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Towards New Neural Correlates of Memory from Deep and Cortex Brain Regions in Deep Brain Stimulation Patients

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Resumo

A estimulação cerebral profunda é um procedimento neurocirúrgico que envolve a implantação de elétrodos no cérebro, que o estimulam a partir de um neuroestimulador implantável. A estimulação a altas frequências dos núcleos talâmicos anteriores é utilizada como um tratamento eficaz para epilepsia refratária.

Os núcleos anteriores do tálamo (NAT) são um agrupamento de núcleos localizados na extremidade rostral do tálamo. Como se trata de um importante componente do Circuito de Papez, acredita-se que esse grupo nuclear desempenha uma importante função durante a aquisição de memórias. Alguns estudos já conseguiram identificar correlatos neurais relacionados com a codificação e recuperação de memórias nos NAT, mas o conhecimento nessa área ainda é limitado. Da mesma forma, os efeitos de estimulação profunda dos NAT ainda são desconhecidos. Verifica-se, no entanto, que lesões desse grupo nuclear podem levar a sérias perdas de memória de reconhecimento. Embora não haja resultados objetivos que apontem para a deterioração de memória durante este tipo de tratamento, há ainda uma preocupação sobre essa possibilidade.

O novo neuroestimulador da Medtronic, o Percept™ PC, dá aos investigadores a oportunidade de gravar sinais eletrofisiológicos profundos durante o tratamento de estimulação cerebral profunda. Com este tipo de tecnologia, é possível explorar não só os efeitos da estimulação cerebral profunda nos NAT, como também as respostas eletrofisiológicas desse grupo nuclear durante a codificação e recuperação de memórias.

A dissertação que se segue apresenta um protocolo experimental que visa estudar os efeitos da estimulação profunda dos NAT na memória de reconhecimento. O protocolo experimental foi prototipado utilizando sistemas de aquisição de EEG de baixo custo e testado com voluntários saudáveis. Replicaram-se os resultados reportados na literatura, pois encontram-se dois potenciais relacionados a eventos ligados à memória de reconhecimento - o FN400, associado à memória de familiaridade, e o LPC (do inglês: *late positive component*), associado à memória de recordação. Contudo, os resultados não foram estatisticamente significativos, uma vez que o número de participantes foi pequeno (um grupo de 7 voluntários).

Infelizmente, não conseguimos realizar a experiência planeada com o paciente de estimulação cerebral profunda, porque este desenvolveu uma infecção sobre o estimulador que teve de ser retirado. No entanto, fizemos uma simulação bem-sucedida da experiência na Unidade de Monitorização de Epilepsia do Centro Hospitalar Universitário de São João com um voluntário saudável. Os resultados obtidos com o hardware médico foram semelhantes aos obtidos durante as experiências realizadas fora da clínica. O protocolo experimental está pronto para ser implementado na Unidade de Monitorização de Epilepsia. Como passo seguinte, deverão ser realizados testes piloto com a população alvo.

Abstract

Deep brain stimulation is a neurosurgical procedure involving the implantation of electrodes to deliver electrical stimuli from an implanted pulse generator. High-frequency stimulation of the anterior nucleus of the thalamus has been cemented as an effective treatment for medication-resistant epilepsy.

The anterior nucleus of the thalamus (ANT) is a cluster of nuclei located in the rostral end of the thalamus. As an important component of the Papez Circuit, the ANT is thought to play an important role in memory acquisition. A few studies have already identified neural correlates of memory encoding and retrieval in the ANT, but knowledge on the topic is still limited. Likewise, the effects of ANT-DBS on human cognition are still widely unknown. However, ANT lesions have been verified to lead to severe declines in memory recognition. While no objective memory deterioration has been observed in patients undergoing this type of neurostimulation, there is a general concern over that possibility.

Medtronic's novel neurostimulator, the Percept™ PC, has provided researchers with the opportunity to chronically record deep electrophysiological signals from patients undergoing DBS treatment. With this kind of technology, it is possible to study the effects of DBS on the ANT and its electrophysiological responses during memory encoding and retrieval.

The following dissertation presents an experimental protocol aimed at studying the effects of ANT-DBS on recognition memory performance. The experimental setup was prototyped using low-cost consumer-grade EEG hardware and tested with healthy volunteers. Following a failed round of experiments, we were successful in replicating previous studies. Two well-established event-related potentials linked to successful memory retrieval were observed – the FN400, associated with familiarity-driven judgements, and the late positive component (LPC), associated with recollection-driven judgements. However, results weren't statistically significant, as the number of participants was small (a group of 7 volunteers).

We were unable to carry out the planned experiment with a patient undergoing ANT-DBS, as he suffered from a hardware-related infection, resulting in the removal of the stimulator. We did, however, implement a successful simulation of the protocol at Centro Hospitalar Universitário de São João's Epilepsy Monitoring Unit (EMU) with a healthy proband. Results obtained with the medical hardware were comparable to those obtained during the out-of-clinic experiments. The experimental protocol is ready to be implemented at the EMU. As a next step, pilot tests with the target population should be conducted.

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Abbreviations

AAC	Amplitude-amplitude coupling
AD	Anterodorsal nucleus
aDBS	Adaptive Deep Brain Stimulation
ADC	Analog-to-Digital Converter
AM	Anteromedial nucleus
ANOVA	Analysis of variance
ANT	Anterior Nuclei of the Thalamus
ATN	Anterior thalamic nuclei
AV	Anteroventral nucleus
BSS	Blind Source Separation
CFC	Cross-frequency coupling
CHUSJ	Centro Hospitalar Universitário de São João
DBS	Deep Brain Stimulation
Dm	Difference in subsequent memory
DM	Dorsomedial nucleus of the thalamus
EEG	Electroencephalography
EMU	Epilepsy Monitoring Unit
ERP	Event-related Potential
fMRI	Functional magnetic resonance imaging
GC	Granger Causality
HFS	High-frequency stimulation
IC	Independent Component
ICA	Independent component analysis
IML	Internal medullary lamina
IPG	Implanted Pulse Generator
LD	Lateral dorsal nucleus
LFP	Local field potential
LPC	Late Positive Component
MDSR	Median seizure frequency reduction
MRI	Magnetic resonance imaging
MSR	Mean seizure frequency reduction
MTT	Mammillothalamic tract
PAC	Phase-amplitude coupling
PD	Parkinson disease
PDP	Process Dissociation Procedure
PET	Positron Emission Topography
PFC	Phase-frequency coupling
PPC	Phase-phase coupling

RK	Remember-Know
ROC	Receiver-operating characteristics
SANTE	Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy
SME	Subsequent memory effects
STN	Subthalamic nucleus
vEEG	Video- electroencephalography

Chapter 1

Introduction

1.1 Context

The anterior nucleus of the thalamus (ANT) is a cluster of nuclei located in the rostral end of the thalamus. As an important component of the hippocampal-diencephalic-cingulate network [1], the ANT is thought to play an important role in memory acquisition. Several human and animal studies of focal ATN lesions have confirmed them to impair long-term memory, leading to encoding deficits akin to those induced by hippocampal lesions [2–4]. Furthermore, both electrophysiological and neuroimaging studies have observed that the ANT plays an important role in episodic memory, particularly during memory encoding [5, 6] and recollection-based memory retrieval [7–10].

Deep Brain Stimulation (DBS) is a neuromodulation treatment involving the implantation of electrodes to deliver highly focal electrical stimuli to a target subcortical structure [11, 12]. DBS has been an established therapy for many medication-refractory movement disorders, such as Parkinson disease (PD), but over the years its applications have expanded beyond the treatment of movement disorders. Among novel DBS applications, the electrical stimulation of the ANT for the treatment of medication-refractory epilepsy offers a promising future.

The results of the first and only randomized controlled clinical trial on ANT-DBS for the treatment of epilepsy have supported both its efficacy and safety [13, 14]. ANT-DBS was initially reported to be linked with memory deficits; while long-term follow-ups observed no significant deterioration in cognition scores, many are wary of its potential effects on memory performance. Just last year, an expert panel made up of ten european neurologists and four neurosurgeons agreed that history of memory deficit should be thoroughly evaluated when considering potential candidates for ANT-DBS [15]. All experts also agreed that memory and cognitive performance should be monitored on a regular basis. These worries are not entirely unfounded, but direct evidence of the effects of ANT-DBS on memory performance is scarce.

Apart from a behavioral study by [16], we found no direct evidence of the effects of electrical stimulation of the ANT in memory performance. To our knowledge, electrophysiological

studies on the topic are non-existent. However, other studies attempting to investigate the impact of electrical stimulation of deep brain structures have found a wide range of effects. For instance, direct electrical stimulation of the hippocampus has been shown to improve memory performance [17, 18], whereas others have reported it to have no effect [19] or even impair it [20, 21].

1.2 Motivation

Although DBS is a promising field whose indications are expanding steadily, one must be cautious of its associated risks and potential detrimental long-term effects. Identifying potential risks and benefits is a crunch of any medical treatment. For ANT-DBS, there is a need to further our understanding of its effects on human cognition, to assure the welfare of its patients in the future.

Assessing memory impairment is commonly done through behavioral testing (e.g. as done in [20]). However, there have also been several attempts to map memory impairment to a variety of neurophysiological correlates, namely event-related potentials (ERPs) [22]. Memory function in ANT-DBS patients, however, has only really been investigated through periodic performance assessments [23].

Medtronic’s novel Percept™ PC neurostimulator provides researchers with the long-awaited opportunity to record electrophysiological signals directly from target subcortical structures. By the end of June 2020, the novel Percept™ PC was implanted in one of the first epileptic patients in the world, at the University Hospital S. João, Portugal¹. The patient is now undergoing ANT-DBS treatment and many other patients are expected to be implanted with the novel neurostimulator in the future.

The Percept™ PC neurostimulator is a powerful tool that has the potential to revolutionize depth electroencephalography memory studies as we know them. For one, using the neurostimulator’s ability to record directly from the implanted leads rids researchers of the limitations associated with relying on externalized DBS electrodes, which include but aren’t limited to microlesion effects, patient fatigue and time restrictions. Moreover, its ability to record from deep structures while stimulating opens up the possibility to compare and contrast neural activity recorded for different stimulation parameters.

1.3 Contributions

Furthering our understanding of the effects of ANT-DBS on human cognition is necessary to evaluate the potential risks of lasting cognitive impairment. The following dissertation devised a streamlined approach to propel this line of investigation. The principal contributions of this thesis are:

¹Portugal is the first in the world to implant neurostimulator with long-term monitoring in epileptic patients. Available at: <https://www.inesctec.pt> (Accessed 20-01-2020)

1. Creating a new experimental protocol for assessing memory impairment in ANT-DBS patients with drug-resistant epilepsy undergoing video-electroencephalography (vEEG) monitoring at the Epilepsy Monitoring Unit (EMU) of Centro Hospitalar Universitário de São João (CHUSJ);
2. Assembling a low-cost consumer-grade experimental setup intended to study the neurophysiological correlates of recognition memory, including but not limited to ERPs;
3. Validating the experimental paradigm with a group of healthy probands, by replicating literature findings on the electrophysiological correlates of recognition memory.

1.4 Dissertation Outline

Besides this introduction, the remainder of this dissertation is composed of four other chapters:

- Chapter 2 provides an overview on deep brain stimulation of the anterior nucleus of the thalamus, from fundamental aspects of state-of-the-art DBS to the ANT's role in memory processing and epilepsy.
- Chapter 3 reviews commonly used methods and techniques for studying the neural mechanisms underlying human memory. This chapter provides a short review on well-established electrophysiological correlates of recognition memory, namely ERPs measured through scalp electroencephalography, and novel findings from intrathalamic recording studies. Additionally, fundamental concepts necessary for ERP analysis are also discussed.
- Chapter 4 presents all developed experimental protocols to be implemented in- and out-of-clinic, including the experimental setup and the employed memory paradigm.
- Chapter 5 reports on all experiments performed out-of-clinic, so as to validate the experimental setup and the memory paradigm.
- Chapter 6 reports on the pilot experiments conducted at the EMU.
- Chapter 7 presents the main conclusions of this work and provides suggestions on improvements to the protocol and posterior future work.

Chapter 2

ANT-DBS for Drug-Resistant Epilepsy

2.1 The Fundamentals of Deep Brain Stimulation

Deep brain stimulation is a non-lesional neuromodulation technique involving the implantation of electrodes in specific areas of the brain, to deliver constant or intermittent electrical stimuli from an implanted pulse generator (IPG) [11, 12]. While electrodes are commonly inserted bilaterally, some treatments require unilateral stimulation. The IPG is implanted on the chest or abdominal wall and the electrodes are connected to it through subcutaneous extension cables (see Fig. 2.1).

DBS provides an opportunity to directly interface with dysfunctional circuitry and allows for the external adjustment of stimulation parameters to optimize treatment performance while reducing adverse effects [11, 12]. Other advantages include its minimally invasive nature, long-term efficacy, and reversibility.

Its multiple perks over other surgical approaches for neurostimulation have cemented its status as an established therapy for many medication-refractory hypokinetic and hyperkinetic movement disorders such as Parkinson disease, essential tremor and dystonia [11, 12]. Additionally, DBS has been used for multiple other neurological diseases, including epilepsy, neuropathic pain and obsessive-compulsive disorder. DBS is currently under investigation for a wide range of other treatment-resistant conditions, such as depression, Alzheimer disease, Tourette syndrome, addiction, anorexia nervosa and schizophrenia.

2.1.1 Mechanisms of Action

While its mechanisms of action are not entirely understood, the current consensus is that DBS acts via multiple, complex mechanisms. DBS is thought to modulate local and network-wide neural activity, induce changes in synaptic plasticity, and may, additionally, have neuroprotective and neurogenic effects [24].

Initial DBS studies postulated that high-frequency stimulation inhibits local neuronal elements and reduces the output of the target nucleus, as clinical effects of DBS resembled those of neuroablation surgery [24–26]. This inhibition hypothesis was supported by experimental evidence that showed a reduction in neural activity at the stimulation site.

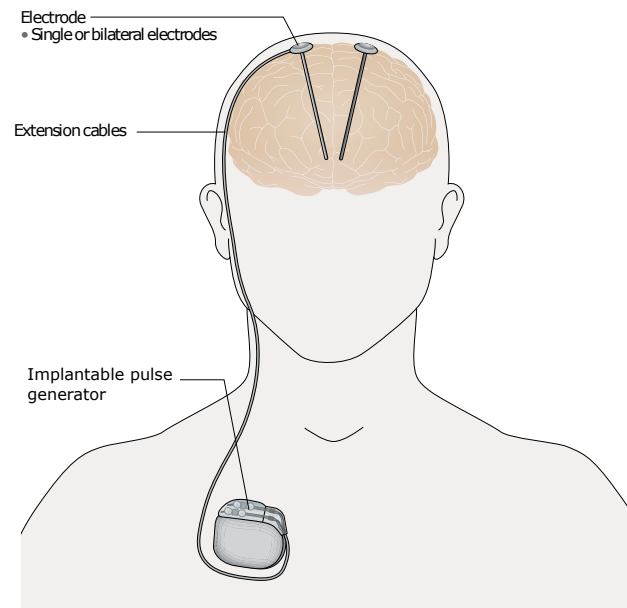


Figure 2.1: Current DBS systems include a single or a pair of electrode leads connected to an IPG through subcutaneous cables. Adapted from [11].

DBS-induced somatic inhibition near the stimulating electrode has been linked to multiple mechanisms, such as depolarization block and the activation of inhibitory afferents to the cell body [24, 26]. However, it is safe to assume that inhibition is not the lone mechanism of DBS, as previous subthalamic nucleus (STN) DBS studies have attested that only a limited population of STN neurons shows complete cessation of firings, with other STN neurons exhibiting residual neuronal activity [26].

High-frequency stimulation (HFS) has also been thought to incite the direct excitation of neural activity, by activating axons and dendrites in the targeted area [12, 24, 25]. There have been several reports of downstream neural activity being either downregulated or upregulated during HFS [25]. These studies have verified that the effects of HFS on downstream nuclei activity were linked to whether the connections from the target nucleus to the downstream nuclei were inhibitory or excitatory in nature. DBS has also been reported to affect upstream nuclei by exciting afferent axons antidromically, meaning the action potential propagates toward the soma instead of away from it [24–26].

In short, experimental evidence seems to suggest that HFS is capable of directly activating axonal and dendritic processes traversing or adjacent to the target nuclei, while inhibiting the activity of the somata.

2.1.2 Surgical and Technical Aspects

The standard DBS treatment process can be split into three steps: preoperative planning, surgical implantation and postoperative assessment [27].

During preoperative planning, magnetic resonance imaging (MRI) of the patient's brain is merged with a brain atlas, to obtain precise stereotactic coordinates for the target region and rule out potential conditions that may jeopardize the implantation [27, 28].

DBS implantation involves two surgical procedures: during the first surgery, the electrodes are implanted into the brain; the impulse generator is implanted during a second procedure. [28, 29]. Using rigid frames attached to the patient's skull, burr holes are drilled at the planned entry points [27, 28]. DBS electrodes are inserted once the optimal target is identified. The electrode's position is verified by postoperative MRI, computed tomography scanning, or, if available, intra-operative fluoroscopy [27, 28]. As mentioned earlier, the patient undergoes a second surgery for the subcutaneous implantation of the IPG, usually below the clavicle. The second procedure is performed immediately after the first surgery or on a separate occasion [28]. Lead extenders are tunneled down the patient's neck and connected to the pulse generator [27].

The implantation of the leads alone has been reported to trigger immediate clinical improvements in patients, due to a phenomenon known as the "microlesion effect" [27–29]. For that reason, postoperative assessments performed shortly after DBS surgery should be done with care. Approximately two to four weeks after DBS surgery, patients are submitted to a programming session to fine-tune stimulation parameters. This session repeats itself at subsequent follow-ups [30]. Programmable variables include electrode polarity, frequency, amplitude and pulse width [29]. Optimal DBS settings depend on the individual characteristics of the patient, the disease being treated, the targeted symptoms, and the neuroanatomical target chosen for stimulation [12]. The main objective of stimulation parameter adjustment is to maximize the beneficial effects of therapy, avoid the occurrence of adverse effects and minimize energy costs to improve the longevity of the IPG.

The effectiveness of DBS treatment is highly dependent on the optimization of the stimulation parameters. This complex programming process requires multiple programming sessions, rigorous monitoring and can take clinicians up to 6 months to obtain optimal results [30]. In epilepsy, for example, parameters are optimized according to patient feedback and seizure frequency [27], which can be cumbersome to monitor.

2.1.3 Adaptive DBS

Advancements in DBS have been primarily geared towards enhancing therapy efficacy and reducing adverse effects. Anticipated innovations in the field of deep brain stimulation include electrode and IPG improvements, optimized programming, and better stimulation paradigms [11].

The current conventional DBS paradigms are slowly being replaced by adaptive models. Adaptive DBS (aDBS) covers responsive and closed-loop control paradigms, in which a biomarker, such as the patient's neuronal activity, is recorded, decoded and used to identify pathological states and adapt the stimulation strategy accordingly [31, 32].

The main goal of aDBS is to only provide the necessary stimulation parameters whenever the patient's state demands it. Just by simply limiting the delivery of stimulation, these paradigms have been shown to prolong IPG battery life [33, 34]. Furthermore, closed-loop DBS implementations

in PD patients have not only mitigated DBS-induced side effects, but have also yielded increased therapeutic benefits [33, 35, 36].

Biomarkers used for aDBS should be highly correlated with the patient's clinical state. Many physiological signals have been proposed for closing the feedback loop, the most prevalent choice being Local Field Potentials (LFP), recordings of neural activity from deep brain structures [32]. Until now, most of the human studies on aDBS using LFPs have been related to PD [34, 37] and tremor [38]. However, Pizarro et al. [39, 40] suggest that LFPs recorded from the ANT may be used for effective closed-loop control for the treatment of epilepsy in the future.

2.1.4 Percept™ PC

Medtronic's novel neurostimulator, was launched in the European Union in early 2020¹ and approved by the FDA later the same year². The Percept™ PC is the first and only clinically approved DBS system capable of chronically recording signals from deep brain structures while delivering stimulation, thanks to its BrainSense™ technology. Its predecessor, the Activa® PC+S system, while also capable simultaneously sensing and stimulating, was only available for investigational use to a select few. BrainSense™ allows clinicians to monitor the subcortical neural activity of their patients in real time and associate it with symptoms, treatment response, and disease progression.

Until now, most of the LFP recording studies in literature have been performed soon after DBS surgery through externalized DBS electrodes prior to IPG implantation [41]. Only a small number of studies have used the Activa® PC+S for the study of changes in neural activity in parkinsonian patients [42, 43].

The creation BrainSense™ technology has granted researchers greater access to LFP recordings of deep brain structures. This technology has the potential to streamline the identification of biomarkers that correlate to symptoms or predict therapy effectiveness. Furthermore, studying LFPs recorded during stimulation may provide valuable insights into the mechanisms of DBS and its effects on deep brain structures. For these reasons, the Percept™ PC has been designated the precursor of aDBS.

Time domain data measured by the neurostimulator is always sampled at 250 Hz, unless otherwise specified. The Percept™ PC possesses four sensing features, whose characteristics have also been summarized in Table 2.1.

- *BrainSense™ Survey* – provides a broad spatial overview of LFP signals from both cerebral hemispheres while stimulation is off. The survey is done in two passes with 6 electrode channels recorded concurrently. The first pass records stimulation compatible pairs, while the second pass uses adjacent contact pairs.

¹Medtronic Receives CE Mark Approval for the Percept™ PC Neurostimulator DBS System with BrainSense™ Technology. Available at: <https://news.medtronic.com> (Accessed on 20-12-2020)

²FDA Approves “New Era” DBS Device. Available at: <https://news.medtronic.com/fda-approval-percept> (Accessed on 20-12-2020)

Table 2.1: Type of LFP data recorded for each BrainSense™ feature. Adapted from (UC202013068EE©MEDTRONIC2020).

Features	BrainSense™					
	Survey			Timeline	Events	Streaming
	<i>LfpMTD</i>	<i>LfpM</i>	<i>IS</i>			
Domain	Time	Frequency	Time	Power	Frequency	Time
Time length	20 s	20 s	15 min	Indefinite	30 s	15 min
Channels	12	12	6	2	2	2
Stimulation	OFF	OFF	OFF	ON/OFF	ON/OFF	ON/OFF
Use	In-clinic	In-clinic	In-clinic	In and out-clinic	In-clinic	In-clinic

Headers: LfpMTD - LfpMontageTimeDomain, LfpM - LfpMontage, IS - Indefinite Streaming

- *BrainSense™ Timeline* – records LFP power data in the selected frequency band. The neurostimulator measures raw time domain data, converts it to the frequency domain and calculates the power of a 5 Hz wide frequency band specified by the clinician.
- *BrainSense™ Events* – also referred to as LFP Snapshots, these are recorded when the patient records an event. When triggered, the neurostimulation measures 30 seconds of LFP time domain data and converts it to the frequency domain. Time domain data of the snapshot is not stored.
- *Brainsense™ Streaming* – real-time LFP power recordings in a selected frequency band. Streaming can be used to collect time domain recordings from the selected channels for offline analysis.

2.2 The Anterior Nucleus of the Thalamus

While several other anatomical targets have been identified for neuromodulation of medication-refractory epilepsy, the ANT's size, extensive cortical and subcortical connections, and distance from blood vessels make it a preferred target [27].

2.2.1 Anatomical Considerations

The dorsal thalamus, usually simply referred to as the thalamus, is an ovoid portion of the diencephalon, approximately positioned in the center of the brain above the brainstem [44]. It is composed of two symmetrical gray matter masses, which are connected through the interthalamic adhesion. It is a target structure of the basal ganglia, receives and processes sensory and motor inputs from the brain stem and cerebellum, and has reciprocal connections, via thalamic radiations, with the cerebral cortex [44,45]. As a result, it is often considered to function as the primary gateway to the cerebral cortex.

As can be seen in Fig. 2.2, the thalamus is comprised of multiple nuclei, clusters of densely packed neurons which perform a common function [44]. It is laterally enveloped by a layer of white matter known as the external medullary lamina, which separates it from a layer of cells that make up the reticular nucleus [44, 45]. The internal medullary lamina (IML), another bundle of white matter, divides the thalamus into four nuclear masses: anterior, medial, lateral, and intralaminar.

The anterior thalamic nuclei (ATN), located in the most rostral part of the thalamus, encompass the anterodorsal (AD), the anteroventral (AV), and the anteromedial (AM) nuclei [44, 45] within the IML and the lateral dorsal nucleus (LD) [47]. Despite being separated from the remaining nuclei, the LD is considered to be a part of the ATN, as it shares many of its limbic connections, and has similar electrophysiological properties [47].

Each of the four nuclei has different anatomical connections and is thought to fulfill distinct functional roles. Neurons in the AV, for example, possess widespread direct hippocampal projections and show high coherence with theta oscillations of the hippocampus [2, 23]. In addition to its possible role in memory consolidation [48], the AD's involvement in spatial navigation has been extensively characterized in rodents [1, 48, 49]. The AM is assumed to engage in executive and emotional processing, given its connections with the orbitofrontal region [47].

In animal studies, the ANT is frequently subdivided into its smaller nuclei. For that reason, it is frequently referred to as multiple nuclei [23]. This division is rarely made in human studies, as

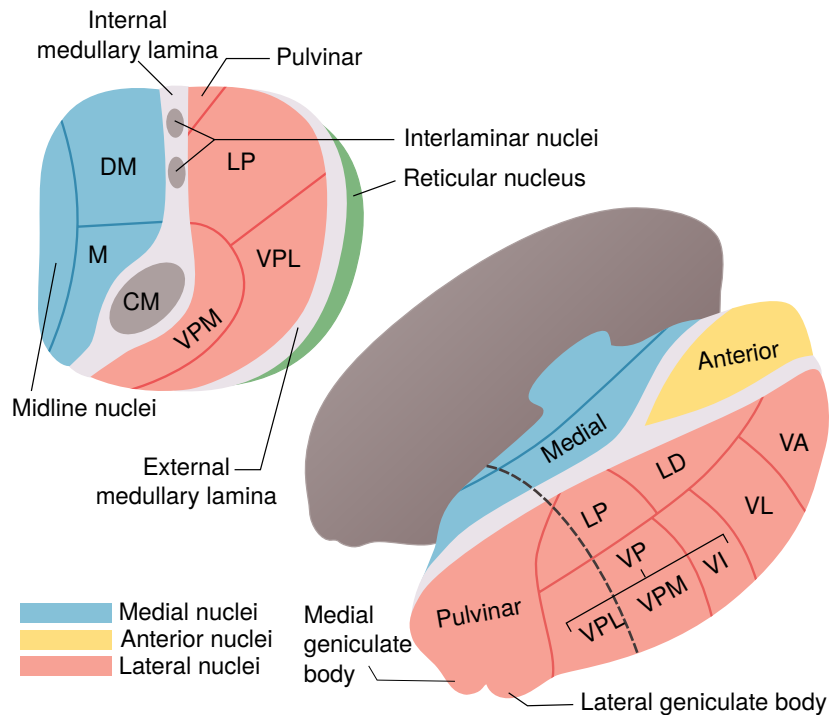


Figure 2.2: Anatomical representation of the thalamus and its nuclei. The schematic to the right includes one of the paired portions of the thalamus, with the reticular nucleus and external medullary lamina removed. The schematic to the left corresponds to a section of the thalamus at the level of the dashed line seen on the schematic to the right. Adapted from [46].

current readily available neuroimaging techniques lack the necessary spatial resolution to perform its subdivision accurately. Therefore, the ANT is often referred to as a singular nucleus in human literature. In this work, the anterior nuclear group is referred to as ANT, for the sake of simplicity.

2.2.2 The ANT's involvement in the hippocampal-diencephalic-cingulate network

Commonly referred to as the Papez circuit, the hippocampal-diencephalic-cingulate network is an important circuit within the limbic system crucial for hippocampal-based memory processes [1, 49]. This circuit was initially thought to be linked to emotional processing [50], but later research found that not to be the case [1]. The ANT, a key component of this pathway, is thought to play a critical role in episodic memory processing [51–53]. Its main components and connections are represented in Fig. 2.3.

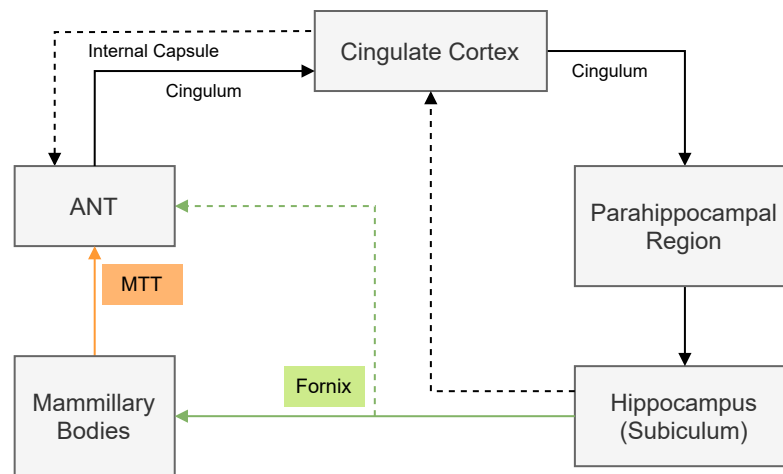


Figure 2.3: Schematic representation of the major connections of the hippocampal-diencephalic-cingulate network. Connections described by the classical Papez circuit are represented with solid lines, updated connections are represented with dashed lines. Adapted from [49].

The hippocampal-diencephalic-cingulate network begins with the hippocampal formation's extensive connections to the fornix, which in turn projects to the mammillary bodies [44, 51, 52]. Additionally, the fornix provides a direct pathway from the hippocampus to the ANT [51, 52]. The mammillary bodies project to the ANT as well, via the mammillothalamic tract (MTT). The ANT possesses efferent thalamic radiations that target the cingulate cortex. Through the cingulum bundle, the cingulate cortex projects back to the parahippocampal region [44]. The circuit is completed with a subsequent projection to the hippocampus [44, 51, 52].

2.2.3 The Role of the ANT in Memory Processing

The thalamus is known to be intricately involved in memory processing, yet how its nuclei contribute to the different underlying memory processes it participates in is unclear. Lesions of the

ANT, the mammillary bodies and the MTT have been consistently correlated to diencephalic amnesia [2,4,54]. These studies have contributed to the notion that the connections between the ANT and hippocampus heavily support episodic memory.

Studies in laboratory animals show that anterior thalamic lesions lead to severe declines in memory performance. These deficits have been observed in paradigms of delayed non-matching-to-position, associative memory, and allocentric spatial memory tasks [4,55]. A frequently cited primate study by Parker and Gaffan [56], showed a drastic drop in performance during an object-in-place recognition memory paradigm following ANT lesioning. In rats these lesions had no apparent effect on single item recognition memory, but impaired object-place associative recognition [57].

Evidence of the ANT's presumed role in human recognition memory comes from neuropathological and neuroimaging studies. Neuropathological literature on Korsakoff's syndrome [3], a common form of diencephalic amnesia, and intrathalamic vascular infarcts has linked anterior thalamic lesions to recollection deficits [58]. Patients with damages of the MTT and ANT have demonstrated recognition deficits characterized by impaired recollection and intact familiarity [54,57,58]. Previous neuroimaging studies have found that, during information retrieval, the ANT shows greater responses during recollection [8–10]. In their recent functional MRI study, Kafkas et al. [9] observed that the ANT's support of recollection was material-general, meaning it did not depend on the content of the visual stimulus.

2.2.4 The Role of the ANT in Epilepsy

The putative role of the ANT in epilepsy was first established following several animal studies. In rhesus monkeys, ipsilateral ANT lesions led to a significant decrease in both seizure frequency and duration [59]. Further investigation showed bilateral HFS of the ANT and mammillary bodies in rats increased the dose threshold for pharmacologically induced motor seizures, implicating the involvement of the Papez circuit in seizure propagation [60,61].

Evidence supporting the involvement of the thalamus during epileptic seizures started accumulating with the advancement of neuroimaging techniques in the early 21st century. Multiple clinical studies using functional magnetic resonance imaging (fMRI) [62,63] and Positron Emission Topography (PET) [64,65] have confirmed the involvement of the thalamus during seizures.

