend - to the field of AUD [205]. Hence, it remains uncertain whether or not the impaired preparatory activity observed in BDs is related to the one observed in ADIs.

Another aspect of our results is that, contrary to our predictions, MEPs were strongly inhibited in all muscles for BDs, except in a very specific condition, when MEPs were elicited in the right FDI (and to some extent in the right ADM too) in right hand trials. These findings clearly question the first reading of the data we made in our prior work on ADIs [132] where we proposed a deficit of preparatory inhibition based on observations that were limited to the prime mover (i.e. FDI), as this was the standard in most past studies where task-irrelevant muscles were usually not considered. As a consequence, the question remains wide open as to whether or not inhibitory processes are genuinely deficient in BDs and in ADIs during action preparation or if these individuals rather suffer from an excessive facilitation of prepotent motor representations. An issue for future investigations.

Noteworthy, inhibitory control only account for a small part of the BDs' behaviour, as a binge drinking pattern is usually linked to both cognitive and

emotional impairments [510]. For instance, BDs have been reported with impaired behavioural and cerebral processing of emotional bursts [335], a disadvantageous decision making [511, 512], premature neurocognitive aging [513], increased motor impulsivity [514], less positive mood and depressive symptoms [323, 515] as well as shortened working memory capabilities [323] and elevated alcohol cue-reactivity [516]. It is important to consider therefore that it is the combination of all these characteristics *plus* a lack of inhibitory control that are likely to be equally the cause but also the consequence of binge drinking [290].

To shed light on whether altered preparatory inhibition might represent a common biological marker of addiction, our study on BDs was followed by the one on GDPs. GDPs represent the only population classified as suffering from an NSRD in the DSM-V as it appears that *gambling behaviours activate reward systems similar to those activated by drugs of abuse and produce some behavioural symptoms that appear comparable to those produced by the SUDs* [198]. In this experiment, although we observed several alterations of some aspects of inhibitory control in the sample of GDPs tested in the study, we measured a similar level of preparatory inhibition in GDPs and HCs. As a result, it seems more likely that the lack of motor suppression - or the excess of facilitation - observed in AD patients [132] represents the consequence of the neurotoxic effects of alcohol rather than the cause of excessive drinking. These findings, although interesting, should be taken with caution as our study suffer from several limitations discussed in Section 5.5. Eventually, future studies should extend investigations into preparatory inhibition to other SRDs and NSRDs to enhance our understanding of inhibitory control and more specifically of preparation inhibition as a potential biological marker of these conditions.

6.4 Methodological considerations

6.4.1 The conceptualisation and definition of the resting motor threshold

For the studies included in this thesis - but generally for all our published studies -, we utilised the relative frequency method to assess the rMT [60]. As a result, we considered the rMT as being the "minimal TMS intensity required to evoke MEPs of at least 50 μV peak-to-peak in all the required muscles for at least 5 out of 10 consecutive trials". This protocol slightly differs from the one proposed by Rossini et al. (1994) in which the rMT was considered as being the lowest stimulus intensity required to induce a MEP in - precisely - 5 out of 10 trials [60]; a method later proven mathematically invalid [517]. Of critical importance however, when utilising at least 5 positive MEPs out of 10 trials [518], it has been assessed that the measurement accuracy (i.e., Awiszus (2012) defined a motor threshold estimation procedure sufficiently accurate for a given subject if *"the probability to obtain a diagnostically acceptable estimator for this subject exceeds 0.95"* [519]) is only acceptable in 47.6% of the subjects [39, 519], whilst defining the rMT as the "smallest stimulus strength with at least 3 MEPs out of 6 trials" is sufficiently accurate for 0.8% subjects only [519]. Fortunately, when using 10 MEPs out of 20 trials, accuracy ramps up and reaches 96.2% [519]. In summary, it can be said that, if possible, a criterion of 10 out of 20 trials should be used both for research and clinical studies in the future in order to obtain more reliable and reproducible results [39].

