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Final Degree Project

Biomedical Engineering Degree

“ The neural basis of serial biases in spatial working memory“

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ABSTRACT

Transcranial magnetic stimulation (TMS) is a technique that stimulates the brain using electromagnetic pulses. This technology has a wide range of uses, from the treatment of certain pathologies, such as drug-resistant depression, to its use in research related to neuronal functionality. Serial dependence refers to a cognitive phenomenon where an individual's perception, or memory of a current stimulus, is influenced by the previous stimulus. This thesis consisted of an experiment involving 12 participants in which TMS was used to study the nature of serial dependence in spatial working memory (WM) as part of the line of research on serial dependence carried out by the Compte Lab. Participants performed a WM task while we applied TMS stimulation and we collected behavioral and EEG data. With the support of previous work, this thesis seeks to provide additional data and establish a direction for future analyses and studies in the field. Therefore, the objectives of this thesis are: firstly, to replicate the results previously obtained by the Compte Lab in order to strengthen the hypotheses put forward with regard to serial dependency and the effect that the TMS pulse has on it [5]. Secondly, to conduct new analyses with respect to the side the brain is being stimulated and the visual hemifield of stimulus appearance. Finally, to obtain the electroencephalogram (EEG) to investigate neural responses to TMS pulses in this task. The objectives of replication of the results with respect to temporality were met, but future analysis of the EEG data obtained is required to corroborate them. The objectives regarding the validation of previous results on the hemifields in which the stimuli appear were also met. No robust conclusions could be drawn regarding the effect of TMS when it was applied in one hemisphere or the other. This was due to the fact that the dataset was divided into too many different subgroups. With so few data per subplot, it was not possible to draw conclusions. The goal of conducting the experiment and obtaining EEG data in each session was successfully achieved.

Key words: Behavior Analysis, Biomedical Engineering, Neural Mechanisms, Serial Dependence, TMS, Working Memory.

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GLOSSARY OF ABBREVIATIONS

CSV - Comma-Separated Values

ECoG - Electrocorticography

EEG - Electroencephalogram

EMG - Electromyography

EM - Electromagnetism

EROS - Event-Related Optical Signal

EU - European Union

fMRI - functional Magnetic Resonance Imaging

IDIBAPS - Instituto de Investigaciones Biomédicas August Pi i Sunyer

ITI - Inter-Trial Interval

MEP - Motor Evoked Potential

MEG - Magnetoencephalography

NIRS - Near-Infrared Spectroscopy

NMDA - N-Methyl-D-Aspartate

NMDAR - N-Methyl-D-Aspartate Receptors

PERT - Program Evaluation and Review Techniques

PET - Positron Emission Tomography

PFC - Prefrontal Cortex

dlPFC - Dorsolateral Prefrontal Cortex

RMT - Resting Motor Threshold

SPECT - Single Photon Emission Computed Tomography

TMS - Transcranial Magnetic Stimulation

US - Ultrasound

WBS - Work Breakdown Structure

WM - Working Memory

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1. INTRODUCTION

The brain is the organ that enables us to feel, think and perform all other kinds of functions, both cognitive and many others which regulate the rest of the human body. It is made up of hundreds of millions of neurons that communicate through electrical stimuli and chemical signals to create, in a coordinated way, what is arguably the most complex object in the universe.

Embedded in human nature is the unstoppable drive to satisfy curiosity and gain a greater understanding of both the environment in which we live and ourselves. One of the greatest questions that mankind has asked itself since the beginning of time is as simple yet fundamental as: Who are we? Understanding the nature of the self has been one of the greatest brainteasers of philosophers, physicians, physicists and most, if not all, human beings who have ever walked the Earth. Within the self, consciousness, which is the most obvious and mysterious feature of our mind, is the one of greatest interest [1].

Historically, WM has been seen to be strongly linked to consciousness. The ability to temporarily store and manipulate information forms the basis of what it is considered to be the attributes of consciousness. However, it should be noted that recently it has been shown that WM also operates outside the consciousness domain, as it functions in areas of the unconscious [2]. Therefore, it is clear that going deeper and obtaining answers about the very nature of WM will make a contribution in the direction of a better understanding of what is called consciousness and, consequently, who we are.

Technological advances have helped us gain a better understanding of the anatomy and functioning of the brain. There are tools that are used to obtain neuronal signals, monitor and diagnose, such as different types of scanners or the EEG, and others that are employed to stimulate and treat the organ, such as the TMS. The latter, besides being a tool for treating certain neurological pathologies such as treatment-resistant depression [3], has also proven to be a very useful tool for studying the brain's functionality [4].

Here, it is pertinent to acknowledge the importance of the profile of the Biomedical Engineer. During these years we have been trained in such a manner that we have obtained a biological knowledge base which allows us to understand the bases of these kinds of problems, and at the same time we have also been instructed in the technological field to obtain optimal solutions for each scenario. In this study we will use techniques such as MRI, EEG, EMG, TMS and a set of technologies to obtain and study different signals directly involved in spatial WM, which will consequently allow us to study the nature of this kind of memory and, in a way, contribute to the understanding of who we are.

1.1 Motivation and Origin of the project

This project is born out of the groundwork established by the research that the Compte lab has carried out previously on the subject of spatial WM, and on the work I had done in my internship with them, which consisted on designing and refining the clinical case planning, looking at all the limitations and studying the different alternatives to overcome them, as well as learning to use the different laboratory machinery, and dealing with the recruitment and scanning of the subjects who were submitted to the trial.

In the search for answers to understand in greater depth the neurological mechanisms that govern spatial WM, this collaborative work between IDIBAPS and the Hospital Clinic (which is part of the UB), aims to be able to continue contributing to a line of research carried out at IDIBAPS under the tutelage of Albert Compte, with the final aim of filling gaps in the literature in relation to serial dependence in the spatial WM (see definitions in section 2.1), as well as to verify certain theories on the topic and to shed more light on the possibility of identifying biomarkers for anti-NMDAR encephalitis, schizophrenia and other disorders related to the hypofunction of NMDAR.

1.2 Objectives

There are three main objectives in this thesis. They are based on expanding and validating data obtained from previous studies by the Compte lab. These three objectives are the following:

- Validation of previous results: to replicate the TMS experiment that the team conducted earlier to address the mechanisms governing serial biases in spatial WM [5]. More data is needed and further analysis to be able to validate these results.

- Bilateral and hemispheric dominance: to extend the previous TMS study, as there was only TMS stimulation on the right cerebral hemisphere [5]. In this way, the establishment of a better basis for bilaterality in WM will be possible. Based on the behavioral results obtained just by stimulating one side, the goal is to verify if these results are generalized when stimulating the other hemisphere. There are also different questions that need to be addressed, such as whether there is a predominant side when it comes to spatial WM, or whether hemispheric dominance shows individual differences in which it can be observe that the hemisphere in which WM has a greater influence varies according to the hemispheric dominance of each subject.

- Neural basis of spatial WM perturbations: to lay the groundwork for future work and analysis. The previous study had no registration of EEG signals during the TMS stimulation [5]. This experiment is aimed to settle the basis for further investigation on how perturbations of spatial WM are reflected at the neural level. Therefore in this experiment the EEG helmet will be added to obtain more signals, not only to understand how both hemispheres communicate

between them as previously mentioned, but also of the mechanisms governing serial biases in spatial WM. Analysis of this data is beyond the scope of this thesis.

This will be done through a volunteer recruitment, data collection and subsequent analysis of the behavioral data. It is important to remark that this is an hypothesis-based study, as it is aimed to replicate exploratory findings that the group made with respect to the laterality of spatial biases. The previous studies on which this thesis is built are explained in detail in section 2.2 State of the Art.

1.4 Limitations

In order to carry out this project, a set of limitations in several different areas were encountered. Primarily there was a time limitation, as the final degree project subject has a deadline for the project set in June 2023 and therefore it is not possible to exceed it in time. Within the time constraints, the availability of the experimentation room was also an important limitation. It being a shared laboratory in which different projects are carried out, on certain occasions this issue has limited our use of it. There were also limitations encountered when it came to learning how to work in the lab, as the staff who had to instruct me and myself had to fit in the same timetable, and often the inability to coincide delayed the project.

As a result of the cyber-attack on the Hospital Clínic in March of 2023, our project suffered limitations both in communication and in obtaining certain data, which slowed down the project. In addition, the space of the laboratory and its distribution forced us to readjust the project from our main idea, as it limited our ability to move the TMS machine or its positioning (see section 6.2). Finally, when dealing with software, each one has its own particular limitations, but none of them were noticeable constraints.

1.5 Location of the project

The project has been carried out in different locations. The offices in the Brain Circuits and Behaviour Lab and IDIBAPS offices at the Esther Koplowitz Centre were used to meet, discuss the different aspects of the project, check the progress and employ the different equipment (computers, photocopiers, etc.). It was also used the MRI room number 23, on the ground floor of the Hospital Clinic, which hosts the MR scanner used for research purposes. Finally, the TMS experiment was carried out at the UB Faculty of Medicine, specifically in the laboratory of David Bartrés located in the Department of Psychiatry and Clinical Psychobiology, Psychology Unit (5701), which is part of the Institute of Neurosciences of the Universitat de Barcelona. In this laboratory, I was taught by Rubén Perellón on how to handle all the machinery necessary to carry out the experiments. The data analysis and the Python coding was carried out at home.

2. BACKGROUND

In order to understand the fundamental concepts on which the work is based, as well as the context in which it is set, it is important to expose the main ideas that constitute the academic framework of the thesis. To enable the reader a correct reading of the work and an understanding of the ideas that will be presented in point *2.2 State of the Art*, some definitions of technical terms that will later be used are described beforehand (*2.1 General Concepts*).

2.1 General Concepts

As mentioned before, here certain concepts which are worth understanding before reading the work that has been carried out will be explained. The idea is to clarify technical concepts which the reader may not be familiar with beforehand.

2.1.1 Working Memory

WM is a term that refers to a system in the brain that provides the ability to manipulate and temporarily store information needed to perform cognitively complex tasks, such as reasoning, learning or understanding language [6]. It must be understood that there are differences between WM, short-term memory and long-term memory. The difference between long-term and short-term memory is that short-term memory has demonstrated temporal decay and chunking capacity limits. It is more difficult to differentiate between WM and short-term memory, as it depends on one of three different definitions given in the literature, which conceive of WM in relation to short-term memory as: short-term memory applied to cognitive tasks, a multicomponent system that maintains and manipulates short-term information, and as the use of attention to manage short-term memory [7]. For the purposes of this thesis, we do not further emphasize the difference between these terms, as we are only concerned with memory maintenance.

2.1.2 Spatial Memory

Spatial memory involves the storage and recall of information in the brain related to the representation of the environment in memory. This helps to plan a route to a desired place, remember the location of a specific object (crucial in this project) or recall where an event occurred [8]. This thesis is interested in spatial WM. This refers to the part of spatial memory devoted to short-term storage, maintenance and manipulation.

2.1.3 Spatial Working Memory Tasks

These tasks are intended to measure an individual's capability to maintain and manipulate information in the face of distractions or competing demands for attention. Subjects are shown visual stimuli on a screen for a brief stimulation time. Then the stimulus is removed and, after a memory delay, the subject must indicate where the stimulus appeared. The time between the moment where the stimulus is removed and the moment when the subject is allowed to make a response is known as the 'Delay Period'.

2.1.4 Serial Dependence in Visual Perception

Visual serial dependence refers to the bias caused by a previously sensed visual stimulus. It occurs because the memory of a previous event induces an error in the subject's memory, affecting the report of the current stimulus. The nature of this effect is still under investigation. Research has established that the bias does not just depend on one stimulus directly affecting the next stimulus because of the timing of their appearance, but also because of the similarity of both visual stimuli [9].

2.1.5 Dorsolateral Prefrontal Cortex

The brain is divided in two hemispheres, the left and the right. Each hemisphere has a set of fissures (sulci) that subdivide the cerebral cortex (cerebral gray matter that covers the hemispheres of the brain) into different lobes according to their function. The six distinct lobes in the human brain are: the frontal lobe, the parietal lobe, the occipital lobe, the temporal lobe, the insular lobe and the limbic lobe [10]. Our point of interest lies around the frontal lobe. This lobe is involved in motor and language functions, as well as in various cognitive processes, such as memory, attention and executive functions. It is also of great importance in mood, personality and moral and social reasoning [11]. In it the prefrontal cortex (PFC) is found, which is the largest part of the frontal lobe [12]. More specifically this study wants to set the focus on a subregion of the PFC, the dlPFC. This region undergoes a prolonged maturation period that lasts until adulthood [13]. It is a functional region of great importance because it connects to various brain and pathway areas, for example, it is the end point of the dorsal pathway, which is of great importance to how we interact with stimuli in space [14]. It is involved in executive functions, which include planning, cognitive flexibility and, for our interest, WM [15].

2.1.6 Persistent Activity

When a stimulus appears, the brain reacts upon it and neurological activity occurs as a consequence. Persistent activity refers to supra-threshold neural activity that remains after the stimulus itself has disappeared. It is a substantial change in the discharge of action potentials which overlasts the stimulus [16].

2.1.7 Decoding Neuronal Activity & Decoding Strength

In this context, decoding refers to the ability to obtain, through the use of computational algorithms, information about the brain activity taking place at a specific location. Decoding strength refers to the accuracy and reliability of the decoding process. In other words, it gives the degree to which, given a pattern of neural activity, the content of the WM can be efficiently extracted.

This concept can be clarified by looking at its mathematical formulation, with the equation $y \backsim w \cdot x$. '*y*' corresponds to the behavior or task, which is proportional to the decoder (*w*) multiplied by the neural activity (*x*). This enables to illustrate that decoding refers to the ability to obtain information about a behavior, such as the memorization of a visual stimulus on a screen, by studying the neural activity associated with that specific behavior.

2.1.8 Attractor Dynamics

In the field of neuroscience, "attractor dynamics" is understood as the collective neuronal network function that enables the stabilization of information encoding. It is a plausible mechanism for WM in dlPFC, as these neurons not only respond to the stimulus, they remain active during the Delay period, when the stimulus is no longer present. This activity represents the information about the stimulus being held in memory. The full understanding of this phenomenon is still to be achieved [17][18]. 'Attractor-based' mechanics are thought to be the processes that create and maintain persistent activity states.

2.1.9 Bump Attractor Dynamics

In experiments with monkeys, a relationship has been observed between the precision in recalling information and the variability of PFC activity. When recalling a spatial location, a "bump" of neural activity representing that location is established in the PFC. Attractor dynamics provides a framework to understand this mechanistically in what is termed a "bump attractor" model. The precision of the

memory is determined by the size and stability of that attractor [19]. This “bump” appears because a model of neurons that respond to similar stimuli excite each other effectively, while neurons that respond to different stimuli inhibit each other. This creates a network structure where neurons with similar selectivity are strongly connected and located close to each other, forming a ring-like pattern (Figure 1a). Neurons that have less similarity in their selectivity have weaker connections and are located further apart on the ring. The inhibitory connections in the network provide a constant level of inhibition throughout the network. The tuning curves of the neurons involved reflect a continuous representation of space (Figure 1b). This suggests that the neural activity patterns in the PFC exhibit a smooth and continuous representation of spatial information during WM tasks [20].

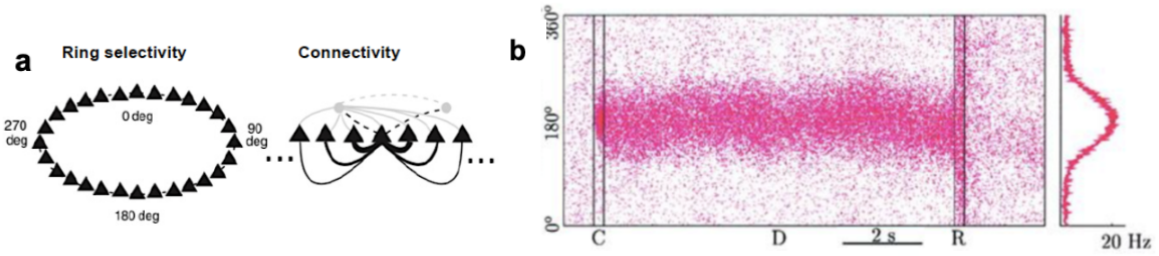


Figure 1. Bump attractor model a) Ring-like pattern of neurons with similar b) Bump of neural activity during the task. The bump appears in the cue ‘C’, time when the stimulus is presented, it is maintained during the delay ‘D’ and it disappears after the response ‘R’. Adapted from [21].

2.1.10 Activity-Silent

An alternative framework for WM maintenance was proposed by Mark Stokes [22]. According to this approach, WM representations are not encoded by persistent spike activity patterns, but instead by plastic synaptic modifications that are continuously updated by inputs from other brain regions. This allows the prefrontal cortex to maintain information in WM even when external stimulation is absent. This form of WM is what Stokes defines as ‘actively-silent’, because the memory is not reflected in spiking neuronal activity. Unlike 'actively-maintained' WM, in which persistent activity emerges because attention is focused on immediately relevant information, 'activity-silent' WM can hold multiple representations simultaneously in a distributed manner. ‘Activity-silent’ mechanisms are ongoing, low-level selective processes, which are present even with no external input or task-related activity.

2.1.11 Transcranial Magnetic Stimulation (TMS)

TMS is a non-invasive procedure which consists in directly stimulating the nerve cells in the brain with electromagnetic pulses that are generated by a coil [23]. These pulses produce a weak electrical

current that can increase or decrease the neuronal activity in specific parts of the brain. At a clinical level, doctors are still learning to optimize the use of TMS, but it has been shown that it can be a useful tool for different mental disorders. For example, some men and women with depression can achieve improvements with TMS treatments when they do not respond to medication or psychotherapy [24]. It is also a very useful tool used in research.

2.1.12 Resting Motor Threshold (RMT)

RMT is understood as the stimulus intensity that causes a minimum motor response in a resting muscle during single TMS pulses applied over the motor hotspot. TMS studies use this parameter to understand the power with which subjects are to be stimulated during experiments. It should be obtained at the beginning of each experiment as there are variations between subjects (thickness of the different tissues, amount of hair, potential needed for stimulation, etc.) and variation for the same subject depending on the moment of stimulation [25].

2.2 State of the Art

This work is conceived to fill gaps in the literature and to continue in the line of research related to spatial WM that is carried out at IDIBAPS in Albert Compte's team. Therefore, here I will explain in depth where this research stands, emphasizing those studies that are of direct relevance to this thesis.

2.2.1 Neural basis of serial dependence studied in humans using TMS

Historically, the mechanism governing WM has always been thought to be persistent neuronal spiking. Albert Compte's team, led by João Barbosa, proved by studying monkeys and humans that there is an interaction between attractor dynamics that control neural spiking during mnemonic periods (learning periods) and activity-silent mechanisms in the PFC, which result in neural reactivations of old memories, causing biases in subsequent stimulus memories. This mechanism has been proposed to underlie serial dependence [5]. To study the effect of these reactivations, they carried out a spatial WM task and applied TMS pulses randomly to influence serial dependence.

The task itself is based on a series of steps that are repeated for each trial. It starts with a fixation period, in which the mouse cannot be moved from the center of the screen; then the subject is stimulated with a single-pulse TMS in randomly selected trials; then comes the cue, which is the period in which the visual stimulus appears on the screen (this stimulus is a dot or a square that

pseudo-randomly shows up at any point on the circumference of the fixation site at a predetermined radius); once the stimulus disappears there is a delay period in which the mouse remains fixed in the center of the screen, and finally there is the response period in which the cursor can move and the subject presses on the place where they consider that the stimulus has appeared. When the subject responds, the mouse can be moved back to the center of the screen and the next trial begins. With this task it is possible to study the serial error, which is the error in the response due to the intervention of the memory of a previous stimulus, and with the EEG it is also possible to study the neuronal activation during the different moments of the task and the underlying mechanisms at each moment [5].