The ANT, in particular, has been implicated in the initiation and propagation of mesial temporal lobe seizures [66]. Moreover, a recent intrathalamic recording study has proven that ANT activity can be used to detect the onset of mesial temporal epileptic seizures [39,40], further reinforcing the ANT's involvement in seizure propagation.

2.3 Clinical Studies on ANT-DBS

Deep Brain Stimulation of the anterior nucleus of the thalamus is an alternative treatment option for drug-resistant intractable epilepsy [12,27]. By the end of the 20th century, several preclinical studies had already postulated about the anticonvulsant effects of HFS of the ANT. In Mirski

et al. [61], the authors suggest that the focal stimulation of the ANT may be a viable treatment for intractable seizures in humans. Subsequent animal studies have also supported this notion. In 2004, Hamani et al. [67] confirmed that bilateral anterior thalamic stimulation produced significant protection against pharmacologically induced status epilepticus in rats.

These promising results led to multiple small-scale noncontrolled studies in human epileptic patients and one large-scale randomized controlled clinical trial (see Table 2.2).

Table 2.2: Clinical studies of ANT-DBS for the treatment of Epilepsy. Adapted from [27, 68, 69].

Study	Year	N	Stimulation parameters	FU (months)	Primary outcomes
[70]	1987	6	60–70 Hz, 3.5–3.8 V, 300 μ s	42	4/6 RR
[71]	2002	5	100 Hz, 10 V, 90 μ s, 1 min on/5 min off, alternating left and right sides	12–21	54% (24–89%) MSR 5/6 RR
[72]	2004	5	100 Hz, 1–10 V, 90 μ s, 1 min on/10 min off, 5 min offset*	6–36	48% (57–98%) MSR
[73]	2006	3	130 Hz, 1.5–7 V 90 μ s, 1 min on/5 min off, alternating left and right sides	2–30	75.4% (50–90.6%) MSR 3/3 RR
[74]	2007	4	175 Hz, 4.1 V, 90 μ s, 1 min on/5 min off	36	75.6% (53–92%) MSR 4/4 RR
[75]	2007	4	90–110 Hz, 4–5 V, 60–90 μ s, continuous	33–48	49% (35–76%) MSR 1/4 RR
[13] (SANTE)	2010	110	145 Hz, 5 V, 90 μ s, 1 min on/5 min off	3 blind 24 total	40% (on) vs 15% (off) MDSR 56% MDSR, 54% RR 70.5% (0–100%) MSR 13/15 RR
[76]	2012	15	100–185 Hz, 1.5–3.1 V, 90–150 μ s, continuous	24–67	7/9 RR
[16]	2012	9	100–185 Hz, 1.5–3.1 V, 90–150 μ s, continuous	>12	7/9 RR
[14] (SANTE)	2015	83	145 Hz, 5 V, 90 μ s, 1 min on/5 min off	60	69% MSR 68% RR
[77]	2015	2	4–8 Hz, 3.5–4 V, 90 μ s, 0.4 s on/0.1 s off	3	53% SR, 80% SR 2/2 RR
[78]	2015	6	140 Hz, 4 V, 90 μ s, 1 min on/4 min off	>36	3/5 RR
[79]	2015	9	145 Hz, 5 V, 90 μ s, 1 min on/5 min off	28	7/9 RR
[80]	2016	16	>100 Hz, 2.4–7 V, 90 μ s	52	65 % MSR at 3 years 11/16 RR
[81]	2016	2	145 Hz, 5 V, 90 μ s	18, 12	61% SR, 75% SR 2/2 RR
[82]	2016	15	140 Hz, 5 V, 90 μ s, 1 min on/5 min off	25	10/15 RR
[83]	2018	1	140 Hz, 5–7 V, 90 μ s, 1 min on/5 min off	40	87% MSR
[84]	2018	16	140 Hz, 5 V, 90 μ s, 1 min on/5 min off	24	12/16 RR

Headers: N - Number of Subjects; FU - Follow-up

Outcomes: RR - Responders Rate (Seizure reduction $\geq 50\%$); SR - Seizure Frequency Reduction; MSR - Mean Seizure Frequency Reduction; MDSR - Median Seizure Frequency Reduction.

* Stimulation on one side was offset by 5 min from stimulation on the opposite side.

2.3.1 SANTE Trial

Published in 2010, the SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) study was a multicenter, double-blind, randomized controlled clinical trial for the investigation of ANT-DBS for the treatment of medication-resistant localization-related epilepsy [13]. One hundred and ten patients with medication-refractory epilepsy, received bilateral DBS of the ANT. One month after implantation, participants entered a 3-month blinded phase and were randomly assigned to stimulation ($n=54$, 145 Hz, 5 V, 90 μ s, 1 min on/5 min off) or no stimulation ($n=55$, 0 V) regimens. Following the blinded phase, all participants received stimulation for 9 months. After 13 months, participants entered a long-term follow-up in which stimulation parameters and concomitant medication could be adjusted freely. Five years later, Salanova et al. [14] published the results of the long-term follow-up study.

At the end of the blinded phase, the stimulation group saw a greater decrease of seizure frequency compared to controls [13]. After 25 months of follow-up, the trial reported significant improvements in seizure frequency, with a median seizure frequency reduction (MDSR) of 56%. Out of the eighty one (74%) patients that completed the follow-up period, 54% achieved a 50% or greater reduction in seizure frequency. Six patients were seizure-free for a 3-month segment following the 2 years of stimulation. The mean seizure reduction (MSR) improved gradually, reaching a 69% reduction at 5 years [14]. The 50% responder rates improved to 68%, with 11 participants reporting complete seizure freedom for at least 6 months. ANT-DBS treatment efficacy in epilepsy was shown to vary with the region of seizure origin, with temporal onset epilepsies being more responsive [13, 14].

2.3.2 Noncontrolled Studies

The first uncontrolled, open-label clinical studies on ANT-DBS involved a small number of patients, and distinct stimulation parameters. Despite the significant differences between them, all studies showed clinical benefits with minimal adverse events (MSR 24-92%). Multiple authors discussed the occurrence of a microlesion effect, similar to the experience of DBS in movement disorders, with immediate seizure reduction (SR) with the insertion of the electrodes alone. Kerrigan et al. [72] reported that in 4 patients, cessation of stimulation led to an immediate increase in seizure frequency and intensity, which was reversed when stimulation was resumed, supporting its anti-ictal effects.

Several other open-label case studies reported on the efficacy and safety of ANT-DBS following the publication of the SANTE trial. In concordance with the SANTE trial, most studies report MSR above 50%. Krishna et al. [80] reported on three patterns of seizure control: (1) sustained benefit without stimulation initiation, dubbed the prolonged insertional effect; (2) immediate and sustained benefit following stimulation; and (3) delayed stimulation benefit. Nine patients reported the occurrence of an insertional effect, whose duration ranged from 2 to 4 months. One patient experienced a prolonged insertional effect that lasted 36 months. Among 5 nonresponders, 1 patient reported an increase of 200% in seizure frequency. Nora et al. [83] reports the similar case of

a patient who responded to ANT-DBS therapy with the occurrence of atypical seizures and novel visual symptoms. Lowering the stimulation voltage alleviated these symptoms and subsequent stimulation yielded a favorable long-term response.

2.3.2.1 Side Effects

Side effects and complications of ANT-DBS are close to those observed for other indications, such as STN-DBS for the treatment of PD [69]. Safety data for ANT-DBS is not as extensively documented due to limited patient data [27].

Over the 5-year follow-up of the SANTE study, the most frequent adverse effects following implantation were paresthesias at the implant site (22.7%), implant site pain (20.9%), and implant site infection (12.7%) [14]. Discomfort (9.1%), product inefficiency (8.2%), lead malposition (8.2%), and sensory disturbances (8.2%) were also commonly reported [14].

Small open-label studies have also reported varied other side effects. Lee et al. [76] observed that patients experienced unforeseen side effects, including altered sexual libido, altered seizure type, altered context for seizures and the ability to predict the onset of upcoming seizures. Voges et al. [79] noted that high voltage nocturnal stimulation induced sleep arousal and disturbed sleep. Nocturnal DBS voltage reduction decreased stimulation-induced sleep arousals and improved neuropsychiatric symptoms in some patients, without compromising therapy benefits.

2.4 Effects of ANT-DBS in cognition

Little is currently known about the neuropsychological side effects of ANT-DBS. Most of the data on the cognitive effects of ANT-DBS pertain to animal studies or human studies on the treatment of medication-refractory epilepsy.

Some animal studies observed enhancement effects on hippocampal neurogenesis following anterior thalamic HFS [85, 86]. Hamani et al. [87] verified that high current (500 μ A) ANT stimulation impaired spatial memory in rats and disrupted memory acquisition. In vivo electrophysiological recordings revealed a reduced firing rate of gyrus dentate cells following high current stimulation, leading the authors to believe that ANT DBS may influence the activity of the hippocampal formation. However, it should be mentioned that according to the authors, ANT stimulation at 100 μ A, which generates an approximate charge density to the one used in humans, did not yield any negative effects. Heschem et al. [88] too detected no changes in performance following ANT-DBS in experimental rat models of dementia.

At the end of SANTE's blinded phase, a significantly greater number of patients in the stimulated group reported adverse effects relating to depression (14.8%) and memory impairment (13%) compared to control (1.8%, 1.8%) [13]. However, neuropsychological test scores for mood and cognition did not differ between them. The 5-year and extended 7-year long-term follow-ups revealed no significant deterioration in cognition or depression scores [14, 89].

Interestingly enough, a small study reported on positive side effects of ANT stimulation. Oh et al. [16] investigated the cognitive outcomes of ANT-DBS following at least 12 months of stimulation. During this study, nine patients who were enrolled for bilateral ANT-DBS implantation underwent preoperative and postoperative cognitive and behavioral assessments. Therapy was associated with improvements in both word fluency and delayed verbal memory. There were no significant changes in general abilities, information processing or executive function.

Hartikainen et al. [90] and Sun et al. [91] investigated the effects of ANT-DBS in emotional control by subjecting twelve patients undergoing ANT-DBS treatment to a reaction time test. The study found immediate effects of ANT-DBS on emotion-attention interaction, as patients subjected to stimulation experienced prolonged reaction times due to threat-related emotional distractors (Wilcoxon signed rank test; $Z=-2.2014$, $p=0.03$). Additionally, an ERP analysis on six of the patients revealed a statistically significant increase in centro-parietal N2-P3 peak-to-peak amplitude (Wilcoxon signed rank test; $Z=-2.2014$, $p=0.03$) for emotional distractors compared to neural distractors during stimulation, indicating an increased attention allocation to threat.

Chapter 3

Studying the Neural Correlates of Memory

3.1 Neuronal Activity

When studying neuronal activity, one must consider its behavior in the time domain or in the time-frequency domain. Depending on the chosen approach one can identify distinct neuronal responses such as induced or on-going oscillations and event-related potentials [92].

3.1.1 Neuronal Oscillations

Neural oscillations are transient, rhythmic fluctuations in electrical brain activity observed in a variety of temporal and spatial scales [93]. Neural oscillations are visible in recordings from both cortical and deep structures and reflect the activity of a wide range of neural population sizes, depending on the recording method [94].

Oscillatory rhythms have been categorized into canonical frequency bands, including delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (15-30 Hz) and gamma (>30 Hz) [92, 94]. Each band can be partitioned into finer subdivisions, such as the low (30-80 Hz) and high (80 -200 Hz) gamma sub-bands [94]. Each of these frequency bands have been associated with distinct sensory, motor and cognitive processes, but many of their precise functions remain uncertain [94, 95].

Neural oscillations are hypothesized to play an active role in neural communication and synchronization. Not only that, but low frequency oscillations, such as theta rhythms, are thought to modulate neural activity over large spatial regions, while high frequency oscillations, such as gamma rhythms, modulate the activity of nearby neural populations [94].

3.1.1.1 Cross-Frequency Coupling

Neural computation and communication is hypothesized to occur via a phenomenon known as cross-frequency coupling (CFC), in which multiple neural oscillations in different frequency bands interact with one another [94, 96]. There are three properties that can be used to characterize any

oscillation: amplitude, frequency, and phase. Accordingly, the four principal types of CFC are phase-frequency coupling (PFC), phase-phase coupling (PPC), phase-amplitude coupling (PAC), and amplitude-amplitude coupling (AAC) [96–98].

CFC has been observed over the human brain between various frequency bands, for multiple task conditions, but has primarily been investigated in memory studies [99]. The strength of PAC, in particular, is proven to be entrained by sensory, motor and cognitive events [94].

Multiple studies have contributed to the notion that CFC phenomena are behind the transient coupling of cortical and subcortical activity [94, 98]. For instance, amplitude modulations in gamma oscillations have been found to be robustly coupled with the phase of theta oscillations during multiple behavioral tasks. This type of CFC has been observed over the neocortex during word recognition [100]), between frontal and parietal regions during successful long-term memory encoding [101]) and in the hippocampus during working memory maintenance of multiple items [102]). Studies have also recently discovered the occurrence of CFC between frontal and thalamic oscillations during memory encoding tasks [5, 103]).

3.1.2 Event-Related Potentials

Event-related potentials are small voltage variations in electrical brain activity elicited by specific events or stimuli. ERPs are generated in response to a variety of sensory, motor, or cognitive events and are time locked to the stimulus [104, 105]. In turn, ERP components consist of voltage peaks and deflections that can be categorized by their latency, morphology, and topography.

ERP components are commonly referred to using acronyms comprised of a letter (N or P), representing polarity, followed by a number, indicative of the component's latency or ordinal position in the waveform [104]. For example, the N100 (or N1) is a negative deflection in voltage that often occurs 100 milliseconds following stimulus onset. In contrast, the P300 is a positive peak, that occurs approximately 300 milliseconds after the stimulus, anywhere between 250 and 700 milliseconds (see Fig. 3.1). ERP component latencies are therefore variable.

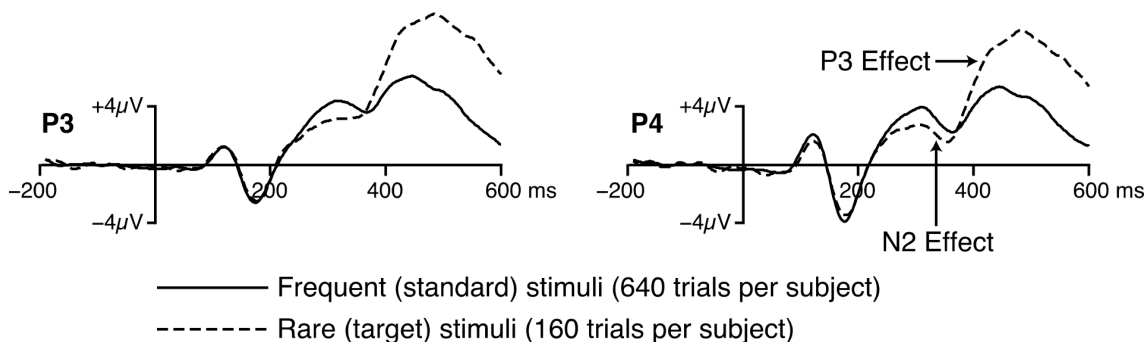


Figure 3.1: Example of grand averaged ERPs recorded from two parietal electrodes. The data are from a subset of 12 participants who participated in an oddball task. The oddball paradigm involves the presentation of frequently repeated stimuli, which is unexpectedly interrupted by deviant stimuli, triggering an event-locked response. Adapted from [106].

ERPs elicited by memory retrieval have been identified in parietal and frontal regions of the cortex [107]. Recent intrathalamic recording memory studies have identified ERP-like activity in the thalamus as well [6, 7, 108].

3.1.3 Recording Neurophysiological Signals

3.1.3.1 Electroencephalography

Electroencephalography (EEG) is the recording of electrical brain activity via specialized electrodes [104, 109]. One may classify EEG as invasive (intracranial EEG) or non-invasive. For the sake of simplicity, in this document we will strictly refer to EEG as the non-invasive recording of signals from the scalp.

The International 10-20 System is a group of standard positions in which electrodes are placed along the scalp relative to anatomical landmarks on the skull [104], as shown in Fig. 3.2. Each electrode location is labeled with a letter, indicative of the cortical area in which it is located, and a number, whose parity depends on what hemisphere is it placed over. This standard electrode positioning system was created in order to ensure EEG studies were comparable and reproducible.

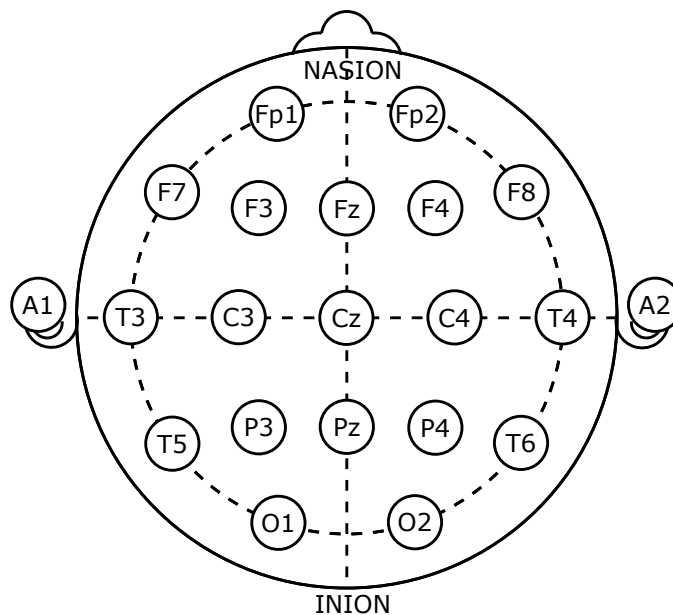


Figure 3.2: Scalp electrode locations for the international 10-20 system. (Adapted from [104])

EEG recordings are widely used in cognitive neuroscience research, given their great temporal resolution. Furthermore, this approach is safe, easy to use by researchers and relatively inexpensive [104]. However, EEG recordings are prone to signal artifacts, such as external electromagnetic noise and physiological noise induced by cardiac signals, muscular contractions, or ocular movements. EEG recordings may also vary greatly throughout and between sessions due to impedance issues, such as changes in skin potentials [110].

3.1.3.2 Local Field Potentials

A LFP can be defined as a voltage deflection reflecting the collective activity of large neuronal populations. LFPs are recorded by small-sized electrodes that penetrate the cortex. While EEG mainly records activity from superficial cortical layers, LFP recordings, also known as depth EEG, can sample electrical events directly from deeper brain structures [109].

LFP signals are robust, stable over time, and have an exceptionally high signal-to-noise ratio compared to other signal modalities used in neuroscientific research [111]. Invasive recordings are also suitable for measuring higher-frequencies such as the high gamma-band (>70 Hz), which are usually greatly attenuated by the skull [110]. Nevertheless, LFP signals can still be contaminated by artifacts, namely DBS induced artifacts [112].

As was mentioned previously, until recently, many LFP recording studies were performed through externalized DBS electrodes preceding the implantation of the impulse generator, given the ethical implications of invasive intracranial recording [113]. The novel Percept™ PC is capable of chronically recording LFPs from target deep brain nuclei, allowing researchers to conduct longer, higher complexity studies.

3.2 Experimental Paradigm Selection

Memory tasks for long-term memory studies have been used in a variety of research modalities, from brain imaging works to EEG recording studies. Most paradigms follow a basic outline with participants being asked to attend to a variety of stimuli and recall them once a given amount of time has passed. Having a proper understanding of the cognitive processes underlying memory formation and retrieval is essential for designing a suitable experimental protocol.

3.2.1 Human Memory

Memory refers to the ability to encode and store information within the brain and retrieve it later, if necessary. There are two broad types of memory: long-term and short-term (working) memory. While short-term memory saves information for a few seconds, long-term memory saves information for a theoretically unlimited amount of time [51, 104]. Long-term memory is split into declarative (explicit) and nondeclarative (implicit) memory [51, 114]. Declarative memory is characterized by the conscious retrieval of encoded information and encompasses both semantic and episodic memory. Episodic memory refers to the conscious memory of past personal events and experiences at a given context, time and location [54, 114, 115].

Memory formation involves three fundamental sequential processes: 1) encoding, which converts perceived information into a construct that can be stored; 2) retention, which stores the encoded information; and 3) retrieval, which allows the stored information to become accessible again [104]. It is generally accepted that memory retrieval can be triggered by one the following memory processes: the identification of previously encountered occurrences when later

re-exposed to them (recognition), and the independent retrieval of previously encountered occurrences (recall) [55, 116].

The relationship between episodic memory and recognition is still under debate, as two types of memory are believed to contribute to recognition performance [116]. According to dual-process theories, recognition hinges on a form of cued recall, known as recollection, and on a second process known as familiarity [116, 117]. Recollection entails recalling details associated with a previous encounter with the stimulus that cannot be inferred from the current encounter alone; in turn, a sense of familiarity involves knowing that a stimulus was previously encountered without recalling any contextual information.

3.2.2 Episodic Memory Tasks

Memory studies that investigate episodic memory examine the activity recorded during the initial perception and memorization of an event, during information retrieval from memory after a considerable amount of time has passed or both [118]. They rely on specialized cognitive tests, in which participants attend to a series of stimuli and are then tested on their memory of it. To decorrelate evoked activity across stimulus presentation, interstimulus intervals are often jittered randomly. Memory tasks are commonly divided into three parts, including an encoding (or study), a distraction, and a retrieval phase. The distraction phase that follows encoding ensures that retrieval is based on long-term memory alone. Although not compulsory, the participant may be given an unrelated task to avoid rehearsal.

3.2.2.1 Memory Encoding

During memory encoding, a group of stimuli, be it visual or auditory, is sequentially presented to the participant. The latter may be instructed to solely memorize the presented stimuli, or to perform an incidental encoding task associated with it [118]. Several studies, such as [22, 103, 119–122], have devised memory tasks where unrelated items are presented sequentially and the participant is instructed to judge whether it is “pleasant” or “unpleasant”. According to the authors, rating each item encourages the participant to reflect on its meaning or appearance, deepening encoding. While other variations of this task exist, they usually require the participant to make binary decisions pertaining to the stimuli. For example, during the procedure used by Sweeney-Reed et al. [5] photographic scenes were sequentially shown to the participant, who was prompted to make a judgement on whether the presented stimuli depicted an indoors or outdoors setting.

3.2.2.2 Memory Retrieval

In experimental episodic memory tasks, the retrieval phase tests whether the stimuli presented during encoding were memorized successfully. Memory retrieval tests can involve the recognition or recall of previously studied items, depending on whether participants are provided with complete or partial reminders of a specific stimuli, or no reminders whatsoever [116, 123]. Cued recall

paradigms provide users with specific partial cues for items, while free recall paradigms involve no specific cueing. Recognition paradigms present the stimulus in its entirety.

The standard "Old/New" recognition paradigm, is the simplest and most commonly used single-item recognition test, in which items that are presented during the encoding phase, are later presented in a new random order, interspersed with novel items (for examples, see [7, 103, 108]). Participants are tasked with judging whether stimuli were previously encountered during the memory encoding task ("old") or not ("new"). A limitation of the standard "Old/New" recognition tests is that individual judgements cannot be exclusively linked to recollection [5, 118]. Indeed, during single-item recognition tasks both familiarity and recollection processes contribute for successful memory retrieval [57].

3.2.2.3 Estimating Recognition Memory Performance

A participant's performance in a "Old/New" memory test can be assessed using two measures: the proportion of correctly recognized old items, the hit rate, and the proportion of incorrectly recognized new items, the false alarm rate [124]. Researchers have since adopted the use of signal detection theory to derive two indices of recognition, which can be used to characterize memory performance, by combining these two measures.

According to the classic signal detection model for recognition memory, a participant's ability to discriminate between old and new items is estimated by the discriminability index (d'), also known as d -prime [124, 125]. The d' is given by

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate}) \quad (3.1)$$

, where $Z(x)$ is the inverse-normal transform function. The d' is undefined for hit or false alarm rates equal to 1 or 0, as the inverse-normal transform approaches infinity for these values [124, 125]. The log-linear rule, proposed by [124], is a commonly used transformation that bypasses this limitation by adding 0.5 to the hit and false alarm frequencies and increasing the total number of old or new items by 1.

The second measure derived from signal detection theory is the response bias (C) [124, 125]. A conservative bias will produce positive C values, whereas a liberal bias will produce negative C values. The response bias is given by the following equation:

$$C = -\frac{1}{2} \left(Z(\text{hit rate}) - Z(\text{false alarm rate}) \right) \quad (3.2)$$

3.2.3 Recollection vs. familiarity

Several authors believe that the memory processes that recollection and familiarity are supported by separate regions of the cortex [54, 55, 117]. The hippocampus is thought to support recollection-driven recollection, whereas the perirhinal cortex is thought to support familiarity-driven recognition. However, distinguishing the contributions of recollection and familiarity during recognition

memory tasks is not straightforward [57, 118]. Neglecting to do so can lead to inaccurate conclusions about the type of brain activity produced during information retrieval.

3.2.3.1 Task-dissociation Methods

Task-dissociation methods distinguish both memory processes by identifying paradigms that rely primarily on one of the two [57, 117]. For example, while single-item recognition involves both familiarity and recollection processes, free recall and associative item recognition relies exclusively on recollection. Thus, by comparing recall or associative recognition performance to that of single-item recognition, it is possible to make inferences about the contributions of recollection and familiarity to overall performance [57, 117]. Response-speed methods have also been proposed to separate the contributions of the two processes, as familiarity is expected to be faster than recollection [117].

Task-dissociation methods may be intuitive and easy to implement, but they often produce inherently ambiguous results [117]. What is more, the comparison of performances between tasks is usually problematic, since the overall accuracy on free recall or associative recognition tests is generally lower [57].

3.2.3.2 Process-estimation Methods

The drawbacks of task-dissociation approaches have prompted the creation of process-estimation methods, which seek to derive parameter estimates from a set of mathematical models to quantify the contribution of both processes to overall performance [57, 117]. Frequently used process-estimation methods include the Remember-Know (RK) paradigm, the Process Dissociation Procedure (PDP) and receiver-operating characteristic (ROC) curve analysis.

The RK procedure requires participants to indicate, for all recognized items, whether they “remember” any information about the study event or whether they simply “know” that the item was previously shown, i.e. the item is familiar to them [57, 116]. This method assumes that recollection and familiarity processes are independent [117]. Therefore, the probability of giving a “remember” response can be used as an index of recollection ($R = hit_{remember}$). Conversely, since participants are instructed to give “know” responses when an item is familiar and not recollected [$hit_{know} = F \times (1 - R)$], the probability that an item received a “know” response given it was not recollected is used as an index of familiarity [$F = hit_{know} / (1 - R)$]. The RK procedure has been criticized for relying on the participant’s understanding of the distinction between recognition and familiarity, but recommendations for increasing the reliability of the paradigm exist (see [116] for a comprehensive review).

PDP involves the encoding of two separate sets of items in distinct contexts, e.g. words being displayed on a screen versus words being spoken through speakers [57]. The encoding phase is followed by two tests: the inclusion and the exclusion tests. During the inclusion test participants identify test items that were previously studied, regardless of context, while in the exclusion test,

participants are only asked to identify items from a specific context and exclude the rest. Recollection and Familiarity indexes can be derived from the participant's performance in the inclusion and exclusion tests [e.g., $R = hit_{inclusion} - hit_{exclusion}$ and $F = hit_{exclusion} / (1 - R)$] [117].

Finally, multiple authors have observed that recollection and familiarity recognition processes produce distinctly shaped ROCs [57, 117]. Therefore, it stands to reason that they can be used to examine the underlying processes of recognition memory. In this context, the probability curve describes the relationship between the hit and false alarm rates across a range of response criteria. It is possible to obtain ROCs from standard tasks, e.g. the "Old/New" recognition test, by requiring participants to rate how confident they are in their response. It is common for the confidence rating method to use a six-point scale ranging from 1 (sure new) to 6 (sure old). Fitting a dual-process equation to the observed ROC provides estimates for recollection and familiarity.

3.3 Neural Correlates of Recognition Memory

Studies on the neural correlates of recognition memory have investigated neural activity during memory encoding, retrieval, or both. Memory processes that arise during encoding and result in successful retrieval are referred to as subsequent memory effects (SMEs). Neural processing differences between the correct identification of studied and unstudied items during retrieval are commonly referred to as old/new effects.

A significant amount of evidence for the neural dissociation between recollection and familiarity processes has been derived from EEG studies of retrieval-related activity [107]. Nevertheless, both encoding, and retrieval memory processes have also been characterized using intracranial EEG recordings in neurosurgical patients undergoing treatment for intractable epilepsy [126].

3.3.1 EEG Recording Studies

For the purpose of this dissertation, we have limited our review of EEG correlates of retrieval and encoding to ERP signatures, as they have been extensively studied using a wide variety of experimental paradigms.

3.3.1.1 Neural Correlates of Encoding

ERP SMEs have also been referred to as Dm effects, for "Difference in subsequent memory". Previous encoding studies have identified an increased positivity for subsequently remembered items compared to items that are subsequently forgotten [127, 128]. The most prominent Dm effect consists of a posterior positive deflection 400-800 ms following stimulus presentation.

While several studies have found distinct Dm effects for familiarity and recollection processes, reported findings are inconsistent. Some authors have found that subsequently recollected items elicited a significant increased positivity compared to subsequently missed items, while subsequently familiar items did not [127]. Duarte et al. [129] found that subsequently familiar items

elicited topographically distinct effects from subsequently recollected items. Others studies have reported mixed [130, 131], or null results [132].

3.3.1.2 Neural Correlates of Retrieval

Generally, ERPs elicited by the correct identification of studied items are more positive than those elicited by the correct identification of a new item. Several studies have identified two distinct ERP components associated with the processes of recollection and familiarity (see Fig. 3.3). Furthermore, recent studies have gone on to prove both effects are associated with subjectively perceived memory confidence.

The parietal old/new effect, also dubbed the late positive component (LPC), is a positive deflection that occurs over parietal sites between 500 and 800 ms following stimulus onset and exhibits a left-sided maximum [107, 120] (see Fig. 3.3A). The LPC has been linked to recollection, as it is greater for behavioral responses thought to reflect recollection-driven recognition, such as correct source judgements. Studies using the RK paradigm have also reported on the occurrence of the LPC for “remember” responses in contrast to “know” responses [129, 133]. Additionally, the LPC shows an increased positive deflection exclusively for high-confidence hits [119, 134, 135].

The FN400, also known as the early mid-frontal effect, is a negative deflection that occurs 300-500 ms after stimulus onset over medial frontal sites and is related to familiarity [107] (see Fig. 3.3B). The FN400 is attenuated for studied item hits and similar lure false alarms, which are thought to be more familiar than novel items [136, 137]. This effect is also elicited by “know”

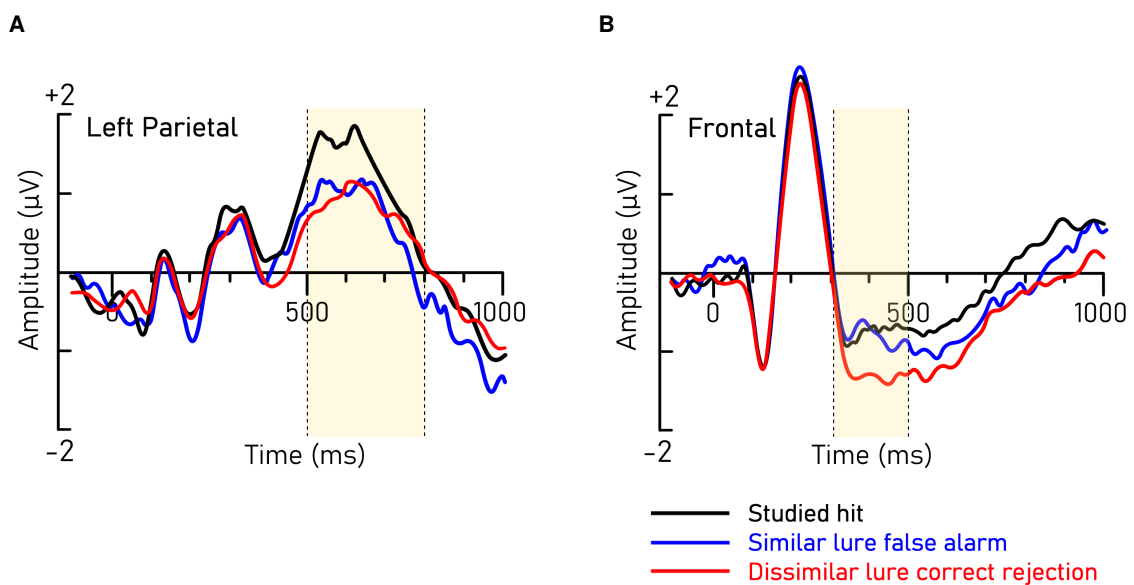


Figure 3.3: Grand average ERPs elicited during a word recognition test with highly similar lures (Adapted from [107]). (A) Waveforms from left parietal sites (electrode cluster including P3) with the LPC effect highlighted by the shaded area. (B) Waveforms from frontal sites (electrode clusters including F3 and F4) with the FN400 effect highlighted by the shaded area.

responses [129,133]. The underlying processes of the FN400 have been disputed and some authors consider it to be a correlate of conceptual priming, a form of implicit memory that contributes to familiarity-driven recognition [107]. Nevertheless, the FN400 has been proven to be unaffected by factors that modulate conceptual priming [138] and is topographically distinct from conceptual priming ERP effects [139]. Additionally, the FN400 varies linearly with subjectively perceived memory confidence, with high-confident correct rejections yielding greater negative deflections [134,135].