6.4.2 The use of a multi-muscle hotspot technique

Being able to collect MEPs in different muscles at the same time is of great interest as it allows one to investigate the extent of the facilitatory and inhibitory influences that target the CS tract at a particular moment. In Chapter 1 & 2, we were able to measure MEPs linked to the FDI and ADM muscles in both hands simultaneously using double-Coil$_{1ms}$. In these studies, the locus of stimulation was determined as the optimal scalp position for eliciting a contralateral MEP in the FDI. In Chapter 4, we went a little further measuring MEPs in the FDI, ADM and APB muscles of both hands through coupling double-Coil$_{1ms}$ with a multi-muscle hotspot technique. Contrary to the first method, the goal of the multi-muscle hotspot technique is not the find the hotspot of a particular muscle, but rather, to determine the optimal place for eliciting consistent MEPs in 3 different muscles of the contralateral hand.

In my opinion, this procedure is really interesting and this, even in tasks designed for index finger movements only. Previous studies suggest indeed that preparatory inhibition may be underestimated in task relevant effectors due to concurrent facilitatory influences producing an opposite boost in MEP amplitudes, especially in the prime mover [349, 154]. In contrast, because preparatory inhibition is a rather global effect surpassing the relevant muscles [22], MEPs in surrounding effectors, which are irrelevant to the task, provide a particularly pure measure of preparatory inhibition (preserved from any facilitatory input), probably even more dependable when the innervation diverges. As a result, the multi-muscle hotspot technique allows one to obtain dependable MEPs from several effectors that are each characterised by a different function or innervation - some of them likely targetted by inhibitory influences only. Ultimately, in the case of Quoilin et al. 2018 [132], the use of this method would have permitted to assess whether abnormal preparatory

inhibition was at play in ADIs in a relevant effector only or whether it was measured in irrelevant motor representations as well.

6.4.3 Inhibition for preparatory inhibition or arousal?

Many studies suggest that without inhibition, one's attention would be overwhelmed by irrelevant information. In addition, with a lack inhibitory capabilities, one could not battle against inappropriate urges. The role of inhibition in the generation of goal-directed behaviours is also heightened by a study where subjects with prefrontal brain damage grabbed anything that was in front on them [520], probably because these objects provided them with *affordances* that, in normal situations, are inhibited to avoid the motor system from being activated.

Although these observations are convincing, there is a major concern that inhibition may not be the best explanation for the aforementioned behaviours. Just on the base on computational efficiency, inhibition seems unlikely. Why would cortical and subcortical areas be constantly engaged in the active inhibition of multiple cortical and subcortical loci instead of simply amplifying the relevant information? In addition, the mere damage of the PFC and the inappropriate endeavours that follow should not be considered as a proof for inhibition. One should indeed be cautious when trying to extrapolate the role of an area from examining the effect of a lesion: when you glasses are broken, repairing them with a spot of glue does not make you think that they were initially *glue deficient* or that the absence of glue might explain your poor vision.

The same principles apply for preparatory inhibition where studies generally involve a comparison of MEPs triggered during the task (i.e., usually referred to as "*at delay*") to a baseline condition. In some studies, baseline

measurements are obtained at rest inside experimental blocks [127, 132], in others outside the experimental blocks [521, 522] and in some in both conditions [132, 189]. Critically, these baseline conditions strongly differ with regard to the level of arousal, vigilance or attention that is required. As a result, relying on a baseline condition or another can lead to very contrasting conclusions [365].

Take for example Figure 5.4 in Chapter 5. Having used MEPs elicited at $\text{TMS}_{Baseline-out}$ instead of $\text{TMS}_{Baseline-in}$, one might suppose that the level of inhibition exhibited by GDPs would have been higher that the one exhibited by HCs, eventually changing the reading of our results. Obviously, we considered this option and this analysis would not have altered the interpretation of our data. This consideration suggests however that the choice of a condition over another can have dramatic consequences for the interpretation of data [51, 365]. What we call preparatory inhibition might in fact reflect - at least in part - other aspects of action preparation such as the level of arousal and/or the level of vigilance expressed at baseline [48, 51].