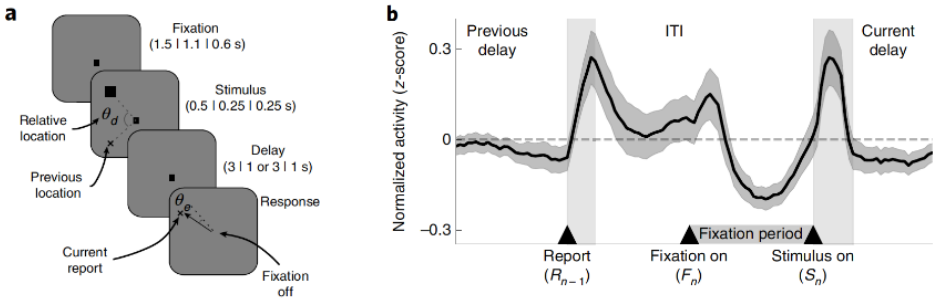


Figure 2. Spatial working memory task a) Successive steps of spatial WM task b) Neural activity during the task. Adapted from [5].

Electrophysiological data recorded in this task has helped clarify a number of questions surrounding spatial biases in WM. It has proved the interaction between bump-attractor dynamics, responsible for activity-based mechanisms, and activity-silent mechanisms in the PFC, whose purpose is to retain information in the PFC and is reactivated with previous stimuli in the spatial WM. In this type of task, it is seen that the delay period is characterized by bump-attractor dynamics in the monkey PFC, which correlates with behavioral precision (Figure 1b). This activity disappears between trials and is reactivated before the next trial, which will enhance the bias. It is the activity-silent mechanisms that carry information from one trial to the next, linking periods of persistent activity that are a priori disconnected from one another. The delay-period attractor dynamics imprints activity-silent mechanisms that retain information between trials and allow reactivations to recapitulate attractor states. This is shown in Figure 3.

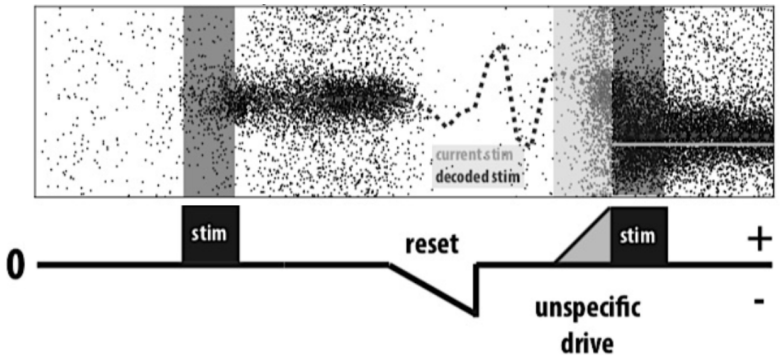


Figure 3. Simulation of neural activity across trials. Two different bump attractors after both stimuli are seen. The interesting thing is how the first bump disappears after the response is given, but it has a little reactivation before the second stimulus, causing a spatial bias. Adapted from [5].

In the following graph (Image 4), simulations of a computational model that implements this mechanism show the rate tuning (black line) and the synaptic tuning (blue line) in a neural network model designed to perform this task. It is clear that in the mnemonic period both are at their maximum, due to the persistent bump-attractor activity. After this period, the neurons encounter a hyperpolarizing input that resets the baseline level of the network state for the duration of the ITI (blue triangle). What this reflects is the absence of fire-rate tuning, but the synaptic tuning remains, although there is a decay. This synaptic tuning permanence allows for a rate tuning reactivation due to a nonspecific input drive (light blue line). Importantly, simulations and experimental data show that these reactivations are linked to increased serial dependance [5].

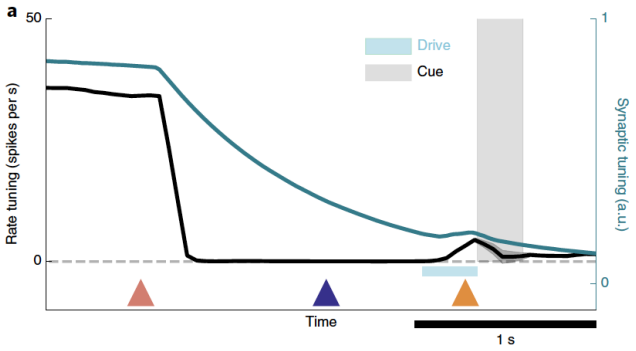


Figure 4. Rate and synaptic tuning during DELAY period [5]. Mnemonic period (red triangle), inter-trial interval (blue triangle) and reactivation (yellow triangle).

The use of TMS has shown that there are memory reactivations when applied in the delay period if those memories are behaviorally relevant. Without TMS it is seen that there is an attractor behavior per se. This means that when there is a certain spatial distance between one stimulus and the next, the response to the second stimulus will have an error, a certain shift, and will tend towards the previous stimulus (attractor effect). This is due to the mechanisms discussed above. This shift towards the position where the previous stimulus was memorized is evidence that there are remnants of the

memory of the previous stimulus when dealing with the current stimulus. Whether these areas have the function of suppressing non-beneficial evolutionary elements to minimize performance degradation or whether they instead highlight and promote adaptive biases, maintaining the visual representation of the stimulus, is still being studied [27].

Enhanced serial biases after reactivating latent traces from earlier memories are consistent with the view that biases are the by-product of memory-supporting processes. The trace left by the bump-attractor dynamics in the form of activity-silent mechanisms can be reactivated, which causes an error bias towards the earlier memory. This was causally demonstrated by applying a single pulse TMS to the *fixation* periods in the dlPFC, which caused more serial bias. It was tested without TMS, with weak drive (70% of the RMT) and with strong drive (130% of the RMT). As can be seen in Figure 5b, the no drive has the expected shape of the serial bias (as in Figure 5a), while the weak drive increases the bias and the strong drive cancels it out. The hypothesis is based on the fact that the weak drive is able to reinforce the 'actively-silent mechanism', thus making bump attraction stronger. In contrast, the strong drive stimulates too much, not only the neural region where the actively-silent mechanism is located, therefore there is no trace that biases the next bump-attractor dynamics, the whole region will have the same predisposition to reactivate and therefore no bias is observed.

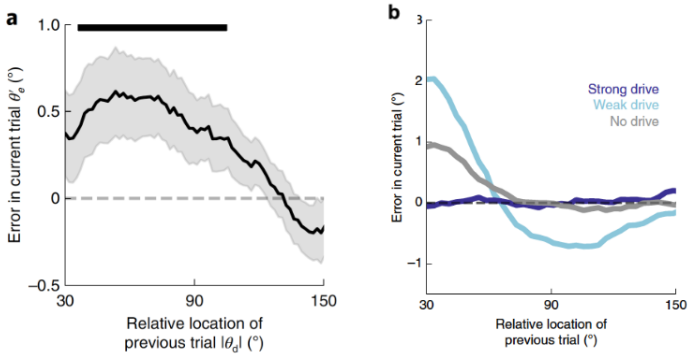


Figure 5. Serial bias a) Serial bias observed in humans b) Serial bias in three different scenarios. Adapted from [5].

Using TMS it was found causal evidence showing that reactivation in the PFC during the fixation-period of activity-silent trance promotes attractive serial biases. This study suggests that these interactions go further and may underlie how memory storage processes work at different time scales. The study has shown an active role of the PFC in generating serial biases, rather than suppressing them as previously thought. This may be because the PFC could generate biases either as a by-product of stable memory retention or actively, in circumstances where past memory traces are behaviorally adaptive; alternatively, strong PFC activation would suppress maladaptive memory remnants in situations where biases are particularly detrimental to behavioral performance, as it was explained in the weak and strong TMS.

This study has yielded very interesting results, but it is necessary to collect new data to give validity and support the conclusions drawn. In particular brain responses were not recorded in TMS experiments before and the unilateral stimulation prevents exploring the laterality dimension of serial biases. Therefore, this thesis will be carried out to collect EEG to be studied in subsequent doctoral theses, while behavioral results will be analyzed in this study.

2.2.2 Laterality of serial biases

Within the question of identifying the neural basis of serial biases, a question of high interest concerns hemispheric-specific basis of serial biases. Again Albert Compte's team, this time led by Melanie Tschiersch, tries to study the laterality of serial biases by studying the effect of the TMS pulse separately when stimuli are presented in one visual hemifield or the other. In the previous study [5], only the right cerebral hemisphere was stimulated using TMS. It would be necessary to see the performance when both hemispheres are stimulated in the same subject, to be able to test whether each subject presents a dominant hemisphere or whether there is a dominant hemisphere generalized throughout the whole dataset with regard to serial biases in spatial WM. Logic suggests that, being a quality derived from visual stimuli (and visual stimuli can appear from any way in the field of vision), it should be a homogeneous quality across both hemispheres.

In Figure 6, it can be seen how the visual field is processed by the brain. It can be observed that the left visual field is processed in the right cerebral hemisphere and vice versa with the right. However, for this information to arrive correctly, the left eye sends information about the left field of vision to the right hemisphere through the optic chiasma (contralateral), while the information about the right field collected by the left eye is sent directly to the primary visual cortex of the same cerebral hemisphere (ipsilateral). The same happens with the right eye in the opposite way, as it is shown in the image. Laterality remains prominent in the early stages of visual cortical processing but progressively reduces as more associative areas are recruited and higher order areas only retain small lateral biases.

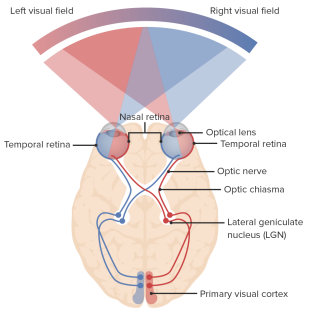


Figure 6. Visual pathways and visual field [26].

As mentioned above, in the team's previous work, TMS stimulation was only applied to the right hemisphere of the brain. Therefore, it has only been possible to study the behavioral results (the quantitative error of where the user pressed on the screen with respect to the real stimulus) when stimulation was performed on this side of the brain. In any case, the results obtained are very interesting. Analysis can be performed to identify differential effects when stimuli are presented contra- or ipsilateral to the TMS hemisphere.

It is observed that when there is stimulation on the side where the next stimulus will be presented, it is seen an increase in serial bias, whether the previous stimulus was on the same side (Figure 7, upper left graph) or the previous stimulus was on the opposite side (middle left graph). This means that, although contralaterally stronger spatial WM mechanisms are produced, ipsilaterally these mechanisms are also triggered. However, when stimulating in the hemisphere opposite to the one in which the next stimulus will appear, it is observed that the serial bias does not occur (Figure 7, right graphs). It is therefore concluded that there is a connection between the two hemispheres in the delay period, but it can be seen that in the fixation period there is no longer a strong connection between the two hemispheres.

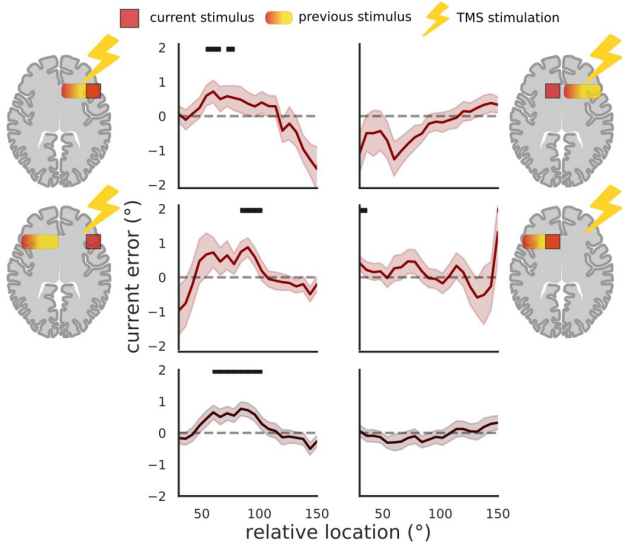


Figure 7. Effect of TMS on serial dependence and laterality of visual stimuli. On the left side: graph when previous and current stimulus are on the same hemisphere as the TMS stimulus (top), graph when previous stimulus is on the other side (middle), overlapping of these two graphs (bottom). On the right side the same, but when the current stimulus is in the other hemisphere.

All this suggests the idea that there are two anatomical zones, one in each cerebral hemisphere, in which the anatomical structures that carry out the neural mechanisms of spatial WM are found. These would be two independent anatomical and functional areas, but which are in turn connected to each other (Figure 8). What is not known is what would happen when TMS stimulation is alternated between the two brain hemispheres, and more data is needed in order to correctly understand the neuronal mechanics underlying these processes.

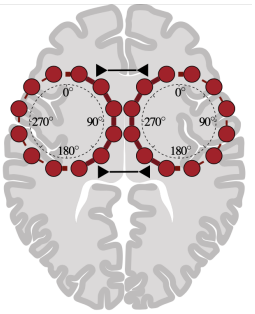


Figure 8. Bump attractor dynamics and their connectedness.

2.2.2 Biomarker for schizophrenia, anti-NMDAR encephalitis and autism

Glutamate is a neurotransmitter that has the functionality to assist in pain perception processes, environmental responses and also plays an important role in memory. One of the receptors it binds to is the NMDA receptor. Certain analgesic drugs such as ketamine or PCP react with these receptors by inhibiting them, resulting in hallucinations and memory loss. These receptors are relevant in various memory mechanisms at different timescales, so they are important for WM [28].

Albert Compte's team has studied how the reduction of the serial biases discussed above suggest deficits in synaptic potentiation in anti-NMDAR encephalitis and schizophrenia [29]. WM was studied in healthy (control) participants, as well as in patients with schizophrenia and patients recovering from anti-NMDAR encephalitis. These groups are of great interest for this study because in anti-NMDAR encephalitis there will be a reduction in information retention capacity as this disease directly affects the glutamate neurotransmitter. In turn, schizophrenia is linked to NMDAR hypofunction [30]. Therefore, deficits in WM are expected to exist in both non-control groups.

The results obtained are very interesting (Figure 9). First, it was observed that for all groups, accuracy decreases equally as the delay period increases (Figure 9a). Even more interestingly, it is observed that there is a smaller bias towards earlier stimuli for patients in the two non-control groups, as expected due to NMDAR hypofunction. This reduction in serial dependence demonstrates a selective disruption between information carried from trial to trial. Anti-NMDAR encephalitis patients were also found to have more similar biases to the control group of patients as they recovered, leading to a potential correlation between psychotic symptoms and reduced serial dependence. Both the strength of positive symptoms and alterations in serial dependence were greater in the schizophrenia group than in the anti-NMDAR encephalitis group (Figure 9d).

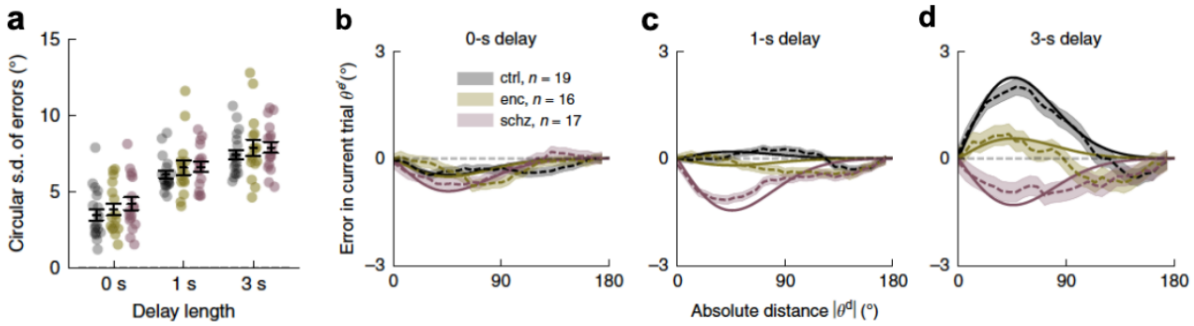


Figure 9. Serial dependance on control, schizophrenia and anti-NMDAR groups [27].

These results open a door to use this type of quantitative study as a biomarker for diseases related to NMDAR hypofunction, which would also include patients with autism [31].

3. MARKET ANALYSIS

In this section we will focus on the different areas related to the various research subjects and technologies covered in this thesis, in order to see the market in which our research is located, as well as the contribution that this thesis can make, in the short and long term, within these sectors.

3.1 Technological Sector

Within this sector, we will focus on the technique of TMS. The use of TMS as a tool has a direct implication for the biotechnology and medical sector. To properly understand the functioning and importance of TMS, a quick review of its history is necessary. The fundamentals of EM were formulated by Michael Faraday and described mathematically by physicist James Clerk Maxwell in the 19th century. Since then, both science and technology have made use of this branch of physics to innovate and bring great advances to society. In 1959, EM began to be used to stimulate nerve tissue [32], laying the foundations for the use of EM for nerve stimulation, whether for treatment, diagnostic or investigative techniques. TMS is one of the technologies that has been developed on the basis of EM phenomena. Initially this technique was used to study brain functionality and to map the motor cortex. In 1995 it was shown that daily repetitive TMS improved the condition of patients with depression [33]. Since then, this tool has been used to try to help patients with different mental problems, such as OCD or treatment-resistant depression. The advantage of using TMS is that it has few side effects compared to other conventional treatments, but there is still a long way to go to explore the potential and to obtain solid long-term results, as well as to develop well-standardized protocols for its application [34]. Figure 10 shows the number of annual articles published in PubMed regarding the TMS technique. It shows an exponential increase with no sign of reaching its peak. Last year was the year with the most publications, with a total of 1250 articles related to this technique. This indicates the importance and potential that this technology has, and how this sector is booming. This project aims to contribute to this sector, as we show the capabilities of this type of technology, promoting research into it and proposing possible improvements.

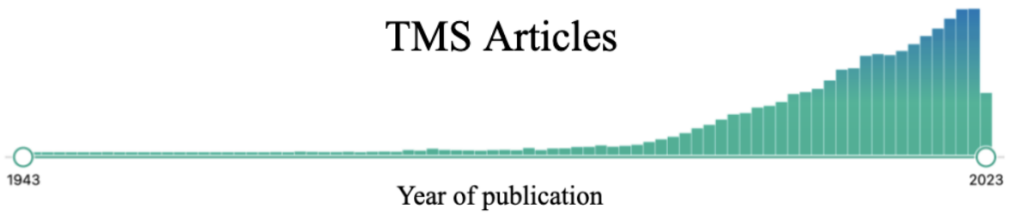


Figure 10. Number of Articles related to TMS over the years. Adapted from Pubmed.

3.2 Pharmaceutical and Medical Sector

The pharmaceutical and medical sectors can also benefit from the contributions of this thesis. Schizophrenia still lacks a biomarker for a clear diagnosis [35]. To date, the diagnosis of schizophrenia requires an assessment by a professional. This method of diagnosis is subject to possible human error and will not be completely homogeneous, as well as complicating early detection. Laying a stronger theoretical foundation for the possibility of developing a biomarker for the diseases schizophrenia and anti-NMDAR encephalitis would bring immense benefits. On the schizophrenia side, it would provide the basis for the development of an accurate biomarker, which would allow more accurate, earlier and more homogeneous diagnoses to be made. For anti-NMDAR encephalitis, it would provide the basis for a new biomarker, as well as a quantitative and alternative way of measuring patient recovery. By improving diagnostics, it consequently opens the door to improved treatment and quality of life for patients suffering from such diseases. It is therefore clear that there is great potential in these markets, both for the improvement in the quality of life of these patients, as well as for the gains in terms of money and logistics that this can generate by reducing the time and treatment needed by patients in health centers. Pharmaceutical or biotechnological companies may benefit from patenting a biomarker that can help to diagnose more effectively and at an earlier stage, as they would benefit financially from this.