The functional association between the LPC and FN400 effects and the recognition processes of recollection and familiarity have also been supported by studies on memory impaired patients. Patients with hippocampal damage, known to exhibit impaired recollection with intact familiarity, exhibited a significant FN400 effect, whereas LPC effects are absent [22,140].

3.3.2 Intrathalamic Recording Studies

While the ANT's putative role in declarative memory encoding has been thoroughly acknowledged, the electromagnetic processes underlying memory processing in the ANT have been scantily analyzed. The ANT's small size and location deep within the brain has limited the number of direct electrophysiological recording studies in humans [5]. In fact, all intracranial recording studies of ANT activity in humans presented in this document are restricted to epilepsy patients undergoing ANT-DBS. In this section, we highlight four intrathalamic recording studies on recognition memory (see Table 3.1) and their findings.

Table 3.1: DBS Studies that performed intracranial recordings of the ANT during memory tasks.

Study	N	Memory Task	Targets	Activity Recorded
[103]	1	Word recognition (visual)	ANT, DM	LFPs and EEG
[5,6,141]	8	Scene photo recognition (visual)	ANT, DM	LFPs and EEG
[108]	3	Scene photo (visual) and word (auditory) recognition	ANT, Hippocampus	LFPs
[7]	4	Modified visual oddball paradigm, Scene photo recognition (visual)	ANT, NAc	LFPs

(Continued)

Study	DBS Electrode Properties			Sampling Frequency
	Diameter	Length	Spacing	
[103]	NR	1.5 mm	1.5 mm	512 Hz
[5,6,141]	NR	1.5 mm	1.5 mm	512 Hz
[108]	1.27 mm	1.5 mm	0.5 mm	1024 Hz
[7]	1.27 mm	1.5 mm	1.5 mm	512 Hz

Headers: N - Number of subjects with contacts in the ANT

Abbreviations: ANT - Anterior nucleus of the thalamus; DM - Dorsomedial nucleus of the thalamus; EEG - Electroencephalography; LFPs - Local Field Potentials; NAc - Nucleus accumbens; NR - Not Reported

The DM communicates with frontal regions, triggering subsequent memory recall.

Staudigl et al. [103] studied thalamocortical communication during long-term episodic memory retrieval. Intrathalamic LFPs from the ANT and dorsomedial nucleus (DM), and surface EEG were recorded from a single participant during memory retrieval. In a recognition memory test, beta phase synchrony between the left DM and frontal surface electrodes was enhanced significantly during retrieval of correctly remembered old items, approximately 300 to 500 ms following stimulus onset. Phase synchrony between frontal electrodes and the ANT was not significant. Neocortical gamma power was found to be modulated by thalamic beta during the identification of correctly remembered old items, suggesting that the DM entrains local neocortical brain activity during human memory retrieval. Additionally, Granger Causality (GC) analysis revealed that dorsomedial thalamic beta predicted frontal activity during successful memory retrieval.

Post-stimulus Neocortical-ANT phase synchrony and PAC predict memory encoding.

Sweeney-Reed and colleagues [5, 6, 141] recorded intrathalamic LFPs from the ANT for eight participants and in the DM for seven. Scalp EEG data were recorded concurrently from frontal electrodes for all eight patients. Recordings were made during both memory encoding and retrieval, but only memory encoding data were analyzed [5].

In their first study [5], the authors compared the post-stimulus electrophysiological activity of the ANT during successful encoding with that of unsuccessful encoding of a series of photographs of indoor and outdoor scenes. Theta phase alignment between frontal and right ANT oscillations was greater during successful encoding, 0.5 to 1.5 s following stimuli presentation. Furthermore, they observed PAC between frontal theta oscillations and right ANT narrowband gamma ($\approx$ 40-50 Hz) during successful encoding. Theta-gamma PAC within the right ANT predicted successful memory encoding. GC revealed that frontal theta predicted right ANT theta activity significantly better. Further analysis of the obtained data revealed that not only was phase alignment in right ANT theta rhythm enhanced during successful encoding, but it was also correlated with within-ANT theta-gamma PAC [6].

Recognition memory processes in the ANT precede the hippocampus.

Štillová et al. [108] recorded event-related potentials elicited by both visual and auditory single-item memory encoding and recognition tasks. Three subjects had electrodes implanted in the hippocampus, and three others in the ANT. P300-like potentials were recorded in the ANT during visual encoding, and visual and auditory recognition of items. During memory retrieval, the observed potentials preceded the ones elicited in the hippocampus.

Pre-stimulus DM theta power predicts right ANT activity during memory encoding.

In 2016, Sweeney-Reed and colleagues investigated pre-stimulus activity [141]. The authors reported a significant increase in theta (4-8 Hz) power in the right DM preceding the presentation of successfully encoded stimuli compared to forgotten ones. This increase in theta power was observed in both the DM and ANT but was not statistically significant in the later. Additionally,

pre-stimulus DM theta power was found to be negatively correlated with post-stimulus right ANT gamma phase alignment. It was also found to be correlated with frontal theta (5-6 Hz) and right ANT narrowband gamma (32-50 Hz) PAC. The authors concluded that ANT activity is possibly modulated by a DM-frontal subsystem.

Signals from the ANT to NAc support memory retrieval.

Bauch et al. [7] recorded intracranial LFPs from the ANT in four epilepsy patients, during memory retrieval. Visual inspection of the grand averaged ERPs showed an amplitude difference between old and new items, 200 to 600 ms following stimulus presentation. Retrieval success in the right ANT was associated with an increase in theta power from 600 to 1000 ms following stimulus onset.

3.4 The Fundamentals of ERP Analysis

ERP studies are a cornerstone of recognition memory studies and have provided a large amount of evidence supporting the underlying processes of memory encoding and retrieval. This section presents some fundamental practices necessary for ERP analysis.

3.4.1 Preprocessing

ERP processing pipelines often begin with offline re-referencing to an adequate virtual reference. For low density electrode montages (under 64 electrodes) over the middle line of the scalp, it is common practice to use the average of the two mastoid electrodes [142]. Averaging over two mastoids assumes that the potentials recorded at those sites is close to neutral.

An important aspect of any type of electrophysiological data preprocessing is its segmentation into epochs according to stimulus or event onset. The adequate length of each epoch can be determined empirically or inferred from the characteristics of well-known related phenomena. ERP studies on the neural correlates of memory often consider 1- to 2-second-long stimulus-locked epochs beginning 500 to 100 ms before stimulus onset.

Before epoching, the raw data may be offline filtered to both denoise and remove unnecessary frequencies from the signal. Before ERP analysis, simple band-pass filters are usually applied to eliminate slow drifts and high frequencies. EEG signals are often filtered between a frequency range of 0.01, 0.05 or 0.1 Hz and 30, or 40 Hz. The reviewed intrathalamic recording studies used widely different bandwidths, ranging from 1-8 Hz [6] to 0.2-40 Hz [108]. Pipelines often include a single low-pass or band-pass filter application before epoching, or a first high-pass filter application and a second low-pass filter application after artifact rejection or ERP extraction.

Epochs contaminated by artifacts, such as eye movements, epileptiform spikes, ECG, etc., can be detected through visual inspection, automated routines, or a combination of both. However, it is recommended that trial data always be visually inspected, to make sure the automated routines are working properly. Some widely used artifact detection algorithms use simple voltage thresholds or moving window peak-to-peak thresholds to mark epochs for rejection. Contaminated epochs

can then either be rejected from the analysis or processed for artifact correction. There are several automated approaches for the correction of artifactual components, but the most commonly used methods are based on Regression and Blind Source Separation (BSS) techniques [143].

Independent component analysis (ICA) is an established BSS technique often used to decompose electroencephalographic signals. Summarily, ICA is a statistical technique capable of separating multi-channel data into a set of independent components (ICs) [144]. ICs corresponding to artifactual sources can be subtracted from the data. Since most artifactual components are easily recognizable by their spatial localization (see Fig. 3.4), ICs are usually represented using scalp topography. While automated labeling algorithms for artifactual component detection exist [145], component labeling should be supervised and artifact identification should be performed manually. In general, it is recommended for ICA to be used on continuous data, since more data usually increases ICA decomposition quality (as long as it is clean, statistically similar data). However, most ERP studies apply ICA to data epochs instead. There are several ICA decomposition algorithms such as Infomax [146], SOBI [147] and FastICA [148].

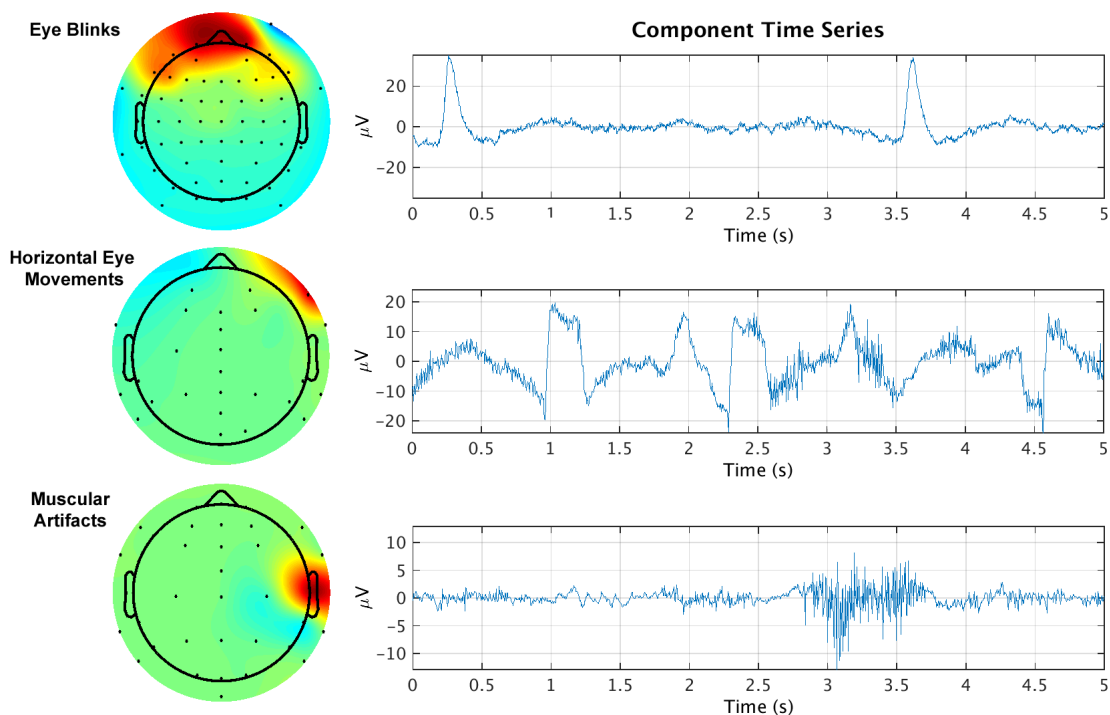


Figure 3.4: Examples of artifactual ICs. Eye and muscle components often yield ICs that are identifiable by their scalp topography (to the left). Eye blinks are also clearly visible in a component's time series plot (to the right). Adapted from the ICLabel project.¹

3.4.1.1 ERP extraction

A great majority of ERP studies employ a simple averaging technique for ERP extraction. Averaging several trials retains the ERP waveform and eliminates irrelevant potentials. This procedure is contingent on the following conditions: (1) the latency and shape of the ERP components are

constant for every trial and (2) the remaining components of the signal, like noise, are unrelated to the event, and therefore, random [104].

Before averaging, epochs are corrected relative to a baseline, which is an epoch deprived of any activity related to the stimuli. Baseline intervals are usually defined before stimulus onset. Trials are first averaged within-subject for each type of stimulus. All individual responses are then averaged a second time, yielding a grand average associated with conditions of interest.

3.4.1.2 ERP Component Measurement

The final steps in ERP analysis involve measuring ERP components of interest and performing statistical analyses of said components. Grand average ERPs are often computed to estimate the general structure of the waveform and detect substantial differences across conditions [149]. This process allows researchers to isolate latencies of interest (time windows) that may include a significant effect. Time windows can also be defined a priori, based on pre-established findings. When measuring ERP component amplitudes, one typically considers measuring the peak amplitude within the time window or calculating the mean voltage within the time window [149, 150]. When measuring ERP latencies, measuring the latency of a local peak within the time window is often the better option.

3.4.1.3 Statistical Significance

Repeated measures analysis of variance (ANOVA) is the dominant statistical method used by cognitive ERP studies [151, 152]. Also known as within-subjects ANOVA, repeated measures ANOVA is used for detecting significant differences between related group means. Independent variables, commonly referred to as within-subject factors, are split into related groups or levels. In ERP analysis, researchers typically consider within-subject factors for condition and electrode position [152]. For example, in a standard RK paradigm, considering ERP measurements from three electrode sites, P3, Pz and P4, one can perform a repeated measures ANOVA analysis with two within-subject factors: condition (recollected hits, familiar hits or correct rejections) and laterality (left hemisphere, midline, or right hemisphere).

Univariate repeated measures ANOVA must meet three assumptions [151]: observation independence between subjects; normality, meaning all possible combinations of the dependent variable should be normally distributed; and sphericity, meaning the variance of the differences between all possible combinations of related groups must be equal. The ANOVA method is rather robust when dealing with small to moderate violations of normality². However, extreme violations of this assumption will render ANOVA analysis unreliable, so non-parametric tests are recommended in those cases. On the other hand, violations of sphericity are quite common and

¹SCCN: Independent Component Labeling. Available at: <https://labeling.ucsd.edu/tutorial/labels> (Accessed 30-05-2021)

²One-way ANOVA with repeated measures in SPSS Statistics - Step-by-step procedure including assumptions. Available at: <https://statistics.laerd.com/spss-tutorials/one-way-anova-repeated-measures-using-spss-statistics.php> (Accessed 20-05-2021)

lead to an increase in probability of a Type I error (false positive). When this assumption is broken Greenhouse-Geisser corrected p-values are reported instead (as e.g. in [119]). Post-hoc tests are conducted when a significant effect is found to determine which related group is causing the effect [151].

Chapter 4

A Protocol for Studying the Neural Correlates of Recognition Memory

This chapter presents the experimental protocol created during this dissertation for studying the effects of ANT-DBS on recognition memory at a clinical environment. The protocol was extended for applications outside of the clinic and can be repurposed for broader studies on the neural correlates of recognition memory.

4.1 Experimental Setup

One of the primary goals of this dissertation was to prepare and pilot test an experimental setup that could be used to investigate the effects of ANT-DBS in episodic recognition memory. Furthermore, we set out to develop a setup that could also be assembled out-of-clinic, to perform short experiments that required the use of visual stimulation.

Special care was taken when making sure the experiment could be performed remotely, as, due to the pandemic, experimenters were instructed to keep physical contact to a minimum and to maintain the safety distance whenever possible. Moreover, at the EMU experimenters were required to remain in the adjacent monitoring room and avoid all contact with the patient, to guarantee their safety.

4.1.1 Outline

An illustration of the experimental setup's general outline is displayed in Fig. 4.1. The devised experimental setup is suitable for performing experiments involving simple cognitive tasks that require the use of visual feedback or stimulation. The experiment routine is presented to the participants through a second monitor, which is connected to a remote computer running the experiment. Instructions, prompts, and stimuli are presented to the participants via the monitor.

The experimental setup includes the EEG acquisition system, which samples the participant's electroencephalographic signals. The acquisition system also samples analog output signals from

a light sensor, which is attached to the monitor screen. The sensor is used to synchronize the visual stimuli with the EEG stream, as both signals are sampled simultaneously by the same device.

Responses given by the participants are recorded via keypresses. Both setups utilize a wireless keypad, so that the participant and experimenter can be at least two meters apart during the experiment. During the experiment, video and audio of the participant is also recorded. In-clinic, this component of the experimental setup is already fully functional and cannot be disabled. Videos recorded are also automatically synchronized to the EEG stream. The vEEG recording can be used to synchronize multiple data streams, such as LFPs recorded using Percept™ PC's BrainSense Technology. The participant may be asked to provide verbal responses during the experiment, which are recorded in the video.

Data collected during the experiment is stored in the main computer and copied to an external storage unit. The system keeps a record of the acquired EEG signals, video and audio recordings of the experiment and responses given by the participants. Information pertaining to the routine itself, such as what stimuli were presented to the participant and in what order, is also stored.

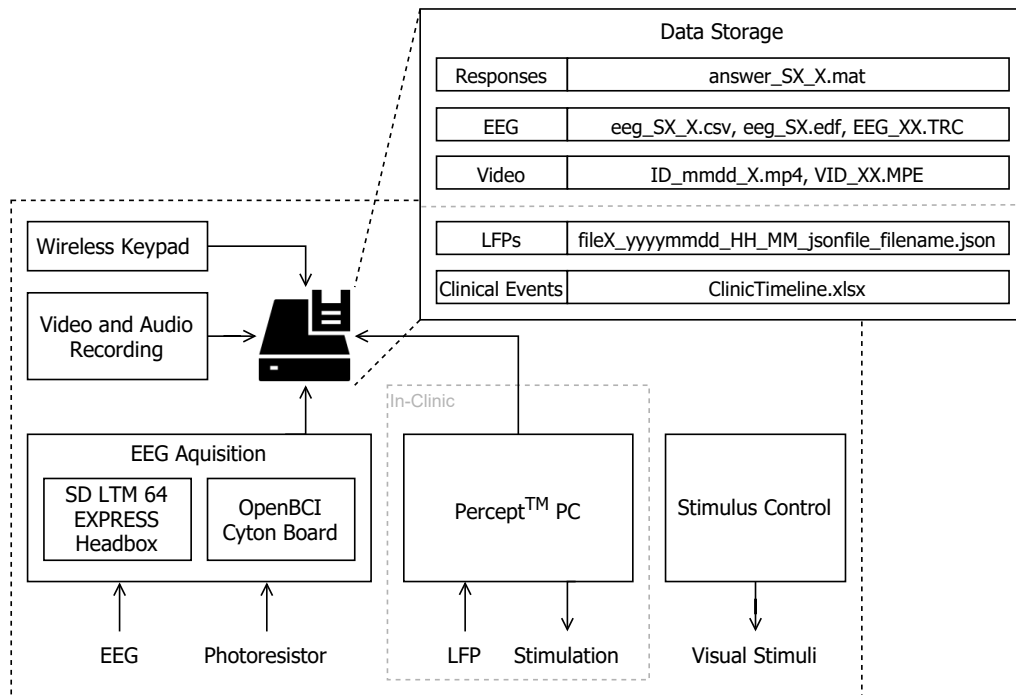


Figure 4.1: Schematic illustration of the general outline of the experimental setup.

4.1.2 EEG acquisition

4.1.2.1 Out-of-Clinic EEG Acquisition using The OpenBCI Cyton Board

The OpenBCI Cyton Board was used during a series of pilot experiments with healthy participants, in preparation for the clinical experiments. The EEG recording setup was thoroughly documented so that it may be reused and repurposed in the future.

The OpenBCI Cyton Board is an affordable, open-source piece of hardware designed to measure electrophysiological signals (see Fig. 4.2). This device was created to sample EEG for low-cost Brain-Computer Interface (BCI) applications but can also be used to sample electromyographic and electrocardiographic signals. The Arduino compatible board includes a biosensing interface with 8 channels, a built-in accelerometer and three auxiliary channels - D11 (A5), D12 (A6) and D13 (A7) - for sampling digital or analog signals. The OpenBCI guide recommends connecting electrodes for EEG measurement using the numbered pins closest to the board, which are connected to the differential analog negative inputs of ADS1299 Analog-to-Digital Converter (ADC) [153]. The analog inputs are connected to a PIC32 microcontroller, which has a 10-bit ADC [154]. Through the OpenBCI USB dongle, the board communicates wirelessly with any computer via Bluetooth. Signals are sampled at a frequency of 250 Hz.

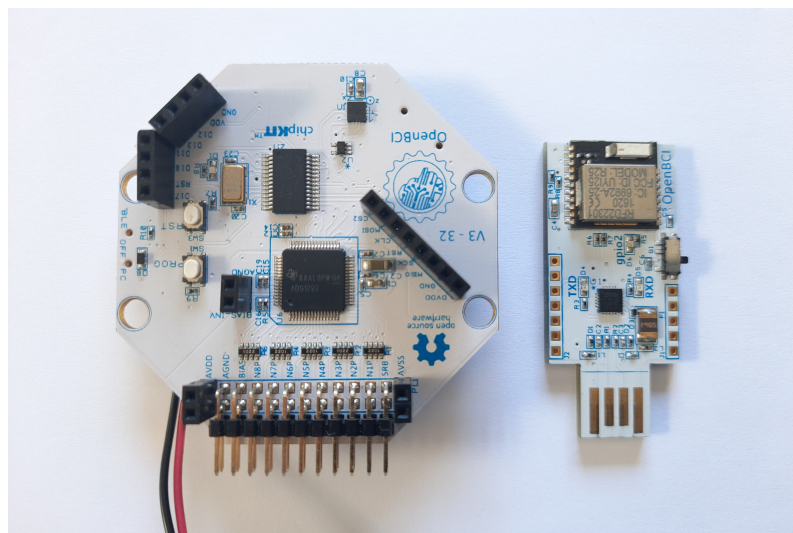


Figure 4.2: The OpenBCI Cyton Board (to the left) and USB dongle (to the right).

OpenBCI provides an open-source software for visualizing, recording, and streaming signals from all OpenBCI Boards. The OpenBCI GUI displays data in real-time and allows users to measure the impedance of each channel. Recorded data can also be saved in .txt format or streamed to a third-party software, such as MATLAB. However, this protocol uses the OpenBCI GUI solely to measure skin-electrode impedances during electrode application and monitor signal quality between blocks. Indeed, data acquisition using the OpenBCI Cyton Board was carried out through BrainFlow¹, an OpenBCI compatible, device agnostic library created to parse electrophysiological data from biosensors.

4.1.2.2 In-clinic EEG Monitoring

The EMU of CHUSJ uses Micromed's SD LTM 64 EXPRESS Headbox, to monitor and record EEG signals from epilepsy patients undergoing vEEG monitoring (see Figures 4.3A and 4.3B). Like any typical clinical EEG system, the electrophysiological signals are amplified, converted to

¹BrainFlow. Available at: <https://brainflow.org/> (Accessed 21-06-2021)

digital signals, and sent to a microcontroller, which stores them. A computer with an installation of the SystemPlus EVOLUTION software is used to monitor the data transmitted from the device in real time. Communication with the computer is made via specific cables.

The device possesses two DC channels with unitary gain (see Fig. 4.3C), which can be used to sample analog signals from other sensors or devices. These 10-bit inputs can be configured to sample a dynamic range of 0.48V or 4.8 V. The 4-pin DC input connector on the Headbox can be connected to standard EEG DIN connectors through the CB LTM DC interface (see Fig. 4.3D).

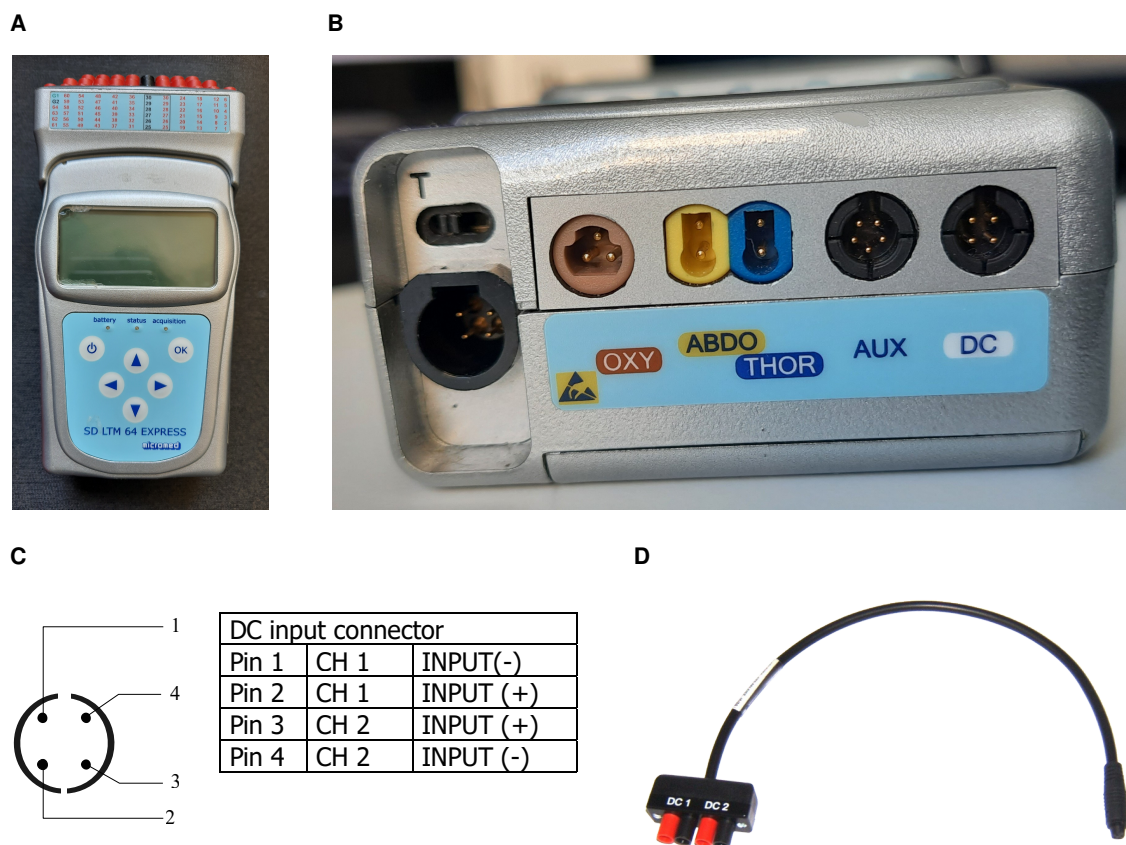


Figure 4.3: EEG acquisition hardware available at the EMU of CHUSJ. (A) SD LTM 64 EXPRESS Headbox with JB LTM 64 EXPRESS Jackbox. (B) SD LTM 64 EXPRESS connector panel. (C) Schematic of the SD LTM 32/64 EXPRESS DC Input Connector. (D) CB LTM DC cable. Red and black connectors correspond to positive and negative inputs for each channel, respectively.

4.1.3 Visual Stimuli Presentation

The stimulation protocol was designed using Psychtoolbox-3 (version 3.0.17), a free MATLAB library for neuroscience research. A subset of functions (see Fig. 4.4) was developed to create stimulation routines following the proposed experimental paradigm (described in full in section 4.2). All code developed for the purpose of this experiment protocol is readily available for consultation in Appendix A.

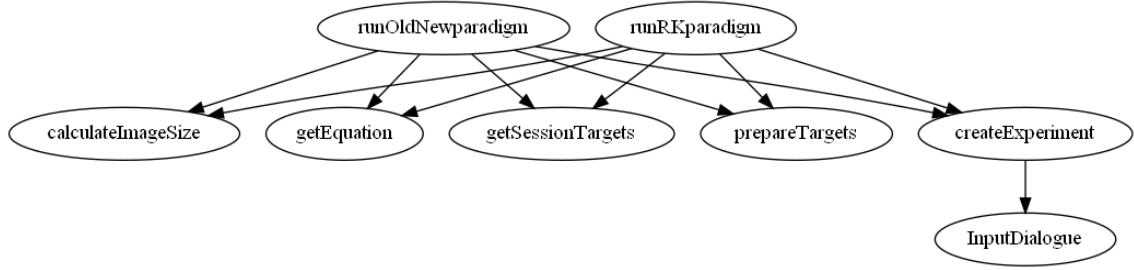


Figure 4.4: Dependency graph for routine scripts generated by M2HTML.

All stimuli are presented on a black background. Images presented to the user are resized automatically to subtend a visual angle of 7.5° (see Fig. 4.5). Image size is determined according to the distance between the computer screen and the participant, which is set by the experimenter. Textual prompts and instructions are available in both Portuguese and English.

To run an experiment routine, the user is required to provide the routine’s identifier and an identifier for the current subject. When running a routine for the first time, a new directory named after the routine’s identifier is created within the “data” directory, which is used to store all generated routines. The user can then define the number of sessions, blocks and stimuli that will be used for that routine. These parameters are stored in a .mat file within that routine’s directory. Therefore, routines can be used for multiple subjects; data obtained for each subject is stored within that routine’s directory, in their respective folder.

A Windows 10 computer with an installation of MATLAB (R2019b) was used to run the experiments. Since Psychtoolbox cannot deactivate Windows’ DWM Composition on Windows 10 systems, it is unable to synchronize the onset of visual stimuli to the display’s vertical retrace and obtain reliable stimulus onset timestamps. For that reason, an external sensor was used to determine precise image presentation timestamps.

4.1.4 Synchronization Between Stimuli Presentation and EEG

A light sensor was used to synchronize the visual stimuli and the EEG stream. The light sensor consisted of a simple voltage divider circuit with a photoresistor (see Fig. 4.6A). The photoresistor was attached to the screen so that the output of the voltage divider increased, whenever the screen got brighter.

When a visual stimulus is presented to the participant, a small white square appears simultaneously on the bottom left corner of the screen (see Fig. 4.5A). The photoresistor is placed above this region, so it detects the moment the stimulus is presented to the user (see Fig. 4.5B). As a result, it is possible to detect the onset of target stimuli with high precision.

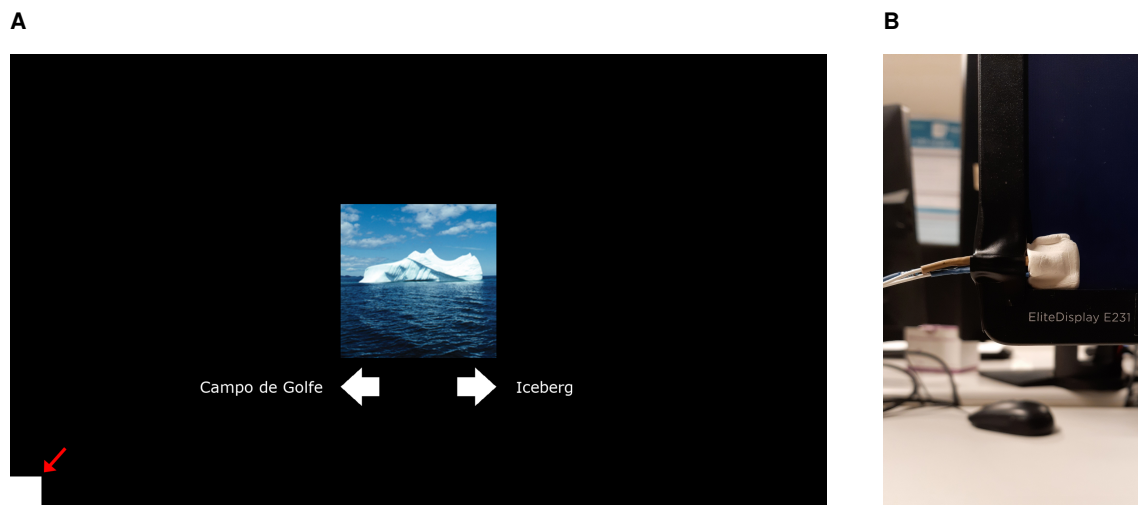


Figure 4.5: Visual stimuli presentation setup. (A) Screen snapshot taken during the presentation of an image. The red arrow points to the region the photoresistor is placed in. (B) Photoresistor firmly attached to the corner of the external monitor.