This fact represents an important matter for future studies who should be cautious before normalising MEPs to baseline measures. Should MEPs be reported in raw data or compared to baseline measures? If the latter option is preferred, should MEPs be expressed as a ratio or difference of baselines taken inside or outside the blocks? Ultimately what do we really compare at TMS_{Delay}, inhibition or arousal ? Maybe both. So many questions, so many appealing issues for future investigations.

6.5 Limits of the current work

6.5.1 The homogeneity of our samples

This thesis has explored several questions going from technical to more clinical fields. Because in each experiment we applied TMS over one's M1, there was always the necessity to recruit subjects. Most of the time, this was done through advertisement on social media. Less often we recruited through health centres, rarely by word-of-mouth.

The need to test participants in our facilities (as TMS devices and accessories cannot be easily transported) means that the vast majority of our subjects were ones that lived nearby our laboratory or a least in Brussels. They were often young (i.e., usually between 18 and 25 years old), right-handed (to conform with previous studies) and studied at the university on the UCL campus (Brussels). A vast majority of them were undergraduate or postgraduate physicians. Hence our samples were often uniform and did not vary with regard to the educational level, age, handedness, etc.

The homogeneity of the participants we tested means that our conclusions might not apply to a population level. To overcome this problem, future studies should include subjects of all backgrounds and all ages together. Of course, this would result in an increase of the variability of the measures and more participants would be needed to obtain dependable results with strong statistical power. Even if costly and time-consuming, such an approach would, however, provide a clearer view of the phenomenon of interest whilst responding to a recurrent critic in research, the low statistical power caused by small samples.

6.5.2 The necessity of larger samples

Why Most Published Research Findings Are False. So is the title of the paper written by John Ioannidis [523]. In this article, the author explains that the probability that a research claim is true depends on many factors that encompass the flexibility of design, the chase of statistical significance, the size of the sample, etc. - to name but a few. In this section, I will only discuss about the latter point: the sample size. I do so because small sample size is a recurrent problem in the field of neuroscience that has been shown to (1) decrease the chance of detecting a true effect and (2) decrease the likelihood that a statistically significant result reflects a true effect [524].

In the current project, our samples never exceeded 20 participants per group except in Chapter 1 where 32 participants were tested. In Chapter 2 for instance, 15 subjects were tested whilst in Chapter 3, only 11 subjects took part in the TMS experiment. These numbers are quite low with regard to some studies [463, 525] but appear higher or somehow similar to most in the field [128, 129, 134, 157, 346, 526, 527].

For the studies that focused on a population suffering from a disorder, the small sample size can be explained by the difficulty to recruit subjects encompassing all the recruitment criteria. In the case of the experiment reported in Chapter 5, for instance, we found ourself with the challenge of finding GDPs that (1) did not show comorbidity, (2) satisfied the criteria for the use of TMS and (3) were willing to participate in the experiment. Finding and testing more subjects during the period of my thesis would have been difficult but probably not impossible.

In the future, studies should increase their sample size to reach high statistical power. This could be achieved through having stronger collaboration

between institutes, hospitals and centres that deal with subjects/patients. From my point of view much could be done in research indeed if the path of collaboration took the lead over competition.

6.5.3 The necessity of longitudinal studies

Using cross-sectional studies in the field of addiction, one cannot draw definite conclusions as to whether the deficit or excess of a variable of interest is more likely to be the cause or the consequence of one's endeavour. In the case of AUD, for instance, it is difficult to say if the lack of preparatory inhibition that was observed in ADIs in Quoilin et al. 2018 [132] is more likely to be the result or the cause of excessive drinking; what came first and what followed? To tackle this issue, future studies could focus on - for instance - young adolescents before the onset of drug intake. Neurophysiological measurements could be taken on a monthly, bi-yearly or yearly basis to assess the neurophysiological correlates associated with one's behaviour - or change of behaviour. Such research would clearly strengthen and deepen our understanding of addictions. They are, however, not easy to perform as they run for many years and require resources and appropriate infrastructures that are sufficiently robust to bear the test of time [528].