3.3 Academic Sector

As mentioned earlier, this is a scientific research work. It is for this reason that the main sector to which this thesis is addressed is academia. The aim of this study is to broaden the knowledge base on TMS and the rest of the technologies used, and especially on the neural basis of serial biases in spatial WM. We can appreciate the surge in research in the field of serial dependence (Figure 11) and the academic pursuit to better understand the mechanisms that govern serial biases and short-term memory. Recently, new research has been done using different technologies such as MEG or fMRI [36][37]. Specifically, this thesis will provide information for Albert Compte's team and IDIBAPS to continue the study of WM or similar areas in which this work can provide valuable knowledge.

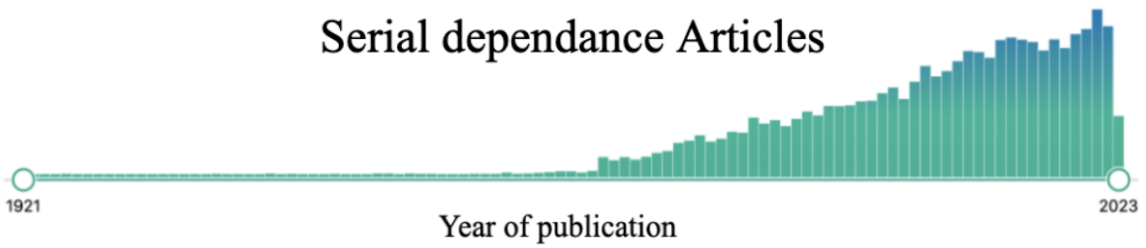


Figure 11. Number of Articles related to ‘Serial dependence’ over the years. Adapted from Pubmed.

4. CONCEPT ENGINEERING

In order to obtain the behavioral curves that determine the serial bias, it is necessary to perform a set of steps, which are reflected in Figure 12. In this section each of these steps will be reviewed and the various options available for each step will be examined, explaining why the final option was chosen. But first, it will be broadly explained how the whole project was carried out.

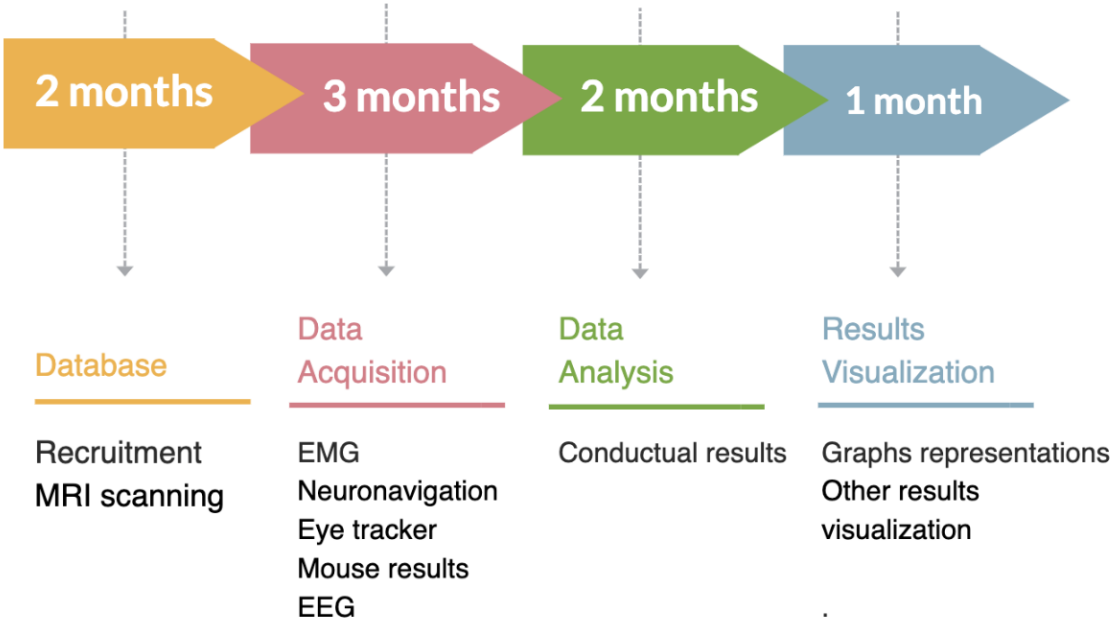


Figure 12. Engineering organization of the project. The four different blocks have listed the different elements that make them up.

At the start of the project, a thorough study of literature related to the subject of the thesis was conducted in order to get to know the different concepts that would be treated later on. While finishing the theoretical foundations study, it was agreed on the objectives of the project as well as on the timeline that was going to be followed to carry out each step. To help us better organize the project, we first created a WBS, which allowed us to create a Gantt diagram, see section 7.3. During the internship period, everything needed for the project to prosper was carried out (understanding of the lab equipment, code for the experiment, recruitment strategy for the subjects, etc.). Once the database of all the subjects was obtained, each one took an MRI image of their brain. The MRIs were co-registered and the subjects were called for the experiment. Each subject performed two experimental sessions of approximately 3 hours each, where behavioral data as well as EEG signals were collected. The EEG signal data were passed to IDIBAPS for further studies done by them, while the behavioral data on serial biases were stored and analyzed for this thesis. Finally, the results have been presented both in this paper and in the presentation slides that will be shown to the evaluation committee.

4.1 Database

Once the subjects who volunteered to participate in this thesis had been recruited, the next step was to obtain a brain image of each of them in order to neuronavigate and know where to position the TMS coil to perform the stimulation. The MRI imaging technique has been used as it is the gold-standard technique for obtaining high-resolution images of different tissues. Another option could be to use faster methods to save time for the subject and the research, as well as to reduce the number of times the subject has to visit the Hospital Clínic. When thinking about rapid imaging methods, the first proposal may be to use US, as it is a non-invasive technique and has the capacity to obtain images in real time. The major drawback of this technique is that the resolution is much lower than that of MRI and the adult skull prevents the correct acquisition of the brain, so it is ruled out. Another possibility is CT scanning. This imaging technique takes less than a second and has a high resolution. The problem with this technique is that subjects are exposed to radiation doses. CT scanning is justified for diagnostic purposes as long as it is necessary, but in this experiment, as the subjects are volunteers and the images are needed for academic purposes, receiving radiation for getting an image just because it is quicker is not justified, so this option is also ruled out [38].

Within the MRI technique, there are several different ways of imaging. T2 is the time it takes for protons to lose phase cohesion and reflects the decay of the transverse magnetisation. T2-weighted images, due to their water enhancing properties (H_2O appears white), are often used to find abnormalities in tissues, as they allow contrast between pathological and healthy tissues to be observed. T2* is a variation of the T2 technique that takes into account magnetic inhomogeneities, which allows the observation of deposition of iron-bearing components (e.g. neuromelanin). Consequently, this technique is used to study conditions such as Parkinson's disease. FLAIR is a technique that selectively suppresses signals from fluids, especially cerebrospinal fluid (CSF), while enhancing signals from other tissues. It is often used to observe lesions that may escape view using T1 and T2 techniques. T1 is the time it takes for protons to align with the magnetic field once they have been perturbed. T1-weighted images are used to visualize anatomical details and give good contrast between different tissues [39]. Therefore, for this experiment, the need to appreciate brain anatomical detail and be able to differentiate between different tissues, the T1-weighted technique is the chosen option. Figure 13 shows the different images obtained from the same subject using different MRI techniques.

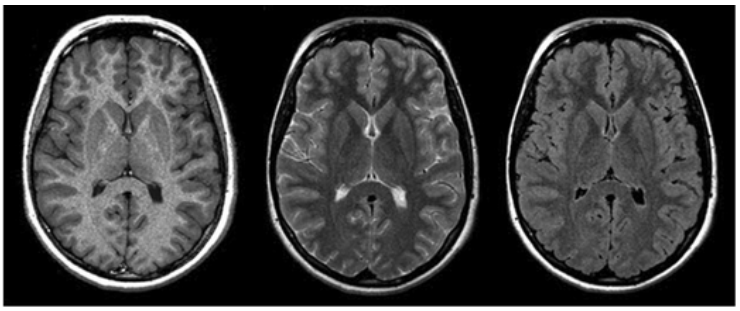


Figure 13. MRI images. From left to right: T1, T2, and FLAIR - weighted. Adapted from [40].

4.2 Data Acquisition

There are two signals that are desired to be collected during the experiments. The first is the neural activation of the brain and at the same time it is also desired to collect the result of the error when performing the task to which the subjects are exposed. The second signal is simpler to collect, as it requires a program that stores the position in which the stimulus appears on the screen and the position in which the subject has pressed their response. In contrast, to detect neural signals there are a number of methods that can be used. Besides the acquisition of these two signals, which are necessary since they will be analyzed, in the experiment it is also necessary to obtain the muscle activation signals in order to establish the RMT at the beginning of each session.

4.2.1 Data acquisition on brain function

In this section, the different methods used to obtain information about neuronal functionality will be evaluated and the advantages and disadvantages of each one will be discussed. This will establish which is the optimal one for this thesis.

4.2.1.1 fMRI

The principle of the fMRI technique is based on detecting which areas of the brain are most active at any given time, as these will receive increased blood flow due to the need for energy. fMRI detects changes that are associated with blood flow in the brain to establish areas of activation [41]. The advantages of this technique are that it is non-invasive, does not require radiation and has good spatial resolution, but on the other hand it requires a dedicated room for its use, it is very expensive, the patient must be completely still and it has a low temporal resolution. Therefore, it is not optimal for our task, which involves fast time scales and requires simultaneous TMS.

4.2.1.2 PET and SPECT

The PET imaging technique uses radioligands (chemical compounds that have radioactive decay and can be traced as they change from reactants to products) to obtain functional images of the brain. Depending on the tracer used, different processes in the body can be observed, so its functionality is wide-ranging, from detecting certain cancers, to bone formation or measuring blood flow. It is widely used in neuroimaging with radioligands such as oxygen-15 to measure blood flow in the brain [42]. The disadvantages it has are the same as fMRI plus the fact that the subject has to receive certain doses of radiation. The difference between PET and SPECT techniques is based on the chemicals and the camera used, so the advantages and disadvantages of SPECT are very similar to those discussed above for PET.

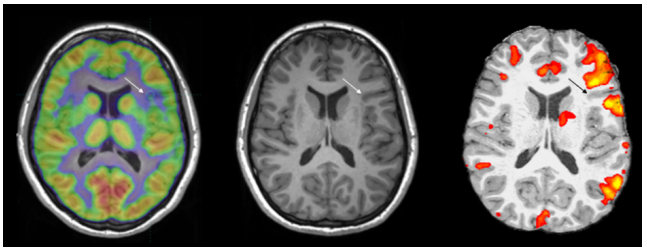


Figure 14. PET scan, MRI and fMRI. Respectively, from left to right. Adapted from [43].

4.2.1.3 Other techniques based on magnetic properties

NMR is a technique based on the principles of nuclear magnetic resonance. It detects magnetic fields around atomic nuclei. It is non-invasive, has high spatial resolution and allows mapping of brain activity by measuring changes in oxygen flow (like fMRI). Like other techniques discussed above, such as fMRI or PET, the equipment is very expensive, can cause claustrophobic episodes and does not tolerate movement of the subject. In addition, it takes time to perform the analysis of the area of interest. MEG is another technique based on magnetic phenomena. In this case, it detects magnetic fields caused by electrical currents in the brain. This requires liquid helium-cooled detectors that capture these magnetic fields, which are worth several million [44]. It has a very high temporal resolution, covers activity throughout the whole brain and is non-invasive. The drawbacks are that it has limited spatial resolution, is sensitive to environmental noise (e.g. magnetic noise produced by electrical equipment), is expensive and requires a specific environment.

4.2.1.4 Optical Techniques

The NIRS technique is based on detecting the location and activity of specific regions of the brain where there has been a rapid change in blood volume through the optical absorption coefficients seen by constantly monitoring hemoglobin levels in the blood. For these reasons, NIRS works well as a quick

screen for possible brain hemorrhages or to study hemoglobin saturation in the microcirculation. The advantages are that it has good temporal resolution, it is a non-invasive technique and the equipment is not overly complex and tolerates certain movements of the subject. The disadvantages on the other hand are that it has a low penetration capacity, so it captures better information from the cortex but has difficulty obtaining information from deeper regions in the brain, and it also has a rather limited spatial resolution [45]. EROS is a technique similar to NIRS. In this case, EROS measures changes in scattering and absorption of light in response to neuronal activity. It has excellent temporal resolution and better spatial resolution than NIRS, but the low penetration capability is inferior even to NIRS [24].

4.2.1.5 Surgical Approach

The ECoG technique records electrical activity by placing electrodes directly on the subject's brain. For this reason, the temporal resolution is extremely high and the spatial resolution is also excellent. It allows a direct measurement of neuronal activity and it can be used for long-term monitoring. For these reasons, it is a highly resolute technique for certain diagnoses, such as establishing epileptogenic zones [46]. However, due to the invasiveness of the process, it is totally dismissed for this study.

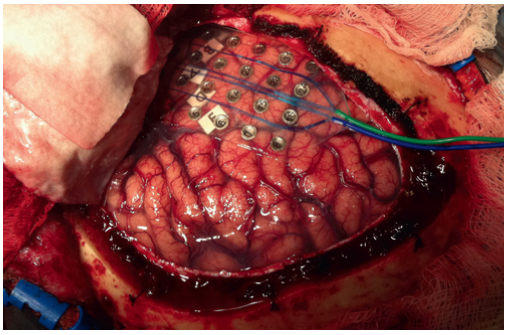


Figure 15. ECoG during brain surgery. Adapted from [47].

4.2.1.6 Selected option: EEG

The technique to be used in this experiment for obtaining neurological data is EEG. It is more cost-effective than most other techniques, and the hardware required is very simple. It allows for some movement of the subject without critically compromising the data, whereas some imaging techniques do not. In the experiment conducted in this thesis, knowing temporally what is happening at any given moment is vital, as it is necessary to analyze what is occurring at precise moments in time. It is non-invasive and non-harmful, as it does not require radiation doses or surgery. Other factors such as the fact that EEG is not prone to cause claustrophobic episodes lend further weight to this technique, and it is also the most comfortable technique for the subject, as they simply wear the EEG helmet, which is not uncomfortable. It is easy to obtain, store and process the information collected by the different electrodes, while spatial 3D techniques have thousands to millions of times more data stream

inputs, so they are limited by hardware and software [48]. With respect to EROS, EEG provides better temporal resolution and has been in the industry for much longer, so there is more information and studies with this technique. It is also necessary to take into account the disadvantage that it does not have as high a spatial resolution as techniques such as fMRI or PET, but in the general computation, it comes out as the optimal option for carrying out the experiment proposed in this thesis (see Section 5.2.4), for everything mentioned previously and because it has a great temporal resolution.

4.2.2 Data acquisition of behavioral results and simultaneous TMS

A form is needed in which information can be stored for each trial. This information must indicate the position in which a visual stimulus has appeared on the screen, the position in which the subject presses on the screen in response to where the stimulus appeared, the number of the trial, the side of stimulation and the RMT, among other parameters. It was decided to use CSV files because they are light, flexible, portable, simple and compatible. Different programs such as Python, R or Matlab can easily create, read and edit them, which is vital in this experiment. Therefore, they are perfectly suited to the task of adding rows with the data of different parameters that are updated in each trial and, at the same time, they allow the reading of this data for subsequent analysis. There are other types of data storage formats that were reviewed but none have qualities that are better than CSV for this thesis. Excel uses a structured and tabular form similar to CSV, but with more features so they are larger files and can present compatibility issues. JSON (JavaScript Object Notation) files are more flexible and versatile than CSV, but tend to be larger than CSV and require more parsing and processing steps. The HDF5 (Hierarchical Data Format) format was also valued. These are versatile and are often used for large datasets. They require specialized libraries and for simple tabular data are more complex to use than CSV. Parquet is another data storage option. It is a columnar file format designed and optimized for big data. For this reason it may be overkill for smaller datasets [49].

4.2.3 Eye tracker

For the subject to be performing the task correctly, they need to look at the center of the screen, where the mouse is located, during the Fixation, Cue and Delay periods. For this reason, we use an eye tracker that is able to detect where the subject is looking at any given moment. The different types of eye trackers have been analyzed in order to use the best possible one for the study.

The cheapest eye trackers are those that are webcam based. They track the eye movement with a conventional webcam, so the accuracy and speed of tracking is quite limited. The next type of eye trackers in order of accuracy are portable eye trackers, which are compact and easy to carry. These should be worn on the patient's head. They are followed by screen-mounted eye trackers, which use

infrared technology and track eye movements with high accuracy. Finally there are the high-end eye trackers, which use various techniques such as retinal photography or corneal mapping to achieve exceptional accuracy.

For our experiment it was decided to use a screen-mounted eye tracker. Portables eye trackers are discarded as they need to be positioned on the subject's head, making it impossible to use TMS together with EEG. Webcam-based eye trackers are discarded due to their low precision, and high-end eye trackers are also discarded, as certain qualities such as eye micromovement are not necessary to know for this experiment; an eye tracker that is capable of correctly tracking eye movements is sufficient.

4.3 Data Analysis

Once the behavioral data has been obtained, it has to be analyzed. The analysis is carried out with the Python programming language. This language is used due to its versatility and the number of libraries developed that are really useful for this case, such as Pandas, NumPy, SciPi or scikit-learn, among others. In addition, it is the program with which the team has worked before for similar analysis, so the advantages and disadvantages of this language are well known, as well as how to get the most out of it. It should be added that it is a very convenient language for working with CSV files, for communication with the TMS machine and with the eye tracker. Matlab would be the alternative option due to the similarity and versatility of the language, but it would take more time to perform certain functions that are already implemented in Python.

In order to obtain the graphs shown in Section 5.3 and the analysis carried out on the behavioral data, in this thesis it has been performed by using the code created by Albert Compte's team for previous studies. The code has been adjusted in order to fit the dataset of this experiment and to be able to carry out the desired analysis. Refer to Annex F to see the code implemented.

4.4 Results Visualization

For the visualization of results I have made use of different techniques. For certain graphs I have used libraries within Python such as matplotlib and seaborn. In addition, other programs have been used to create different graphs and diagrams, such as diagramas.net and Google Slides.

5. DETAILED ENGINEERING

In the previous section we discussed the steps that should be taken to carry out the project and which was the best option for each one of them. Once it has been decided which path to follow, this section will focus on breaking down the execution of each step and explaining in detail how it has been carried out. Additionally, the results obtained will be visualized. The order to be followed will be roughly as dictated by the diagram in Figure 12.

5.1 Detailed Database

This section will explain thoroughly how the database was obtained, taking into account both the subjects and their MRIs which are necessary for the neuronavigation carried out during the experimental phase.

5.1.1 Subjects

Previous Compte Lab studies were conducted with 10 subjects and then replication studies were conducted with 10 more subjects. Therefore, in this study the preliminary idea was to use 20 subjects and to perform a single session on each participant in order to obtain the necessary data that the replication study would also provide. It was decided that in order to better understand how the bilaterality of serial dependence behaves, it was more convenient to use half as many subjects but double the number of sessions. In this way, each subject would have one session where they would start with TMS stimulation on the left cerebral hemisphere and another session where they would start with the stimulation on the opposite hemisphere, so the results obtained would be more robust. Given that there was time to expand the study modestly, the number of subjects was eventually increased to 12.. The choice of the side on which to start stimulating is random for each subject. The database of this experiment is composed of a total of 12 subjects (6 men and 6 women), with a mean age of 23,31 ± 4,06 years. Two participants are left handed and the other 10 are left handed. One participant was only able to attend a single session, bringing the total number of sessions to 23. No subject was excluded from the study, either due to medical problems or at the subject's own request.

5.1.2 MRI Scanning and Stimulation Area

An MRI of each participant was obtained in the hospital clinic to collect the anatomical data required for the source reconstruction. In a Prisma 3 Tesla magnet, the MRI T1-weighted (T1W) picture was

captured. Subsequently, the 3D T1W structural image that was kept in a DICOM dataset was converted to NIfTI (Neuroimaging Informatics Technology Initiative) format.