The sensor can be connected to the OpenBCI Cyton Board directly. The VDD and the ground pins are connected to the voltage divider's input and ground, while the A5 (D11) pin is connected to the output of the circuit. Connecting the voltage divider to an SD LTM 64 EXPRESS Headbox requires the use of a separate power source. The in-clinic setup uses a 3.7 V rechargeable LiPo battery to power the sensor. The sensor's output and ground are connected to the first auxiliary DC channel through the CB LTM DC interface (see Fig. 4.6B).

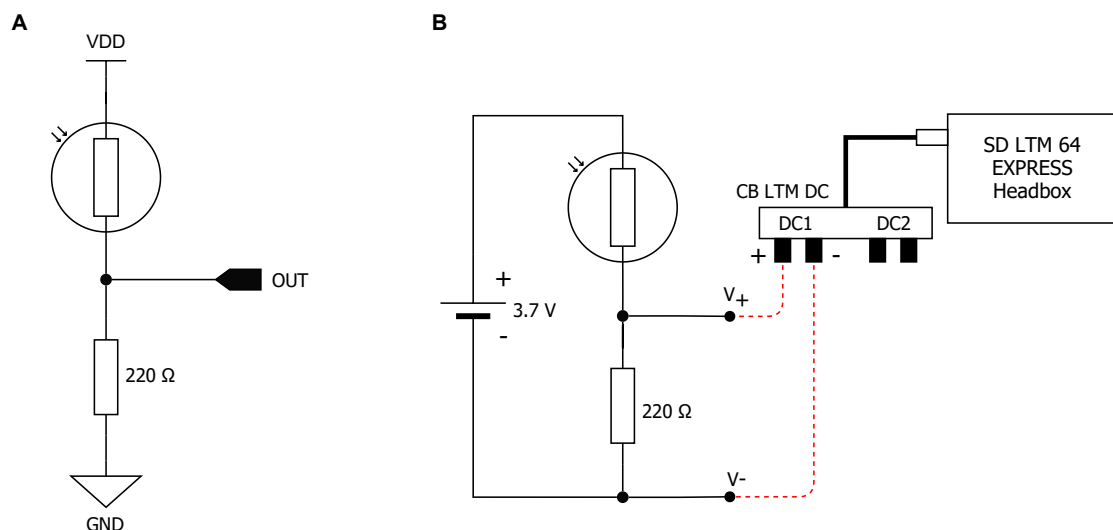


Figure 4.6: Photoresistor circuit used to synchronize stimuli presentation and EEG data. (A) Isolated photoresistor circuit. (B) Schematic illustration of the connection between the photoresistor circuit and the in-clinic EEG acquisition system.

As mentioned previously, EEG signals and analog output signals from the light sensing circuit are sampled simultaneously. As a result, one can easily identify the latency of visual stimulus onset by running a threshold filter across the photoresistor marker channel and extracting rising edges (see Fig. 4.7). The appropriate threshold value depends on the brightness of the screen. Therefore, it should be determined empirically.

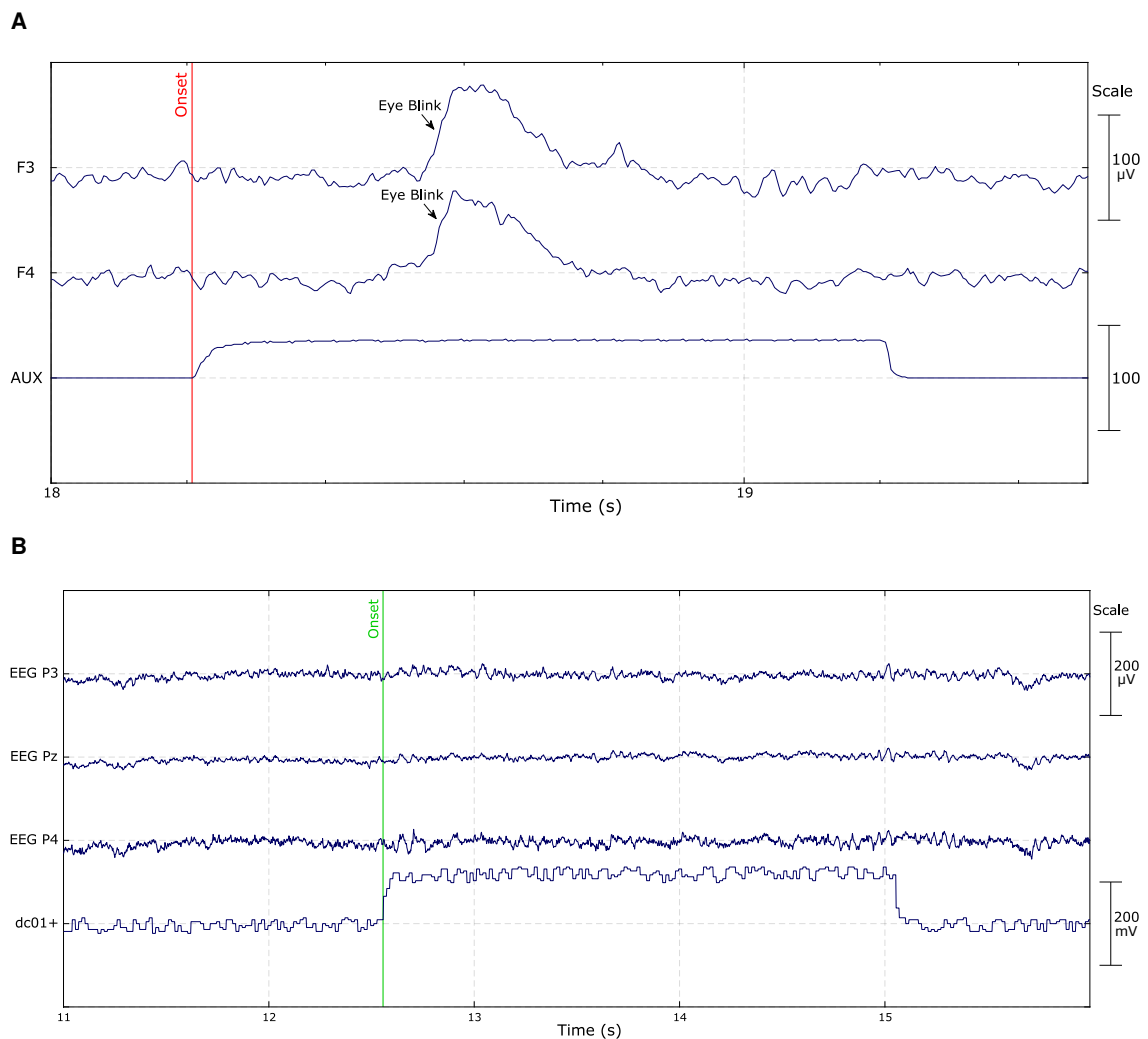


Figure 4.7: Sample photoresistor and EEG trace acquired by the EEG acquisition systems during stimulus presentation. Stimulus onsets can be determined using a simple threshold. (A) EEG trace sampled by the OpenBCI Cyton Board during a simple hardware verification task in which participants are asked to blink following a visual cue. While EEG channels (F3 and F4) are in μV , integer values (ranging from 0 to 1023) are returned for the auxiliary analog channel (AUX). Rising edges above a predefined threshold value of 0 were marked. (B) EEG trace sampled by the SD LTM 64 EXPRESS Headbox during the execution of a cognitive task. EEG channels are in μV and the DC channel is in mV. Rising edges above a predefined threshold value of 50 mV were marked.

4.1.5 Synchronization Between EEG and BrainSense Streams

Data recorded from the Percept PC device is not automatically synchronized with data recorded with external equipment. As a result, prior fine-grained synchronization of vEEG and LFP recordings is necessary.

To achieve this, the BRAIN research group has proposed performing a “head tapping maneuver” once per day. The tapping maneuver involves lightly tapping the region over the DBS leads on the patient’s cranium, producing easily detectable artifacts in both EEG and LFPs data streams (see Fig. 4.8). Additionally, this action is also visible in any video recording, allowing the precise synchronization of video streams as well.

This procedure has already been tested at the EMU of CHUSJ. Results indicate that by performing this type of synchronization, an average synchronization accuracy of ~ 0.5 s can be obtained [155].

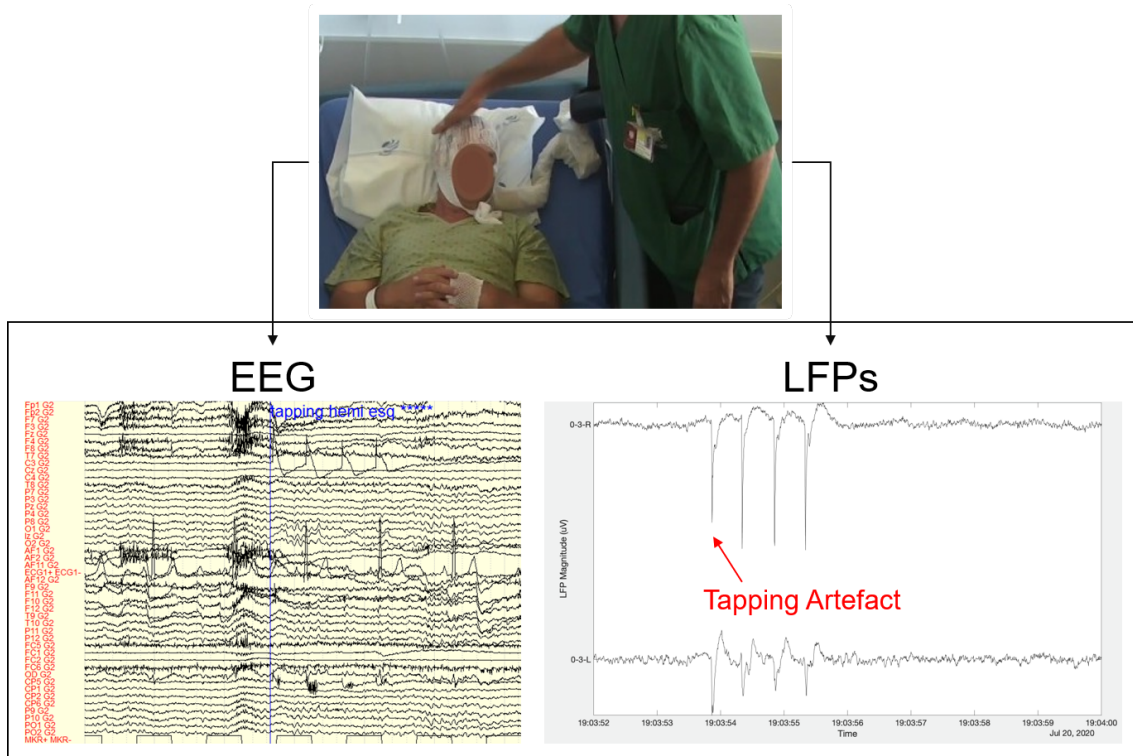


Figure 4.8: Schematic illustration of the Head Tapping Synchronization method. Adapted from [155].

4.2 Experimental Protocol

A common experimental protocol guideline was created to streamline the development of the experimental routines. Both in-clinic and out-of-clinic experimental procedures adhere to the general protocol described ahead.

4.2.1 Stimulus Materials

Stimuli were taken from a large preexisting image set of categorized scenes [156], available for download online². Images are grouped into semantic categories, e.g. “iceberg”, “beach”, etc. Sixty scene categories, each with 60 exemplars, were included. Within every category, stimuli are divided into two sets of 30 items, a set of studied items (“old”) and a set of unstudied items (“new”). Sets can be counterbalanced across participants so that all items are presented as old just as often as they are presented as new.

When generating a new routine, stimuli categories are picked at random. The number of categories picked is dictated by the number of sessions and blocks programmed for that routine. During a single block, users are presented with two image categories. Let n be the number of old stimuli stipulated by the experimenter for a given routine. For every block, two subsets of $n/2$ scenes are created from the new and old image sets. Subsets of two different semantic categories are concatenated to create two final sets of old and new scenes.

4.2.2 Experimental Paradigm

An adapted version of the RK paradigm was chosen for this study. This paradigm was picked over other process estimation methods for the following reasons: unlike PDP, it does not require the execution of two tasks involving different instructions and retrieval cues, which is more appropriate for hospitalized patients; and unlike ROCs, it does not require a large number of responses (≥ 60) from the subject to derive stable estimations of recollection and familiarity, allowing experimenters to perform shorter trials [117]. Nevertheless, we are aware that multiple research groups have reported that many participants, even healthy ones, may struggle to understand and follow the RK instructions [116]. For that reason, in addition to preparing a strict procedure for evaluating the patient’s understanding of the paradigm, a simple “Old/New” test mode was also created, for participants that could not comprehend the instructions.

The experiment consists of multiple blocks of a single-item recognition memory task. Each block includes three phases: study, distraction, and recognition, in that order (see Fig. 4.9). The participant rests for a stipulated amount of time between blocks.

During the first phase, the participant is presented with a set of images (subtending a visual angle of $7.5^\circ \times 7.5^\circ$). Each set contains unique images from two different semantic categories (e.g., images of icebergs and golf courses). Each image remains on the screen for approximately 2500 ms. The participant is prompted to identify what category each image belongs to with a keypad press. Between stimuli, a fixation cross (+) appears on the center of the screen. Interstimulus intervals varied randomly between 1400 and 1600 ms. A 30 s distractor task is carried out following the study phase. During this task, the participant is presented with a series of simple equations, such as $2+3=5$, and must indicate whether they are true or false. The participant is encouraged to judge as many equations as they can within 30 s. Finally, in the recognition phase, the

²Scene Categories. Available at: <http://olivalab.mit.edu/MM/downloads/Scenes.zip> (Accessed 28-01-2021)

old images are presented in a new random order, interspersed with completely new scenes. The participant's objective is to identify the images that they have seen during the study phase, and to report on the memory process that enabled their identification. During recognition, each image is presented centrally on a black background for 2500 ms. Participants are instructed to remain still and withhold their response. Response options are then displayed underneath the image for a given amount of time. Experimenters can implement a 4 s timeout or allow participants to remain on the response screen until a key is pressed. Before conveying their response, participants may be

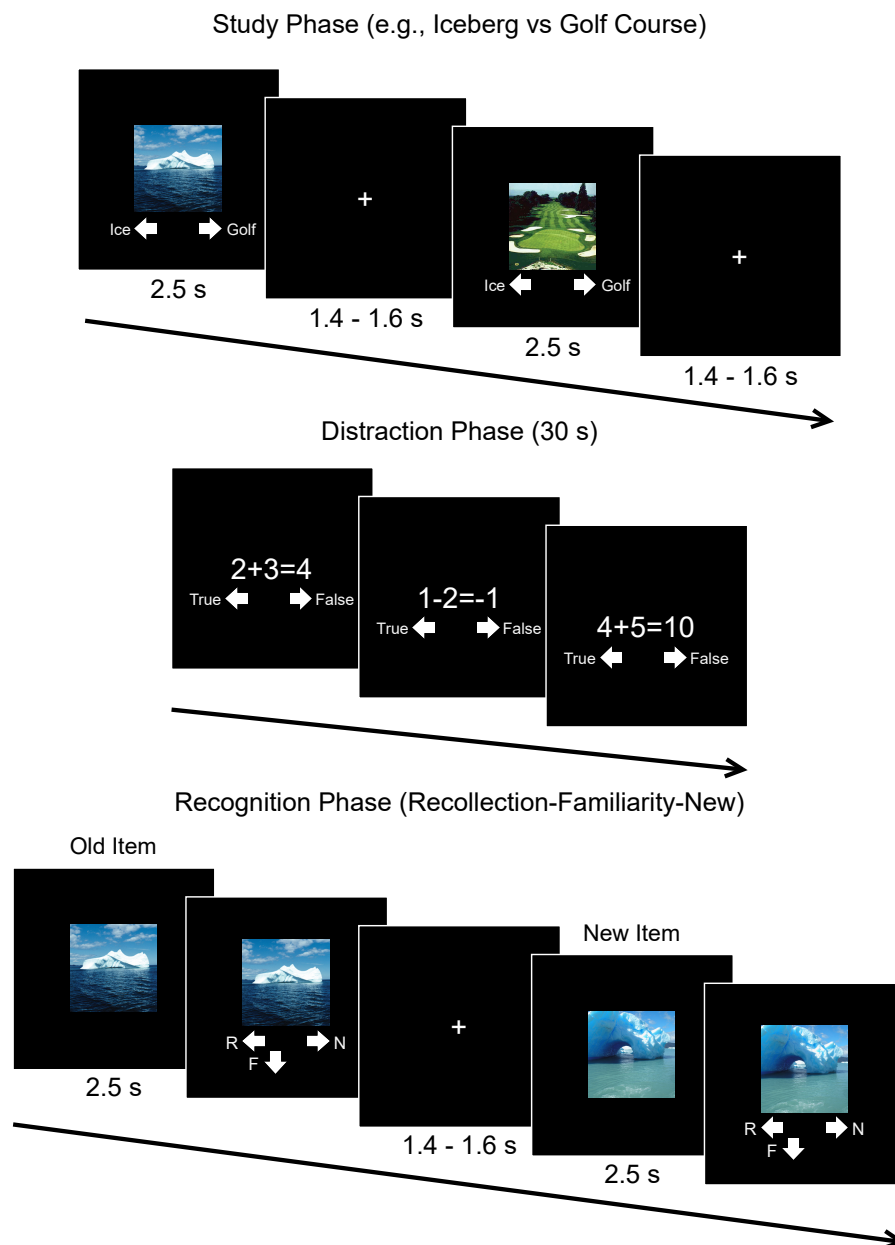


Figure 4.9: Schematic overview of the experimental paradigm. Participants are shown a list of scenes during the study phase. Following a thirty-second-long distraction phase, participants are shown a new list containing both studied ("old") and unstudied ("new") scenes.

prompted to justify their “old” decisions out loud. Participants use the arrow keys on the keypad to select one of the following responses: the down arrow for Familiarity (Familiaridade), the left arrow for Recollection (Recordação) and the right arrow for New (Nova). Participants are instructed to answer “Recollection” whenever their recognition of an image is accompanied by the cued recall of information related to its previous presentation during study, whether it be an association or thought that occurred at the time. Participants are asked to report only spontaneous recollections and avoid dwelling on the decision for too long. In the absence of recollection, participants are instructed to answer “Familiarity”.

Prior to testing, subjects are given detailed instructions outlining the test procedure and the distinction between Recollection and Familiarity. Participants are then asked to complete a practice session, in which responses are justified and corrective feedback is given. Following practice, participants are asked to provide their own understanding of the distinction. The RK instructions were adapted from those implemented by [157], taking into account the modifications recommended by [116], and employed by [9]. The instructions given to all participants are available for consultation in Appendix B.

4.3 Clinical Context

The experiment is intended to be performed on patients with refractory epilepsy, undergoing ANT-DBS treatment at the Epilepsy Monitoring Unit of Centro Hospitalar Universitário de São João. All patient’s daily activities are tracked by the hospital staff using the Clinical Timeline, an excel document. Besides tracking a patient’s activities, the clinical timeline tracks medication intake, epileptic seizures, physical and cognitive tests conducted, and status of administered stimulation. Generally, ANT-DBS patients that undergo vEEG monitoring at the EMU of CHUSJ are scheduled to be hospitalized for five days, starting Monday. Intracranial stimulation is only administered over the last three or two days of monitoring.

During their time at the EMU, the patient is expected to complete six sessions of the recognition memory task, composed of multiple blocks each (see Fig. 4.10). Sessions are scheduled to begin on the third day of monitoring and are spread out over the course of the remaining two days. The first two sessions are performed with stimulation turned off, while the following four sessions are performed with stimulation turned on. Only stimulation parameters employed in standard clinical practice will be used. Overall, participants are expected to complete two sessions without stimulation, two sessions with stimulation at 2 mA and two more sessions with stimulation at 4 mA.

The memory task is introduced to the patient by completing a practice session, on the second day of monitoring. The practice session is also useful for adjusting the number of stimuli shown, as epilepsy patients undergoing ANT-DBS exhibit a substantial heterogeneity in cognitive ability [158]. Regardless, routines should be adapted to the patient’s neuropsychological testing results prior to the practice session. After conferring with EMU coordinator, Ricardo Rego, and clinical

neurophysiologist, Joana Lima, we determined that sessions should not surpass thirty minutes, to not exhaust the patient.

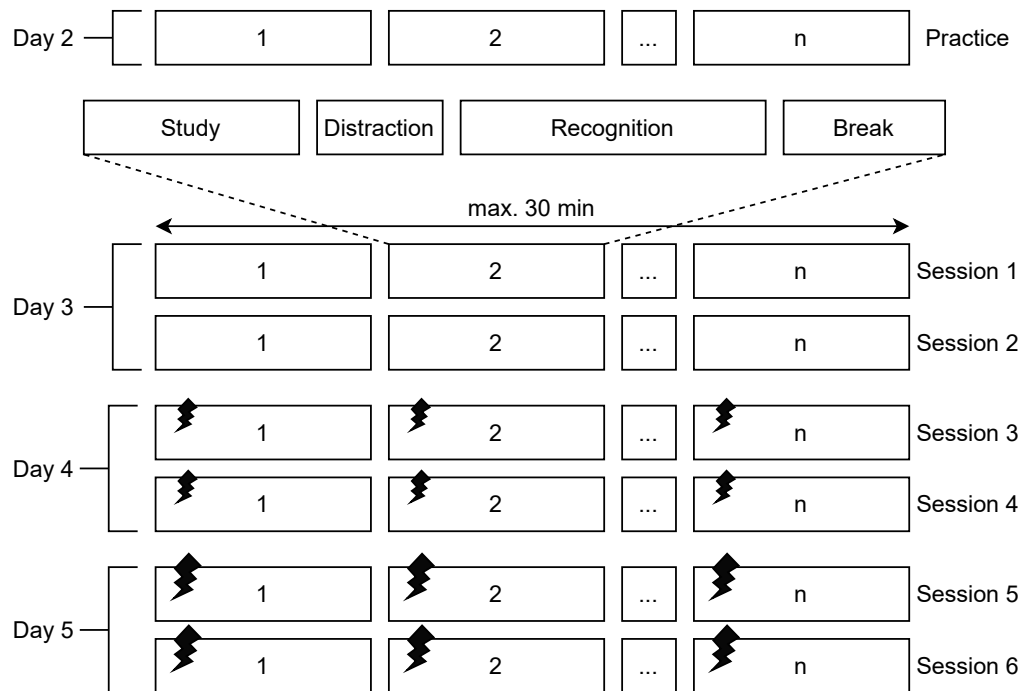


Figure 4.10: Generic outline of the planned clinical protocol for experiments with ANT-DBS patients.

Chapter 5

Out-of-clinic Pilot Experiments

5.1 Estimating The Delay Between Hardware and Software Triggers

Prior studies have shown that for wireless, consumer-grade EEG acquisition systems there may be a considerable delay between the moment a signal is sampled and the moment the packet is delivered to the computer and timestamped [159]. For the Cyton board, timestamps are assigned as soon as the packet is received by the computer, without correcting for this time delay.

The main objectives of this study were fourfold: (1) to verify the whether the photoresistor circuit was operating properly, (2) to investigate the accuracy of BrainFlow’s software triggers, (3) to estimate the delay between the instant the marker is inserted into the data stream by the photoresistor circuit, and the instant said packet reaches the computer, and (4) to verify if said delay changed significantly when using an external monitor for stimuli presentation, as multiple display setups can create unreliable stimuli presentation times on Windows-10 systems.

5.1.1 Methods

Experiment Setup The experiment was carried out using an HP EliteBook 850 G3 laptop. An OpenBCI Cyton board was used to sample the output signal of the photoresistor circuit. During a first run, the photoresistor was attached to the bottom-left corner of the laptop monitor. On a second run, the laptop was connected to an external display, an HP EliteDisplay E231 monitor, through a VGA cable. The photoresistor was attached to the bottom-left corner of the external monitor. Both screens had a refresh rate of 60 Hz. For a description of the setup see section 4.1.

Procedure A full-screen window containing a placeholder image and a white marker (refer to Fig. 4.5A) was shown on the computer monitor, followed by a fixation cross window devoid of a marker. Images and fixation crosses were presented for one and two seconds, respectively. The sequence was repeated one hundred times.

As mentioned previously, individual packet timestamps are not assigned once a packet is sampled, but once it reaches the laptop. Brainflow’s *insert_marker* method allows the user to insert a marker into the data stream, by adding it into the next packet received from the board after its

invocation. Using this method, a marker was inserted into the EEG stream immediately after the completion of the Screen('Flip') command, which Psychtoolbox uses for synchronized stimulus presentation.

Data Analysis The raw signals sampled from the photoresistor circuit were preprocessed using a fifth-order one-dimensional median filter. This step removed unwanted noise, preventing the detection of false edges, and preserved rising edges associated with visual stimuli (see Fig. 5.1). External trigger timestamps were extracted from rising edges above the minimum value recorded by the analog channel, whereas software trigger timestamps were extracted from the marker channel.

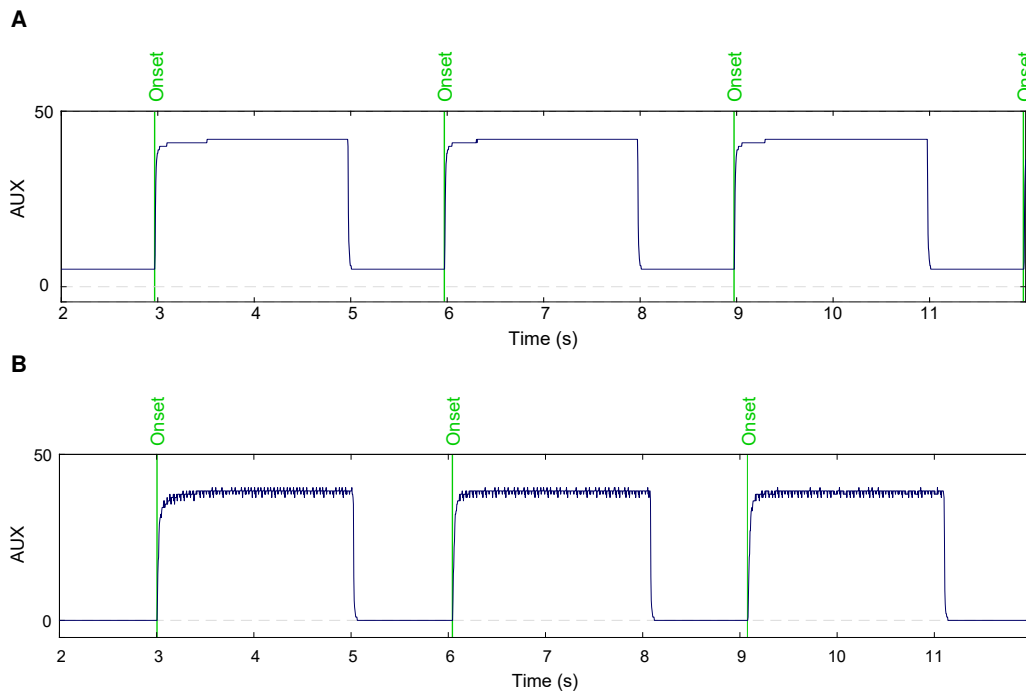


Figure 5.1: Sample photoresistor circuit data acquired during the first three stimuli presentation trials of the latency test. Signals were preprocessed using a fifth-order one-dimensional median filter. (A) Data obtained for the test using the laptop monitor. Events were extracted from rising edges above a predefined threshold value of 5. (B) Data obtained for the test using the external monitor. Events were extracted from rising edges above a predefined threshold value of 0.

5.1.2 Results and Discussion

On average markers inserted by the photoresistor were delayed by 42.39 ms compared to markers inserted by Brainflow, with a standard deviation of 2.31 ms. Using the multi-display setup with an external monitor, we obtained an average delay of 46.28 ms and a standard deviation of 6.79 ms (see Fig. 5.2). These results are somewhat consistent with a previous account by another author [159].

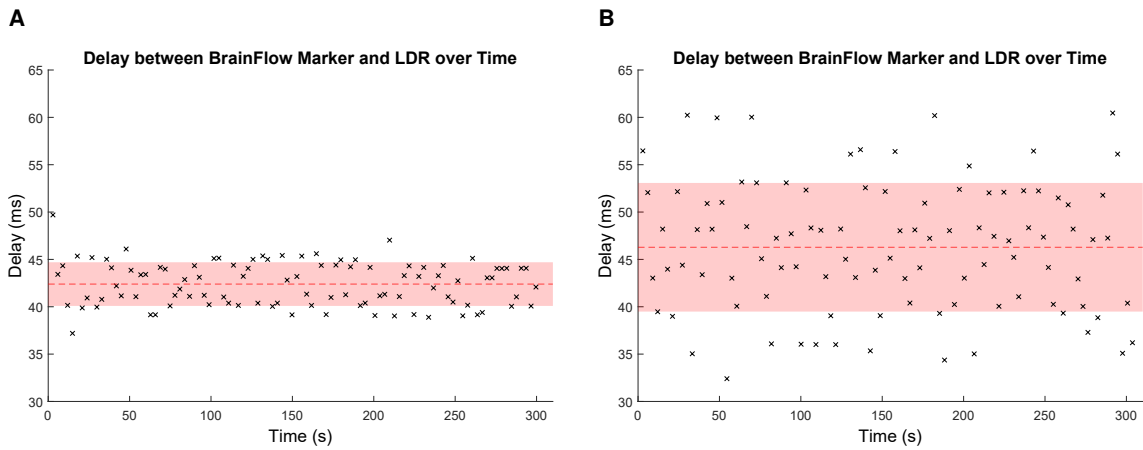


Figure 5.2: Delays between hardware and software-tagged packets over time. The red dashed line indicates the mean, whereas the shaded area covers the standard deviation. (A) Results obtained for single monitor display setup. (B) Results obtained for the multiple monitor display setup.

Delays obtained for the laptop monitor routine appear to follow a bimodal distribution, with two peaks at approximately 40 and 44 ms (see Fig. 5.3). Congruently, most packets tagged by Brainflow preceded rising edges in the photoresistor channel by 10 or 11 packets. In contrast, for the external monitor test delays appear normally distributed.

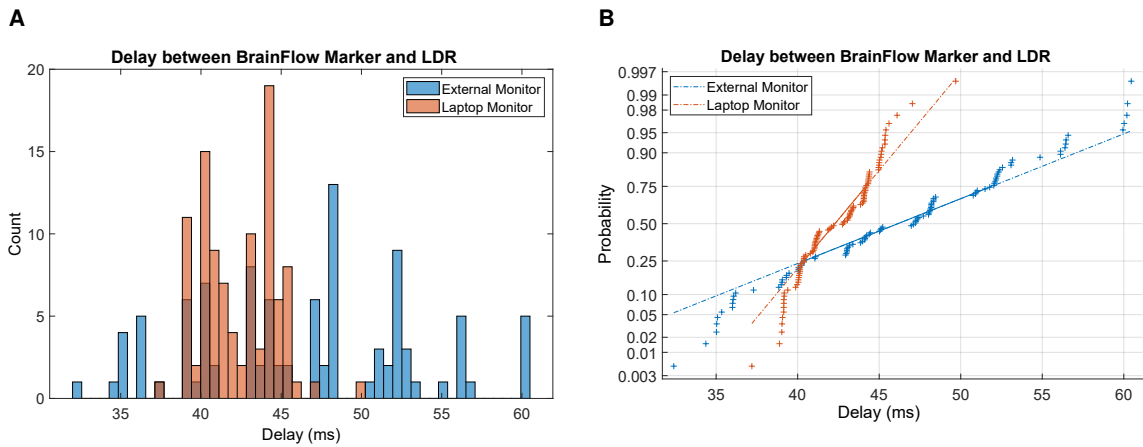


Figure 5.3: Distribution of delays between hardware and software-tagged packets. (A) Packet delay histogram. (B) Normal probability plots for packet delays.

By wiring a photoresistor circuit to the Cyton Board, we were able to accurately tag the onset of visual stimuli. We calculated the lag between packets tagged by Brainflow and packets tagged by the photoresistor to estimate the delay between the moment data is sampled by the board and the moment it is timestamped by the computer. The standard deviation of the delay obtained for the laptop monitor was under 3 ms, which is quite consistent and therefore satisfactory. Using the external monitor, we obtained a slightly longer delay with a wider variance, and a standard deviation above 5 ms. Perhaps counterintuitively, the software triggers preceded the photoresistor

triggers. However, this occurrence may have been caused by two possible contributors: the packet transmission delay and drops in the monitor's refresh rate.