General conclusion

"Reasoning draws a conclusion, but does not make the conclusion certain, unless the mind discovers it by the path of experience."

Roger Bacon

General conclusion

The present thesis has explored three main axes viz., (1) the reliability of double-coil$_{1ms}$ (Chapters 1 and 2), (2) the role of preparatory inhibition for behavioural inhibition (Chapter 3) and (3) the possible alteration of the activity of the motor output pathway in BDs and GDPs (Chapters 4 and 5 respectively).

The results of the first two chapters (Chapters 1 and 2) suggest that double-coil$_{1ms}$ yields equivalent MEPs as does a single-coil TMS method and this, both at rest and within the context of a motor task. This is great news as double-coil$_{1ms}$ allows one to acquire twice the amount of data in a single trial and to observe state-related CSE changes in both hands simultaneously on a trial-by-trial basis. It now starts to be used by other researchers [49, 189, 305, 529] and is likely to participate in the expansion of TMS in a broad range of neurophysiological as well as neurological studies.

The results from Chapter 3 support previous work that has revealed that preparatory inhibition is at play during motor preparation. They also provide additional evidence for a significant decrease of RTs when a SAS is elicited near the go-signal. Limitations in the experimental design prevent us however to shed new light on the role of preparatory inhibition for impulse control abilities.

In Chapter 4, we observed that BDs exhibit an abnormal level of preparatory activity at the level of the motor output pathway though some of our results raise new questions regarding the significance of these observations. That is, are inhibitory processes genuinely deficient in BDs and ADIs during action preparation or do these individuals exhibit excessive facilitation of prepotent motor representations? The question remains wide open and should be explored in future studies. With regard to Chapter 5, our data demonstrated

that although some aspects of inhibitory control are impaired in GDPs, these alterations do not seem to concern preparatory inhibition. As a result, the absence of deficit in preparatory inhibition reported in GDPs makes preparatory inhibition an unlikely common vulnerability marker of whether one is going to develop an addiction or not.

Ultimately, the experiments encompassed in the present thesis make several recommendations for future studies. First, they invite researchers to use double-coil$_{1ms}$ for investigating CSE. Second, they encourage scientists to implement uncommon apparatuses in their experiments for exploring the role of preparatory inhibition. Third, they recommand the use of specific TMS methods to investigate which subpopulation of CS neurons is responsible for the lack of inhibition - or increase of facilitation - observed in BDs and in patients suffering from AUD. Of note, these methods could also be useful for a better understanding of the neural correlates of preparatory inhibition in healthy individuals and in subjects experiencing other types of addictions. Fourth, with regard to the field of addiction, they suggest that it is relevant to make cluster analysis based on the psychological profiles of the subjects. Last, they highlight the fact that future studies should enlarge their sample size as the presence of small samples remains a recurrent problem in the field of neurosciences [524, 530].

Scientific contributions

"Give a scientist a tool and you feed science for a day. Teach a scientist to be open and you feed science for a lifetime"

Anonymous

Articles published in peer-review journals

- **Grandjean J**, Duque J. A TMS study of preparatory inhibition in binge drinkers. NeuroImage: Clinical, Volume 28, 102383, 13 August 2020, online. DOI: 10.1016/j.nicl.2020.102383

- Quoilin C, **Grandjean J**, Duque J. Considering Motor Excitability During Action Preparation in Gambling Disorder: A Transcranial Magnetic Stimulation Study. Front Psychiatry. 2020; 11: 639. Published online 2020 Jun 30. doi: 10.3389/fpsyt.2020.00639

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- **Grandjean J**, Derosiere G, Vassiliadis P, Quemener L, Wilde Y, Duque J. Validation of a double-coil TMS method to assess corticospinal ex-

citability. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, Volume 10, Issue 2, 507.