In order to decide the exact zone in which the TMS stimulation should be performed, regions of interest were selected based on areas frequently identified during spatial WM tasks on the basis of the study's focus on these zones. To select the exact position, we relied on a previous master's thesis by Rebecca Martinez, who performed it under the tutelage of Albert Compte [50]. In Rebecca's study, the results of 52 fMRI studies related to spatial WM were used and underwent an automated meta-analysis on neurosynth.org [51]. With this meta-analysis, a mask was made with those areas where activation related to spatial WM exists. Extrapolating this information to this thesis, the areas of highest activity within the dlPFC were obtained. Initially, the coordinates of interest were (x=40, y=34, z=16) for the right dlPFC and (x=-42, y=31, z=29) for the left dlPFC. These coordinates were problematic as they were too frontal, so when placing the TMS coil in this location, it collided with the support glasses that the subject must wear to be able to neuronavigate during the session. These coordinates were therefore modified and, within the area of interest, less frontal coordinates that allowed the correct positioning of the coil were chosen. These final coordinates are (x=42, y=29, z=26) for the right dlPFC and (x=-35, y=24, z=32) for the left dlPFC, see Figure 16.

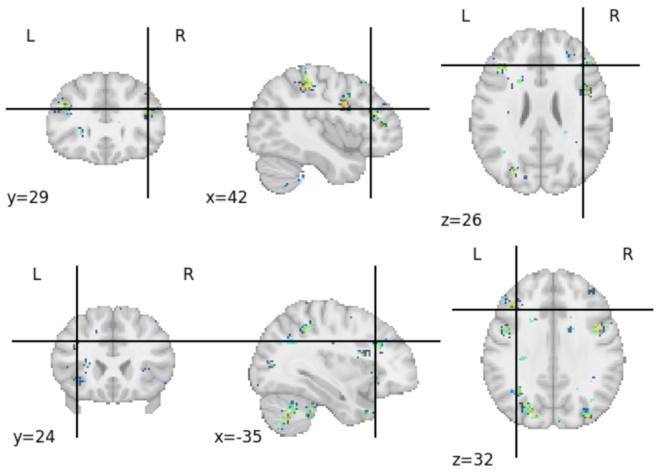


Figure 16. Coordinates of Stimulation. The top row refers to the right hemisphere coordinates and the bottom row to the left hemisphere coordinates.

5.2 Detailed Data Acquisition

A major concern in this thesis lies in the correct data acquisition. In this section, the techniques used for this purpose will be discussed in greater depth.

5.2.1 EEG preparation

To capture the electrical signals produced by the brain, two EEG helmets consisting of 64 active electrodes were used, one for medium head sizes and the other one for bigger heads. Using the standard 64 Ch, the electrode positions used in these helmets are the following: Fp1, Fpz (Ground), Fp2, AF7, AF3, AFz, AF4, AF8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT9, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, FT10, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP9, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, TP10, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO3, POz, PO4, PO8, O1, Oz and O2. For the subsequent analysis of the EEG signal, it is necessary that the signal has the best possible SNR ratio, and that the impedance in each channel is less than 15 kOhm. Subjects are therefore asked to wash their hair and scalp thoroughly before coming to the session and once in the lab, the scalp is cleaned again with diluted alcohol. To reach the desired impeding threshold, it is necessary to go electrode by electrode, separating the hair that lies underneath it and applying a conductive gel.

5.2.2 Determining RMT

The power at which the TMS coil has to fire to have an effect on a person's brain varies from subject to subject and, for the same subject, this power also varies depending on the moment at which the measurement is made. For this reason, before starting each experiment it is necessary to establish what the RMT of the subject is at that precise moment. In order to establish the RMT, it must be studied what is the minimum TMS intensity necessary to evoke MEPs of at least 50 μV in 50% of 5 to 10 consecutive trials [52]. In this study, the reading of the first dorsal interosseous muscle of the right hand was performed, and MEPs had to be observed in at least 3 out of 6 consecutive trials. The RMT study is done with the EEG helmet on as the thickness of the helmet may slightly vary the result. The Signal program allows the visualization of this procedure.

5.2.3 Preparation in advance of the WM task

Subjects are seated in a chair that is positioned approximately 70 cm away from the screen in which the task will be displayed. They have a chin rest that provides support, and this can be adjusted so that the participant is comfortable and their eyes are approximately at the same height as the middle of the screen. The subject, during the fixation, cue and delay periods, must fixate their gaze on the center of the screen, see Section 5.2.4.1. Therefore, when the subject is already seated, the eye tracker has to be calibrated. The eye tracker will send information directly to the computer, and on the screen it will be shown the exact coordinates at which the subject is looking within the limits we have set, or it will show by the terminal that the subject is not looking where they should.

The Brainsight software and the detectors that come with it were used to be able to neuronavigate and know exactly where to position the TMS coil. In order to achieve this, a pair of goggles must be placed to read its position in space thanks to a detector that launches infrared rays and is capable of tracking the position of the subject's head with the goggles on. The position of the fiducial points and the position of each electrode must be registered with the same Brainsight program. This enables the coil to be moved around the subject's head and to know exactly where to position it to stimulate the coordinates of interest. When all the above steps have been successfully completed, the task can be performed.

5.2.4 WM task and TMS

This section will explain in detail the experiment that the subjects must perform as well as the techniques used during this assessment. The EEG helmet data is saved with the Recorder program, while the Python file that runs the experiment saves the behavioral data in a csv file. This file stores for each trial parameters of interest such as: block, stimulation side, trial number, TMS_trial (if it is a trial that triggered TMS or not), position and angle where the stimulus appeared, position and angle where the subject responded. To see each step carried out during the experimental sessions, see Annex E.

5.2.4.1 TMS employed

The TMS stimulation was performed using the Magventure MagPro x100 with MagOption. Two different intensities were used, 70% RMT and 0% RMT (no TMS). Half of the trials are single-pulse monophasic triggers with an intensity of 70% RMT and the other half of the trials are performed without TMS. The arrangement of which trials trigger TMS and which do not is done randomly by the Python file that runs the experiment at the beginning of the trial. The Python file makes use of the MagPy package, which allows the manipulation of TMS parameters and direct interaction with the TMS machine during the experiment.

It has been observed that the location of TMS coil clicking noise can affect the report in motor tasks [53]. To try to minimize this effect, subjects are required to wear earplugs during the task. The earplugs are also of big help in trying to create the least difference between trials with TMS firing at 70% RMT and trials without TMS. The TMS coil makes noise when performing the trials with stimulation, but no noise is produced in the trials without TMS stimulation. The soundproofing avoids possible biases caused by the noise of the machine, as this may create a susceptibility of alerting the subject, which may cause some differences with those trials that do not have noise.

5.2.4.1 WM task employed

It is determined randomly whether to start stimulating firstly the right hemisphere or the left hemisphere of the subject's brain. As each subject performs the experiment twice, the second time they come to the experiment the stimulation will start on the other hemisphere. The task consists of 8 blocks, each one containing 100 trials. Each trial corresponds to a stimulus that is presented at a random angle on the circumference with the center at the fixation point. There is a Fixation period (0,5 s) in which the subject cannot move the cursor from the center of the screen and the TMS pulse is triggered, followed by the presentation of the visual stimulus (0,25 s), also known as the Cue period. When the visual stimulus disappears, there is a Delay period in which the mouse is immobile at the fixation point (1,97 s) and finally a Response period in which the subject has to go with the cursor to the place on the circumference where they think the stimulus appeared and press, and then return to the center to start the Fixation period of the next trial. The first four blocks are performed by stimulating the initial brain hemisphere that was chosen at the beginning of the experiment and the last four blocks are performed by switching the TMS machine on to the other side of the lab, changing the goggle holder for neuronavigation to the other side, making the settings for neuronavigation again and stimulating the other brain hemisphere.

It is important that the subject fixes their gaze on the center of the screen during the Fixation, Cue and Delay periods, as this ensures that they are performing a memory exercise. If it is not verified that they are looking at the center, it is possible that they fix their gaze on the place where the stimulus appeared, wait for the Response period, and then move the mouse to the place where their gaze is fixed, so it would not be a memory exercise, but simply a mechanical exercise.

5.3 Data Analysis of Conductual Results

For each session, a csv file was obtained with the different parameters that define the characteristics of each trial. In order to carry out the study, all the data from all the sessions must be brought together by concatenating the csv files into a single file. Once the csv files have been merged, a total of 18400 trials have been obtained, but a total of 18347 trials have been used. This cleaning is done because of significant errors that are caused by the subjects at the time of the response. If the time of response was too long, more than 10 seconds, or the error to the stimulus location too big, more than 45 degrees, that trial was dismissed. This avoids obtaining incoherent data that is not relevant and does not help in achieving results.

The first thing to be done is an analysis of the population absolute error in degrees when it comes to responding in the trials with and without TMS. The aim of this is to check that there is no uncontrolled factor that affects the participant in such a way that they are more or less accurate when giving their answers in either of the two conditions. Figure 17 displays the results. In yellow we obtain the absolute error in degrees in the trials with TMS and in gray in the trials without TMS. With a null hypothesis predicting that the two data sets compared follow the same probability distribution, a Kolmogorov-Smirnov test has been carried out between the two functions. A p-value of 0.1985 was obtained, which is not strong evidence to reject the null hypothesis, suggesting that the two data sets are not significantly different. Therefore, there are no significant differences that would lead us to suspect any experimental factor that would cause a bias towards either of the two conditions. With this in mind, the study of the data can proceed.

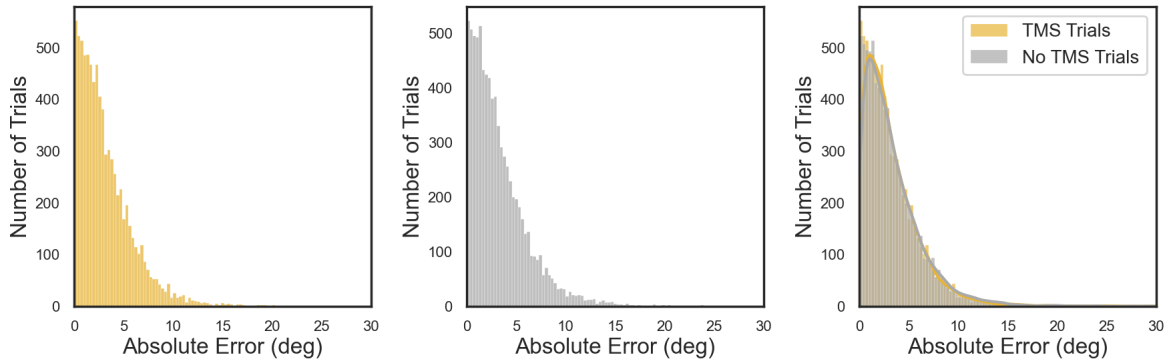


Figure 17. Absolute error in response. From left to right: a) absolute error in trials with TMS, b) absolute error in trials without TMS and c) superposition of the two previous graphs.

With the csv of all the sessions the serial dependence curve is computed. Serial dependence measures the error in the response (in degrees) to the current stimulus in relation to the distance in degrees between the previous and current stimuli. As it is seen in the literature (see Figure 5a) there should be an attractive effect when the relative position of the preceding stimulus is less than approximately 120 degrees and that there is a repulsive effect for relative positions of greater angle. Considering all the results obtained, regardless of whether there was TMS or not, the cerebral hemisphere in which the stimulation was performed or the time of the session in which the trial took place, the results obtained show the curve that should be expected, see Figure 18.

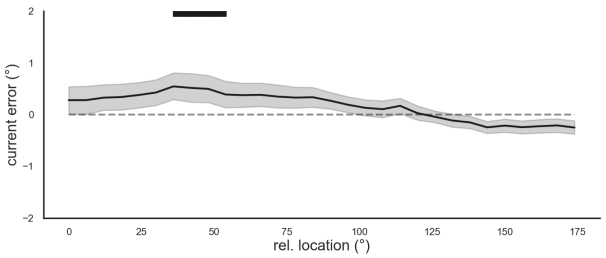


Figure 18. Serial Dependence Obtained. Shading represents ±s.e.m. Error shading represents 68% CI.

5.3.1 Visual Hemifield

The following is a comparative study of the visual hemifields in which the stimulus appears. Figure 19 shows three graphs. The first one indicates in green color when the previous visual stimulus and the current one appeared in the same visual hemifield (left-left or right-right), while in orange color it indicates when they appeared in opposite hemifields. The central graph shows the case when the previous and the current visual stimulus appeared in the same vertical visual field (in green) or when one stimulus appeared in the upper half and the other in the lower half (in orange). The last graph illustrates the difference between the first and second graphs, in which it can be seen that in both cases, when the stimulus appears in the same half of the visual field, either horizontally or vertically, there is a greater serial dependence effect. On the other hand, the results are not robust enough to establish quantitative differences in the effects of biases between verticality and horizontality, which follows the line of thought of Albert Compte's team. This data does not support strong laterality effects in serial dependence compared with the verticality effect.

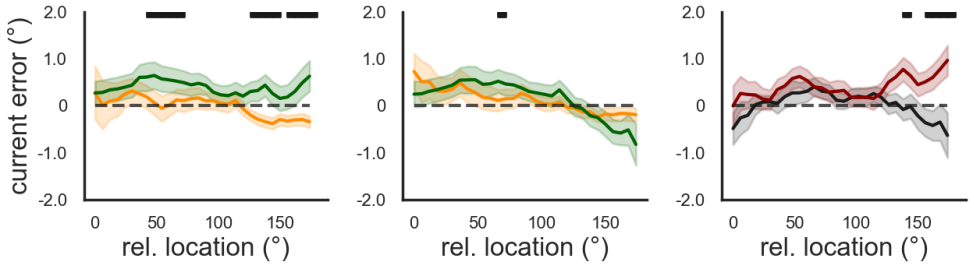


Figure 19. Visual Hemifields Results. From left to right: a) horizontal hemifields, b) vertical hemifields and c) difference between vertical and horizontal hemifields. Shading represents ±s.e.m.

5.3.2 Temporality

An important consideration is to distinguish between the data obtained during the first half of the session and the second half of the session. This is because in the previous study, the data obtained showed that in the first half of the experiment, trials with 70% TMS showed an increase in serial dependence compared to trials without TMS. This effect was severely reduced in the second half of the session [5]. Each half is composed of 4 blocks of 100 trials, giving a total of 400 trials per half-session. The data has been separated into 4 different subgroups in which we iterate between both parts of the session and both conditions (with and without TMS). Figure 20 shows in black the trials with no TMS, in yellow trials with TMS and in red the difference between both conditions. The first row refers to the first half of the session and reveals that TMS has no noticeable effect, while the second row refers to the second half of the session and clearly displays in the trials with TMS the serial dependence curve which is more enhanced than usual. The trials without TMS show a slight serial dependence curve in both scenarios.

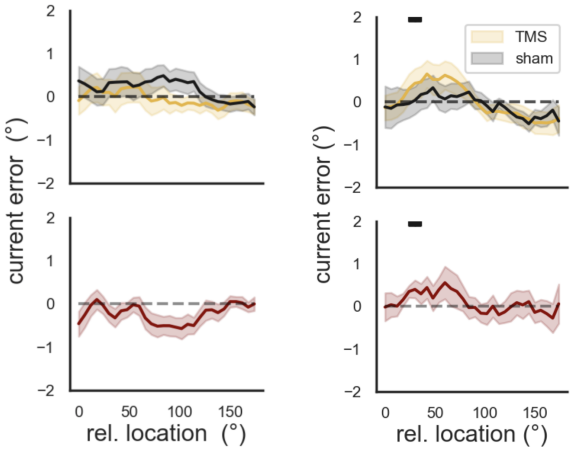


Figure 20. Temporality Results. First column displays the first half of the sessions and the second column the last half. The first row shows the serial dependence of the trials with TMS (yellow) and without TMS (black), while the second row reflects the difference between the two. Shading represents ±s.e.m.

5.3.3 Bilaterality

To study bilaterality, the trials were subdivided according to the hemifield they appeared in, the stimulation side and whether or not there was stimulation. By making so many subdivisions in the dataset available, the number of data with which the analysis is finally carried out is very small, so the results obtained are not clean and it is not possible to draw conclusions or establish hypotheses in this respect, see Figure 21.

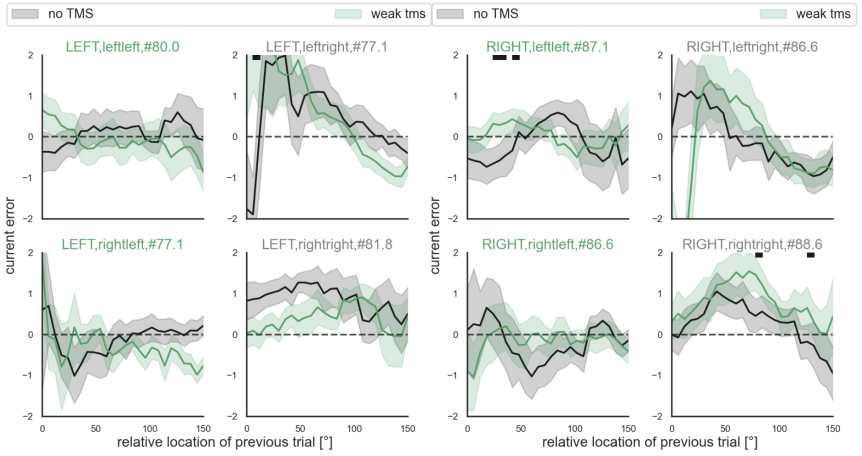


Figure 21. Bilaterality Results. In green it is shown when weak TMS has occurred and in black when there has been no TMS. In each subplot, the brain side being stimulated is shown in capital letters, followed by the visual hemifield in which the previous stimulus appeared and finally the visual hemifield in which the current stimulus appeared. Shading represents ±s.e.m.

6. DISCUSSION

The execution of the experiments and the results displayed in Section 5 open the door to further improvements, interpretations and analyses.

6.1 Results discussion

In section 5.3.1 the behavior results were exposed with respect to the hemifield in which the previous stimulus was presented relative to the current one. Based on the way the brain processes visual information, as explained in section 2.2.2, large serial biases would be expected when both stimuli appear in the same horizontal visual hemifield. The results, as can be seen in Figure 19a, corroborate this hypothesis. On the other hand, an increase in serial bias was also seen when they appear in the same vertical visual hemifield.What would have been expected, understanding the anatomical separation in the vertical axis, is that a notable difference between horizontal and vertical visual hemifields should exist, due to the dorsal and ipsilateral nature in which visual information is stored. However, the results obtained are not significant enough to establish such differences, as can be seen in Figure 19b. From the visual cortex, where there is a clear difference between hemispheres, to the most posterior part of the brain, there is both a horizontal and vertical distribution of information. Therefore, in dlPFC, the difference between verticality and horizontality is not so clear. In this Figure 19b it can be seen that around 50 degrees there is a greater bias towards verticality, which may suggest that there really are indeed differences, but more data should be obtained to verify this hypothesis.

The study with regard to bilaterality has not produced feasible results. Performing so many subgroups for the data gathered resulted in noisy signals with low robustness. This analysis could be of great interest, but more data is needed to be able to draw any conclusions.