The *insert_marker* method adds the requested marker to a queue. Markers from said queue are progressively attached to the newest packet immediately after its timestamping. Assuming that the marker insertion process is close to instantaneous, we can approximate the instant a packet is timestamped to the instant immediately following stimulus onset. Since there is a transmission delay, as this packet is received and timestamped, a new packet containing the photoresistor trigger is sampled by the board. As a result, the photoresistor trigger is only timestamped once it reaches the computer. Nevertheless, it is inaccurate to assume that the packet is timestamped the instant immediately following stimulus onset. The recorded timestamp is closer to the instant the Screen('Flip') command finishes its execution, after the end of vertical retrace. Therefore, in order to obtain an accurate estimate of the transmission delay, we would have to account for the delay between the end of vertical retrace and the software trigger. However, quantifying this delay was impossible, as Psychtoolbox-3 cannot obtain reliable stimulus onset timestamps because of Window's DWM desktop compositor.

While these results are by no means an accurate estimation of the packet transmission delay, they seem to indicate that relying on Brainflow's software triggers may be a viable option for ERP studies, as long as a single display is used and the delay is accounted for during processing.

5.2 Studying Old-new ERP Effects of Recollected and Familiar Items

Tests with healthy probands were carried out to test the robustness of the experiment setup and design. With this experiment, we intended to reproduce the findings reported in literature and begin collecting a database of healthy controls. The ERP waveforms obtained from these participants would later be contrasted with those obtained from epileptic patients at the EMU.

5.2.1 Experiment 1

5.2.1.1 Methods

Participants Twelve healthy volunteers (four women, average age: 24.7 ± 8.1 years) participated in this study. All participants had normal or corrected-to-normal vision. Three participants only completed two blocks due to technical difficulties, and one participant admitted to being distracted during the first block. One participant was excluded from the EEG analysis altogether given the low-quality of the recording. Participants gave written informed consent before participating in the experiment.

Experiment Setup The experiment was carried out using an HP EliteBook 850 G3 laptop. Visual stimuli were presented to the participants on an HP EliteDisplay E231 23-inch monitor with a 60 Hz refresh rate (see Fig. 5.4A). The photoresistor circuit was attached to the bottom-left corner of the external monitor and connected to the D11 analog pin of the Cyton Board, as shown in Fig.

5.4B. Sessions were recorded using a smartphone. Participants conveyed their responses using a wireless keypad. Refer to chapter 4.1 for an in-depth description of the overall experimental setup.

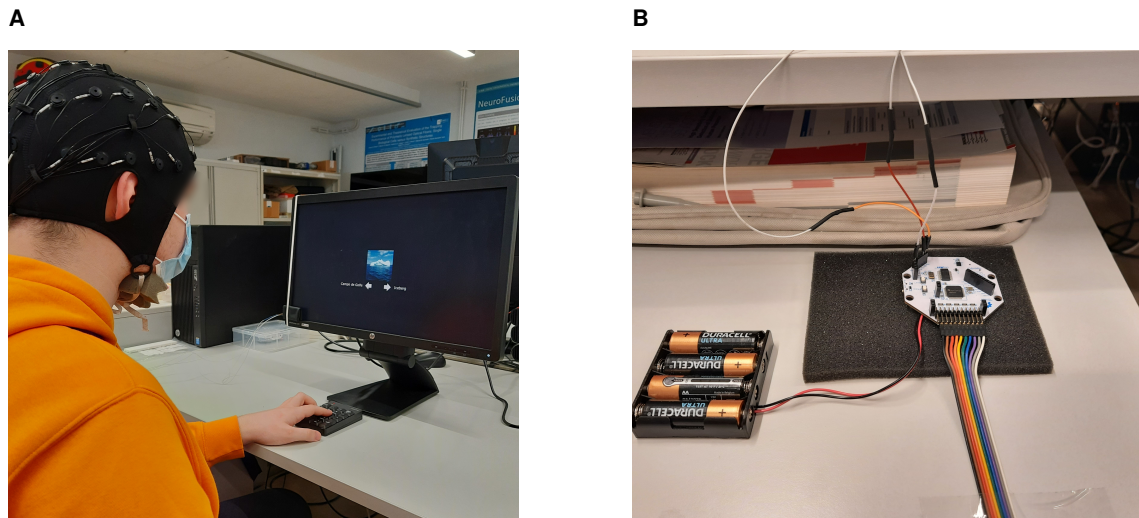


Figure 5.4: Photographs of the out-of-clinic experimental set up. (A) Participants were seated in a comfortable chair at approximately 60 cm from the external monitor and use a keypad to convey their responses. (B) The Cyton Board is used to sample eight EEG channels and the signal from the photoresistor circuit.

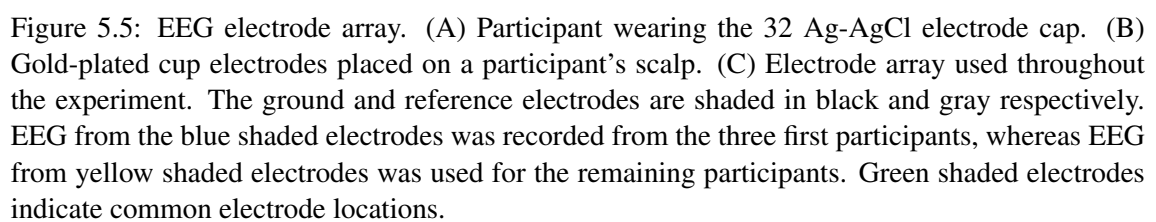
Stimulus Materials Stimuli consisted of 480 images of scenes, grouped into 8 semantic categories. For each participant, category pairs were randomly allocated across four routine blocks. The practice block only required 40 images, whereas regular blocks used 120 images. Stimuli were divided into two subsets of 240 scenes which were counterbalanced across participants so that each subset was “old” just as often as it was “new”. The order of presentation was randomized for both study and recognition phases.

Procedure After giving informed consent, participants were seated in a comfortable chair in a well-lit room at approximately 60 cm from an external monitor. Participants were given clear written instructions, which were read to them by the experimenter, and were shown visual aids related to the memory task (see Appendix B). Before testing, participants completed a practice block in which they performed 20 study trials followed by 40 recognition trials. During practice, they were given corrective feedback for their “recollection” and “familiarity” classifications. Following the practice block, participants provided their interpretation of the distinction between familiarity and recollection and gave examples of their own experiences. Once the electrodes were set up, participants completed three blocks of the single-item recognition memory task, intercalated with 10-minute breaks (see Fig. 4.9). Each block contained 60 study trials followed by 120 recognition trials. During this experiment, participants were asked to justify their “old” responses whenever possible. The experimental paradigm was described in more depth in section 4.2.

EEG Acquisition EEG signals were recorded and amplified with an OpenBCI Cyton board from 8 active electrodes at locations P3, Pz, P4, Fp1, Fp2, F3, Fz, and F4, according to the standard international 10–20 system. Positions P3, Pz, P4, C3, C4, F3, Fz, and F4 were used for the first three participants. This arrangement’s lack of prefrontal electrodes hindered the identification of eye movement and blink artifacts, leading to its replacement. For all participants, the reference electrode was positioned over the vertex (Cz), and the ground electrode over AFz. Two different sized elastic caps with 32 and 64 Ag–AgCl electrodes (Besdata EEG Electrode Cap, Shenzhen Besdata Technology Co., Ltd.) were used throughout the experiment. For the eleventh participant, gold-plated cup EEG electrodes (Dymedix Diagnostics Inc.) were used instead, as the appropriately sized cap was not at our disposal. Signals were sampled at 250 Hz. The electrode-skin impedance was kept below 100 k Ω for all sessions.

Behavioral Data Analysis Video recordings of all participants’ justifications were analyzed to confirm they understood the instructions and make sure their decision criteria remained constant throughout the session. Trials in which participants were visibly distracted during encoding (e.g. whenever they looked away from the computer screen) were discarded from the behavioral analysis. Global memory performance for each block was estimated by the discriminability index (d') and response bias (C). For some participants, false alarm rates were very close to 0 (under 0.05), so both hit and false alarm rates were transformed following the log-linear rule. Additionally, recognition scores for familiarity and recollection were calculated. Recollection was estimated as the proportion of recollected hits minus the proportion of false recollections of novel scenes. Familiarity was estimated by subtracting the familiarity index for false alarms from the familiarity index for hits. Data were analysed using a custom MATLAB (R2019b) script.

EEG Data Analysis Trials in which participants were visibly distracted, spoke prematurely or moved too much were discarded from the EEG analysis. Data were analysed in MATLAB (R2019b) and statistical analyses conducted with SPSS Statistics 27. EEG data were analyzed in EEGLAB (v2021.0) [160], an open source toolbox for MATLAB, and ERPLAB (version v8.10) [161], a plug-in toolbox for EEGLAB designed for ERP analysis. EEG channels recorded from the Cyton Board were inverted prior to analysis, since they were sampled using the analog negative inputs of the board’s primary ADC. Mastoid channels were not recorded for this experiment, so channels were not re-referenced offline. Before filtering, the DC offset of the data was removed. All EEG data were band-pass filtered between 0.1 and 30 Hz (4th order Butterworth filter). The data were then segmented into stimulus-locked epochs (-200 to 1000 ms). Epochs that contained EEG activity above 100 μ V or under -100 μ V were automatically flagged for removal. We also used a 200 ms sliding window, with a 100 ms step, to find epochs containing peak-to-peak activity above 80 μ V. During a final visual inspection of the data the remaining epochs containing undetected artifacts, such as muscle artifacts or saccades, were discarded. The complete ERP processing pipeline is illustrated in 5.6.



For a participant to be included in the analysis, a minimum of 10 artifact-free trials for a given condition was required. We obtained on average: 53 (SD=26) recollection hits, 34 (SD=17) familiarity hits, 1 (SD=2) recollection false alarms, 18 (SD=21) familiarity false alarms, 42 (SD=22) misses, 109 (SD=37) correct rejections, 97 (SD=39) subsequent hits and 43 (SD=22) subsequent misses. For the purpose of this experiment, encoding trials were not analyzed. One participant was discarded from the ERP analysis, as they did not meet the minimum trials requirement.

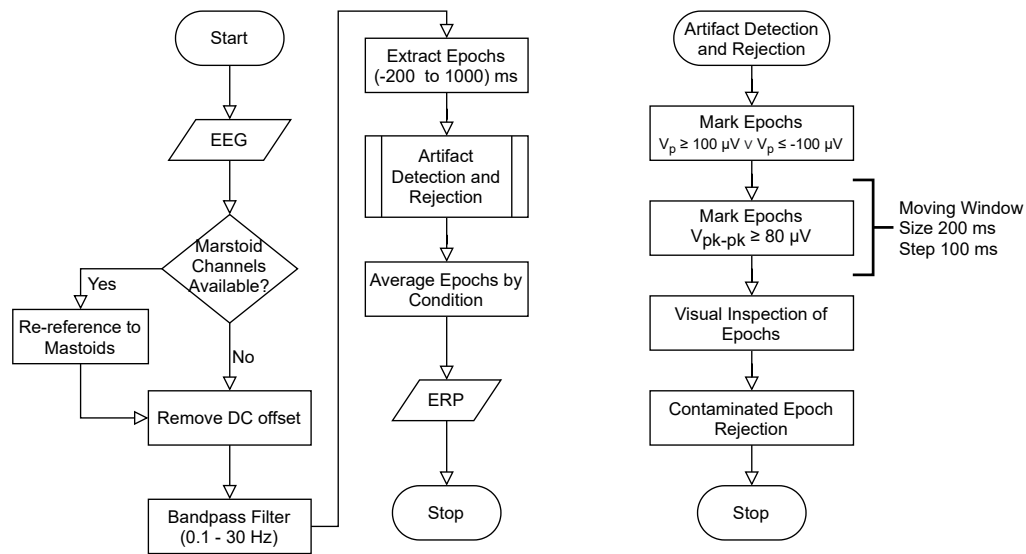


Figure 5.6: ERP processing pipeline used for the out-of-clinic studies.

Statistical Analysis Statistical analyses were conducted with SPSS Statistics 27. Two time windows of interest were selected according to the findings of previous studies on the FN400 and LPC effects. Consequently, frontal amplitudes in the 300-500 ms interval and parietal amplitudes in the 500-800 ms interval were measured. Repeated measures ANOVA analyses were conducted to find statistically significant effects. Two within-subject factors were used: condition (recollection hits, familiarity hits and correct rejections) and laterality (left, midline, right). Greenhouse-Geisser corrected p-values are reported whenever the sphericity assumption is violated. Significant effects were followed up by Bonferroni-adjusted significance tests for pairwise comparisons.

5.2.1.2 Results and Discussion

Behavioral Performance We found a mean hit rate of 0.68 (SD = 0.17) and a false alarm rate of 0.16 (SD = 0.13). Participants obtained an average d' of 1.71 (SD = 0.51) and a C of 0.31 ($D=0.48$), which is indicative of a relatively high performance and a somewhat conservative bias. Finally, we found an average recollection index of 0.41 (SD = 0.18) and an average familiarity score of 0.34 (SD = 0.14). While direct comparisons are difficult, the latter scores are in line with other previous studies that used the RK paradigm (see [117] for a review). Average scores obtained for each participant are displayed in Table 5.1

Compared to other studies in the same vein, this study obtained higher performance scores and lower false alarm rates. A study by Wynn et al., for example, in which participants encoded a set of abstract pictures, obtained an average d' of 1.11 (SD = 0.38), with the same mean hit rate of 0.68 (SD = 0.12), but a much higher false alarm rate of 0.30 (SD = 0.14) [135]. In our study, participants were less willing to classify items as old. We postulated that using sets of highly similar scenes within the same category would increase the false alarm rate. Instead, we observed an opposite effect, with some participants actively dismissing old scenes believing them to be foils.

Table 5.1: Behavioral performance measures obtained for Experiment 1

SUBJECT	no. B	Hit ¹	FA ¹	d'	C	RI	FI
200	2	0.34 (0.01)	0.04 (0.02)	1.37 (0.24)	1.09 (0.15)	0.16 (0.02)	0.18 (0.01)
20C	2	0.73 (0.12)	0.17 (0)	1.58 (0.36)	0.16 (0.18)	0.4 (0.08)	0.39 (0.14)
26E	3	0.78 (0.07)	0.13 (0.01)	1.93 (0.19)	0.17 (0.13)	0.52 (0.07)	0.44 (0.09)
29E	3	0.66 (0.18)	0.07 (0.03)	1.95 (0.6)	0.54 (0.22)	0.44 (0.13)	0.35 (0.21)
2B8	3	0.92 (0.08)	0.37 (0.08)	1.82 (0.29)	-0.57 (0.33)	0.73 (0.14)	0.19 (0.39)
2DA	3	0.82 (0.07)	0.11 (0.04)	2.19 (0.45)	0.17 (0.08)	0.5 (0.03)	0.54 (0.15)
37D	2	0.52 (0.08)	0.09 (0.02)	1.41 (0.06)	0.64 (0.17)	0.27 (0.01)	0.26 (0.08)
3B2	2	0.65 (0.07)	0.02 (0.01)	2.57 (0.12)	0.9 (0.25)	0.23 (0.14)	0.53 (0)
40E	3	0.88 (0.08)	0.19 (0.1)	2.14 (0.7)	-0.15 (0.1)	0.62 (0.24)	0.51 (0.12)
4D4	3	0.46 (0.09)	0.17 (0.06)	0.89 (0.42)	0.54 (0.11)	0.17 (0.16)	0.18 (0.08)
5D4	3	0.76 (0.04)	0.43 (0.08)	0.87 (0.29)	-0.27 (0.1)	0.35 (0.05)	0.2 (0.1)
65E	3	0.66 (0.04)	0.08 (0.03)	1.81 (0.2)	0.49 (0.14)	0.48 (0.11)	0.26 (0.08)
AVERAGED		0.68 (0.17)	0.16 (0.13)	1.71 (0.51)	0.31 (0.48)	0.41 (0.18)	0.34 (0.14)

Headers: no. B - Number of blocks completed; FA - False Alarm Rate; d' - Discriminability index; C - Response bias; RI - Recollection Index; FI - Familiarity Index

¹ Hit and false alarm rates **following** *log-linear* transformation.

On the other hand, it is important to note that memory studies with healthy participants have them encode a greater number of items, usually over 100. Considering our experimental routine was limited to 60 study items per task, the obtained false alarm rate is perfectly reasonable.

The experiment routine generator restricts the maximum number of study items, as it is intended to create routines for patients undergoing ANT-DBS. These patients, namely those with refractory TLE, can experience a broad range of episodic memory dysfunction [162]. We have observed that most memory studies on this population follow the same trend of keeping the amount of study items under 60 [7, 103, 108, 158, 163]. In [7], for example, participants were only exposed to 50 items at study and obtained a mean hit rate of 0.51 (SEM = 0.11), a mean false alarm rate of 0.27 (SEM = 0.11) and a mean d' of 0.75 (SEM=0.12), which is indicative of relatively low memory performance. From these observations, one could deduce that increasing the number of study items would make the memory task too difficult and potentially impair the recognition of old items. Nevertheless, it's worth mentioning that [141], who presented 200 items at study, obtained a comparable mean hit rate of 0.546 (SD = 0.191) and a mean false alarm rate of 0.27 (SD = 19.1), yielding a d' of 0.73. This case is a testament to the fact that there are other factors at play, such as task complexity and inter-subject variability. Designing a more versatile routine generator might be more beneficial in the long run.

Event-related Potentials The grand average ERPs do not reveal any clear significant deflections within the time windows of interest (see Fig. 5.7). The LPC is seemingly absent for all three conditions. Strangely enough, we observed an increased negativity for recollection hits, which directly contradicts the literature (see section 3.3).

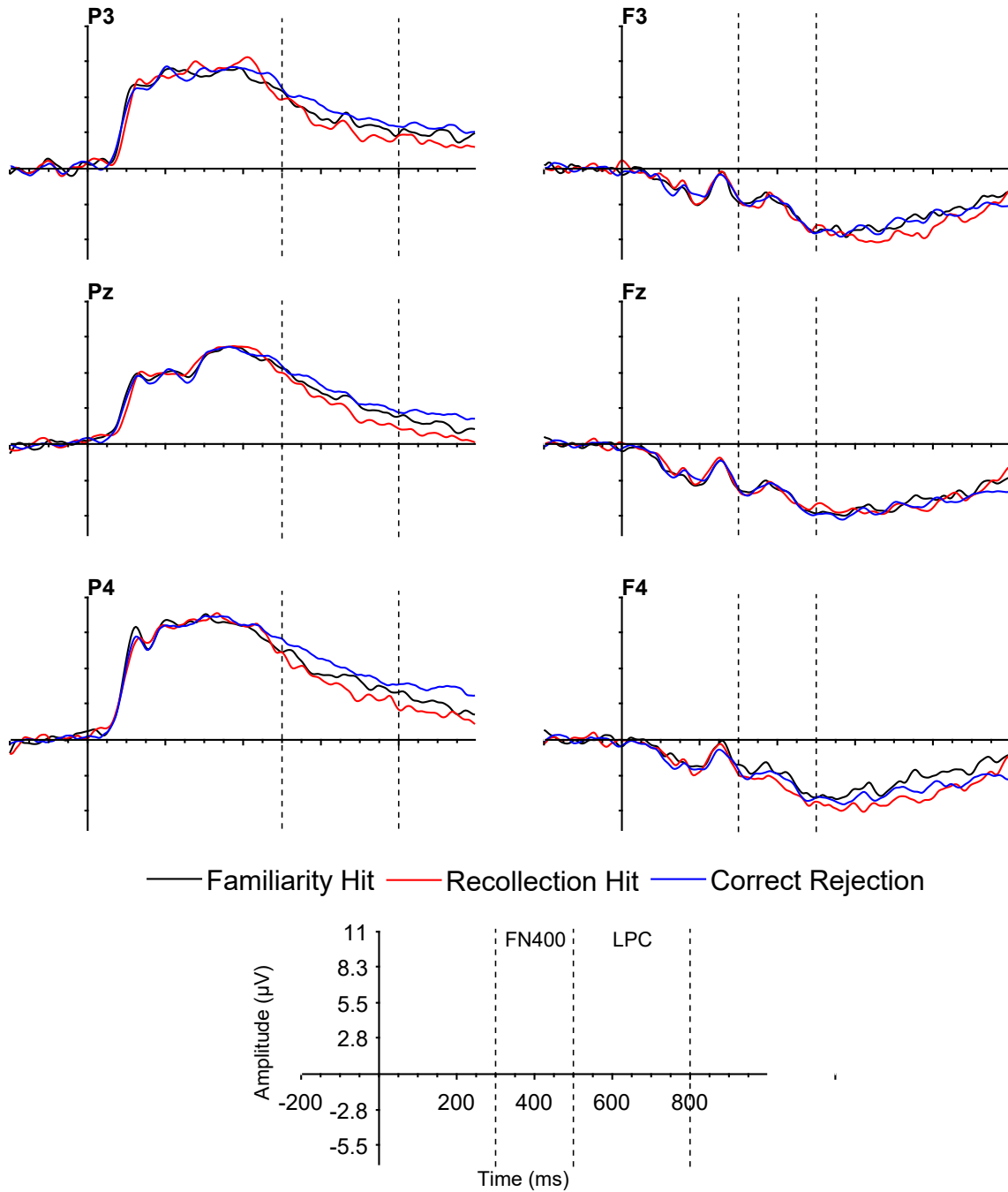


Figure 5.7: Grand average ERP waveforms for the ten participants. Labeled axes common for all graphs are displayed underneath the legend.

FN400 A repeated measures ANOVA analysis revealed no significant effects for condition ($F(2, 18) = 0.148, p = .864, \eta_p^2 = 0.016$) or laterality ($F(2, 18) = 2.210, p = .139, \eta_p^2 = 0.197$). We found no significant interaction between within-subject factors ($F(4, 36) = 1.468, p = .232, \eta_p^2 = .140$).

LPC We found a significant effect of condition ($F(2, 18) = 3.620, p = .048, \eta_p^2 = 0.287$). However, post-hoc Bonferroni-adjusted pairwise comparisons revealed no statistically significant effects, despite showing an amplitude increase for correct rejections compared to recollection responses ($M_{diff} = 1.240, 95\% CI [-0.191, 2.670], p = .095$). No significant effects for laterality ($F(2, 18) = 2.945, p = .078, \eta_p^2 = 0.247$) were found. No significant interaction between within-subject factors was found either ($F(2.104, 18, 936) = 0.700, p = .516, \eta_p^2 = 0.072$).

The FN400 and LPC effects are absent from the computed ERP waveforms, and the parietal ERP waveforms seem to directly contradict previous findings. Upon taking note of the differences between this study and its predecessors, a potential cause for these lackluster results becomes apparent: an erroneous reference selection.

In studies investigating ERP activity at the midline sites, it is a standard practice to re-reference the data offline to the linked mastoids, by subtracting the average of the potentials recorded from two electrodes positioned over the left and right mastoid processes. The scalp electrode array used at the EMU includes a physical reference at FCz but does not include mastoid electrodes. One of the goals of this preliminary study was to begin amassing a database with healthy controls, whose EEG signals would later be compared with those obtained from epileptic patients. In an effort to emulate the clinical setup, a physical vertex (Cz) reference was used throughout this study. In doing so, not only did we overlook the possibility to re-reference the data offline to a virtual reference, but we also neglected to consider the impact that this would have on the ERP waveforms, which are known to be reference-dependent [164]. Not to mention, there is a general consensus that FCz and Oz references create considerable distortions in EEG potentials [165], and should, therefore, be avoided when measuring local activity from cephalic target sites [166].

We suspect that failing to re-reference the data to a more electrically neutral site distorted the ERPs. As a result, the obtained ERPs cannot be directly compared with those reported in literature. A follow-up experiment was conducted to confirm our hypothesis and rectify this issue.

5.2.2 Experiment 2

5.2.2.1 Methods

Participants Seven healthy volunteers (three women, average age: 22 ± 1.3 years) participated in this study. One of the participants could not complete all three blocks, as they were too exhausted to continue.

Experiment Setup The setup was the same as in Experiment I.

Stimulus Materials The follow-up experiment used the same number of stimuli as Experiment I, as the experimental paradigm was also the same. Different images were picked for this experiment so that returning participants would be seeing them for the first time.

Procedure The procedure was the same as in Experiment I.

EEG Acquisition During the follow-up experiment, EEG signals were recorded from 8 active electrodes at locations P3, P4, Fp1, Fp2, F3, F4, TP9 and TP10. For all participants, the reference electrode was positioned over the vertex (Cz), and the ground electrode over AFz. Gold-plated cup EEG electrodes (Dymedix Diagnostics Inc.) were used for all participants instead of the electrode cap. Signals were sampled at 250 Hz. The electrode-skin impedance was kept below 100 k Ω for all sessions.

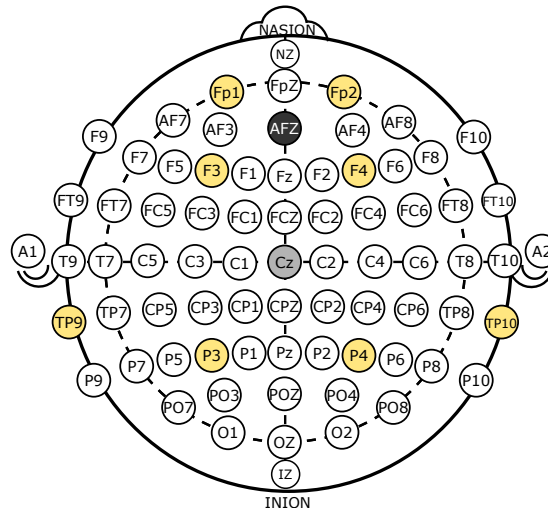


Figure 5.8: Electrode array used throughout the experiment. The ground and reference electrodes are shaded in black and gray respectively. The remaining electrodes are shaded in yellow.

Behavioral Data Analysis The same analyses as Experiment 1 were conducted.

EEG Data Analysis EEG signals were re-referenced offline to the average of the left (TP9) and right (TP10) mastoid channels. For comparison's sake, a copy of all datasets was processed without offline re-referencing. The remaining ERP processing pipeline was described in Experiment I (see Fig. 5.6). One participant was discarded from further analyses, as they did not meet the minimum trials requirement. We obtained on average 53 (SD=33) recollection hits, 42 (SD=22) familiarity hits, 2 (SD=3) recollection false alarms, 21 (SD=12) familiarity false alarms, 42 (SD=14) misses, 109 (SD=29) correct rejections, 93 (SD=29) subsequent hits and 40 (SD=13) subsequent misses.

Table 5.2: Behavioral performance measures obtained for Experiment 2.

SUBJECT	no. B	Hit ¹	FA ¹	d'	C	RI	FI
001	3	0.71 (0.06)	0.15 (0.02)	1.59 (0.11)	0.24 (0.12)	0.19 (0.03)	0.5 (0.04)
002	3	0.71 (0.09)	0.17 (0.13)	1.7 (0.94)	0.29 (0.29)	0.48 (0.16)	0.28 (0.13)
003	3	0.63 (0.02)	0.18 (0.03)	1.25 (0.19)	0.3 (0.04)	0.26 (0.09)	0.32 (0.01)
004	3	0.73 (0.07)	0.35 (0.12)	1.03 (0.1)	-0.11 (0.27)	0.33 (0.05)	0.25 (0.05)
005	3	0.8 (0.09)	0.21 (0.08)	1.68 (0.45)	-0.01 (0.21)	0.58 (0.14)	0.28 (0.13)
006	2	0.44 (0.06)	0.04 (0.02)	1.63 (0.42)	0.96 (0.06)	0.12 (0.06)	0.33 (0.05)
007	3	0.74 (0.12)	0.16 (0.12)	1.76 (0.89)	0.2 (0.12)	0.42 (0.11)	0.42 (0.26)
AVERAGED		0.68 (0.12)	0.18 (0.09)	1.52 (0.27)	0.27 (0.34)	0.34 (0.16)	0.34 (0.09)

Headers: no. B - Number of blocks completed; FA - False Alarm Rate; d' - Discriminability index; C - Response bias; RI - Recollection Index; FI - Familiarity Index

¹ Hit and false alarm rates **following** *log-linear* transformation.

Statistical Analysis The same analyses as Experiment 1 were conducted. Only the re-referenced data were submitted for statistical analysis. Unlike the previous analysis, the laterality factor used had only two levels (right and left hemisphere).

5.2.2.2 Results and Discussion

Behavioral Performance We found a mean hit rate of 0.68 (SD = 0.12) and a false alarm rate of 0.18 (SD = 0.09). Participants obtained an average d' of 1.52 (SD = 0.27) and a C of 0.27 (D=0.34). We found an average recollection index of 0.34 (SD = 0.16) and an average familiarity score of 0.34 (SD = 0.09). Average scores obtained for each participant are displayed in Table 5.2.

Event-related Potentials Grand average ERP waveforms were obtained for vertex and linked mastoid references (see Fig. 5.9 and 5.10). Using the vertex reference, we managed to reproduce the ERPs waveforms obtained for Experiment 1. For frontal sites no clear condition-related negative deflections are visible around the 300-500 ms time window (see Fig. 5.9A). Again, for parietal sites we observed an increased negativity for recollection hits compared to correct rejections (see Fig. 5.10A). Re-referencing the EEG data to the linked mastoids produced drastically different waveforms, consistent with those reported in prior memory studies. The FN400 effect is clearly visible in frontal sites – the negative deflection appears be attenuated for familiarity hits, as is expected (see Fig. 5.9B). Likewise, a late positive deflection characteristic of the LPC was found for recollection hits (see Fig. 5.10B). Further visual inspection of the frontal ERP waveforms revealed the occurrence of a late frontal positive effect for recollection hits, after approximately 800 ms. While this finding is beyond the scope of the current study, its worth mentioning that a similar effect has been proposed to reflect post-retrieval processing [167]. This effect may be worth exploring in future follow-up analyses.

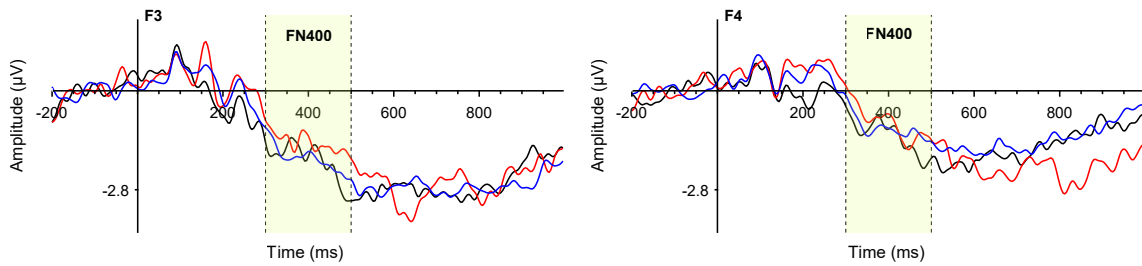
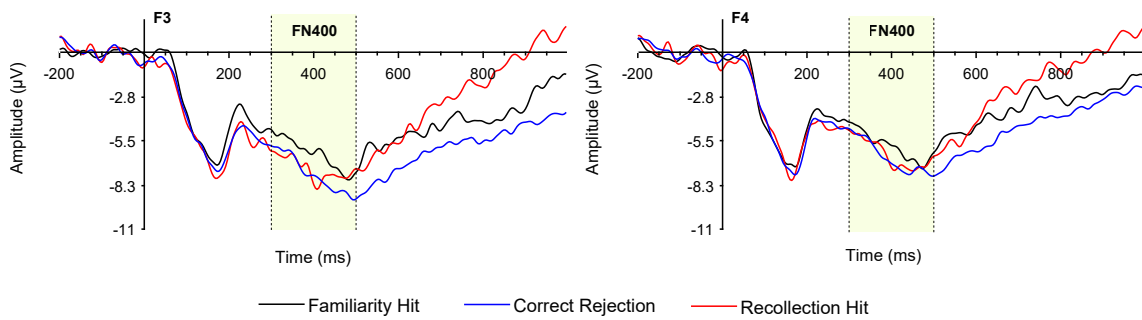
A**B**

Figure 5.9: Grand average frontal ERPs waveforms. (A) Frontal ERPs for vertex reference. (B) Frontal ERPs for linked mastoid reference.