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- Vassiliadis P, Derosiere G, **Grandjean J**, Duque J. Motor training strengthens corticospinal suppression during movement preparation. bioRxiv, page 2020.02.14.948877, 2020.

- Derosiere G, Thura D, Van hemelrijck S, **Grandjean J**, Cisek P, Duque J. Time-dependent impact of urgency on corticospinal excitability during action selection.

Presentations during conferences with scientific committee

Oral presentations

- **Grandjean J**, Derosiere G, Vassiliadis P, de Wilde Y, Quemener L, Duque J. (2018, September). Assessing the reliability of a new double-coil TMS method to measure corticospinal excitability bilaterally. EURON PhD days. Brussels - Belgium.

- **Grandjean J**, Derosiere G, Vassiliadis P, de Wilde Y, Quemener L, Duque J. (2016, November). Validation of a Double-Coil TMS Method to Assess Corticospinal Excitability. Annual Conference of the IoNS PhD day. Brussels - Belgium.

Poster presentations

- Vassiliadis P, **Grandjean J**, Derosiere G, Duque J. (2019, October). Training-related modulation of preparatory activity in the motor system. Program No. 312.09. 2019. Society for Neuroscience (SfN). Chicago, USA.

- **Grandjean J**, Warnauts C, Lancelon E, Fierens A, Verdure M, Duque J. (2019, May). Is preparatory inhibition altered in binge-drinkers? A TMS experiment. 13th National Congress of the Belgian Society for Neuroscience. Brussels, Belgium.

- **Grandjean J**, Vassiliadis P, Derosiere G, de Wilde Y, Quemener L, Duque J. (2018, September).Validation of a new double-coil TMS method to assess corticospinal excitability bilaterally. Belgian Brain Congress (BBC). Liege, Belgium.

- Derosiere G, Thura D, Van Hemelrijck S, **Grandjean J**, Cisek P, Duque J. (2018, May). Time-dependent impact of urgency on corticospinal excitability during action selection. 28^{th} Neural Control of Movement (NCM) Meeting. Santa Fe, NM, USA.

- **Grandjean J**, Vassiliadis P, Derosiere G, de Wilde Y, Quemener L, Duque J. (2017, December). Investigating the Reliability of a Double-Coil TMS Method to Assess Corticospinal Excitability. 9^{th} IoNS Young Researcher Day. Brussels, Belgium.

- Wilhelm E, **Grandjean J**, Duque J. (2017, July). Testing the influence of various parameters on preparatory motor inhibition: a possible explanation for discrepancies between previous studies? Progress in Motor Control (PMC) conference. Key Biscayne Miami, Florida, USA.

- **Grandjean J**, Vassiliadis P, Derosiere G, de Wilde Y, Quemener L, Duque J. (2017, May). A New Double-Coil TMS Method to Assess Corticospinal Excitability Bilaterally. 12^{th} National Congress of the BSN. Ghent, Belgium.

- Wilhelm E, **Grandjean J**, Duque J. (2017, May). Testing the influence of various parameters on preparatory motor inhibition: a possible explanation for discrepancies between previous studies. 12^{th} National Congress of the BSN. Ghent, Belgium.

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- Wilhelm E, **Grandjean J**, Duque J. (2017, May). Testing the influence of various parameters on preparatory motor inhibition: a possible explanation for discrepancies between previous studies. 27^{th} Neural Control of Movement (NCM) Meeting. Dublin, Ireland.

- **Grandjean J**, Derosiere G, Vassiliadis P, Quemener L, de Wilde Y, Duque J. (2017, March). Validation of a Double-Coil TMS Method to Assess Corticospinal Excitability. 2^{nd} International Brain Stimulation Conference. Barcelona, Spain.

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Colophon

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