The most interesting issue that has been found in this data deals with the temporality of the trials, see section 5.3.2. During the previous study conducted by Joao, it was observed that the trials with TMS showed a large serial bias in the first half of the experiment, while in the second half of the experiment this effect was not noticeable. Our results show just the opposite, see Figure 20. To understand the reason for this discrepancy, the conditions under which both results were obtained must be evaluated. In the experiment carried out by Joao, three different intensities were used: no TMS, weak TMS (70% RMT) and strong TMS (130% RMT). It was observed that with strong TMS there was no effect on serial bias. The hypothesis was that strong TMS saturated the synapses, thus homogenizing the neuronal area for the next stimulus and therefore there was no area predisposed to be reactivated [5]. Comparing the conditions and results of the two experiments, the hypothesis drawn is that in the first

experiment the strong TMS ends up fatiguing the area of interest, so the effect of the weak TMS is mitigated in the second half. In contrast, this fatigue effect is not seen in the experiment carried out in this thesis. Therefore, the hypothesis is that a period of activation is needed for the TMS week to have a maximum serial bias effect. This activation was very early in the previous experiment, helped by the strong TMS condition.

EEG data will provide further insight into this hypothesis. If there is an increase in decoding strength, in other words, more neural activity related to attractor dynamics as the experiment progresses, then this hypothesis will gain further weight.

6.2 Methodology discussion

On the experimental side, the discussion can be divided into two main blocks: issues related to the way in which the experiment has been conducted, and issues related to the improvement in the subject's cognitive performance. Starting with issues related to the way in which the experiment has been conducted, the initial idea was to change the stimulation side after each block. Due to the limited space of the lab room, the complexity of moving the machine with the distribution of the lab and all the cables that lay on the ground, and the need for a co-registration after each change, it was decided that this idea could not be carried out. For this reason, instead of making seven changes on the stimulation side in each session, only one was made in the middle of the session. To be able to carry out the main idea, a support would have been required to see the subject's position and to be able to neuronavigate without this being lateral, so that the pre-registration would not have to be repeated any more times. At the same time, a larger and better designed laboratory would have also been needed to avoid having so many cables on the floor and to facilitate the movement of the TMS machine.

For certain subjects with a lot of hair, it was difficult to obtain optimal impedance values for the EEG recording. This was especially the case with female subjects who had very long hair. Some electrodes, no matter how much time and gel was used, could not completely clear the signal, especially the electrodes positioned behind the ears, which with long hair remained loose, without making firm contact with the scalp. A possible solution would be to try to choose subjects with short hair. This would reduce the preparation time as well as improve the quality of the EEG signals obtained.

With regard to cognitive performance, there are two issues to take into account: the subject's visual and cognitive fatigue, as well as avoiding possible environmental biases. Some subjects have commented that they find it difficult to maintain attention in the exercise due to the monotony of the experiment and the lack of attractiveness for the participant. Therefore, the design of certain functions that are more engaging but do not affect the cognitive processes can be carried out. A ranking at the end of each

block, some statistics or scoreboard can make the subject more motivated and make the task less monotonous. This will make them pay more attention to the task and could lead to more accurate results, as well as improve the experience of the participants when carrying out the experiment.

Finally, there is the factor of biases caused by knowing when there is TMS and when there is not. When the stimulus is applied, the subject hears the coil and has the sensation of a tapping in the head. Participants wear earplugs during the sessions but these allow considerable noise to pass through. Coupled with the monotony of the exercise, some subjects reported that on certain occasions the sensation of TMS drew their attention back to the task and prepared them to respond, whereas when there were several trials without TMS consecutively, they were more likely to become distracted and lose concentration. The absolute error results suggest that there is no significant difference between responding to trials without TMS and trials with TMS (see Figure 17), but this issue should not be overlooked. Improved soundproofing of the subject, or the use of a coil capable of making noise and, if possible, mimicking the sensation of TMS during trials without TMS, should be considered.

7. EXECUTION PLAN

To reach the final objective of the thesis, it has been necessary to carry out an exhaustive organization, as there are several tasks that depend on each other and have to be carried out in a correct manner. A clear plan, a breakdown of tasks and a time study at the beginning of the thesis has been essential to achieve the objectives within the established timeframe. In this section it will be studied the different tasks that had to be carried out during the entire thesis period, as well as the organization and timetable so that everything could be executed correctly. For this purpose, a WBS has been executed, which allows a visual breakdown of the different tasks, followed by a PERT diagram, permitting the time coordination of the different tasks, and ending with a GANTT diagram, which enables the visualization of the time layout of the whole project.

7.1 WBS

The WBS is based on breaking down the project scope into those tasks that are essential for the completion of the thesis. It has a hierarchical structure, in which the total project is divided into smaller blocks, which in turn are subdivided into individual tasks. Breaking down the tasks that need to be carried out in this way provides an overview of what needs to be done, as well as identifying which tasks appear to be more urgent and which will require more time and work. Figure 17 shows the WSB made for this thesis.

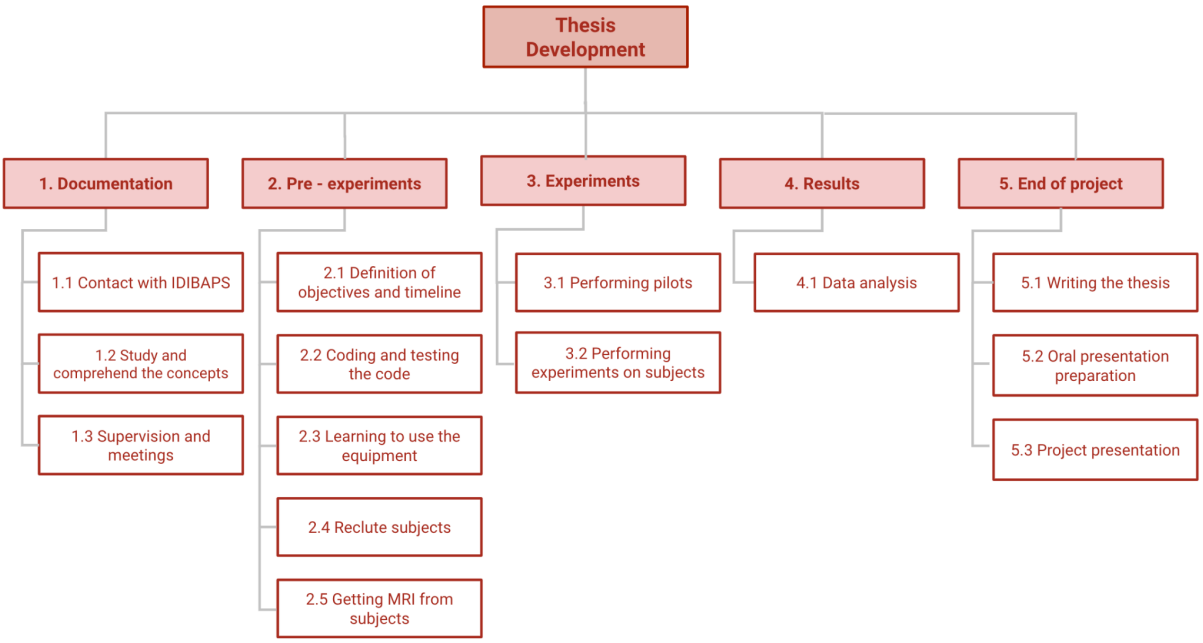


Figure 22. WBS of the project.

Definitions of the different tasks shown on Figure 17 can be found in the dictionary available in Annex A.

7.2 PERT Diagram

It is crucial to know which tasks are dependent on other ones, as well as those which take more time to complete. The PERT diagram allows to visualize the dependency between tasks as well as the critical tasks, which are the ones that are absolutely necessary to perform so that the rest of the project can continue without provoking any time lags. In order to make the PERT diagram, the different tasks must be identified, as well as the dependencies that exist between them and the time that each one takes to complete. This can be visualized in Table 1.

Table 1. Identification, precedences and timing of tasks.

WBS ID	PERT ID	Previous Task	Time (days)
1.1	A	-	1
1.2	B	A	21
1.3	C	A	126
2.1	D	A	2
2.2	E	D	30
2.3	F	D	30
2.4	G	D	21
2.5	H	G	7
3.1	I	E, F	14
3.2	J	H, I	20
4.1	K	J	14
5.1	L	B, K	40
5.2	M	L	7
5.3	N	M	1

With the information obtained in Table 1 it is possible to construct the PERT diagram of the project. It is of interest to see which is the critical path, and for this the PERT diagram must be made and the early and late time of each activity must be determined. The early time refers to the minimum time needed to complete the task and the late time is the maximum time that the activity can be delayed without compromising the pace of the project and the start of other tasks. The critical path is the one in which the activities in the early time and the late time are the same, meaning that any delay in these tasks will cause a delay in the development of the whole project.

The PERT diagram for this thesis can be seen in Figure 17. Each arrow corresponds to an activity and each node has two numbers at the bottom, the one on the left is the early time and the one on the right is the late time.

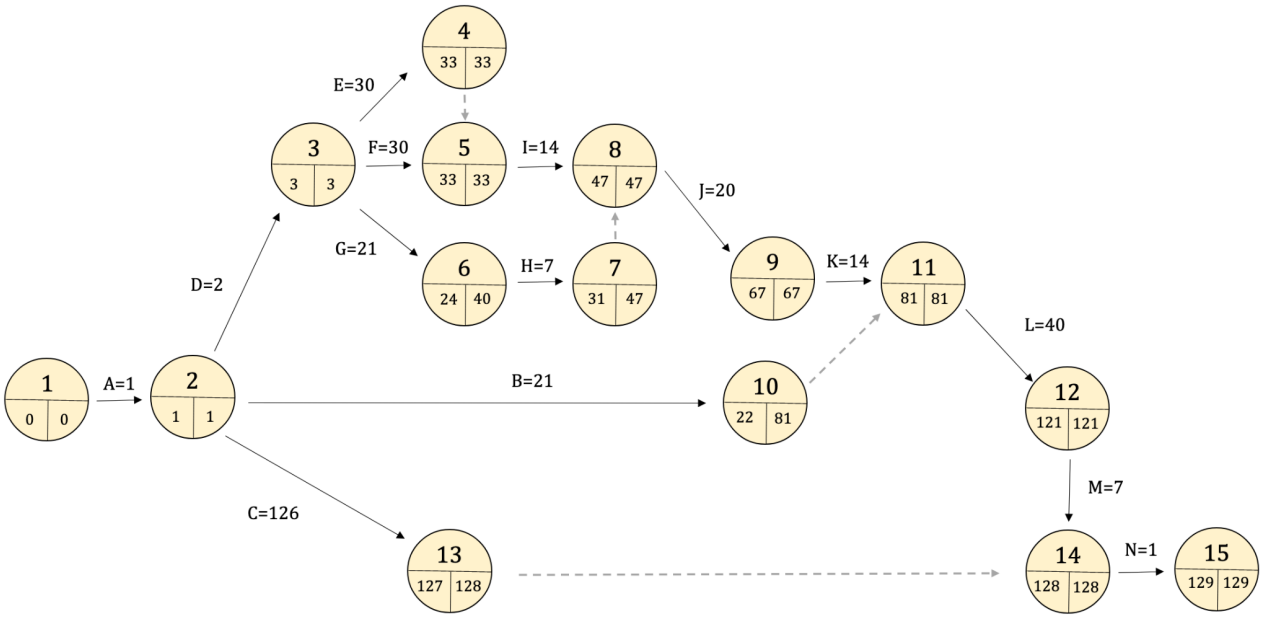


Figure 23. PERT diagram of the project.

It can be seen that in this case the critical path is composed of the activities A-D-(E & F)-I-J-K-L-M-N. The result is reasonable since prior to starting the thesis, the institution must first be contacted, then the objectives must be established, and once this is done, the rest of the work can begin. Furthermore, before starting the experiment, the student performing the thesis must learn how to use the different tools that will be required during the experiments and the code that performs the task must be completed and adjusted to ensure that the task can be executed correctly and with the desired parameters. These tasks take more time than recruiting the participant and obtaining the MRIs. To start the actual experiments, a series of pilots must first be performed to readjust the necessary parameters. Data analysis cannot be performed without the data, but some data analysis can be started before all the experiments are finished, to check the preliminary results that are obtained. Finally, the thesis report can only be written once the results of the analysis have been obtained, and the presentation will be the last thing to be carried out.

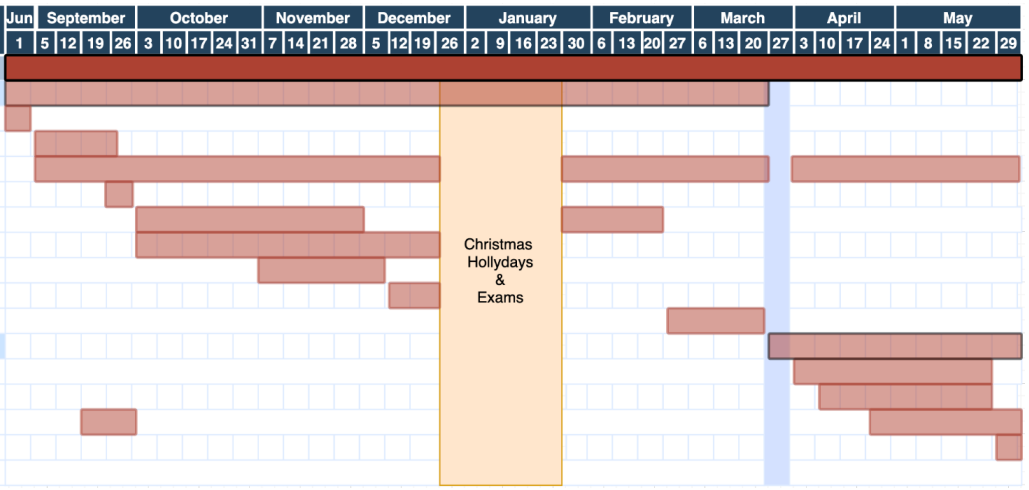
7.3 GANTT Diagram

This section ends with the presentation of the GANTT diagram, as can be seen in Table 2. It is important to note that the temporal duration is not the same as the useful time, but rather the period in which the activity has been carried out. Certain tasks, such as studying the concepts, can be done every day because they can be conducted autonomously at home, while others, such as conducting pilots, require scheduling the time of the subjects and of the professionals who must teach the student

on how to conduct the experiment, the timetable and the availability of the laboratory, as well as the laboratory days on which it is open for work. Therefore, the duration shown in the GANTT diagram corresponds to the period in which the activities were carried out, while the time used in the PERT diagram refers to the useful time of each activity, in other words, the days needed to perform each task.

Table 2. GANTT Diagram of the project.

ID PERT	Task Name	Duration
-	Complete project execution	40 weeks
-	Pre-experiment organization	31 weeks
1.1	Contact with IDIBAPS	1 week
1.2	Study and comprehend the concepts	3 weeks
1.3	Supervision and meetings	33 weeks
2.1	Definition of objectives and timeline	1 weeks
2.2	Coding and testing the code	13 weeks
2.3	Learning to use the equipment	12 weeks
2.4	Reclute subjects	5 weeks
2.5	Getting MRI from subjects	2 weeks
3.1	Performing pilots	4 weeks
-	During and post experiments	9 weeks
3.2	Performing experiments on subjects	8 weeks
4.1	Data analysis	7 weeks
5.1	Writing the thesis	8 weeks
5.2	Oral presentation preparation	1 week
5.3	Proyect presentation	-



8. TECHNICAL VIABILITY

The study has delivered very positive results, but in order to make a proper analysis of the technical feasibility of the project, a SWOT analysis has to be carried out to understand the weaknesses, opportunities, threats and strengths that have been found during these months of work. Table 3 shows the SWOT diagram of the work carried out, and in this section an analysis of each section will be conducted.

Table 3. SWOT Diagram of the project.

	Helpful for the objectives	**Harmful** for the objectives
Internal Origin	**Strengths** S1. Multidisciplinary team S2. Cooperation with competent groups S3. Quality laboratory S4. EEG, TMS and bilaterality	**Weaknesses** W1. Time limitation W2. Previous lack of knowledge W3. Coordination among individuals
External Origin	**Opportunities** O1. Concepts and tools learned O2. Technology and models developed O3. Continuation of the work done	**Threats** T1. Hospital Clinic's hack T2. Costly technology T3. Strong external research groups

8.1 Strengths

Strengths refer to those internal factors that contribute towards the successful completion of the thesis. This study was provided with high-performance machinery that had been used for previous projects, which reduced the total cost of the study while enabling the implementation of these cutting-edge tools. Another great strength has been the fact that this thesis has been carried out jointly by the University of Barcelona, the Hospital Clinic and IDIBAPS. Being leading centers at a national level, they have had at their disposal staff and equipment of the highest caliber that have contributed to the construction of this project. In turn, the fact that we have been able to work with professionals from different fields (doctors, physicists, engineers, psychologists and philosophers) has allowed us to understand various problems in their totality, and to investigate certain concepts and ideas in original ways that could not have been done from the point of view of just one sector.

Moreover, a great strength lies in the foundations on which the work is based, given that the publications that the Compte lab is trying to continue are from articles that they have published in the most prestigious scientific journals (Nature Neuroscience and Nature Communications, among others). When it comes to the experimental aspect, the strengths of the work are the use of non-invasive

techniques and the unprecedented study of bilaterality and EEG with TMS simultaneously applied in humans.

8.2 Weaknesses

Weaknesses are, as with strengths, internal factors within the project. In this case they are factors that hinder the work from being carried out in the optimal way. A clear weakness is the time constraint. Having a limited time frame limits the possibilities that can be undertaken in the project and leaves certain analyses to be carried out in future studies. At the same time, it forces certain tasks to be carried out at a faster speed than would be optimal, such as the recruitment of subjects. With little time available, the subjects recruited are compressed into a very narrow sample niche, and with more time it would have been interesting to analyze a larger or more diverse database, where factors such as age, ethnicity, socio-economic differences could have been parameters to be taken into account.

Another weakness is the limited knowledge of the concepts and technologies used in the project. With an already limited amount of time, part of it has been devoted to learning all these techniques and not to the realization of the project itself. In addition, the scarce prior information required coordination with the professionals who had to supervise these tools, creating greater complexity at an organizational level and taking up the time of these professionals. Finally, being a clinical study carried out between two different centers, a weakness was the organization between all the individuals involved in the project and being able to coordinate with the participants and professionals at the same time.

8.3 Opportunities

Once the factors internal to the project itself have been looked at, it is time to examine those that come from or are projected further afield. This project has presented different opportunities. Firstly, the amount of information learnt during the previous academic formation has allowed a better understanding and quicker adaptation to the working environment, and the knowledge learnt during the thesis could be useful for the future. This thesis is a further step in the continuation of the line of work on serial dependency in WM which, as mentioned in the Market Analysis section, is a growing field of study. It is therefore an important area for further contributions. In turn, the University of Barcelona, the Hospital Clínic and IDIBAPS are centers of the highest national prestige, so it is a great opportunity to work and to be able to continue to perform research work in these establishments.

8.4 Threats

The last point that remains to be analyzed corresponds to those external factors that pose a threat to the objectives of the work. The main threat was the hacking of the Hospital Clínic at the beginning of March. This caused difficulties in maintaining contact with the different professionals and professors who used the network and the institution's e-mail. It also made it difficult to obtain MRI scans of subjects and certain operations performed in the laboratory that required internet access within the hospital.

Another threat lies in the high cost of the tools used (see section 8.1). A failure or breakdown of any of these tools would mean long delays in the project or, depending on the cost, the impossibility of proceeding. For this reason, a lot of caution has been applied in the use of the laboratory equipment. Finally, there is the threat of external research groups capable of carrying out studies with a larger data set or with techniques that could provide more robust results.

9. ECONOMIC VIABILITY

The project was carried out with the support of the investment made by IDIBAPS and the University of Barcelona. The machinery, software, personnel and everything necessary to carry out the tasks that make up the study have a specific cost that must be studied before starting the project to check whether it is feasible to conduct it. This section focuses on the analysis of the necessary costs incurred to complete this thesis.