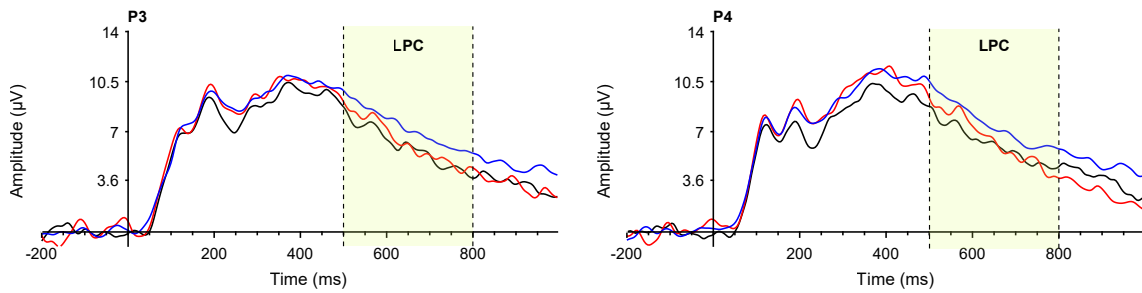
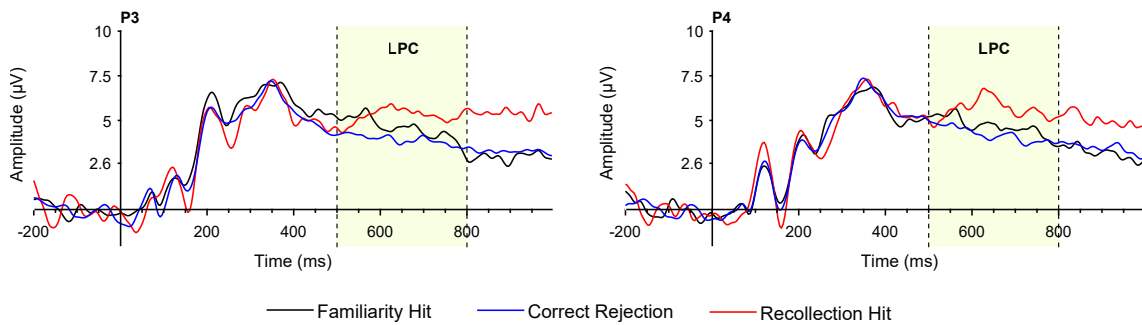
A**B**

Figure 5.10: Grand average parietal ERPs waveforms. (A) Parietal ERPs for vertex reference. (B) Parietal ERPs for linked mastoid reference.

FN400 A repeated measures ANOVA analysis revealed no significant effects for condition ($F(2, 10) = 1.805, p = 0.214, \eta_p^2 = 0.265$) or laterality ($F(1, 5) = 0.954, p = 0.374, \eta_p^2 = 0.160$). We found no significant interaction between within-subject factors ($F(2, 10) = 1.434, p = 0.283, \eta_p^2 = 0.223$).

LPC We found no statistically significant main effects for condition ($F(2, 10) = 2.755, p = 0.111, \eta_p^2 = 0.355$) or laterality ($F(1, 5) = 0.108, p = 0.755, \eta_p^2 = 0.021$). The analysis revealed no significant interaction between within-subject factors ($F(2, 10) = 0.259, p = 0.777, \eta_p^2 = 0.049$).

Despite the grand average ERP waveforms for each condition showing the expected effects, we were unable to find any statistically significant differences in mean amplitude within the time windows of interest. These results are far from discouraging, however, as they likely stem from the low sample size used for our statistical analysis. Regardless, with this follow-up experiment we were successfully able to prove that the previous experiment was jeopardized by the reference choice.

While we were able to reproduce the results reported in ERP recognition memory literature, we ought to mention that the low number of electrodes used in this study limited our analysis by greatly lowering the spatial resolution of the recordings. Computing accurate topographic distributions of the ERP effects was impossible, for example. Additionally, we were unable to perform artifact removal with ICA. As it stands, for most participants ICA decomposition was incapable of fully separating the ocular artifact components. PCA too, was not a viable option, as it has been proven to be unable to perform the separation completely, especially when the artifacts and brain signals have approximate amplitudes [143, 168, 169].

5.3 Final Remarks

The present study assessed the validity of the experimental protocol proposed in chapter 4, through a series of pilot experiments on healthy probands. Results of the synchronization test showed that tagging the neurodata stream using an external photoresistor sensor circumvented Cyton's packet latency issue and the limitations imposed upon Psychtoolbox-3 by the operating system. Following a first round of experiments, we verified that the obtained ERP waveforms were substantially different from the ones reported in literature. After identifying a potential cause for these disparate results, a follow-up experiment with both new and returning participants was carried out. The follow-up experiment was successful, as both LPC and FN400 effects were clearly visible in the computed grand average ERP waveforms. Due to time constraints and other restrictions imposed upon us by the pandemic, however, we were unable to repeat the experiment with enough participants to achieve statistically significant results. Nevertheless, we were able to confirm the validity of the experimental protocol.

While the experimental protocol is ready to be implemented in the clinic, there are several limitations of the paradigm that must not be overlooked. From our experience with the healthy

probands, we believe that implementing the RK paradigm in a clinical environment like the EMU may be difficult. Throughout our experiments, it became clear that the instructions were lengthy, even though they were written clearly and concisely. Considering that multiple tasks would be performed over the course of several days, it is unrealistic to expect that every participant would remember the instructions, and by extension the distinction between recollection and familiarity, perfectly. Each day, there would be a need to re-instruct the participant and repeat the practice sessions, which would drag out the experiment. On the topic of experiment length, we verified that justifying every old response frequently caused participants to ramble, extending the experiment further (some tasks took as long as 30 minutes, when they could have been completed under 20 minutes). This approach did have its advantages as it allowed us to identify erroneous classifications, misclicks or absentminded responses, that would otherwise go undetected. These were very sporadic, however, so monitoring the entire retrieval process might not be worthwhile. Asking participants to justify their responses during the practice sessions to assess their understanding of the paradigm should suffice.

Another drawback of our current implementation of the RK paradigm is its lack of control for memory strength. A recent study suggests that the electrophysiological effects observed for the subjective classification of recollected and familiar items, may instead be linked to mnemonic strength [122]. Notably, their exploratory analysis revealed that strong “Know” responses (familiarity) yielded significantly larger mean amplitudes, within a 500-1000 ms time window, compared to weak “Remember” responses (recollection). The authors do stress, however, that further validation of this effect in future studies is necessary.

For that reason, future comparison studies between the neural signatures of recollection and familiarity responses should include measurements of mnemonic strength, such as perceived memory confidence ratings. One could argue, however, that introducing a perceived confidence rating task to the paradigm would complicate it further. Another option would be to abandon the RK judgements completely and run a simple “Old/New” task with confidence ratings, as these tasks tend to be more intuitive and straightforward. Unfortunately, that would mean forgoing the ability to derive recollection and familiarity indexes for each participant. As was mentioned previously in section 4.2, deriving stable ROCs to estimate the contribution of both processes to recognition performance requires a large number of responses from each participant (≥ 60 per condition). Since we were recommended to keep testing sessions under thirty minutes, this option may not be appropriate. Both tasks have their pros and cons, so it ultimately depends on how receptive the patients will be. Pilot testing with the target population is required.

Chapter 6

In-Clinic Implementation

Two short pilot experiments in the clinic were conducted in preparation for the admittance of a new ANT-DBS patient to the EMU. However, the week before their hospitalization, the patient started showing signs of an infection over the IPG and the extender cables. Therefore, they were unable to proceed with the treatment. This chapter reports on the results obtained during our pilot experiments with a healthy proband at the EMU environment.

6.1 Validating The Hardware Trigger Setup

Before moving onto the cognitive experiment, a shorter mock experiment was carried out to validate the photoresistor trigger circuit. Using the synchronized video, we identified timestamps corresponding to the instant stimuli were presented on the screen and compared them to the timestamps tagged by the photoresistor. The purpose of this experiment was not to obtain a millisecond-precise estimate of the delay between timestamps, but to verify that the photoresistor tags were being consistently inserted into the neurodata stream without major persistent delays.

6.1.1 Methods

Experiment Setup The experiment was carried out using an HP EliteBook 850 G3 laptop, which was set up in the monitoring room. The laptop was connected to an external display, an HP Pavilion 23xi IPS LED Backlit monitor with a refresh rate of 60 Hz, through an HDMI cable and a DisplayPort to HDMI 1.4 Adapter. The external monitor was set up in the patient's room, on top of an overbed table, so it would be facing towards a ceiling-mounted video camera. As depicted in Fig. 6.1, the photoresistor was attached to the bottom-left corner of the external monitor. An SD LTM 64 EXPRESS Headbox was used to sample the output signal of the photoresistor circuit (see section 4.1 for an in depth description of the connection). The DC channels were set to a 4.8 V range (4.69 mV/digit). Through a separate computer with an installation of Micromed's SystemPlus Evolution software, the experimenter monitored the data acquired by the Headbox in real-time.

Procedure We ran a routine composed of two blocks, each with 16 study images and 16 additional novel images, for a total of 96 visual stimuli (see Fig. 4.9, for an outline of the stimulation protocol). The outline of the routine was previously described in detail in chapter 4. The external monitor was recorded at 25 fps using the vEEG camera, which gave us an approximate resolution of 40 ms.

Data Analysis In order to validate the proper synchronization of the visual stimuli with the vEEG stream, the delay between events derived from the video recording and events derived from rising edges in the photoresistor channel was calculated. Since Psychtoolbox-3 cannot synchronize the stimulus onset with the vertical retrace on Windows-10 systems, some of the screens may show incompletely drawn stimuli overlapping the previous screen. Using Micromed's SystemPlus software, we reviewed the video footage of the experiment and flagged two types of events: **onset events**, the very first video frame where the stimulus starts being drawn, sometimes overlapping the previous screen; and **image events**, the first video frame in which the visual stimulus, the image, is completely drawn. Hardware trigger timestamps were extracted from the raw photoresistor signal, from rising edges above 50 mV. This threshold value was determined empirically, so to minimize the detection of false edges. Figure 6.1 shows all event markers defined during this analysis for a single stimulus presentation.

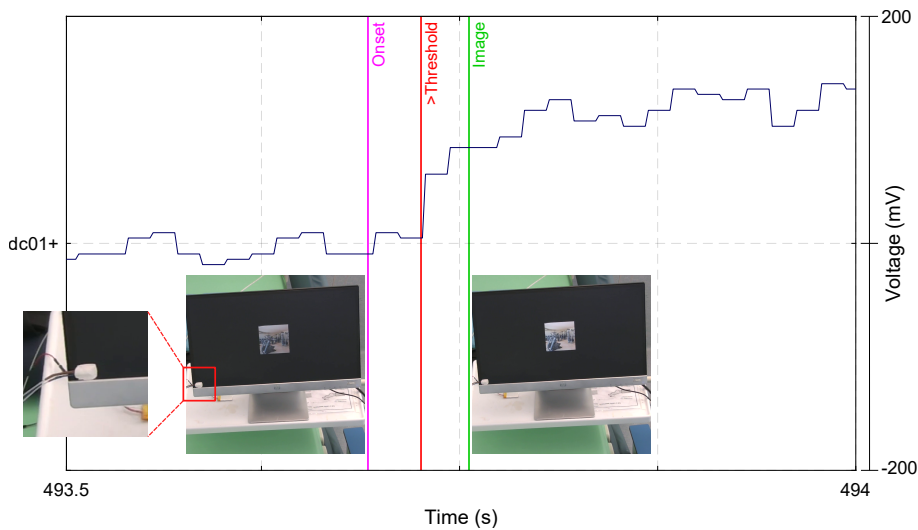


Figure 6.1: Event markers defined using vEEG and rising edges in the photoresistor channel.

6.1.2 Results and Discussion

On average markers defined by the photoresistor were delayed by 35.31 ms compared to the onset events, with a standard deviation of 22.82 ms (see Fig. 6.2A). Conversely, photoresistor markers preceded image events by 3.20 ms, with a standard deviation of 22.89 ms. The delays are normally distributed (see Fig. 6.2B). Considering that all timestamps taken from the video have an

uncertainty of 40 ms, our delay estimates were also affected by the same uncertainty ($\Delta t_{LDR-onset} = 35 \pm 40$ ms and $\Delta t_{LDR-image} = -3 \pm 40$ ms). Even then, we can be sure that the photoresistor timestamps are properly synchronizing the stimulus onset with the EEG stream. To obtain higher precision estimates, one would need to record the experiment at a higher framerate.

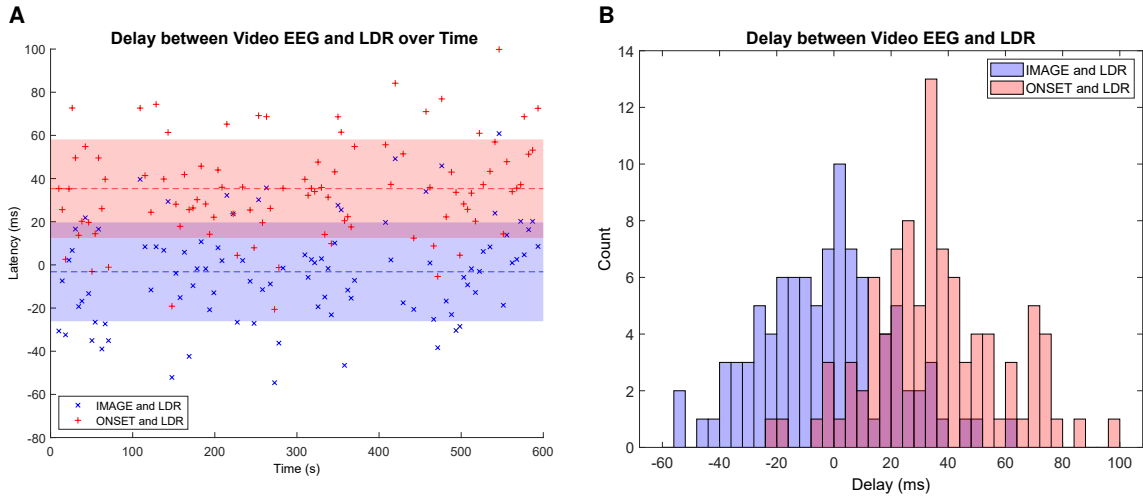


Figure 6.2: Distribution of delays between hardware- and video-tagged timestamps. (A) Delay distribution over time. The dashed lines indicates the mean, whereas the shaded areas cover the standard deviation. (B) Timestamp delay histogram.

A portion of the raw analog signal sampled by the Headbox's first DC channel is displayed in Fig. 6.3. When set to the 4.8 V range, the analog signals sampled from the Headbox appear to be affected by some baseline noise. It is, therefore, difficult to determine the start of the rising edge – the instant immediately following stimulus onset – with precision. While the rising edges of the signal are still easily detectable using a simple voltage threshold, this approach will introduce a constant lag associated with the photoresistor's response time. This delay should, in theory, be constant, so markers should not be jittered too severely. For future experiments, the signal should be sampled using the smaller dynamic range of 0.48 V, to allow the detection of the beginning of the rising edge. A better solution, perhaps, would be to replace the photoresistor altogether with a faster light sensing device, such as a photodiode.

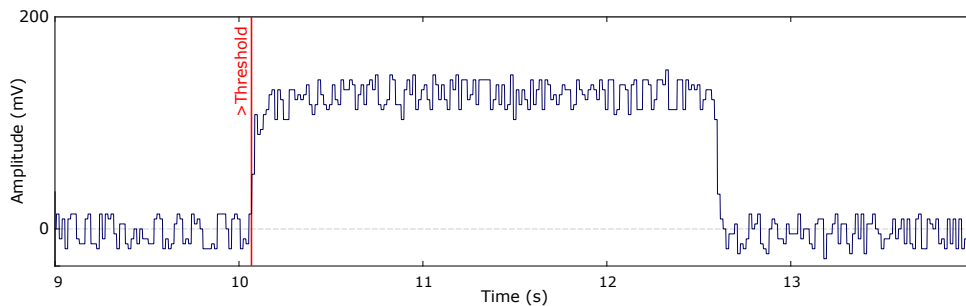


Figure 6.3: Photoresistor circuit signal acquired in-clinic during the presentation of a single stimulus.

6.2 Studying Old-new ERP Effects of Recollected and Familiar Items

6.2.1 Methods

Participant One healthy volunteer (female, 23 years old) participated in this pilot study. The participant was already acquainted with the task, as they participated in the out-of-clinic follow-up experiment.

Experiment Setup The experiment setup was the same as described in the previous section, only this time the external monitor was turned away from the ceiling-mounted video camera, towards the bed (see Fig. 6.4A). The participant sat comfortably on the bed at approximately 60 cm from the external monitor (see Figures 6.4B and 6.4C). The clinicians and the experimenter oversee the experiment from the monitoring room, through the video footage (see Fig. 6.4D). An intercom system allows them to communicate with the participant and provide instructions. Due to a technical issue, the video footage of the experiment was lost.



Figure 6.4: Photographs of the in clinic experimental set up. (A) The external display, set on top of an overbed table, and the photoresistor sensor, attached to the bottom-left corner of the screen. (B) Photograph of the participant sitting on one of the EMU's beds at approximately 60 cm from an external monitor. (C) Photograph of the participant using the wireless keypad to convey their responses. (D) Photograph of the monitoring room, including the laptop used to run the routine and the monitoring screens. An intercom is placed in the leftmost corner of the room.

Procedure Once the electrodes were set up by the EMU’s technician, the participant completed three blocks of the single-item recognition memory task, intercalated with 10-minute breaks. Each block contained 60 study trials followed by 120 recognition trials (see Fig. 4.9). During this experiment, the participant justified their “old” responses whenever possible. Again, the experimental paradigm was described in more depth in section 4.2.

Behavioral Data Analysis The same analysis as the out-of-clinic experiments was conducted. Participant justifications could not be reviewed as the footage for the experiment was lost.

EEG Data Analysis Bad channels were rejected if they flatlined for more than 5 seconds or if the amount of powerline noise exceeded four times the standard deviation from the total channel population mean. Bad sections of data and idle periods between blocks were then rejected based on visual inspection. EEG signals were re-referenced offline to the average of the electrode sites closest to the mastoids: P9, to the left, and P10, to the right. A copy of the dataset was band-pass filtered between 1 and 30 Hz, as previous studies have determined that high-pass filtering the data prior to ICA decomposition improves its quality [170]. The dataset was submitted to ICA decomposition, using EEGLAB’s SOBI algorithm [147]. ICA weights and sphere matrices

were copied to the 0.1 Hz filtered dataset. Ocular and muscular ICs were removed from the data. The remaining ERP processing pipeline was the same as Experiment I. A complete schematic of the extended ERP processing pipeline can be seen in 6.6. We obtained 57 recollection hits, 43 familiarity hits, 18 familiarity false alarms, 75 misses, 155 correct rejections, 102 subsequent hits and 76 subsequent misses.

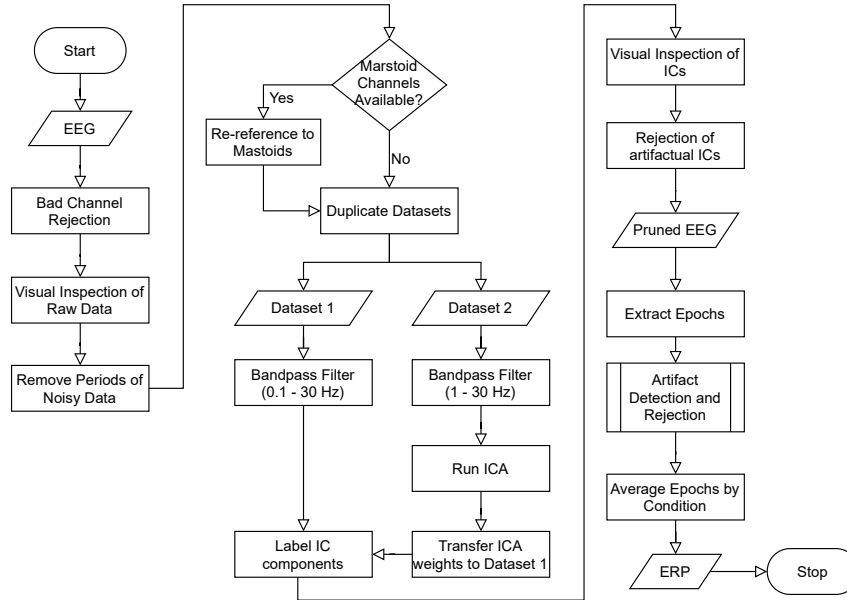


Figure 6.6: ERP processing pipeline used for the in-clinic pilot experiment. The artifact detection and rejection subroutine is the same as the one displayed in Fig. 5.6.

6.2.2 Results and Discussion

Behavioral Performance The participant obtained a mean hit rate of 0.57 ($SD = 0.08$), a mean false alarm rate of 0.12 ($SD=0.06$), a mean d' of 1.38 ($SD=0.48$) and a mean C of 0.51 ($SD=0.12$). The latter is indicative of a somewhat conservative bias. The average calculated recollection index was 0.33 ($SD=0.06$) and the average familiarity index 0.25 ($SD=0.11$). Compared to the out-of-clinic follow-up experiment, the participant's average performance was slightly lower (see scores for Subject 007, in Table 5.2).

Event-related Potentials ERP waveforms for frontal and parietal electrodes are displayed in Figures 6.7 and 6.8 respectively. Visual inspection of the results reveals highly similar ERP waveforms for every condition, within the time windows of interest. A late positive effect is visible 800-1000 ms after stimulus-onset. The lack of visual distinction between the ERPs for each condition is not alarming, since the results acquired during the out-of-clinic follow-up experiment confirm that this participant produces no distinctive effects for the time windows of interest.

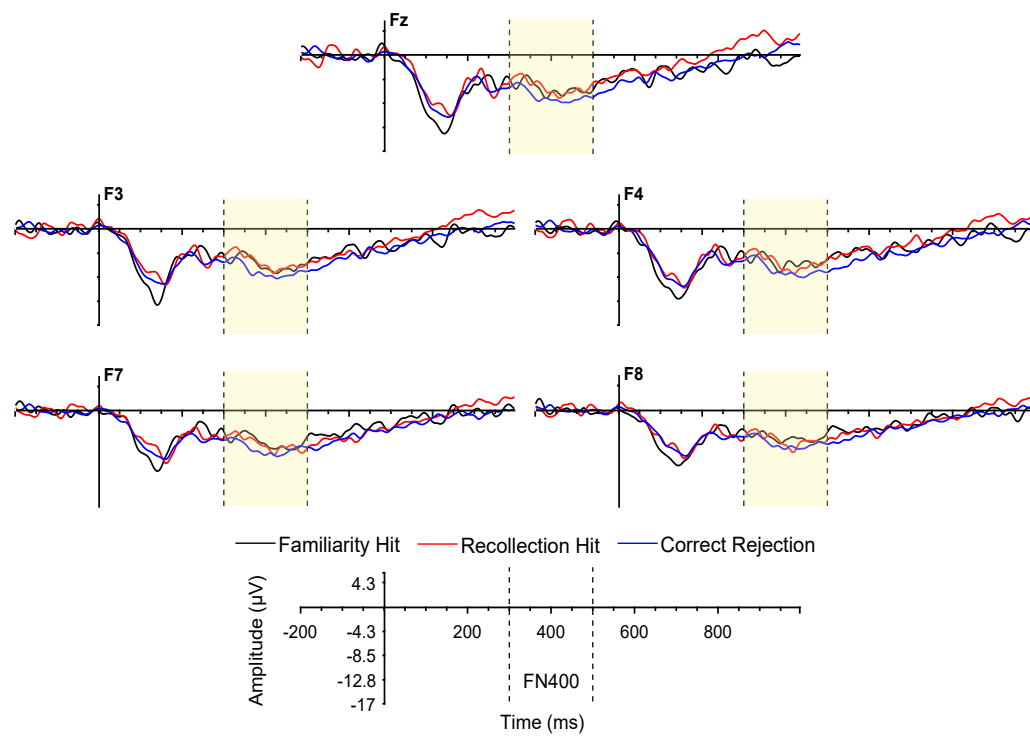


Figure 6.7: Frontal ERP waveforms obtained during the in-clinic pilot. Labeled axes common for all graphs are displayed underneath the legend.

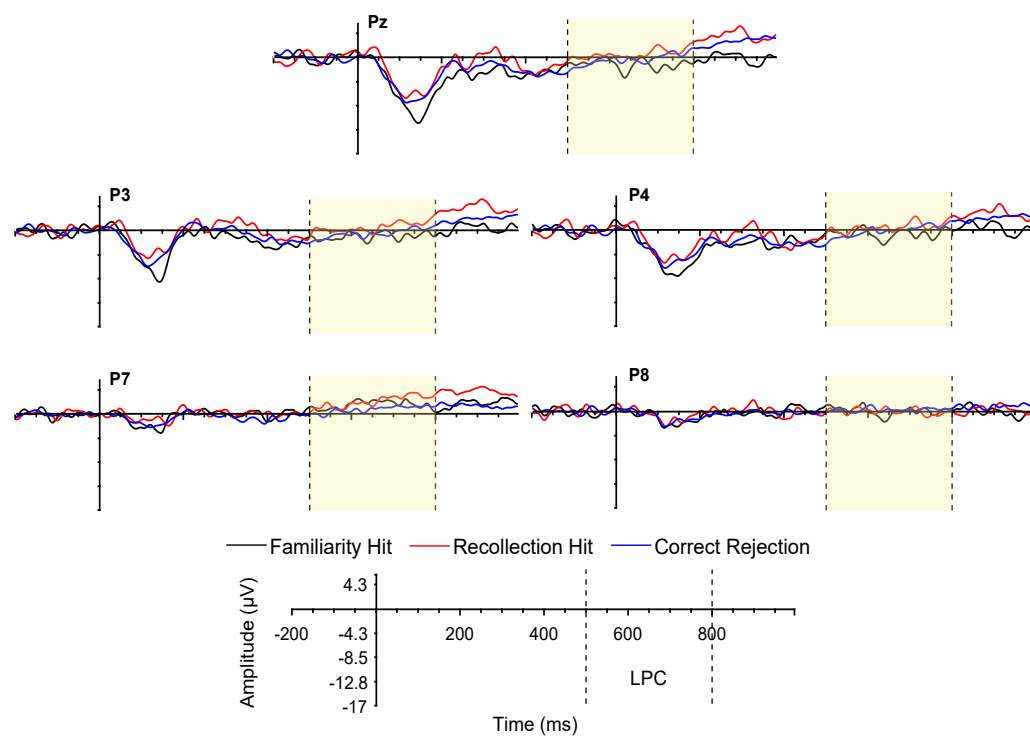


Figure 6.8: Parietal ERP waveforms obtained during the in-clinic pilot. Labeled axes common for all graphs are displayed underneath the legend.

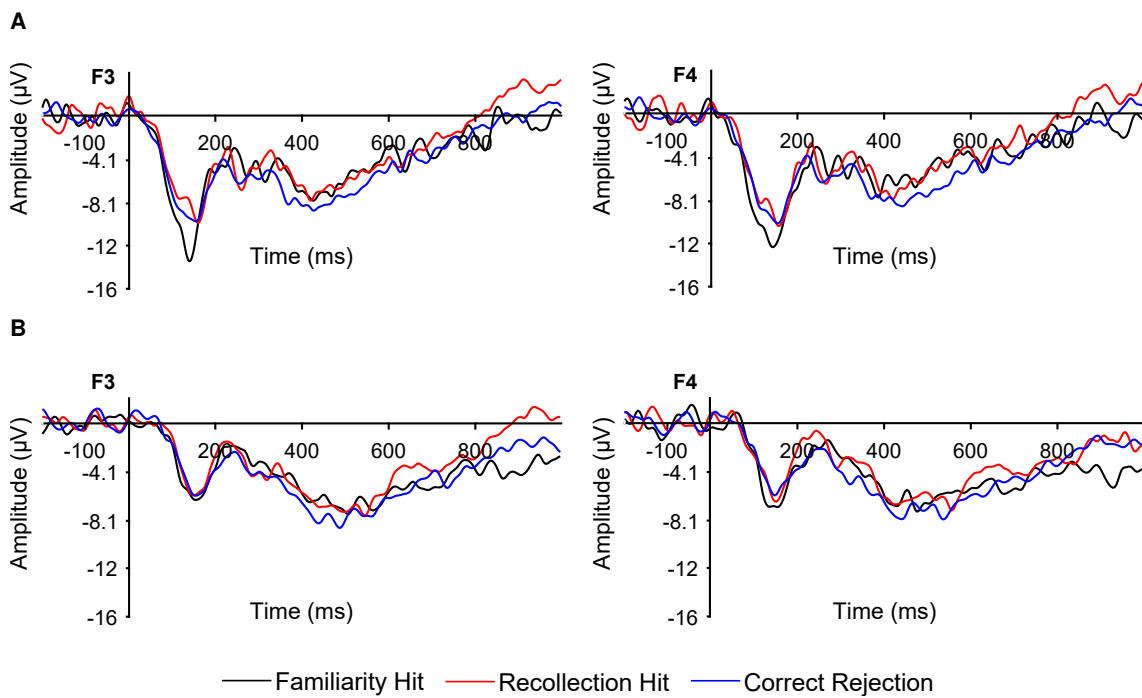


Figure 6.9: Frontal ERP waveforms. (A) Frontal ERPs acquired in-clinic. (B) Frontal ERPs acquired out-of-clinic.

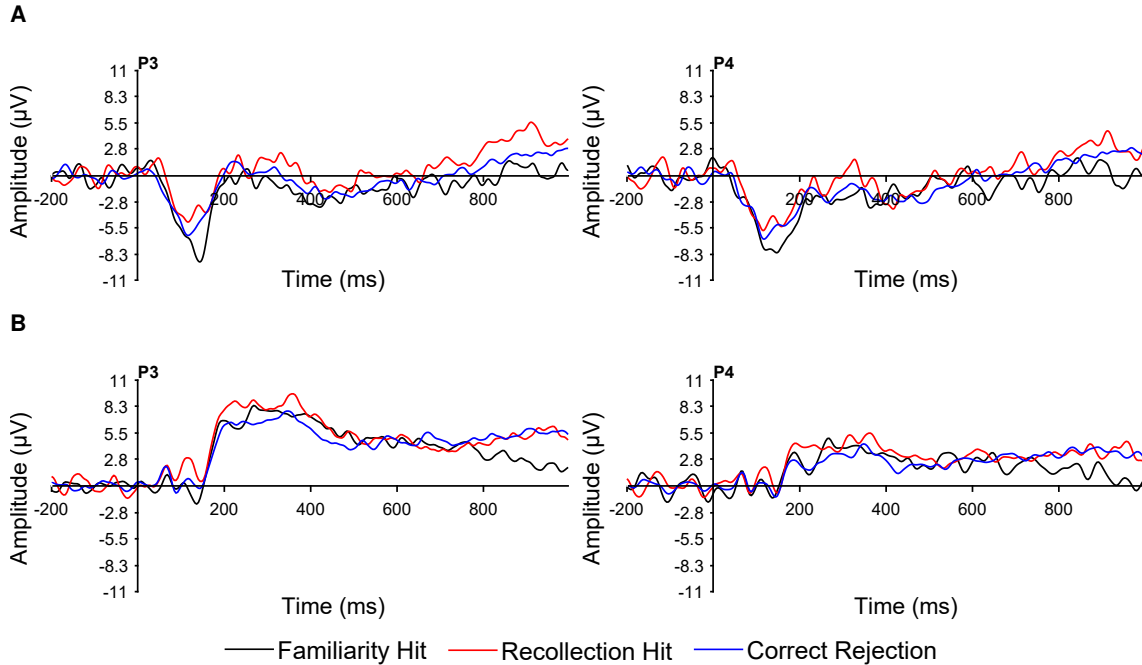


Figure 6.10: Parietal ERP waveforms. (A) Parietal ERPs acquired in-clinic. (B) Parietal ERPs acquired out-of-clinic.