9.1 Material, Software and Licenses Resources

Firstly, we will study the physical elements that have been necessary to carry out the project. A review of the specific element used for each task is provided. The TMS was performed with the *Magventure MagPro x100 with MagOption* machine, and the coil used with this machine is the *MCF-B70*. To collect the EEG signals, two *actiCAP slim electrode 64 caps* helmets were used, they both have different sizes. The EEG signal receptor used was the *BrainProducts 64 channels actiCHAMP plus*. One of the two helmets had problems with the ground electrode and had to be replaced. For the EMG signal, disposable adhesive electrodes were used to sense the signals, as well as the *Digitimer D360R-4 Multi-channel* filter and amplifier and the *CED micro 1401-4* signal recorder. The eye tracker used is the *Tobii Pro Fusion*. As for the computers used in the lab, there are two *BenQ GL2460BH 24" TN FHD 75Hz 1ms* screens, a *PCIEXPRES CONCEPTRONIC* parallel port with two serial ports, an *ILIFE PR100.100 INTEL i5 9400 16GB 500GB 3Y* tower and an *Apple iMac i5*. Table 4 displays the price of all these elements.

Table 4. Costs derived from Physical Materials.

Item	Units	Price/Unit (€)	Total Price (€)
TMS Machine	1	50.000	50.000
TMS Coil	1	4.900	4.900
EEG Helmet	2	4.600	9.200
EEG Recorder	1	28.500	28.500
EEG Ground Electrode	1	90	90
EMG Amplifier	1	6.000	6.000
EEG Recorder	1	4.425	4.425
EEG Gel	3	84,7	254,1
EMG Standard Electrodes x40	3	40	120
EMG Ground Electrodes x20	3	35	105
Eye Tracker	1	6.449	6.449
Computer Screen	2	94,21	188,42
Computer Tower	1	448,27	448,27
Parallel Port	1	12,26	12,26
Apple iMac	1	2.499	2.499
Hairdryer	1	49	49
			113.240,05

On the other hand, we have the annual *Matlab* license and the equipment that allows us to carry out the neuronavigation. The neuronavigation equipment implemented is the *RogueResearch Brainsight Neuronavigation*, which consists of software, an infrared reader and several elements that allow its position to be read by the infrared reader. Table 5 shows the price of these elements.

Table 5. Costs derived from Software and Licenses.

Item	Units	Cost/Unit (€)	Total Cost (€)
Matlab License / year	1	250	250
Neuronavigation Package	1	50.000	50.000
			50.250

9.2 Subject related resources

As it is a clinical trial, it is necessary to take into account the cost that each subject represents to the project. Before the experiment, the subjects have to undergo an MRI scan, which costs 153.50€ each. In addition, each participant is paid 10€ per hour during the experimental sessions. The preparation usually takes 1.5 hours and the experiment itself takes 1.5 hours, so each subject is in the lab for 3 hours per session, which equates to 30€ per session and 60€ per participant.

Table 6. Cost of Subject Related Resources.

Session	Total Sessions	Cost/Unit (€)	Total Cost (€)
MRI	12	153,50	1.842
Experimental Session	24	30	720
			2.562

9.3 Human resources

Finally, the cost of the staff involved in the project must also be taken into account. In this section an estimation has been made, as the salaries of the team members are not known and the student did not receive any payment. It has been estimated that both the thesis tutor and the director should be paid 20€ per hour, and that both have been involved in the project, directly or indirectly, for approximately 100 hours. Staff who have been present at specific times to teach the student how to use certain tools or people who have volunteered to run pilot sessions should also be taken into account. They are different people but we will put them all under 'Technical Staff'. Most of these individuals have not been paid, but we assume a cost of 15€ per hour and a total of 40 hours spent by all of them in total. Finally

there is the student rate. Even if there is no payment, we assume an undergraduate engineer's salary of around 11€ per hour. Having done around 400 hours, the total price would be equivalent to 4,400€. The breakdown of the prices derived from human resources is presented in Table 7.

Table 7. Costs of Human Resources.

Staff	Total Hours	Cost/Hour (€)	Total Cost (€)
Thesis Director	100	20	2.000
Thesis Tutor	100	20	2.000
Technical Staff	40	15	600
Thesis Student	400	11	4.400
			9.000

9.4 Total Costs

Having looked at the different costs, they will be put together to see the total amount of funds that have been necessary for the realization of the project. This information is represented in Table 8. It should be noted that this is an estimation of the budget that would cost to carry out this work from start to finish under ordinary conditions, but much of the machinery used had already been purchased and used for previous experiments and will be used later in future tests. In turn, as discussed in section 8.3, the prices of the professionals who have carried out the project are rough estimations.

Table 8. Total Costs of the Project.

Sector	Cost (€)
Physical Materials	113.240,05
Software and Licenses	20.250
Subject Related	2.562
Human Resources	9.000
	145.052,05

10. REGULATIONS AND LEGAL ASPECTS

The thesis was conducted entirely in Barcelona, and was therefore subject to the legal framework of Catalonia, Spain and the EU. There are several issues to be taken into account in the legal framework, such as the clinical trial itself, the use of the machinery, the personnel authorized to carry out experiments and the patients' data. This section will describe the legal framework within which the project has been developed.

10.1 Project Approval and Device Regulation

In Spain, the regulation of clinical trials is governed by EU regulations and Spanish national legislation, which falls under EU Clinical Trials Regulation No. 536/2014 [54]. This study has been conducted in accordance with this regulation. To this end, the project's protocol was sent and approved by the Ethics Committee for Research on Medicinal Products of the Hospital Clinic of Barcelona, see Annex B. The machinery used during the thesis also complies with the requirements of the EU Medical Device Regulation (MDR) 2017/745 [55].

10.2 Protection of Participant's Data

The participants in this study have participated voluntarily and had the right to stop or withdraw from the experiment at any time. Participants' data are regulated by the General Data Protection Regulation (EU) 2016/679 [56]. Patient information is protected and only identified by a code. Only the student conducting the thesis and authorized personnel have access to the patient data and to this code. In accordance with the regulation, the data of the patients was stored securely at the IDIBAPS offices. Participants were given three different documents to sign. They were given first a consent form upon contact in which they were informed exactly of what the experiment was going to be and all the possible contraindications (see Annex C), then a screening questionnaire before the sessions to make sure that there were no risks for the subject in order to perform the experiment (see Annex D) and finally a document to make the corresponding payment once the sessions were finished.

11. CONCLUSIONS

The goals of this thesis were to validate the results of previous work carried out by the Compte Lab, to shed more light on bilaterality and hemispheric dominance and to provide more information on the neural nature of serial biases in WM memory. For this purpose, we successfully conducted a study with 12 subjects over a total of 23 individual sessions.

I was fully responsible for the main tasks in this project: rigorous study of the literature on the topics involved in this thesis, as well as the previous work that consisted in learning the tools to be used during the experiment, the elaboration of the code used to run the task as well as to store the behavioral data, the recruitment and acquisition of the MRI of the participants and the elaboration of the various pilots prior to the experiments.

During the experimental part, coordination was essential between the other professionals who had to use the same laboratory, myself and the participants who volunteered to contribute by performing the task designed for the study. No participant presented discomfort or decided to stop the test at any time, and none was rejected due to the screening carried out prior to each session. Data collection was laborious but successful, obtaining behavioral and EEG data for all sessions. There have been drawbacks along the way, such as a shortage of material at certain points in the project, or complications due to the Hospital Clínic cyberattack, but with constant reorganization and coordination between all the centers and professionals involved, it has been possible to deal with each one of them in order to continue with the planned project schedule.

The reward of all the procedures discussed above comes with the visualization of the results obtained in the analysis of the behavioral data. The first thing that could be visualized is that the experiment showed the expected pattern of serial dependence when all trials were analyzed together. The analysis of the behavioral data with respect to the hemifields of the presented stimuli gave weight to the hypotheses put forward by Albert Compte's team that there are no major variations between the importance of the horizontal and vertical visual hemifields with respect to the serial biases in the spatial WM, although it leaves open the possibility that there are subtle differences. The fact that there are so little differences between the two directionalities shows that, as the visual information moves from the sensory cortex to more abstract and frontal areas, the information is shared to a larger and more diffuse set of neurons, so the information distribution is homogenized once it reaches the dlPFC and we cannot observe the lateral differences that are evident in the visual cortex region. Serial dependence was found to be greater when the previous and current stimuli appear in the same hemifield, regardless of their directionality. In this way, the objective of giving more strength to the ideas that the Compte Lab has developed with regard to visual hemifields has been successfully achieved.

Exciting results were obtained when trying to replicate the effect of temporality in the TMS trials carried out by João Barbosa [5]. The results were not the same as those obtained in Barbosa's work. In Barbosa's work it was observed that in the first half of the experiments the effect of TMS was very pronounced while in the second half of the experiments there was practically no effect when using weak and strong TMS. In this thesis it has been observed that weak TMS needs to be operating for some time to have visible results in the serial bias. But by evaluating the parameters and results of both studies, interesting hypotheses have been put forward regarding the efficacy and activation of the TMS effect and the TMS intensity employed. If the EEG obtained during the sessions supports the hypothesis put forward in Section 6.1, the replication objective of Barbosa's study will have been a success.

From a personal point of view, this work has allowed me to learn new techniques. I had to work with very sophisticated software and hardware that have served to broaden my knowledge acquired during the degree, as well as the organization between the professionals of the UB, Hospital Clínic, IDIBAPS and the participants of the study. It has been a great opportunity to work with professionals of the highest caliber and a very gratifying way to conclude the Biomedical Engineering degree.

11.1 Future Lines

The project carried out implies a subsequent study, as the amount of EEG data obtained will have to be analyzed in depth by the IDIBAPS and UB teams. This future study will provide more information that will be useful for assessing the different hypotheses surrounding the results obtained in this experiment. The most significant hypothesis is the one regarding the timing of TMS stimulation. If the EEG shows that the decoding strength after a TMS pulse increases during the experiment, at the same time as the effect of TMS on serial bias increases, it will be possible to give more weight to the hypothesis put forward in this thesis, which is that weak TMS, if not combined with strong TMS, needs a period of activation to be able to produce the effect of serial dependence in spatial WM. Understanding the behavior of the brain in response to TMS stimulation can help to optimize this tool, which is useful both in research and in the treatment of certain conditions such as drug-resistant depression. Therefore, if the hypothesis that TMS strong allows TMS weak to have an effect almost automatically but that this effect is diminished due to the saturation produced and that, without TMS strong, there is no saturation and that weak TMS needs a period of activation to reach its maximum potential is given more weight by the EEG data, a more robust study should be conducted in which the effect of such TMS strengths on the dlPFC is examined.

In addition, a larger replication study that implies the manipulation of more data needs to be conducted in order to be able to draw more robust conclusions for the other two conditions studied: hemifields and

bilaterality. In the case of bilaterality, we have seen that it has not been possible to draw any conclusions, therefore a better knowledge of the bilaterality effect in spatial WM has not been achieved. This is due to the fact that, by reducing the dataset into so many subgroups, the analysis was ultimately performed on a very small number of trials, so the results obtained are not conclusive. When studying the hemifields, we have seen that they slightly follow the expected hypothesis, in which there are no notable differences between the directionality in which the previous and current stimuli appear, but there are differences if these stimuli appear in different hemifields (one above and one below or one on the left and one on the right). From the data obtained, it seems that there are differences when the relative distance between previous and current stimuli are around 50 degrees, with the vertical visual hemifield showing a greater serial dependence than the horizontal visual hemifield. A replication study can be conducted in order to verify this hypothesis.

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[56] 'REGLAMENTO (UE) 2016/ 679 DEL PARLAMENTO EUROPEO Y DEL CONSEJO - de 27 de abril de 2016 - relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la Directiva 95/ 46/ CE (Reglamento general de protección de datos)'.

ANNEXES

Annex A. WBS Dictionary

1. Documentation

WBS ID	Name	Description
1.1	Contact with IDIBAPS	To start the project, Albert Compte and his team were contacted, and it was decided to carry out the thesis together.
1.2	Study & comprehend concepts	To understand exactly what concepts needed to be worked with, an arduous research task had to be carried out.
1.3	Supervision & meeting	Monitoring and refinement sessions were conducted throughout the project.

2. Pre - Experiments

WBS ID	Name	Description
2.1	Definition of objectives & timeline	A clinical trial involves many factors and tasks to be conducted successfully, from the decision on how to conduct the actual experiment to the data analysis. Therefore, careful organization and a clear definition of the objectives are important at the beginning of the project.
2.2	Coding and testing the code	The code had to be adapted to the characteristics of the experiment in question, as well as an interface to present the subject's parameters, to save the data correctly and to communicate with the different devices such as the eye tracker or the TMS machine.
2.3	Learning to use the equipment	There are many high-value tools, both software and hardware, that have had to be learned to be used efficiently and safely to conduct the experiments.
2.4	Recruit subjects	The experiment must be done on healthy and voluntary participants. Therefore, the potential participants should be contacted and explained in detail what the experiment consists of, the protocol and the sheet with contraindications must be passed on to them.
2.5	Getting MRI from subjects	Subjects who have agreed to participate in the experiment are scheduled to undergo an MRI scan.

3. Experiments

WBS ID	Name	Description
3.1	Performing pilots	Before starting the actual experiments, a series of pilots should be carried out to check that everything goes according to plan, and to refine those things that need to be improved.
3.2	Performing experiments	Participants should be scheduled when the lab is available. They must fill in the pre-session screening and the experiment is carried out. Each subject must perform the experiment twice.

4. Results

WBS ID	Name	Description
4.1	Data analysis	An analysis of the behavioral data is carried out to draw conclusions with rigor.

5. End of project

WBS ID	Name	Description
5.1	Writing the thesis	All work done during the thesis must be written down and adjusted to the format required for its subsequent evaluation.
5.2	Oral presentation preparation	Before presenting and defending the thesis, it is necessary to prepare the presentation and internalize everything done to make a good defense in front of the examining board.
5.3	Project presentation	The end of the project is reached when the thesis is presented and defended before an examining board.

Annex B. Dictum of the ethics committee on research involving medicinal products

CLÍNIC BARCELONA
Hospital Universitari

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

ANA LUCIA ARELLANO ANDRINO, Secretario del **Comité de Ética de la Investigación con medicamentos del Hospital Clínic de Barcelona**

Certifica:

Que este Comité ha evaluado la propuesta del promotor, para que se realice el estudio:

CÓDIGO:
DOCUMENTOS CON VERSIONES:

CIF – G-08431173

Tipo	Subtipo	Versión
Protocolo		V2. 21/9/2022
Hoja Información de Paciente		V2. 21/9/2022

TÍTULO: La base neuronal dels biaixos serials en memòria de treball espacial
PROMOTOR:
INVESTIGADOR PRINCIPAL: ALBERT COMPTE BRAQUET; MARIA CENTENO SOLADANA

y considera que, teniendo en cuenta la respuesta a las aclaraciones solicitadas (si las hubiera), y que:

- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
- Que se han evaluado la compensaciones económicas previstas (cuando las haya) y su posible interferencia con el respeto a los postulados éticos y se consideran adecuadas.
- Que dicho estudio se ajusta a las normas éticas esenciales y criterios deontológicos que rigen en este centro.
- Que dicho estudio cumple con las obligaciones establecidas por la normativa de investigación y confidencialidad que le son aplicables.
- Que dicho estudio se incluye en una de las líneas de investigación biomédica acreditadas en este centro, cumpliendo los requisitos necesarios, y que es viable en todos sus términos.

Este CEIm acepta que dicho estudio sea realizado, debiendo ser comunicado a dicho Comité Ético todo cambio en el protocolo o acontecimiento adverso grave.

y hace constar que:
1º En la reunión celebrada el día 08/09/2022, acta 15/2022 se decidió emitir el informe correspondiente al estudio de referencia.

Reg. HCB/2022/0840

Mod_04 (V4 de 18/06/2018) PR

Página 1/3

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Tel. 93 227 54 00 Fax 93 227 54 54
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Generalitat de Catalunya Departament de Salut

UNIVERSITAT DE BARCELONA

CLÍNIC BARCELONA Hospital Universitari

2º El CEIm del Hospital Clínic i Provincial, tanto en su composición como en sus PNTs, cumple con las normas de EMA/CHMP/ICH/135/1995
3º Listado de miembros:

Presidente:
- JOSEP MARÍA MIRÓ MEDA (Médico Enfermedades Infecciosas, HCB)

Vicepresidente:
- JULIO DELGADO GONZÁLEZ (Médico Hematólogo, HCB)

Secretario:
- ANA LUCIA ARELLANO ANDRINO (Médico Farmacólogo Clínico, HCB)

Vocales:
- JOSE RIOS GUILLERMO (Estadístico. Plataforma de Estadística Médica. IDIBAPS)
- OCTAVI SANCHEZ LOPEZ (Representante de los pacientes)
- MARIA JESÚS BERTRAN LUENGO (Médico Epidemiólogo, HCB)
- JOAQUÍN SÁEZ PEÑATARO (Médico Farmacólogo Clínico, HCB)
- SERGI AMARO DELGADO (Médico Neurólogo, HCB)
- EDUARD GUASCH CASANY (Médico Cardiólogo, HCB)
- MARINA ROVIRA ILLAMOLA (Farmacéutico Atención Primaria, CAP Eixample)
- PAU ALCUBILLA PRATS (Médico Farmacólogo Clínico, HCB)
- JOSE TOMAS ORTIZ PEREZ (Médico Cardiólogo, HCB)
- ELENA CALVO CIDONCHA (Farmacéutica Hospitalaria, HCB)
- CECILIA CUZCO CABELLOS (Enfermera, HCB)
- PAULA MARTÍN FARGAS (Abogada, HCB)
- SALVATORE BRUGALETTA (Médico Cardiólogo, HCB. Miembro del CEA, HCB)
- XAVIER CANALS-RIERA (Ingeniero Telecomunicaciones)
- FRANCESC XAVIER CORBELLE (Informático, HCB)
- JOSEP DÍAZ CORT (Licenciado en Ciencias Físicas. Catedrático en Informática)
- GASPAR MESTRES ALOMAR (Médico, Angiología, Cirugía Vascular, HCB)
- MARTA FRANCH SAGUER (Abogada)
- ANNA MARÍA GUIJARRO PÉREZ (Servicio de Atención a la Ciudadanía, HCB)
- BEGOÑA ROMAN MAESTRES (Doctor en Filosofía)

CIF – G-08431173

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, este se ausentará de la reunión durante la discusión del proyecto.

Para que conste donde proceda, y a petición del promotor,

Motivo: Certifico la precisión e integridad de este documento
Fecha: 2022.10.06 12:33:55 +02'00'

Reg. HCB/2022/0840

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Annex C. Participant consent form

Hoja de consentimiento de participante

Título del estudio: “La base neuronal de los sesgos serials en memoria de trabajo espacial”

Yo, (nombre y apellidos del participante): ……..

He leído la hoja de información que se me ha entregado sobre el estudio.
He leído las hojas de información sobre la EMT y entiendo los riesgos que puede tener.
He podido hacer preguntas sobre el estudio
He recibido suficiente información sobre el estudio
He hablado con (nombre del investigador): .....
Comprendo que mi participación es voluntaria
Comprendo que puedo retirarme del estudio:
1. Cuando quiera
2. Sin tener que dar explicaciones
3. Sin que esto repercuta en mis cuidados médicos

De conformidad con lo que establece el Reglamento UE 2016/679 del Parlamento Europeo y del Consejo de 26 de abril de 2016 relativo a la protección de las personas físicas en cuanto al tratamiento de datos personales y la libre circulación de datos, declaro haber sido informado de la existencia de un fichero o tratamiento de datos de carácter personal, de la finalidad de la recogida de éstos y de los destinatarios de la información.

Consiento que los posibles resultados obtenidos con mi participación en el estudio sean fuente de publicaciones científicas, siempre que se vele por mi completo anonimato. Ante la presente información que el Responsable del estudio me ha facilitado, y habiendo entendido ésta, ofrezco mi consentimiento al tratamiento de:

☐ Mis datos personales para llevar a cabo el proyecto de investigación.

☐ Mis datos personales para ser recontactado en el futuro con el fin de llevar a cabo proyectos de investigación afines al presente o de la misma área de investigación.

Presto libremente mi conformidad para participar en el estudio.

Firma del participante: Firma del investigador:

Fecha: ____/____/____ Fecha: ____/____/____

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para mí salud:

o SI o NO

V2. 21/9/2022

Annex D. Pre-session screening questionnaire

Datos Sesión

CódigoNombre participante:
Nombre Investigador: Fecha:

Cuestionario Screening

1. ¿Ha padecido alguna vez convulsiones o un ataque de epilepsia? ☐Sí ☐No
2. ¿Alguien en tu familia sufre o ha sufrido epilepsias? ¿Quién? ☐Sí ☐No
3. ¿Ha padecido sincopes o pérdidas de consciencia? Explica en qué ocasión ☐Sí ☐No
4. ¿Ha sufrido algún trauma que haya sido diagnosticado cómo conmoción cerebral o que estuviera asociado a pérdida de consciencia? ☐Sí ☐No
5. ¿Tiene problemas de audición o tiene zunzunes en el oído? ☐Sí ☐No
6. ¿Tiene implantes cocleares? ☐Sí ☐No
7. ¿Está embarazada o piensa que lo podría estar? ☐Sí ☐No
8. ¿Tiene algún metal en la cabeza (excepto en la boca)? ☐Sí ☐No
9. ¿Tiene algún neuroestimulador implantado (eg.DBS, epidural/subdural, VNS...)? ☐Sí ☐No
10. ¿Tiene marcapasos implantado o válvula intracardíaca? ☐Sí ☐No
11. ¿Toma medicaciones? ¿Cuáles? Especifique abajo ☐Sí ☐No
12. ¿Ha recibido EMT antes? ☐Sí ☐No
13. ¿Tuvo una reacción adversa? ☐Sí ☐No
14. ¿Le han hecho cirugía cerebral? ☐Sí ☐No
15. ¿Padece alguna enfermedad neurológica? ☐Sí ☐No
16. ¿Padece alguna enfermedad psiquiátrica? ☐Sí ☐No
17. ¿Sufre habitualmente dolores de cabeza severos? ☐Sí ☐No

Firma Investigador:

V2. 21/9/2022

Annex E. Lab Procedure

Lab Procedure
Luis Doreste Cabrera

STEPS DONE THE DAY OF THE EXPERIMENT

0. PRIOR PREPARATION:

Before the subject arrives we must do as much preparation as possible. We must wash our hands with soup once we enter the lab. The image of the subject's MRI must be prepared on the program Brainsight (shown on *STEPS DONE BEFORE THE EXPERIMENT*). The preparation consists on:

- Put the table and chair where the subject will be seated.
- Put an arm on the seat of the chair so that the EEG helmet cables can be placed without pulling the patient's head down.
- Put the EEG machine on the side of the lab where we will start stimulating.
- Prepare at least 3 syringes with the EEG helmet conduction gel inside.
- Turn on the computers and open all the different software that will be used. Programs on the computer used to obtain the signals and display the experiment on the screen: *Signal* (for the EMG), *Recorder* (for the EEG), *Virtual Studio Code* (with the Python code of the experiment), *Tobii Fusion Pro* (for the eye tracker calibration). In the MAC we use the *Brainsight* program to coregister the MRI images, put the stimulation coordinates and neuronavigation (the coregistration is explained down). *Brainsight* will show us where to put the TMS to properly stimulate exactly where we want.
- Turn on the different machines: TMS machine, EEG and EMG recorder. If we don't turn them on, an error will appear when we try to run the programs mentioned before. The EMG battery has a green cable which is used to charge it. Before we start we have to replace the green charging cable with the green one that connects the battery with the signal reader. Once the experiment is over, connect the battery again with the green cable that charges it.
- Place the eye tracker in its place.

Once the patient is in the room, the subject must fill the pre-session screening questionnaire and a thorough explanation must be taken. If the subject has any piercing or other metallic objects in the ear or mouth it must be removed. Mobile phones, laptops or other informatic instrumentation must be carefully stored to avoid risk of getting damaged by the TMS machine.

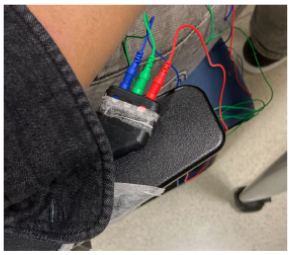
1. EMG:

In this step we will measure the power at which we must use the TMS so that it stimulates the cerebral cortex but using the least possible intensity. First of all, we must clean the head of the subject with some alcohol to get rid of the oil and fat that the scalp segregates (IMPORTANT: ask the subject to wash their head before coming to the session). Then we put the EEG helmet on the head and the earplugs. There is a medium and a small helmet, depending on the size of the subject's head (the small one is fine unless the head is big, this normally happens with male subjects). To put the helmet on, place the front part of the helmet one and a half centimeters below the hairline. Once on, check that there are no folds and that the electrodes are not too tight. This is important because having the helmet adds another layer and therefore changes the actual threshold. It is important to measure it in this way as it will be in the same conditions that the subject will be in when we do the experiment.

With the previous steps done, we have to clean with alcohol the area in which we are going to place the electrodes (the interior part of the index finger and at the ulnar styloid process). Then we put the three different electrodes.

To obtain the same result every time, we use this color code:

- Red: reference
- Green: ground
- Blue: active



And position them in the following way:
We tape the connector to the chair so that it does not pull on the electrodes. We also roll the electrodes' wires and tape them. By doing this we avoid tension in the arm and we obtain a signal with less noise.

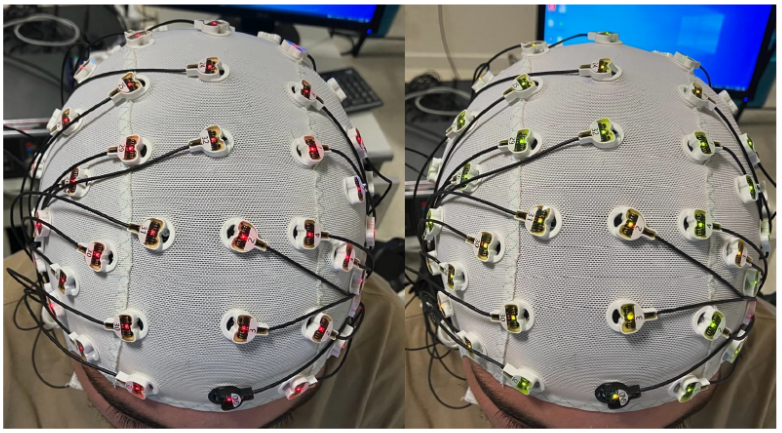
The *Signal* program allows us to observe the muscle activation:

> Inside the program, we click on 'For show' and see that signal quality. The 50 Hz noise has to be within the two marked lines, if not, we must clear better with more alcohol in the zone where the electrodes are. The next thing is to set 'Setup A' (the one designed for the experiment) on the TMS machine, and start stimulating with an amplitude of 30%. This setup triggers automatically, so we have to be careful when we set it on. We put the TMS on the motor cortex area and see if there is an action potential in the signal program. We have to navigate around this area with the TMS coil. If we don't find anything, we go up to 40%, then we go up 5% at a time until we see the potential represented on the screen (it must overpass the two black lines). We must count 3 out of 6 potentials for it to be valid. Once we have achieved this, we go down little by little until we lose the 3/6. The last value where we achieved 3/6 potentials is the TMS potential.

2. EEG

The helmet is already placed in the head (as explained in the previous steps). With the *Recorder* program, there is an impedance button next to an eye button. This will allow us to see the status of the different electrodes. The electrodes are shown in red and once the impedance improves, they turn green. With the syringes we move the hair carefully and fill each electrode with the product. We must see that the electrodes turn green. It is often necessary to let the liquid settle to see this change of color. When done, we put the glasses with the holder with the three spheres on the subject in order to be able to neuronavigate.

While the product is getting settled, we record the position of the electrodes and the points of interest on the head with the *Brainsight* software (IMPORTANT!! this, and the rest of neuronavigation procedures are explained in the neuronavigation part down below. It is important to read that part carefully, because it has important steps that need to be carried out before going on to the next part which is running the experiment).



3. RUNNING THE EXPERIMENT

With all the preparations in place, the next step is to run the Python program. Just before running it, we must calibrate the eye tracker. This step is simple to open the software *Tobii Fusion Pro* and to select our eye tracker (it will be the only one that appears). Me then presses to calibrate and the subject must look at the white spots that appear until they explode. If the subject is too far away, we won't be able to calibrate. Once this is done, we must place the TMS coil right where the *Brainsight* tells us. We run the Python code and a screen will appear on which we must fill in the subject code, the side on which we will start to stimulate, the block on which we will start (it will be 1 unless we pause the experiment at a given moment), the power of the TMS threshold and if we want to do the first 5 practice trials or not (we can skip the practice trials on the second session). We are stimulating one side for 4 consecutive blocks and then change sides for the last 4 blocks. In this change we have to be very careful when moving the TMS machine around (specially with the cables). We have to change the balls that help to know the position of the subject from one side of the goggle to the other side and we also have to repeat the landmarks step (described below in neuronavigation).

4. TIDY UP

Once we have carried out the experiment we have to collect everything. We close all the programs, the only one we have to be especially careful with is the recorder, as we have to press the red square button and then the red stop button that appears. We remove the EEG helmet from the subject and let them wipe and dry their hair. While we collect the eye tracker, we switch off the computers and collect anything we have used that should go in the trash. When the sink is free, we clean the syringes that are reused (the tip goes in the trash) and the EEG headset, being very careful not to get wires and connectors wet. We have to go electrode by electrode getting the gel off. Once this is done, we must put the helmet on top of a towel or paper to let it dry. De wires must be positioned at a higher altitude than the wet hat so no water goes to the connectors.

STEPS DONE BEFORE THE EXPERIMENT AND NEURONAVIGATION DURING

The first thing we must do is to gather the subjects that are willing to contribute to this project. Then we compute an MRI of their brain. With this image, we must do a preprocess so that we can neuro navigate when they come to the lab and we can put the coordinates we want to stimulate with the TMS.

We must turn the DICOM images of the MRI into Nifti. With this image, we run the code made by Rubén to get the matrix and different images that will be later used:

[native_coords] = MNIfunc2native ('/Users/brainsight/Documents/MatlabTools/spm12', '*path_T1_image*', [-42 10 30]).

When the transformation is done, we will use the software *Brainsight* on the Mac:

We go to the software and press on 'New Project', assuming that it is the first time the subject has come to the experiment (if not we open an existing Project and we go directly to the New Online Session). There are a number of different steps that must be followed on this software:

1. Add the image: by going to atlas, pressing the first dropdown and we add the matrix done previously with matlab (T1…). Careful because when we want to add an image or a matrix on *Brainsight*, it will open directly on the subject that was used before. This can cause an accidental error of getting another subject's images.

2. Overlay: here we add the tissues: BET image is the brain (open).

3. ROI: we skip this step.

4. Reconstruction: here we will add three different overlays:
    - New: Skin: compute skin -> close.
    - New: Curvilinear from overlay (it uses the BET) -> compute -> close.
    - New: Surface from overlay -> compute -> close.

5. Landmarks: here we must add the three fiducial points. For the three points we must mark on the image of the subject's head where we want them, then press new and add the name: NAS for the nose, LPA for the left pre auricular and RPA for the right pre auricular.

6. Targets: we compute the places we want to stimulate. Some steps must be done:
    - Down right of the screen:
        - Coordinate system: we press MNI.
        - Crosshairs origin: here we put the coordinates we want. In this case:
            - Right coordinates (DERECHA): 42(x), 29(y), 26(z).
            - Left coordinates (IZQUIERDA): -35(x), 24(y), 32(z).
    - Upper left of the screen:
        - New: trajectory -> name (IZQUIERDA and DERECHA like shown above).
        - Snap to: snap to curvilinear brain & optimize trajectory -> skin & snap (it's like this by default).
        - Sometimes the point is very deep on the subject's brain and the trajectory is just wrong, it will indicate that the point of stimulation is from beneath for example. In these cases, instead of choosing 'trajectory' we choose 'marker'.

Neuronavigation steps

All the previous steps should be done before the subject is in the room to maximize time. Once the subject is with us and has the EEG helmet on, we must create a new online session to calibrate the neuronavigation. These are some simple extra steps:

1. Firstly we create a new online session from the subject's database. In this new online session we put the IZQUIERDA and DERECHA targets of stimulation.

2. Input output (IOBox): we close the two eyelashes icon on the legend located on the upper right corner and press on the 'Use switch'.

3. Polaris: in this step we will see the camera range. We need to assure, using the pistol with the three spheres, that the subject's head is inside this range and that it can read where this pistol is around the head. We might need to move the infrared camera that reads the position around so that it is able to see where the subject's head is, or even the subject and the table if needed.

4. Registration: there is a cable connected to the MAC with a button at the end. Using the pistol, we place the tip on the three previously marked fiducial points (NAS, LPA and RPA) and press the button at the end of the cable to correlate the previously virtually marked points with their position in real space.

5. Validation: here we will get different points around the head ('extreme' points like the center, sides, back) in order to minimize the error. Then, we will place back the pistol at the known points (fiducials) and look at the distance eros. If the error is small, the numbers will appear in green and we can continue on to the next step, if not, we will have to repeat the registration step or even go back and repeat the landmarks step.

6. Electrodes: with the pistol, we will place it on top of the different electrodes and mark it in the same way as performed on the validation step. We go to add from -> file -> the one from the subject's database starting 'BP64_…_new_order.txt'). This file has all the names of the electrodes that our EEG helmet uses.

7. Perform: 'Driver' is what the camera follows, by default it will get the pointer (the pistol). We must change it and put in the TMS coil (MCF-B70). Careful because there are two coils with nearly the exact name. The placebo has a '-P' at the end, and we don't want to use it. The screen will guide us so that we stimulate at the place and direction desired in the subject's head. With all this done, we can start the experiment.

Annex F. Behavioral Analysis Code

Behavior Data Analysis - Albert Compte's Lab

Adapted by Luis Dorste Cabrera

Load of the different libraries used throughout the code:

In [ ]:
```
import numpy as np   #For numerical computation in Pythom
import pandas as pd   #For data manipulation and analysis
import matplotlib.pyplot as plt   #For creating visualizations
from matplotlib.legend import _get_legend_handles_labels
import seaborn as sns   #For more visually appealing and informative statistical graphics
from scipy.io import loadmat   #For reading Matlab file formats
from scipy.stats import *   #For statistical functions and probability distributions
from scipy.optimize import curve_fit   #For curve fitting and optimization
from cmath import phase
from numpy import array
from scipy.sparse import csr_matrix   #For sparse matrix representations
import urllib   #For accessing URLs
import pickle   #For object serialization and deserialization in Python
import glob     #For searching for files in a directory tree
try:
    from sklearn.linear_model import LinearRegression
except ModuleNotFoundError:
    %pip install scikit-learn   #For machine learning models for linear regression and logistic regression
    from sklearn.linear_model import LinearRegression
from sklearn.linear_model import LogisticRegression
from sklearn.model_selection import train_test_split   #For model selection and evaluation
from sklearn.model_selection import LeaveOneOut
from sklearn.metrics import accuracy_score   #For evaluating the accuracy of classification models
from sklearn import preprocessing   #For preprocessing data before machine learning
try:
    import statsmodels.formula.api as sf
except ModuleNotFoundError:
    %pip install statsmodels   #For specifying statistical models in Python using formulas
    import statsmodels.formula.api as sf
from sklearn import metrics
from random import randint
from numpy.linalg import inv
import math
import io
import io
try:
    from circ_stats import *
except ModuleNotFoundError:
    %pip install circ_stats
    from circ_stats import *
from patsy import dmatrices
import statsmodels.api as sm
try:
    import helpers as hf
except ModuleNotFoundError:
    %pip install helpers
    import helpers as hf
from helpers2 import *
import statsmodels.formula.api as smf


sns.set_theme()
sns.set_style("white")
sns.set_context("poster")

import matplotlib.pylab as pylab
params = {'legend.fontsize': 24,
          'figure.figsize': (17, 6),
          'figure.facecolor': (0.0, 0.0, 0.0, 0.0),
         'axes.labelsize': 24,
         'axes.titlesize':24,
         'xtick.labelsize':16,
         'ytick.labelsize':16}

pylab.rcParams.update(params)
```

We load the csv file, create labels for each stimulation side, convert degrees between 0 and 360 to -pi to pi, calculate the distances between the points and the error (difference between target and response).

In [2]:
```
df_tms = pd.read_csv("todos.csv", delimiter=';')

RIGHT = 1
LEFT = 0

# convert target angle from (0,360) to (-pi,pi)
df_tms["target_angle"] = [np.deg2rad(df_tms.target_angle[i])-2*np.pi if np.deg2rad(df_tms.target_angle[i])>np.pi
                          else np.deg2rad(df_tms.target_angle)[i] for i in df_tms.index]
df_tms["report_angle"] = [np.deg2rad(df_tms.report_angle[i])-2*np.pi if np.deg2rad(df_tms.report_angle[i])>np.pi
                          else np.deg2rad(df_tms.report_angle)[i] for i in df_tms.index]
# calculate, serial dependence params
df_tms["prevcurr"] = circdist(roll(df_tms.target_angle,1), df_tms.target_angle)
df_tms["err"]=circdist(df_tms.report_angle,df_tms.target_angle)

## remove random guesses
df_tms=df_tms[(df_tms.err.abs()<radians(45))].reset_index(drop=True)

## calculate TMS intensity
df_tms["tms_abs"] = df_tms.RMT * df_tms.tms_intensity
df_tms["prev_tms"] = roll(df_tms.tms_intensity,1)

df_tms.insert(6,'tms_int', [1 if df_tms.tms_intensity[i]==0.7 else 0 for i in df_tms.index])

df_tms.rename(columns={"target_angle": "target", "report_angle": "response", "err": "error"}, inplace=True)

#print(df_tms)
#df_tms.head()
```

The function calculates running averages of the err array over a specified range of target values, with the range defined by w2. w2 is the angular window used for averaging, because the serial bias is only a small bias on top of the large variance of responses around the target.xx are the sampled angles from -pi/0 to pi:

In [3]:
```
def runningAvg(err,target,xx,w2):
    n=0
    m_err=[]
    std_err=[]
    count=[]
    cis=[]
    uf_err = err.copy()
    points_idx=[]
    for i,t in enumerate(xx):
        # wi=w[i]
        idx=abs(circdist(target>=t))<w2/2
        m_err.append(circ_mean(err[idx]))                  #array of the mean error
        std_err.append(circstd(err[idx])/sqrt(sum(idx)))   # "" of the standard error
        count.append(sum(idx))                             # "" of the number of points included in each mean error
        points_idx.append(idx)                             # calculation
    return [array(err),array(m_err),array(std_err),count,points_idx,n,uf_err]
```

This step simply consists of creating markers for the hemifields and checking that it is able to correctly differentiate between them:

In [7]:
```
df_tms['hemifield'] = ['left' if (df_tms['target'][i]<-np.pi/2) |\
                       (df_tms['target'][i]>np.pi/2)\
                       else 'right' if (df_tms['target'][i]>-np.pi/2) &\
                       (df_tms['target'][i]<np.pi/2)\
                       else 'border' for i in df_tms.index]
df_tms['topdown'] = ['top' if (df_tms['target'][i]>0) & (df_tms['target'][i]<np.pi)\
                     else 'down' if (df_tms['target'][i]<0) & (df_tms['target'][i]>-np.pi)\
                     else 'border' for i in df_tms.index]

df_tms['hemifield_prev'] = np.roll(df_tms.hemifield,1)
df_tms['topdown_prev'] = np.roll(df_tms.topdown,1)
df_tms['error_prev'] = np.roll(df_tms.error,1)

OPP = 0
SAME = 1
BORDER = 2

df_tms['same'] =  [BORDER if ((df_tms.hemifield_prev[i]=='border') | (df_tms.hemifield[i]=='border'))\
           else SAME if (df_tms.hemifield_prev[i]==df_tms.hemifield[i])\
           else OPP for i in df_tms.index]
df_tms['same_td'] =  [BORDER if ((df_tms.topdown_prev[i]=='border') | (df_tms.topdown[i]=='border'))\
           else SAME if (df_tms.topdown_prev[i]==df_tms.topdown[i])\
           else OPP for i in df_tms.index]


df_tms['prevcurr_hemi'] = [df_tms.hemifield_prev[i]+df_tms.hemifield[i] for i in df_tms.index]
# remove random guesses, only use PFC stimulation
#df_tms=df_tms[(df_tms.err.abs()<radians(45))].reset_index(drop=True)

df_tms=df_tms[(df_tms.error.abs()<radians(45))].reset_index(drop=True)
```

To study the population absolute error between the trials without and with TMS:

In [11]:
```
tms_trials = df_tms[df_tms.tms_int==1]
no_tms_trials = df_tms[df_tms.tms_int==0]

# Calculate the absolute error for both datasets
tms_trials['abs_error'] = np.abs(np.rad2deg(tms_trials['error']))
no_tms_trials['abs_error'] = np.abs(np.rad2deg(no_tms_trials['error']))

# Set the number of bins for the histograms
num_bins = 100
bns = linspace(0,30,num_bins)

# Create a figure with three subplots
fig, axs = plt.subplots(1, 3, figsize=(18, 6))

# Plot the histogram of TMS trials
sns.histplot(data=tms_trials, x='abs_error', label='TMS Trials', bins=bns, ax=axs[0], color='#e8b436ff')
axs[0].set_xlim(0, 30)  # Set the x-axis range
axs[0].set_xlabel('Absolute Error (deg)')
axs[0].set_ylabel('Number of Trials')

# Plot the histogram of No TMS trials
sns.histplot(data=no_tms_trials, x='abs_error', label='No TMS Trials', bins=bns, ax=axs[1], color='darkgray')
axs[1].set_xlim(0, 30)  # Set the x-axis range
axs[1].set_xlabel('Absolute Error (deg)')
axs[1].set_ylabel('Number of Trials')

# Plot the histogram of TMS and No TMS trials combined
sns.histplot(data=tms_trials, x='abs_error', kde=True, label='TMS Trials',
             bins=bns, ax=axs[2], color='#e8b436ff', alpha=0.7)
sns.histplot(data=no_tms_trials, x='abs_error', kde=True, label='No TMS Trials',
             bins=bns, ax=axs[2], color='darkgray', alpha=0.7)
axs[2].set_xlim(0, 30)  # Set the x-axis range
axs[2].set_xlabel('Absolute Error (deg)')
axs[2].set_ylabel('Number of Trials')
axs[2].legend(fontsize='small')

plt.tight_layout()  # Adjust the spacing between subplots
plt.show()

from scipy import stats
stats.kstest(tms_trials.abs_error, no_tms_trials.abs_error)
```

To plot the serial dependence of all trials. Functions from other files (helpers) are used, which will be covered later on:

In [12]:
```
subjects = df_tms.subject.unique()
allsbias = zeros([len(subjects),len(xxx)])
allsbias_std = zeros([len(subjects),len(xxx)])
SB_subjects = []
pvals = zeros([len(subjects)])
DoG = []
for sub_i,(sub, subject) in enumerate(df_tms.loc[df_tms.tms_int>=0.0].groupby("subject")):
    sbias_all = compute_seria_from_pandas(subject,xxx,flip)
    allsbias[sub_i] = sbias_all[2]
    allsbias_std[sub_i] = sbias_all[3]

figure(figsize=(4,4))

# plot serial bias curve using the function plot_serial in helpers2, there you can see that error bars are s.e.m.
plot_serial(allsbias,"k",label="")
pvalues=perm_test_nan_onesided(allsbias,np.zeros((allsbias.shape)),n_perms=10000)/2
plot_sigs([],"k",[],pvalues=pvalues,upper=[1.9,2])
yticks([-1,0,1])
plt.ylim([-1,1])
plt.ylabel('mean error (deg)')
plt.xlabel('distance previous-current (deg)')
plt.show()
```

Hemifields Study

We first configure some plotting parameters. Then we subdivide the data into different categories, depending if the previous and current stimuli are on the same hemifield, and if the hemifield is up-down or left-right:

In [13]:
```
import seaborn as sns
#%matplotlib inline
#%config InlineBackend.figure_format = 'svg'

sns.set_theme()
sns.set_style("white")
sns.set_context("poster")

#poster
import matplotlib.pylab as pylab
params = {'legend.fontsize': 22,
          'figure.figsize': (16, 6),
          'figure.facecolor': (0.0, 0.0, 0.0, 0.0),
         'axes.labelsize': 24,
         'axes.titlesize':24,
         'xtick.labelsize':16,
         'ytick.labelsize':16}


pylab.rcParams.update(params)
```

In [14]:
```
OPP = 0
SAME = 1

from matplotlib.ticker import FormatStrFormatter

df_notms = df_tms.loc[df_tms.tms_intensity==0]

subjects = df_notms.subject.unique()
sameOppbias = zeros([len(subjects), 3, len(xxx)])
sameTopDown = zeros([len(subjects), 3, len(xxx)])
for sub_i,(sub, subject) in enumerate(df_notms.groupby("subject")):
    for sameOpp_i, (so, sameOpp) in enumerate(subject.groupby('same')):# for opposite, same hemifield
        sbias_all = compute_seria_from_pandas(sameOpp,xxx,flip)
        sameOppbias[sub_i, sameOpp_i] = sbias_all[2]
    for topDown_i, (td, topDown) in enumerate(subject.groupby('same_td')):# for top, down
        sbias_all = compute_seria_from_pandas(topDown,xxx,flip)
        sameTopDown[sub_i, topDown_i] = sbias_all[2]
```

```
number_perms = 10000

figure(figsize=(13,4))

subplot(131)
plot_serial(sameOppbias[:,OPP,:],"darkorange",label="opp")
plot_serial(sameOppbias[:,SAME,:],"darkgreen",label="same")
pvalues=perm_test(sameOppbias[:,SAME,:],sameOppbias[:,OPP,:],n_perms=number_perms)/2
plot_sigs([],"k",[],pvalues=pvalues,upper=[1.9,2])
plt.yticks([-2.0,-1.0,0,1.0,2.0],['-2.0','-1.0','0','1.0','2.0'])
plt.xlabel('rel. location (°)')
plt.ylabel('current error (°)')

subplot(132)
plot_serial(sameTopDown[:,OPP,:],"darkorange",label="opp")
plot_serial(sameTopDown[:,SAME,:],"darkgreen",label="same")
pvalues=perm_test(sameTopDown[:,SAME,:],sameTopDown[:,OPP,:],n_perms=number_perms)/2
plot_sigs([],"k",[],pvalues=pvalues,upper=[1.9,2])
plt.ylabel('')
plt.yticks([-2.0,-1.0,0,1.0,2.0],['-2.0','-1.0','0','1.0','2.0'])
plt.xlabel('rel. location (°)')

subplot(133)
compare_td = sameTopDown[:,SAME,:]-sameTopDown[:,OPP,:]
compare_so = sameOppbias[:,SAME,:]-sameOppbias[:,OPP,:]
plot_serial(compare_td,"k",label="topdown")
plot_serial(compare_so,"darkred",label="hemifield")
pvalues=perm_test(compare_so,compare_td,n_perms=number_perms)/2
plot_sigs([],"k",[],pvalues=pvalues,upper=[1.9,2])
plt.yticks([-2.0,-1.0,0,1.0,2.0],['-2.0','-1.0','0','1.0','2.0'])
plt.xlabel('rel. location (°)')

plt.tight_layout()
plt.show()
```

Temporality Study

We get the data of the first half and the second one:

In [17]:
```
LOW_TMS = 1 # only meaningful for PFC
NO_TMS = 0

tms_intensities = df_tms.tms_intensity.unique()
locations = df_tms.location.unique()
subjects = df_tms.subject.unique()

allsbias_all = zeros([len(subjects),len(locations),len(tms_intensities),len(xxx)])
allsbias_first = zeros([len(subjects),len(locations),len(tms_intensities),len(xxx)])
allsbias_last = zeros([len(subjects),len(locations),len(tms_intensities),len(xxx)])
allsbias_all_sem = zeros([len(subjects),len(locations),len(tms_intensities),len(xxx)])
allsbias_first_sem = zeros([len(subjects),len(locations),len(tms_intensities),len(xxx)])
allsbias_last_sem = zeros([len(subjects),len(locations),len(tms_intensities),len(xxx)])
SB_subjects_tms = {'0.0':[], '0.7':[]}
DoG_tms = {'0.0':[], '0.7':[]}
params_tms = {'0.0':[], '0.7':[]}
for sub_i,(sub, subject) in enumerate(df_tms.groupby("subject")):
    for loc_i, (loc,location) in enumerate(subject.groupby("location")):
        for tms_i, (tms,tms_int) in enumerate(location.groupby("tms_intensity")):
            sbias = zeros(len(xxx))
            sbias_first = zeros(len(xxx))
            sbias_last = zeros(len(xxx))
            sbias_sem = zeros(len(xxx))
            sbias_first_sem = zeros(len(xxx))
            sbias_last_sem = zeros(len(xxx))


            n_sessions = len(tms_int.session.unique())
            for sess_i, (_,session) in enumerate(tms_int.groupby("session")):
                sbias_all_first = compute_seria_from_pandas(session[:int(len(session)/2)],xxx,flip)
                sbias_all_last = compute_seria_from_pandas(session[int(len(session)/2):],xxx,flip)
                sbias_all = compute_seria_from_pandas(session,xxx,flip)
                sbias += sbias_all[2]
                sbias_first += sbias_all_first[2]
                sbias_last += sbias_all_last[2]
                sbias_sem += sbias_all[3]
                sbias_first_sem += sbias_all_first[3]
                sbias_last_sem += sbias_all_last[3]
            n_sessions = len(tms_int.session.unique())
            for sess_i, (_,session) in enumerate(tms_int.groupby("session")):
                sbias_all_first = compute_seria_from_pandas(session[:int(len(session)/2)],xxx,flip)
                sbias_all_last = compute_seria_from_pandas(session[int(len(session)/2):],xxx,flip)
                sbias_all = compute_seria_from_pandas(session,xxx,flip)
                sbias += sbias_all[2]
                sbias_first += sbias_all_first[2]
                sbias_last += sbias_all_last[2]
                sbias_sem += sbias_all[3]
                sbias_first_sem += sbias_all_first[3]
                sbias_last_sem += sbias_all_last[3]

            allsbias_all[sub_i,loc_i,tms_i] = sbias/n_sessions
            allsbias_first[sub_i,loc_i,tms_i] = sbias_first/n_sessions
            allsbias_last[sub_i,loc_i,tms_i] = sbias_last/n_sessions
            allsbias_all_sem[sub_i,loc_i,tms_i] = sbias_sem/n_sessions
            allsbias_first_sem[sub_i,loc_i,tms_i] = sbias_first_sem/n_sessions
            allsbias_last_sem[sub_i,loc_i,tms_i] = sbias_last_sem/n_sessions
```

First half of experiments (second just have to change allsbias_first to allsbias_last)

In [18]:
```
RIGHT = 1
LEFT = 0
fig = plt.figure(figsize=(3.5,7))
subplot(2,1,1)
plot_serial(allsbias_first[:,RIGHT,LOW_TMS,:],'#e8b436ff', label='TMS') # Last half uses allsbias_last instead
plot_serial(allsbias_first[:,RIGHT,NO_TMS,:],"k", label='sham')
pvalues=perm_test_nan_onesided(allsbias_first[:,RIGHT,LOW_TMS,:],allsbias_first[:,RIGHT,NO_TMS,:],n_perms=100000)/2
plot_sigs([],"k",[],pvalues=pvalues,upper=[1.9,2])
yticks([-2,-1,0,1,2])
xticks([])
legend(fontsize=16)

subplot(2,1,2)
diff = allsbias_first[:,RIGHT,LOW_TMS,:]-allsbias_first[:,RIGHT,NO_TMS,:]
plot_serial(diff,'darkred')#
pvalues=perm_test_nan_onesided(diff,np.zeros((diff.shape)),n_perms=100000)/2
plot_sigs([],"k",[],pvalues=pvalues,upper=[1.9,2])

fig.add_subplot(111, frameon=False)
plt.tick_params(labelcolor='none', top=False, bottom=False, left=False, right=False)
plt.xlabel('rel. location [°]')
plt.ylabel('current error')
plt.show()
```

Bilaterality Study

SD analysis based on left-left, left-right, right-left, right-right trials

Data is subdivided into eight subgroups depending on the side it appeared, the side of stimulation and the stimulation intensity:

In [20]:
```
LOW_TMS = 1 # only meaningful for RIGHT
NO_TMS = 0


OPP=0
SAME=1

tms_intensities = df_tms.tms_intensity.unique()
locations = df_tms.location.unique()
subjects = df_tms.subject.unique()
num_targetcombis = 4 # consecutive targets can be: left-left, right-left, left-right, right-right (4 options)

allsbias_all = zeros([len(subjects),len(locations),len(tms_intensities),num_targetcombis,len(xxx)])
allsbias_all_sem = zeros([len(subjects),len(locations),len(tms_intensities),num_targetcombis,len(xxx)])
numTrials_all = zeros([len(subjects),len(locations),len(tms_intensities),num_targetcombis])
allsbias_last = zeros([len(subjects),len(locations),len(tms_intensities),num_targetcombis,len(xxx)])

for sub_i,(sub, subject) in enumerate(df_tms.groupby("subject")):
    for loc_i, (loc,location) in enumerate(subject.groupby("location")):
        for tms_i, (tms,tms_int) in enumerate(location.groupby("tms_intensity")):
            for same_i, (same,same_hemi) in enumerate(tms_int.groupby("prevcurr_hemi")):

                sbias = zeros(len(xxx))
                sbias_first = zeros(len(xxx))
                sbias_last = zeros(len(xxx))
                n_sessions = len(same_hemi.session.unique())
                for sess_i, (_,session) in enumerate(same_hemi.groupby("session")):
                    sbias_all = compute_seria_from_pandas(session,xxx,flip)
                    sbias += sbias_all[2]
                    sbias_all_last = compute_seria_from_pandas(session[int(len(session)/2):],xxx,flip)
                    sbias_last += sbias_all_last[2]

                allsbias_all[sub_i,loc_i,tms_i,same_i] = sbias/n_sessions
                allsbias_last[sub_i,loc_i,tms_i,same_i] = sbias_last/n_sessions
                numTrials_all[sub_i,loc_i,tms_i,same_i] = len(same_hemi)
```

RIGHT side (left side is the same, just changing RIGHT to LEFT)

In [21]:
```
fig = figure(figsize=(10,10))

combinations = np.unique(tms_int.prevcurr_hemi)
titles=["full", "first", "last"]
allsbias = allsbias_last # only check out last half of trials
for same_i, (same,same_hemi) in enumerate(tms_int.groupby("prevcurr_hemi")):
    subplot(2,2,same_i+1)
    plot_serial(allsbias[:,RIGHT,NO_TMS,same_i,:],"k", label='no TMS')
    plot_serial(allsbias[:,RIGHT,LOW_TMS,same_i,:],sns.xkcd_rgb["greenish"],label="weak tms")
    pvalues=perm_test_nan_onesided(allsbias[:,RIGHT,LOW_TMS,same_i,:],allsbias[:,RIGHT,NO_TMS,same_i,:],
                                   n_perms=10000)/2
    plot_sigs([],"k",[],pvalues=pvalues,upper=[1.9,2])
    ylabel("")
    xlabel("")
    yticks([-2,-1,0,1,2])
    if same_i<=1:
        xticks(xticks()[0],"")
    ylim(-2,2)
    xlim(xxx2[0],150)
    if (same == 'leftleft') | (same == 'rightleft'):
        title('RIGHT,'+same+',#'+str(np.round(np.mean(numTrials_all[:,RIGHT,:,same_i]),1)),
              color=sns.xkcd_rgb["greenish"])
    else:
        title('RIGHT,'+same+',#'+str(np.round(np.mean(numTrials_all[:,RIGHT,:,same_i]),1)), color='grey')
    if same_i==0:
        fig.legend(bbox_to_anchor=(0., 1, 1., .102), loc='lower left',
               ncol=2, mode="expand", borderaxespad=0.)

plt.tight_layout()
fig.add_subplot(111, frameon=False)
plt.tick_params(labelcolor='none', top=False, bottom=False, left=False, right=False)
plt.xlabel('relative location of previous trial [°]')
plt.ylabel('current error')
```

Functions by Heike Stein from other files used in the code above

Relevant functions used above:

In [ ]:

```
def compute_seria_from_pandas(pandas,xxx,flip=None):
    return compute_serial(pandas.response.values,pandas.target.values,\
        pandas.prevcurr.values,xxx,flip)

def compute_serial(report,target,d,xxx,flip=None):
    n=0
    err=circdist(report,target)
    m_err=[]
    std_err=[]
    count=[]
    cis=[]
    uf_err = err.copy()
    if flip:
        err = np.array([sign(d[i])*err[i] if sign(d[i])!=0 else err[i] for i in range(len(err))])
        d=abs(d)
    points_idx=[]
    for i,t in enumerate(xxx):
        # wi=w[i]
        idx=abs(circdist(d,t))<w2/2
        m_err.append(circ_mean(err[idx]))
        std_err.append(circstd(err[idx], low=-np.pi, high=np.pi)/sqrt(sum(idx)))
        count.append(sum(idx))
        points_idx.append(idx)
    return [array(err),d,array(m_err),array(std_err),count,points_idx,n,uf_err]

def cross_validate(y,X,subj=None):
    if subj==None:
        y_train,y_test, X_train,X_test = ms.train_test_split(y, X, test_size=.33)
    else:
        y_train,y_test, X_train,X_test = ms.train_test_split(y, X, test_size=.33,
        stratify=subj)
    glm     = sm.OLS(y_train, X_train).fit()
    y_pred  = glm.predict(X_test)
    return np.mean(np.square(y_pred.values-y_test.values.flatten()))


def serial_bias(prevcurr, error, window, step):
    xxx = np.arange(-np.pi, np.pi, step)
    m_err=[]; std_err=[]
    for t in xxx:
        idx = abs(circdist(prevcurr,t))<window/2
        m_err.append(sps.circmean(error[idx], low=-np.pi, high=np.pi))
        std_err.append(sps.circstd(error[idx], low=-np.pi, high=np.pi)/np.sqrt(np.sum(idx)))
    return np.array(m_err), np.array(std_err)


def folded_bias(prevcurr, error, window, step):
    xxx = np.arange(-np.pi, np.pi, step)
    t_err=[]; err = []
    for t in xxx:
        idx = (prevcurr>=t-window/2) & (prevcurr<t+window/2)
        if t-window/2 < -np.pi:
            idx = (prevcurr>=t-window/2) & (prevcurr<t+window/2) | (prevcurr>np.pi-(window/2-(np.pi-np.abs(t))))
        if t+window/2 > np.pi:
            idx = (prevcurr>=t-window/2) & (prevcurr<t+window/2) | (prevcurr<-np.pi+(window/2-(np.pi-np.abs(t))))
        t_err.append(list(error[idx]))
    for t in reversed(range(int(len(xxx)/2))):
        err.append([x*-1 for x in t_err[t]]+t_err[-t-1])
    m_err   = [sps.circmean(x, low=-np.pi, high=np.pi) for x in err]
    se_err  = [sps.circstd(x, low=-np.pi, high=np.pi)/np.sqrt(len(x)) for x in err]
    return np.array(m_err), np.array(se_err)
```