The frontal ERPs derived from EEG acquired at the EMU are very structurally similar to the frontal ERPs obtained for the same participant during the out-of-clinic experiment (see Fig. 6.9). Both waveforms possess a clear negative deflection around 150 ms post-stimulus, the visual N1 component, followed by a positive deflection at approximately 200 ms, the P2 component. The FN400 component for the ERPs acquired in the clinic appears to peak slightly earlier for ERPs acquired in-clinic, in comparison with those acquired out-of-clinic. In contrast, there is a considerable difference in shape for the parietal ERPs (see Fig. 6.10). Considering the reference electrodes used for both experiments were not the same, some differences in waveform shapes are expected. It is possible that picking P9 and P10 as approximations of the mastoid electrodes had a greater impact in nearby parietal and occipital electrodes. Future analysis should consider using alternatives, such as T9 and T10. Regardless, conclusions drawn from this visual comparison should be accepted with some reservations.

As stated previously, throughout this in-clinic experiment, we were unable to tag the onset of the photoresistor response, as we did for the out-of-clinic experiments. For this reason, we anticipated the occurrence of a short time drift between the ERP waveforms, linked to the photoresistor's response time. In an attempt to detect it, we measured the peak latency of the N1 and FN400 components for the ERP waveforms obtained for correct rejections averaged across frontal sites (electrodes F3 and F4). Said waveforms are displayed in Fig. 6.11.

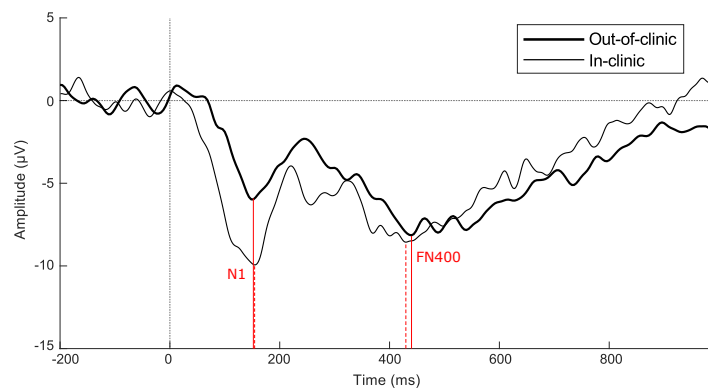


Figure 6.11: Averaged ERP waveforms across frontal electrodes obtained in- and out-of-clinic. Latency measurements for the N1 and FN400 components are indicated by the red lines.

The latency of the N1 component seen in the in-clinic frontal waveform (154.3 ms) was only approximately 2 ms removed from the latency of the N1 component seen in the out-of-clinic waveform (152.0 ms). We also found that, the FN400 component for the in-clinic waveform peaked at about 429.7 ms post-stimulus, whereas the out-of-clinic waveform showed a trough at 440.0 ms. Since we only found a considerable difference for the FN400 component, we can assume that the anticipated time drift might be negligible. One might say the variability found for the FN400 component is likely the result of distortions caused by high-frequency noise contamination or component overlap [171]. As it stands, we recognize the dangers of relying on peak latency measurements alone to characterize ERP components and advise this conclusion be accepted with reservations.

Scalp Topography Maps Since a denser electrode array was used, we were able to compute scalp topography maps of this participant's difference waveforms. In this analysis, ERP waveforms for correct rejections were subtracted from familiarity and recollection hits for both time windows of interest (see Fig. 6.12).

An examination of the scalp topographies for the 300-500 ms time window shows a maximal attenuation of the FN400 component for familiarity hits over frontal scalp sites, as expected [121, 133, 137]. Recollection hits appeared to be more positive than correct rejections over central midline electrodes. This positive central effect in the 300-500 ms interval has been previously observed for correct source judgements, which are also thought to reflect recollection driven recognition [172].

The scalp topography maps for the 500-800 ms time window show an increased mean amplitude for recollection hits over right prefrontal, central and left parietal sites, which is consistent with previous findings [121, 129, 133, 137]. Compared to correct rejections, familiarity hits appeared to be more negative over posterior sites, and more positive for right frontal and prefrontal sites. To our knowledge, this phenomenon has not been reported in any of the previous literature, and is likely a byproduct of re-referencing to the average of the posterior sites P9 and P10.

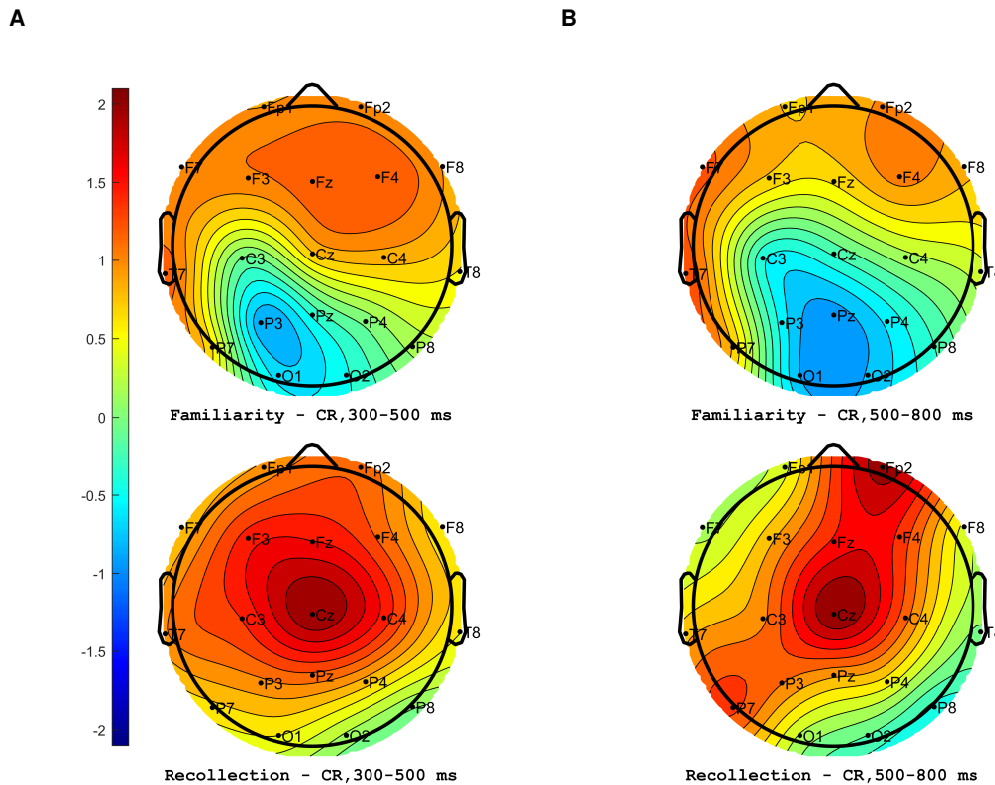


Figure 6.12: Scalp topographies for difference waveforms. Top row includes "familiarity hits" vs "correct rejections", while the bottom row includes "recollection hits vs. correct rejections". The colored barplot for A is also applicable to B. (A) Mean amplitude (in μV) within the 300-500 ms time window. (B) Mean amplitude (in μV) within the 500-800 ms time window.

6.3 Final Remarks

This chapter presented the pilot experiments performed at the EMU to validate the experimental setup, in preparation for the admittance of a new ANT-DBS patient into the monitoring unit. We begun by confirming that the EEG stream was tagged correctly whenever stimuli were shown. Using vEEG, we identified timestamps corresponding to the instant stimuli were shown on the screen and compared them to the timestamps tagged by the photoresistor. However, millisecond-precision delays between the stimulus onset and the photoresistor timestamp could not be calculated, given the insufficient temporal resolution of the vEEG recording.

We then replicated the out-of-clinic follow-up experiment with a returning subject. ERP waveforms obtained for the participant were consistent with those obtained out-of-clinic, except for posterior sites. Re-referencing the data to electrodes P9 and P10 to emulate the mastoid electrodes is the likely cause for this discrepancy. In case we cannot request for the addition of mastoid electrodes to the electrode array used at the EMU, looking into an alternative referencing scheme may be necessary; performing future experiments with the current reference scheme would hinder our findings' comparability with other studies. Scalp topographies of difference wave comparisons were consistent with prior literature findings, further validating the experimental routine. Due to time constraints during EMU visits and access restrictions owed to the pandemic, we were unable to have other participants partake in the clinical experiment. Notwithstanding, one may argue that testing with other returning healthy probands would be unnecessary.

Unfortunately, the patient that was supposed to undergo vEEG monitoring at the EMU was unable to proceed with the ANT-DBS treatment, due to an infection. Consequently, since no LFP recordings were obtained throughout this work, we did not get the chance to prepare any processing pipelines to analyse them, nor begin our investigation into potential intrathalamic neural correlates of memory. Nevertheless, the setup is fully functional and ready to be used at the EMU. Following up on the previously expressed concerns over the experimental paradigm, we recognize that we have yet to validate it with its target demographic. More than anything, in order to further validate the protocol and routine, experiments with epilepsy patients ongoing vEEG monitoring, not necessarily patients undergoing ANT-DBS, should be performed.

Chapter 7

Conclusions and Future Work

With this dissertation we set out to develop an experimental protocol aimed at studying the effects of ANT-DBS on recognition memory performance and, by extension, find neurophysiological evidence supporting these potential effects.

The experimental setup was prototyped outside the clinic using low-cost consumer-grade EEG hardware and tested with healthy volunteers. Throughout its development, the out-of-clinic setup was thoroughly documented so that it may be reused and repurposed in the future for other EEG studies. The experiments with healthy probands focused on studying two well-established ERP correlates of successful memory retrieval – the FN400, associated with familiarity-driven judgements, and the LPC, associated with recollection-driven judgements. By our second experiment with healthy volunteers, we were able to replicate the results reported in the literature. While we were unable to carry out the planned experiment with the ANT-DBS patient, we implemented a successful simulation of the protocol at CHUSJ’s EMU with a healthy proband. Results obtained with the medical hardware were comparable to those obtained during the out-of-clinic experiments.

Going forward, we ought to restructure the experimental paradigm to account for mnemonic strength, as recommended in [122]. This can be easily implemented by prompting participants to provide confidence ratings following each RK judgement. As we mentioned previously, understanding subjective RK reports might be difficult for cognitive impaired patients, so implementing a simpler version of the task with confidence judgements alone might be advantageous. Nonetheless, we already have simplified “Old/New” routines prepared, for patients who fail to understand the instructions. Other improvements to the routine scripts should strive to improve their versatility. Increasing the maximum number of stimuli that can be presented at encoding, for example, would be a good start. This would, of course, go hand in hand with splitting the encoding and retrieval phases into smaller blocks, to avoid exhausting the participants. It would also be beneficial to separate encoding and retrieval phases into two executable scripts, so that the retrieval phase could be carried out after a longer amount of time has passed – this would be particularly useful for fMRI studies, in which participants often perform one of the phases inside the scanner. The aforementioned changes, some of which have already begun to be implemented, should only

require a few adjustments to the current version of the routine generator.

The limitations of the out-of-clinic setup have also already begun to be addressed. We have recently acquired and tested an OpenBCI Daisy Module, which can be mounted onto the Cyton Board, increasing the number of acquisition channels to 16. However, on its own the Cyton+Daisy Module can only sample data with a sampling frequency of 125 Hz. Pairing the Board with the OpenBCI WiFi Shield increases the sample rate up to 8000 Hz by streaming the acquired neurodata over WiFi ¹. Expanding the out-of-clinic setup to include this hardware would greatly broaden its applications. More tests with this setup will be required, however, as the WiFi shield is known to have some reliability issues. It's worth noting that no changes need to be made to the current scripts, since the streaming library we used, BrainFlow, is board agnostic and compatible with the Cyton+Daisy with WiFi shield.

After expanding the out-of-clinic setup, while waiting for the next ANT-DBS patient to be implanted with a Percept PC System, a revised cognitive experiment can be carried out with a wider subject demographic. Compiling a database of healthy controls will allow us to perform a comparative study with patients suffering from refractory epilepsy. Regardless, as soon as another ANT-DBS patient is admitted to the EMU for a week-long monitoring session, we will be ready to advance with the study.

¹WiFi Shield Getting Started Guide - OpenBCI Documentation. Available at: <https://docs.openbci.com/docs/> (Accessed 16-05-2021)

Appendix A

Experiment Routine Generator Scripts

This chapter includes a compilation of all scripts developed for generating stimulation routines following the experimental protocol described in section 4.2. Some of the improvements discussed in chapter 7, namely the inclusion of confidence ratings, have already been implemented in preparation for future experiments.

```
1 function runRKparadigm(experimentID, subjectID, varargin)
2 % Implementation of a recognition memory task following the RK procedure.
3 %
4 % @file runRKparadigm.m
5 %
6 % The function runRKparadigm uses Psychtoolbox to present a group of scenes
7 % following the Remember/Know procedure. The experiment is divided into an
8 % encoding, distractor and retrieval phase. Control for mnemonic strength
9 % is implemented through confidence ratings following successful RK
10 % judgments
11 %
12 % SYNTAX:
13 %   runRKparadigm(experimentID, subjectID)
14 %   runRKparadigm(experimentID, subjectID, session)
15 %   runRKparadigm(____, 'distanceFromScreen', value, 'selfpaced', value,...)
16 %
17 %
18 % INPUT:
19 %       experimentID:      identifier given to the experimental
20 %                          procedure, as well as the folder containing
21 %                          both all parameters unique to this group of
22 %                          experiments and collected data. (char)
23 %
24 %       subjectID:         identifier given to the subject
25 %                          participating in the experiment, as well as
26 %                          the folder containing all data related to
27 %                          them. (char)
28 %
```

```

29 %      session:                number of the session. Each session is
30 %                             composed by multiple blocks that contain
31 %                             an encoding, distractor and retrieval
32 %                             phase. (int)
33 %
34 %      distanceFromScreen (m): distance the subject is from the screen
35 %                             (double)
36 %
37 %      selfpaced:              indicates if the retrieval phase is
38 %                             self-paced (bool)
39 %
40 %      useConfidenceRating:    ask for confidence ratings following RK
41 %                             judgements (bool)
42 %
43 % Ana S S Cardoso, BRAIN group, INESC-TEC Porto, Jun/2021
44 %
45 % ...
-----

46
47 %% Parse Input Information, Load Experiment Data
48 % Script starts by clearing the workspace and screen. Input parameters are
49 % processed and validated. Parameters for the requested experiment are
50 % loaded.
51
52 % Clear the workspace and the screen
53 sca;
54 close all;
55
56 % Initialize default parameters
57 defaultSession = 1;
58 defaultDistance = 0.5;
59
60 % Initiate input parser
61 p = inputParser;
62
63 addRequired(p, 'experimentID', @(x) validateattributes(x, {'char'}, ...
64     {'nonempty'}));
65 addRequired(p, 'subjectID', @(x) validateattributes(x, {'char'}, ...
66     {'nonempty'}));
67 addOptional(p, 'session', defaultSession, @(x) validateattributes(x, ...
68     {'numeric'}, {'nonempty', 'scalar'}));
69 addParameter(p, 'distanceFromScreen', defaultDistance, @(x) ...
70     validateattributes(x, {'double'}, {'nonempty', 'scalar', '>', 0.2, '<', 1}))
71 addParameter(p, 'selfpaced', false, @(x) ...
72     validateattributes(x, {'logical'}, {'nonempty', 'scalar'}))
73 addParameter(p, 'useConfidenceRating', false, @(x) ...
74     validateattributes(x, {'logical'}, {'nonempty', 'scalar'}))
75
76 parse(p, experimentID, subjectID, varargin{:});

```

```

77
78 % Load experiment parameters. If no experiment with this ID has been
79 % created show a warning to the user and create a new experiment.
80 try
81     params = load(fullfile('.',data',experimentID,'params.mat'));
82 catch
83     warning(['Unable to read parameter file.\n\n' ...
84         'Experiment %s may not exist in the current directory.\n\n'...
85         'Creating Experiment...'],...
86         experimentID)
87     % create a new experiment and load parameters
88     [exitCode, message] = createExperiment(experimentID, 'Memory');
89     if exitCode
90         warning(message,exitCode);
91         return
92     end
93     params = load(fullfile('.',data',experimentID,'params.mat'));
94 end
95
96 % Check if subject exists, create a new subject folder if it doesn't
97 subjectPath = fullfile('.',data',experimentID,subjectID);
98 if ~isfolder(subjectPath)
99     mkdir(subjectPath);
100 end
101
102 % Check if session is within the number of planned sessions
103 if params.numSessions < p.Results.session
104     error('Error. \nThis experiment does not possess more than %d. sessions'...
105         , params.numSessions);
106 end
107
108 sessionString = num2str(p.Results.session); % To be appended to filenames
109
110 % If this experiment has a training session (S = 1), use the parameters
111 % specified on creation
112 if isempty(params.training)
113     sessionString = num2str(p.Results.session-1); % Accounting for training ...
114         session.
115     if p.Results.session == 1
116         params.numBlocks = params.training.numBlocks;
117         params.numImages = params.training.numStim;
118     end
119 end
120
121 %% List off available languages
122 % Starts by requesting the user to select one of the available languages
123 % for the experiment

```

```

124 availableLanguages = {'English (EN)', 'Português (PT)'}; % Text displayed to ...
    user
125 languageCodes = {'EN', 'PT'}; % Codes used to identify the language
126
127 [idx,tf] = listdlg('ListString', availableLanguages,...
128     'SelectionMode','single');
129
130 % if the user selects 'Cancel' from the input dialogue the function returns
131 % exit code 1
132 if ~tf
133     return
134 end
135
136 language = languageCodes{idx}; % Selected language
137
138 %% Initialization of BrainFlow
139 % This experiment is compatible with OpenBCI Boards. A pop-up window
140 % prompts the user to decide if the current experiment will use the OpenBCI
141 % Board. If so, a new board object is created. The board is configured for
142 % accordingly before starting to stream.
143
144 % Use Brainflow?
145 answer = questdlg('Use Brainflow?', 'Brainflow Setup', ...
146     'Yes', 'No', 'Yes');
147
148 switch answer
149     case 'Yes'
150         % List off supported Boards
151         [ ~ , supportedBoards] = enumeration('BoardIDs');
152
153         [pickedBoard,tf] = listdlg('ListString', supportedBoards,...
154             'SelectionMode','single', 'ListSize', [200 300]);
155
156         % if the user selects 'Cancel' from the input dialogue the function ...
157         % returns
158         % exit code 1
159         if ~tf
160             return
161         end
162
163         %
164         if ~isempty(dir([subjectPath, '\eeg_S', sessionString...
165             , '_*.csv']))
166             error('Error.\nRecordings for session %s already exist in %s. ...
167                 \nIf you do not wish to lose this data, back up your files. ...
168                 If you wish to repeat this session, delete them before ...
169                 proceeding.', ...
170                 sessionString, subjectPath)
171         end

```

```

168
169     BoardShim.set_log_file('brainflow.log'); % Set log file
170     BoardShim.enable_dev_board_logger();      % Set log level to TRACE
171
172     boardParams = BrainFlowInputParams();      % Initialize ...
           parameters struct
173     % Assign Serial port. Only works from M2019b onwards
174     boardParams.serial_port = char(serialportlist("available"));
175
176     % Create a new "board" and prepare the session
177     board_shim = ...
           BoardShim(int32(BoardIDs.(supportedBoards{pickedBoard})), ...
           boardParams);
178     board_shim.prepare_session();
179
180     board_shim.config_board('/2'); % Turn on analog reading
181
182     disp('Using The Requested Board.')
183     useBrainflow = true;
184     case 'No'
185         disp('No board will be created.')
186         useBrainflow = false;
187     otherwise
188         return
189 end
190
191 %% Initialization of Psychtoolbox
192 % Default settings for Psychtoolbox are set; measures related to the
193 % screen are retrieved. A first black window is drawn and shown
194
195 % Here we call some default settings for setting up Psychtoolbox
196 PsychDefaultSetup(2);
197
198 % On windows 8 and 10, Psychtoolbox cannot deactivate the desktop
199 % windows manager. Synchronization tests will always fail, causing
200 % the program to crash. These lines deactivate both the tests and a
201 % warning screen that succeeds it.
202 Screen('Preference', 'SkipSyncTests', 1);
203 Screen('Preference', 'VisualDebugLevel', 0);
204
205 % Get the screen number, gives us a number for each of the screens
206 % attached to computer. Using multiple screens with Windows is not
207 % recommended.
208 screens = Screen('Screens');
209
210 % Select maximum of these numbers, so that external monitor is chosen
211 % by default, if existent
212 screenNumber = max(screens);
213

```

```

214 % Get screen's values for black and white
215 white = WhiteIndex(screenNumber);
216 black = BlackIndex(screenNumber);
217
218 HideCursor; % Hide mouse cursor
219
220 % Open an on screen window using PsychImaging and color it black
221 [window, windowRect] = PsychImaging('OpenWindow', screenNumber, black);
222
223 % Set the blend function for the screen - Support Transparency
224 Screen('BlendFunction', window, 'GL_SRC_ALPHA', 'GL_ONE_MINUS_SRC_ALPHA');
225
226 % Get the size of the on screen window in pixels
227 [screenXpixels, screenYpixels] = Screen('WindowSize', window);
228
229 % Get the centre coordinate of the window in pixels
230 [xCenter, yCenter] = RectCenter(windowRect);
231
232 % Measure the vertical refresh rate of the monitor
233 ifi = Screen('GetFlipInterval', window);
234
235 % Retrieve the maximum priority number and set max priority
236 topPriorityLevel = MaxPriority(window);
237 Priority(topPriorityLevel);
238
239 % Setup the text type for the window
240 Screen('TextFont', window, 'Monospaced');
241 Screen('TextSize', window, 36);
242
243 %% Load Resources
244 % Necessary icons and textual prompts are loaded. Image stimuli aren't
245 % loaded here, only a cell array containing the chosen categories for this
246 % session and a struct array with metadata related to each stimulus.
247
248 % Load image stimuli list
249 [imageStruct, imageCategories] = getSessionTargets(experimentID, ...
    subjectPath, ...
250     language, p.Results.session);
251
252 % Load visual prompts
253 [i,map,alpha] = imread('.\resources\arrows\left.png');
254 i = ind2rgb(i,map); i(:, :, 4)=alpha;
255 arrowLeft = Screen('MakeTexture', window, i);
256 [i,map,alpha] = imread('.\resources\arrows\right.png');
257 i = ind2rgb(i,map); i(:, :, 4)=alpha;
258 arrowRight = Screen('MakeTexture', window, i);
259 [i,map,alpha] = imread('.\resources\arrows\down.png');
260 i = ind2rgb(i,map); i(:, :, 4)=alpha;
261 arrowDown = Screen('MakeTexture', window, i);

```



```

262
263 clear i
264
265 % Path to text files containing dialogue for the requested language
266 switch(language)
267     case 'PT'
268         txtfile = './resources/text/messages_pt.csv';
269     case 'EN'
270         txtfile = './resources/text/messages.csv';
271 end
272
273 % Load text prompts
274 try
275     messages = readcell(txtfile, 'Delimiter', '\t');
276 catch
277     [~, messages, ~] = xlsread(txtfile); % For backwards compatibility
278 end
279
280 %% Set Keyboard Map
281 % Maps each key on the keypad to a response (to a char)
282
283 KbName('UnifyKeyNames');
284 escapeKey = KbName('ESCAPE'); % Assign escape key
285
286 % Keys for encoding
287 keymap.encoding = containers.Map({ KbName('4'), ...
288     KbName('6') }, {1,2});
289
290 % Keys for retrieval
291 keymap.retrieval = containers.Map({KbName('4'), ...
292     KbName('2'), KbName('6') }, ...
293     {'R','F','N'}); % R - Recollection; F - Familiarity; N - New
294
295 % Keys for confidence ratings
296 if p.Results.useConfidenceRating
297     keymap.confidence = containers.Map({KbName('4'), ...
298         KbName('2'), KbName('6') }, ...
299         {'1','2','3'}); % 1 - not sure; 2 - a bit sure; 3 - definitely sure
300 end
301
302 % Initialize array with all keys that will be used
303 idx = [cell2mat(keys(keymap.retrieval)),escapeKey];
304 keysInterest=zeros(1,256);
305 keysInterest(idx)=1;
306
307 %% Set Interval Durations
308
309 stimulusDuration = 2.500; % stimulus presentation ...
    duration

```

```

310 stimulusFrames = round(stimulusDuration / ifi); % number of frames to wait for
311
312 isi = [1.400, 1.600]; % interstimulus duration
313 isiFrames = round(isi / ifi); % number of frames to wait for
314
315 pauseDuration = 30.000; % distraction phase duration
316 pauseFrames = round(pauseDuration / ifi); % number of frames to wait for
317
318 answerDuration = 4.000; % answer timeout
319 answerFrames = round(answerDuration / ifi); % number of frames to wait for
320
321 %% Set Visual Parameters
322 % Set the size of stimuli, markers and others and set their position on the
323 % screen.
324
325 % SET THE POSITION AND SIZE OF ALL IMAGE STIMULUS -----
326
327 % Calculate height of images to be displayed
328 imageHeight = calculateImageSize(screenNumber, p.Results.distanceFromScreen);
329
330 % Prepare box to draw the images in
331 theRect = [0 0 imageHeight imageHeight]; % Image is squared
332 destinationRect = CenterRectOnPointd(theRect, xCenter,...
333     yCenter);
334
335 % DETERMINE THE POSITIONS OF THE ARROW ICONS -----
336
337 % Positions used for arrow keys prompts (RK judgements)
338 theRect = [0 0 imageHeight/4 imageHeight/4]; % Image is squared
339 destinationLeft = CenterRectOnPointd(theRect, xCenter-imageHeight*3/8,...
340     yCenter+imageHeight*11/16);
341 destinationRight = CenterRectOnPointd(theRect, xCenter+imageHeight*3/8,...
342     yCenter+imageHeight*11/16);
343 destinationCenter = CenterRectOnPointd(theRect, xCenter,...
344     yCenter+imageHeight);
345
346 % Positions used for confidence rating prompts
347 destinationLeftCentered = CenterRectOnPointd(theRect, ...
348     xCenter-imageHeight*3/8,...
349     yCenter);
350 destinationRightCentered = CenterRectOnPointd(theRect, ...
351     xCenter+imageHeight*3/8,...
352     yCenter);
353 destinationCenterCentered = CenterRectOnPointd(theRect, xCenter,...
354     yCenter+imageHeight*5/16);
355 % -----
356
357 % Prepare square indicator in the corner of the screen. The photoresistor
358 % will be place above it.

```

```

357 theRect = [0 0 150 150];
358 indicatorRect = CenterRectOnPointd(theRect, 0, screenYpixels);
359
360 % SET TEXT PROMPT COORDINATES -----
361
362 % Calculate the width of a single character
363 textRect = Screen('TextBounds', window, 'A');
364 fontWidth = textRect(3)-textRect(1);
365 numCharPerLine = floor(screenXpixels/fontWidth);
366
367 % Set coordinates for each text prompt. Text prompts appear
368 % besides each arrow icon.
369
370 topTextCoord_y = (yCenter+imageHeight*11/16)-textRect(4)/2; % Used for
371                                                              % top text prompts
372 newTextCoord_x = xCenter+imageHeight*5/8; % Translate text horizontally ...
373                                     (right)
374
375 textRect = Screen('TextBounds', window, messages{6}); % Get text coordinates
376 rememberCoord_x = xCenter-(textRect(3)+imageHeight*5/8); % Translate text ...
377                                     horizontally (left)
378
379 textRect = Screen('TextBounds', window, messages{7});
380 knowCoord_x = (xCenter)-(textRect(3)+imageHeight*2/8);
381
382 botTextCoord_y = (yCenter+imageHeight)-textRect(4)/2; % Used for bottom text
383
384 if p.Results.useConfidenceRating
385     textRect = Screen('TextBounds', window, messages{13}); % Get text ...
386                                     coordinates
387     conf_1_Coord_x = xCenter-(textRect(3)+imageHeight*5/8); % Translate ...
388                                     text horizontally (left)
389
390     textRect = Screen('TextBounds', window, messages{14});
391     conf_2_Coord_x = (xCenter)-(textRect(3)+imageHeight*2/8); % Align Center
392
393     conf_3_Coord_x = xCenter+imageHeight*5/8; % Translate text horizontally ...
394                                     (right)
395 end
396
397 % -----
398 % Set fixation cross parameters
399
400 fixCrossDimPix = 40; % Set the size of the arms of the fixation cross
401 xCoords = [-fixCrossDimPix fixCrossDimPix 0 0]; % Set the coordinates
402 yCoords = [0 0 -fixCrossDimPix fixCrossDimPix];
403 allCoords = [xCoords; yCoords];
404 lineWidthPix = 4; % Set the line width for the fixation cross
405

```

```

401 %% Initiate Stimulus Presentation
402 % The task loop begins here. First, a list of images is sequentially
403 % presented to the participant. Afterwards, the participant is shown random
404 % equations and must determine if they're correct. Finally, the participant
405 % is shown a new sequence of images. Consult
406 % Experiment_Routine_Instructions.pptx for more details.
407
408 % Create keyboard queue to read subject inputs
409 KbQueueCreate([],keysInterest);
410 KbQueueStart();
411
412 for block = 1:params.numBlocks
413     encodingResponse = cell(params.numImages,1); % Assign cell to save
414                                           % encoding answers
415     if useBrainflow % Begin streaming into a .csv file with Brainflow
416         streamerParams = ['file://data/', experimentID, '/', ...
417             subjectID, '/eeg_S', sessionString...
418             , '_', num2str(block), '.csv:w'];
419         board_shim.start_stream(225000, streamerParams);
420     end
421
422     startTime = posixtime(datetime('now'));
423
424     % Prepare target images for the current block
425     twoCategories = imageCategories(block,:); % Pick two categories
426     [Targets, allImages, idxOldImages] = prepareTargets(imageStruct,...
427         twoCategories,params.numImages, subjectID);
428     % Targets - struct containing data related to every target that will be
429     % presented during the current block, including its name, folder,
430     % category and label (Old or New). RK judgments given to each one of
431     % them during retrieval are saved in this struct under "response";
432     % confidence ratings under "confidence_rating"
433     % allImages - Array of image matrices
434     % idxOldImages - Indices of images that will be presented during
435     % encoding
436
437     % Write instruction message for subject
438     DrawFormattedText(window, [messages{1}, '\n', messages{3}], ...
439         'center', 'center', white, numCharPerLine);
440
441     % Update the display to show the instruction text:
442     Screen('Flip', window);
443
444     KbQueueWait(); % Wait until key is pressed
445
446     % Get X coordinates of text
447     textRect = Screen('TextBounds', window, twoCategories{1});
448     leftTextCoord_x = xCenter-(textRect(3)+imageHeight*5/8);
449     rightTextCoord_x = xCenter+imageHeight*5/8;

```

```

450
451 % Draw prompts
452 DrawFormattedText(window, [messages{11}, '\n', messages{3}], ...
453     'center', 'center', white, numCharPerLine);
454 Screen('DrawTextures', window, [arrowRight, arrowLeft]...
455     , [], [destinationRight; destinationLeft]);
456 Screen('DrawText', window, twoCategories{1}, leftTextCoord_x , ...
457     topTextCoord_y, white);
458 Screen('DrawText', window, twoCategories{2}, rightTextCoord_x, ...
459     topTextCoord_y, white);
460
461 % Flip to screen
462 Screen('Flip', window);
463
464 KbQueueWait(); % Wait until key is pressed
465
466 %% Begin Encoding Stage
467 % Old images are presented sequentially on the screen
468
469 % Draw the fixation cross in white on the "back"
470 Screen('DrawLines', window, allCoords, ...
471     lineWidthPix, white, [xCenter yCenter], 2);
472
473 vbl = Screen('Flip', window); % flip to fixation screen
474
475 % Initialize loop counter
476 counter = 0;
477
478 while counter ≠ params.numImages
479     counter = counter + 1;
480
481     % Create image texture and draw it on the "back"
482     imageTexture = ...
483         Screen('MakeTexture', window, allImages(idxOldImages(counter)));
484     Screen('DrawTextures', window, imageTexture, [], destinationRect);
485
486     % Draw indicator rectangle in the corner of the screen
487     Screen('FillRect', window, white, indicatorRect);
488
489     % Draw prompts
490     Screen('DrawTextures', window, [arrowRight, arrowLeft]...
491         , [], [destinationRight; destinationLeft]);
492     Screen('DrawText', window, twoCategories{1}, leftTextCoord_x, ...
493         topTextCoord_y, white);
494     Screen('DrawText', window, twoCategories{2}, rightTextCoord_x, ...
495         topTextCoord_y, white);
496
497     vbl = Screen('Flip', window, vbl + (isiFrames(randi([1,2])) - 0.5) ...
498         * ifi);

```

```

497
498     if counter ≠ params.numImages
499         % Draw the fixation cross in white
500         Screen('DrawLines', window, allCoords,...
501             lineWidthPix, white, [xCenter yCenter], 2);
502
503         vbl = Screen('Flip', window, vbl + (stimulusFrames - 0.5) * ifi);
504     else
505         % Create empty screen
506         Screen('FillRect', window, black)
507
508         % Flip to empty screen
509         vbl = Screen('Flip', window, vbl + (stimulusFrames - 0.5) * ifi);
510     end
511
512     [pressed, firstPress]=KbQueueCheck(); % At the end of each trial
513                                         % check for keypad presses
514
515     if pressed
516         [¬,idx]=max(firstPress);
517         if firstPress(escapeKey)
518             break;
519         end
520         try
521             encodingResponse{counter} = ...
522                 twoCategories{keymap.encoding(idx)};
523         catch
524             encodingResponse{counter} = [];
525         end
526     end
527
528     KbQueueFlush();
529
530     %% Begin Distractor Stage
531     % Equations are presented sequentially to the participant during a
532     % given amount of time
533
534     % Get X coordinates of text
535     textRect = Screen('TextBounds', window, messages{4});
536     leftTextCoord_x = xCenter-(textRect(3)+imageHeight*5/8);
537
538     while (GetSecs - vbl) ≤ pauseDuration
539         [str, ¬] = getEquation(1);
540
541         Screen('TextSize', window, 42);
542         DrawFormattedText(window, str, 'center', 'center', white);
543
544         % Draw prompts

```

```

545         Screen('DrawTextures', window, [arrowRight, arrowLeft]...
546             , [], [destinationRight;destinationLeft]');
547
548         Screen('TextSize', window, 36);
549         Screen('DrawText',window, messages{4}, leftTextCoord_x,...
550             topTextCoord_y, white);
551         Screen('DrawText',window, messages{5}, rightTextCoord_x,...
552             topTextCoord_y, white);
553
554         Screen('Flip', window);
555
556         KbQueueWait()
557         break; % Uncomment to skip the break
558     end
559
560
561     %% Begin Retrieval Stage
562     % Previously shown images are presented again, intermingled with novel
563     % images.
564
565     retrievalTime = posixtime(datetime('now'));
566
567     % Write instruction message for subject
568     DrawFormattedText(window, [messages{2},'\n',messages{3}]]...
569         , 'center', 'center', white, numCharPerLine);
570
571     % Update the display to show the instruction text:
572     Screen('Flip', window);
573
574     KbQueueWait();
575
576     % Draw the fixation cross in white
577     Screen('DrawLines', window, allCoords,...
578         lineWidthPix, white, [xCenter yCenter], 2);
579
580     % Flip to fixation cross
581     vbl = Screen('Flip', window);
582
583     % Reset counter
584     counter = 0;
585     exitLoop = false;
586
587     while ~exitLoop && counter ≠ 2*params.numImages
588
589         counter = counter + 1;
590
591         % Create texture with image and draw it on the backscreen
592         imageTexture = Screen('MakeTexture',window, allImages{counter});
593         Screen('DrawTextures', window, imageTexture, [], destinationRect);

```

```

594
595 % Draw indicator rectangle in the corner of the backscreen
596 Screen('FillRect', window, white, indicatorRect);
597
598 % Flip to backscreen
599 vbl = Screen('Flip', window, vbl + (isiFrames(randi([1,2])) - 0.5) ...
        * ifi);
600
601 % Draw image Texture on the backscreen
602 Screen('DrawTextures', window, imageTexture, [], destinationRect);
603
604 % Draw RK prompts in backscreen
605 Screen('DrawTextures', window, [arrowRight, arrowLeft, ...
        arrowDown], [], [destinationRight; destinationLeft; ...
        destinationCenter]);
606
607 % Add arrowUp and destinationGreen for Guess
608
609
610 Screen('DrawText', window, messages{6}, rememberCoord_x, ...
        topTextCoord_y, white);
611
612 Screen('DrawText', window, messages{7}, knowCoord_x, ...
        botTextCoord_y, white);
613
614 % Screen('DrawText', window, messages{8}, guessTextCoord_x, ...
615 % botTextCoord_y, white); % Uncomment for Guess
616 Screen('DrawText', window, messages{9}, newTextCoord_x, ...
        topTextCoord_y, white);
617
618
619
620 % Flip to answer screen
621 vbl = Screen('Flip', window, vbl + (stimulusFrames - 0.5) * ifi);
622
623 KbQueueFlush()
624
625 if p.Results.selfpaced
626     while true % While answer isn't given
627         [pressed, firstPress]=KbQueueCheck();
628         [¬, idx]=max(firstPress);
629         if pressed
630             try
631                 Targets(counter).response = keymap.retrieval(idx);
632                 break;
633             catch
634                 if firstPress(escapeKey)
635                     exitLoop = true;
636                     break;
637                 end
638             end
639         end
640     end
641 else

```



```

642         % Implement timeout loop
643         while (GetSecs - vbl) ≤ answerDuration
644             % Check what key was pressed during the test
645             [pressed, firstPress]=KbQueueCheck();
646             [¬, idx]=max(firstPress);
647             if pressed
648                 try
649                     Targets(counter).response = keymap.retrieval(idx);
650                     break;
651                 catch
652                     if firstPress(escapeKey)
653                         exitLoop = true;
654                         break;
655                     end
656                 end
657             end
658         end
659     end
660
661     KbQueueFlush()
662
663     % If confidence ratings are required the next screen prompts the
664     % user for those.
665     if p.Results.useConfidenceRating && pressed
666         Screen('DrawTextures', window, [arrowRight, arrowLeft, ...
667             arrowDown], [], ...
668             [destinationRightCentered; destinationLeftCentered; ...
669             destinationCenterCentered]);
670         % Add arrowUp and destinationGreen for Guess
671
672         Screen('DrawText', window, messages{13}, conf_1_Coord_x, ...
673             topTextCoord_y - imageHeight*11/16, white);
674         Screen('DrawText', window, messages{14}, conf_2_Coord_x, ...
675             botTextCoord_y - imageHeight*11/16, white);
676         Screen('DrawText', window, messages{15}, conf_3_Coord_x, ...
677             topTextCoord_y - imageHeight*11/16, white);
678
679         % Flip to answer screen
680         vbl = Screen('Flip', window);
681
682         KbQueueFlush()
683
684         if p.Results.selfpaced
685             while true % While answer isn't given
686                 [pressed, firstPress]=KbQueueCheck();
687                 [¬, idx]=max(firstPress);
688                 if pressed
689                     try

```

```

689         Targets(counter).confidence_rating = ...
690             keymap.confidence(idx);
691         break;
692     catch
693         if firstPress(escapeKey)
694             exitLoop = true;
695             break;
696         end
697     end
698 end
699 else
700     % Implement timeout loop
701     while (GetSecs - vbl) ≤ answerDuration
702         % Check what key was pressed during the test
703         [pressed, firstPress]=KbQueueCheck();
704         [~,idx]=max(firstPress);
705         if pressed
706             try
707                 Targets(counter).confidence_rating = ...
708                     keymap.confidence(idx);
709                 break;
710             catch
711                 if firstPress(escapeKey)
712                     exitLoop = true;
713                     break;
714                 end
715             end
716         end
717     end
718 end
719
720 % Flip to fixation cross (Or dark screen)
721 if counter ≠ 2*params.numImages
722     % Draw the fixation cross in white
723     Screen('DrawLines', window, allCoords,...
724         lineWidthPix, white, [xCenter yCenter], 2);
725 end
726
727 vbl = Screen('Flip', window); % Right after answer is given
728 end
729
730 %% Break Between Blocks
731
732 % Stop Stream
733 if useBrainflow
734     board_shim.stop_stream();
735 end

```

```

736
737     % Save images shown and responses given during this block
738     encodingTargets = [encodingResponse, num2cell(idxOldImages')];
739
740     if ~isempty(params.training) && p.Results.session == 1
741         subjectFilename = ['answers_Training_', ...
742             num2str(block), '.mat'];
743     else
744         subjectFilename = ['answers_S', sessionString, ...
745             '_', num2str(block), '.mat'];
746     end
747     save(fullfile(subjectPath, subjectFilename), ...
748         'startTime', 'retrievalTime', 'Targets', 'encodingTargets');
749
750     clear idxOldImages encodingResponse encodingTargets...
751         encodingAndRetrievalTime startTime retrievalTime Targets
752
753     if block ≠ params.numBlocks
754         % Draw text and flip to break screen
755         DrawFormattedText(window, messages{10}, 'center', 'center', white);
756         vbl = Screen('Flip', window);
757
758         % Wait a minute or move on when key is pressed
759         KbQueueWait([], 0, vbl + (pauseFrames*2 - 0.5) * ifi);
760     end
761
762 end
763 %% Terminate correctly
764 % Release stream and keyboard queue, Clear the screen
765
766 % Release Board
767 if useBrainflow
768     board_shim.release_session();
769 end
770
771 % Release Keyboard Queue
772 KbQueueRelease();
773
774 % Clear the screen.
775 sca;
776 end

```



```

1 function runOldNewparadigm(experimentID, subjectID, varargin)
2 % Implementation of an "Old/New" recognition memory task.
3 %
4 % @file runOldNewparadigm.m
5 %
6 % The function runOldNewparadigm uses Psychtoolbox to present a group of

```

```

7 % scenes following a standard "Old/New" task. The experiment is divided
8 % into an encoding, distractor and retrieval phase. Control for mnemonic
9 % strength is implemented through confidence ratings following successful
10 % "Old/New" judgements
11 %
12 % SYNTAX:
13 %   runOldNewparadigm(experimentID, subjectID)
14 %   runOldNewparadigm(experimentID, subjectID, session)
15 %   runOldNewparadigm(____, 'distanceFromScreen', value, 'selfpaced', value,...)
16 %
17 %
18 % INPUT:
19 %       experimentID:      identificator given to the experimental
20 %                          procedure, as well as the folder containing
21 %                          both all parameters unique to this group of
22 %                          experiments and collected data. (char)
23 %
24 %       subjectID:         identificator given to the subject
25 %                          participating in the experiment, as well as
26 %                          the folder containing all data related to
27 %                          them. (char)
28 %
29 %       session:           number of the session. Each session is
30 %                          composed by multiple blocks that contain
31 %                          an encoding, distractor and retrieval
32 %                          phase. (int)
33 %
34 %       distanceFromScreen (m): distance the subject is from the screen
35 %                               (double)
36 %
37 %       selfpaced:         indicates if the retrieval phase is
38 %                          self-paced (bool)
39 %
40 %       useConfidenceRating: ask for confidence ratings following
41 %                          Old/New judgements (bool)
42 %
43 % Ana S S Cardoso, BRAIN group, INESC-TEC Porto, Jun/2021
44 %
45 % ...
-----
46
47 %% Parse Input Information, Load Experiment Data
48 % Script starts by clearing the workspace and screen. Input parameters are
49 % processed and validated. Parameters for the requested experiment are
50 % loaded.
51
52 % Clear the workspace and the screen
53 sca;
54 close all;

```

```

55
56 % Initialize default parameters
57 defaultSession = 1;
58 defaultDistance = 0.5;
59
60 % Initiate input parser
61 p = inputParser;
62
63 addRequired(p, 'experimentID', @(x) validateattributes(x, {'char'}, ...
64     {'nonempty'}));
65 addRequired(p, 'subjectID', @(x) validateattributes(x, {'char'}, ...
66     {'nonempty'}));
67 addOptional(p, 'session', defaultSession, @(x) validateattributes(x, ...
68     {'numeric'}, {'nonempty', 'scalar'}));
69 addParameter(p, 'distanceFromScreen', defaultDistance, @(x) ...
70     validateattributes(x, {'double'}, {'nonempty', 'scalar', '>', 0.2, '<', 1}))
71 addParameter(p, 'selfpaced', false, @(x) ...
72     validateattributes(x, {'logical'}, {'nonempty', 'scalar'}))
73 addParameter(p, 'useConfidenceRating', false, @(x) ...
74     validateattributes(x, {'logical'}, {'nonempty', 'scalar'}))
75
76 parse(p, experimentID, subjectID, varargin{:});
77
78 % Load experiment parameters. If no experiment with this ID has been
79 % created show a warning to the user and create a new experiment.
80 try
81     params = load(fullfile('.', data, experimentID, 'params.mat'));
82 catch
83     warning(['Unable to read parameter file.\n\n' ...
84         'Experiment %s may not exist in the current directory.\n\n'...
85         'Creating Experiment...'], ...
86         experimentID)
87     % create a new experiment and load parameters
88     [exitCode, message] = createExperiment(experimentID, 'Memory');
89     if exitCode
90         warning(message, exitCode);
91         return
92     end
93     params = load(fullfile('.', data, experimentID, 'params.mat'));
94 end
95
96 % Check if subject exists, create a new subject folder if it doesn't
97 subjectPath = fullfile('.', data, experimentID, subjectID);
98 if ~isfolder(subjectPath)
99     mkdir(subjectPath);
100 end
101
102 % Check if session is within the number of planned sessions
103 if params.numSessions < p.Results.session

```

```

104     error('Error. \nThis experiment does not possess more than %d. sessions'...
105           , params.numSessions);
106 end
107
108 sessionString = num2str(p.Results.session); % To be appended to filenames
109
110 % If this experiment has a training session (S = 1), use the parameters
111 % specified on creation
112 if ~isempty(params.training)
113     sessionString = num2str(p.Results.session-1); % Accounting for training ...
114           session.
115     if p.Results.session == 1
116         params.numBlocks = params.training.numBlocks;
117         params.numImages = params.training.numStim;
118     end
119 end
120 %% List off available languages
121 % Starts by requesting the user to select one of the available languages
122 % for the experiment
123
124 availableLanguages = {'English (EN)', 'Português (PT)'}; % Text displayed to ...
125           user
126
127 languageCodes = {'EN', 'PT'}; % Codes used to identify the language
128
129 [idx, tf] = listdlg('ListString', availableLanguages, ...
130                   'SelectionMode', 'single');
131
132 % if the user selects 'Cancel' from the input dialogue the function returns
133 % exit code 1
134 if ~tf
135     return
136 end
137
138 language = languageCodes{idx}; % Selected language
139
140 %% Initialization of BrainFlow
141 % This experiment is compatible with OpenBCI Boards. A pop-up window
142 % prompts the user to decide if the current experiment will use the OpenBCI
143 % Board. If so, a new board object is created. The board is configured for
144 % accordingly before starting to stream.
145
146 % Use Brainflow?
147 answer = questdlg('Use Brainflow?', 'Brainflow Setup', ...
148                 'Yes', 'No', 'Yes');
149
150 switch answer
151     case 'Yes'
152         % List off supported Boards

```

```

151     [ ~ ,supportedBoards] = enumeration('BoardIDs');
152
153     [pickedBoard,tf] = listdlg('ListString', supportedBoards,...
154         'SelectionMode','single', 'ListSize', [200 300]);
155
156     % if the user selects 'Cancel' from the input dialogue the function ...
157         returns
158     % exit code 1
159     if ~tf
160         return
161     end
162
163     %
164     if ~isempty(dir([subjectPath, '\eeg_S',sessionString...
165         , '_*.csv']))
166         error('Error.\nRecordings for session %s already exist in %s. ...
167             \nIf you do not wish to lose this data, back up your files. ...
168             If you wish to repeat this session, delete them before ...
169             proceeding.',...
170             sessionString, subjectPath)
171     end
172
173     BoardShim.set_log_file('brainflow.log'); % Set log file
174     BoardShim.enable_dev_board_logger(); % Set log level to TRACE
175
176     boardParams = BrainFlowInputParams(); % Initialize ...
177         parameters struct
178     % Assign Serial port. Only works from M2019b onwards
179     boardParams.serial_port = char(serialportlist("available"));
180
181     % Create a new "board" and prepare the session
182     board_shim = ...
183         BoardShim(int32(BoardIDs.(supportedBoards{pickedBoard})), ...
184         boardParams);
185     board_shim.prepare_session();
186
187     board_shim.config_board('/2'); % Turn on analog reading
188
189     disp('Using The Requested Board.')
190     useBrainflow = true;
191     case 'No'
192         disp('No board will be created.')
193         useBrainflow = false;
194     otherwise
195         return
196     end
197
198     %% Initialization of Psychtoolbox
199     % Default settings for Psychtoolbox are set; measures related to the

```

```

193 % screen are retrieved. A first black window is drawn and shown
194
195 % Here we call some default settings for setting up Psychtoolbox
196 PsychDefaultSetup(2);
197
198 % On windows 8 and 10, Psychtoolbox cannot deactivate the desktop
199 % windows manager. Synchronization tests will always fail, causing
200 % the program to crash. These lines deactivate both the tests and a
201 % warning screen that succeeds it.
202 Screen('Preference', 'SkipSyncTests', 1);
203 Screen('Preference', 'VisualDebugLevel', 0);
204
205 % Get the screen number, gives us a number for each of the screens
206 % attached to computer. Using multiple screens with Windows is not
207 % recommended.
208 screens = Screen('Screens');
209
210 % Select maximum of these numbers, so that external monitor is chosen
211 % by default, if existent
212 screenNumber = max(screens);
213
214 % Get screen's values for black and white
215 white = WhiteIndex(screenNumber);
216 black = BlackIndex(screenNumber);
217
218 HideCursor; % Hide mouse cursor
219
220 % Open an on screen window using PsychImaging and color it black
221 [window, windowRect] = PsychImaging('OpenWindow', screenNumber, black);
222
223 % Set the blend function for the screen - Support Transparency
224 Screen('BlendFunction', window, 'GL_SRC_ALPHA', 'GL_ONE_MINUS_SRC_ALPHA');
225
226 % Get the size of the on screen window in pixels
227 [screenXpixels, screenYpixels] = Screen('WindowSize', window);
228
229 % Get the centre coordinate of the window in pixels
230 [xCenter, yCenter] = RectCenter(windowRect);
231
232 % Measure the vertical refresh rate of the monitor
233 ifi = Screen('GetFlipInterval', window);
234
235 % Retrieve the maximum priority number and set max priority
236 topPriorityLevel = MaxPriority(window);
237 Priority(topPriorityLevel);
238
239 % Setup the text type for the window
240 Screen('TextFont', window, 'Monospaced');
241 Screen('TextSize', window, 36);

```



```

242
243 %% Load Resources
244 % Necessary icons and textual prompts are loaded. Image stimuli aren't
245 % loaded here, only a cell array containing the chosen categories for this
246 % session and a struct array with metadata related to each stimulus.
247
248 % Load image stimuli list
249 [imageStruct, imageCategories] = getSessionTargets(experimentID, ...
250     subjectPath, ...
251     language, p.Results.session);
252
253 % Load visual prompts
254 [i,map,alpha] = imread('.\resources\arrows\left.png');
255 i = ind2rgb(i,map); i(:, :, 4)=alpha;
256 arrowLeft = Screen('MakeTexture',window,i);
257 [i,map,alpha] = imread('.\resources\arrows\right.png');
258 i = ind2rgb(i,map); i(:, :, 4)=alpha;
259 arrowRight = Screen('MakeTexture',window,i);
260 [i,map,alpha] = imread('.\resources\arrows\down.png');
261 i = ind2rgb(i,map); i(:, :, 4)=alpha;
262 arrowDown = Screen('MakeTexture',window,i);
263 % [i,map,alpha] = imread('.\resources\arrows\up.png');
264 % i = ind2rgb(i,map); i(:, :, 4)=alpha;
265 % arrowUp = Screen('MakeTexture',window,i); % Uncomment for Guess
266
267 clear i
268
269 % Path to text files containing dialogue for the requested language
270 switch(language)
271     case 'PT'
272         txtfile = '.\resources\text\messages_pt.csv';
273     case 'EN'
274         txtfile = '.\resources\text\messages.csv';
275 end
276
277 % Load text prompts
278 try
279     messages = readcell(txtfile, 'Delimiter', '\t');
280 catch
281     [~, messages, ~] = xlsread(txtfile); % For backwards compatibility
282 end
283
284 %% Set Keyboard Map
285 % Maps each key on the keypad to a response (to a char)
286
287 % Key mapping
288 KbName('UnifyKeyNames');
289 escapeKey = KbName('ESCAPE'); % assign escape key

```

```

290
291 % Keys for encoding
292 keymap.encoding = containers.Map({ KbName('4'), ...
293     KbName('6') }, {1,2});
294
295 % Keys for retrieval
296 keymap.retrieval = containers.Map({KbName('4'), ...
297     KbName('6') }, ...
298     {'R', 'N'}); % R - Remembered ('Old'); N - New
299
300 % Keys for confidence ratings
301 if p.Results.useConfidenceRating
302     keymap.confidence = containers.Map({KbName('4'), ...
303         KbName('2'), KbName('6') }, ...
304         {'1', '2', '3'}); % 1 - not sure; 2 - a bit sure; 3 - definitely sure
305 end
306
307 % Initialize array with all keys that will be used
308 idx = [cell2mat(keys(keymap.confidence)), escapeKey];
309 keysInterest=zeros(1,256);
310 keysInterest(idx)=1;
311
312 %% Set Interval Durations
313
314 stimulusDuration = 2.500; % stimulus presentation ...
    duration
315 stimulusFrames = round(stimulusDuration / ifi); % number of frames to wait for
316
317 isi = [1.400, 1.600]; % interstimulus duration
318 isiFrames = round(isi / ifi); % number of frames to wait for
319
320 pauseDuration = 30.000; % distraction phase duration
321 pauseFrames = round(pauseDuration / ifi); % number of frames to wait for
322
323 answerDuration = 4.000; % answer timeout
324 answerFrames = round(answerDuration / ifi); % number of frames to wait for
325
326 %% Set Visual Parameters
327 % Set the size of stimuli, markers and others and set their position on the
328 % screen.
329
330 % SET THE POSITION AND SIZE OF ALL IMAGE STIMULUS -----
331
332 % Calculate height of images to be displayed
333 imageHeight = calculateImageSize(screenNumber, p.Results.distanceFromScreen);
334
335 % Prepare box to draw the images in
336 theRect = [0 0 imageHeight imageHeight]; % Image is squared
337 destinationRect = CenterRectOnPointd(theRect, xCenter, ...

```

```

338     yCenter);
339
340 % DETERMINE THE POSITIONS OF THE ARROW ICONS -----
341
342 % Positions used for arrow keys prompts (Old/New)
343 theRect = [0 0 imageHeight/4 imageHeight/4]; % Image is squared
344 destinationLeft = CenterRectOnPointd(theRect, xCenter-imageHeight*3/8,...
345     yCenter+imageHeight*11/16);
346 destinationRight = CenterRectOnPointd(theRect, xCenter+imageHeight*3/8,...
347     yCenter+imageHeight*11/16);
348
349 % Positions used for confidence rating prompts
350 destinationLeftCentered = CenterRectOnPointd(theRect, ...
351     xCenter-imageHeight*3/8,...
352     yCenter);
353 destinationRightCentered = CenterRectOnPointd(theRect, ...
354     xCenter+imageHeight*3/8,...
355     yCenter);
356 destinationCenterCentered = CenterRectOnPointd(theRect, xCenter,...
357     yCenter+imageHeight*5/16);
358 % -----
359
360 % Prepare square indicator in the corner of the screen. The photoresistor
361 % will be place above it.
362 theRect = [0 0 150 150];
363 indicatorRect = CenterRectOnPointd(theRect, 0,...
364     screenYpixels);
365
366 % SET TEXT PROMPT COORDINATES -----
367
368 % Calculate the width of a single character
369 textRect = Screen('TextBounds', window, 'A');
370 fontWidth = textRect(3)-textRect(1);
371 numCharPerLine = floor(screenXpixels/fontWidth);
372
373 % Set coordinates for each text prompt. Text prompts appear
374 % besides each arrow icon.
375
376 topTextCoord_y = (yCenter+imageHeight*11/16)-textRect(4)/2; % Used for
377 % top text prompts
378 newTextCoord_x = xCenter+imageHeight*5/8; % Translate text horizontally ...
379 (right)
380
381 textRect = Screen('TextBounds', window, messages{12}); % Get text ...
382 coordinates
383 rememberCoord_x = xCenter-(textRect(3)+imageHeight*5/8); % Translate text ...
384 horizontally (left)
385
386 botTextCoord_y = (yCenter+imageHeight)-textRect(4)/2; % Used for bottom text

```

```

382
383 if p.Results.useConfidenceRating
384     textRect = Screen('TextBounds', window, messages{13}); % Get text ...
385         coordinates
386     conf_1_Coord_x = xCenter-(textRect(3)+imageHeight*5/8); % Translate ...
387         text horizontally (left)
388
389     textRect = Screen('TextBounds', window, messages{14});
390     conf_2_Coord_x = (xCenter)-(textRect(3)+imageHeight*2/8); % Align Center
391
392     conf_3_Coord_x = xCenter+imageHeight*5/8; % Translate text horizontally ...
393         (right)
394 end
395
396 % -----
397 % Set fixation cross parameters
398
399 fixCrossDimPix = 40; % Set the size of the arms of the fixation cross
400 xCoords = [-fixCrossDimPix fixCrossDimPix 0 0]; % Set the coordinates
401 yCoords = [0 0 -fixCrossDimPix fixCrossDimPix];
402 allCoords = [xCoords; yCoords];
403 lineWidthPix = 4; % Set the line width for the fixation cross
404
405 %% Initiate Stimulus Presentation
406 % The task loop begins here. First, a list of images is sequentially
407 % presented to the participant. Afterwards, the participant is shown random
408 % equations and must determine if they're correct. Finally, the participant
409 % is shown a new sequence of images. Consult
410 % Experiment_Routine_Instructions.pptx for more details.
411
412 % Create keyboard queue to read subject inputs
413 KbQueueCreate([], keysInterest);
414 KbQueueStart();
415
416 for block = 1:params.numBlocks
417     encodingResponse = cell(params.numImages,1); % Assign cell to save
418         % encoding answers
419     if useBrainflow % Begin streaming into a .csv file with Brainflow
420         streamerParams = ['file://data/', experimentID, '/', ...
421             subjectID, '/eeg_S', sessionString...
422             , '_', num2str(block), '.csv:w'];
423         board_shim.start_stream(225000, streamerParams);
424     end
425
426     startTime = posixtime(datetime('now'));
427
428     % Prepare target images for the current block
429     twoCategories = imageCategories(block,:); % Pick two categories
430     [Targets, allImages, idxOldImages] = prepareTargets(imageStruct,...

```

```

428         twoCategories,params.numImages, subjectID);
429     % Targets - struct containing data related to every target that will be
430     % presented during the current block, including its name, folder,
431     % category and label (Old or New). RK judgments given to each one of
432     % them during retrieval are saved in this struct under "response";
433     % confidence ratings under "confidence_rating"
434     % allImages - Array of image matrices
435     % idxOldImages - Indices of images that will be presented during
436     % encoding
437
438     % Write instruction message for subject
439     DrawFormattedText(window, [messages{1},'\n',messages{3}],...
440         'center', 'center', white, numCharPerLine);
441
442     % Update the display to show the instruction text:
443     Screen('Flip', window);
444
445     KbQueueWait(); % Wait until key is pressed
446
447     % Get X coordinates of text
448     textRect = Screen('TextBounds', window, twoCategories{1});
449     leftTextCoord_x = xCenter-(textRect(3)+imageHeight*5/8);
450     rightTextCoord_x = xCenter+imageHeight*5/8;
451
452     % Draw prompts
453     DrawFormattedText(window, [messages{11},'\n',messages{3}],...
454         'center', 'center', white, numCharPerLine);
455     Screen('DrawTextures', window, [arrowRight, arrowLeft]...
456         , [], [destinationRight;destinationLeft]');
457     Screen('DrawText',window, twoCategories{1}, leftTextCoord_x , ...
458         topTextCoord_y, white);
459     Screen('DrawText',window, twoCategories{2}, rightTextCoord_x, ...
460         topTextCoord_y, white);
461
462     % Flip to screen
463     Screen('Flip', window);
464
465     KbQueueWait(); % Wait until key is pressed
466
467     %% Begin Encoding Stage
468     % Old images are presented sequentially on the screen
469
470     % Draw the fixation cross in white on the "back"
471     Screen('DrawLines', window, allCoords,...
472         lineWidthPix, white, [xCenter yCenter], 2);
473
474     vbl = Screen('Flip', window); % flip to fixation screen
475
476     % Initialize loop counter

```

```

477     counter = 0;
478
479     while counter ≠ params.numImages
480         counter = counter + 1;
481
482         % Create image texture and draw it on the "back"
483         imageTexture = ...
            Screen('MakeTexture', window, allImages{idxOldImages(counter)});
484         Screen('DrawTextures', window, imageTexture, [], destinationRect);
485
486         % Draw indicator rectangle in the corner of the screen
487         Screen('FillRect', window, white, indicatorRect);
488
489         % Draw prompts
490         Screen('DrawTextures', window, [arrowRight, arrowLeft]...
            , [], [destinationRight; destinationLeft]);
491         Screen('DrawText', window, twoCategories{1}, leftTextCoord_x, ...
            topTextCoord_y, white);
492         Screen('DrawText', window, twoCategories{2}, rightTextCoord_x, ...
            topTextCoord_y, white);
493
494         vbl = Screen('Flip', window, vbl + (isiFrames(randi([1,2])) - 0.5) ...
            * ifi);
495
496
497     if counter ≠ params.numImages
498         % Draw the fixation cross in white
499         Screen('DrawLines', window, allCoords, ...
            lineWidthPix, white, [xCenter yCenter], 2);
500
501         vbl = Screen('Flip', window, vbl + (stimulusFrames - 0.5) * ifi);
502     else
503         % Create empty screen
504         Screen('FillRect', window, black)
505
506         % Flip to empty screen
507         vbl = Screen('Flip', window, vbl + (stimulusFrames - 0.5) * ifi);
508     end
509
510     [pressed, firstPress]=KbQueueCheck();
511
512     if pressed
513         [¬, idx]=max(firstPress);
514         if firstPress(escapeKey)
515             break;
516         end
517         try
518             encodingResponse{counter} = ...
                twoCategories{keymap.encoding(idx)};
519         catch
520

```

```

523         encodingResponse{counter} = [];
524     end
525 end
526 end
527
528 KbQueueFlush();
529
530 %% Begin Distractor Stage
531 % Equations are presented sequentially to the participant during a
532 % given amount of time
533
534 % Get X coordinates of text
535 textRect = Screen('TextBounds', window, messages{4});
536 leftTextCoord_x = xCenter-(textRect(3)+imageHeight*5/8);
537
538 while (GetSecs - vbl) ≤ pauseDuration
539     [str, ~] = getEquation(1);
540
541     Screen('TextSize', window, 42);
542     DrawFormattedText(window, str, 'center', 'center', white);
543
544     % Draw prompts
545     Screen('DrawTextures', window, [arrowRight, arrowLeft]...
546         , [], [destinationRight;destinationLeft]);
547
548     Screen('TextSize', window, 36);
549     Screen('DrawText', window, messages{4}, leftTextCoord_x,...
550         topTextCoord_y, white);
551     Screen('DrawText', window, messages{5}, rightTextCoord_x,...
552         topTextCoord_y, white);
553
554     Screen('Flip', window);
555
556     KbQueueWait()
557     break; % Uncomment to skip the break
558 end
559
560
561 %% Begin Retrieval Stage
562 % Previously shown images are presented again, intermingled with novel
563 % images.
564
565 retrievalTime = posixtime(datetime('now'));
566
567 % Write instruction message for subject
568 DrawFormattedText(window, [messages{2}, '\n', messages{3}]...
569     , 'center', 'center', white, numCharPerLine);
570
571 % Update the display to show the instruction text:

```

```

572     Screen('Flip', window);
573
574     KbQueueWait();
575
576     % Draw the fixation cross in white
577     Screen('DrawLines', window, allCoords,...
578         lineWidthPix, white, [xCenter yCenter], 2);
579
580     % Flip to fixation cross
581     vbl = Screen('Flip', window);
582
583     % Reset counter
584     counter = 0;
585     exitLoop = false;
586
587     while ~exitLoop && counter ≠ 2*params.numImages
588
589         counter = counter + 1;
590
591         % Create texture with image and draw it on the backscreen
592         imageTexture = Screen('MakeTexture',window, allImages{counter});
593         Screen('DrawTextures', window, imageTexture, [], destinationRect);
594
595         % Draw indicator rectangle in the corner of the backscreen
596         Screen('FillRect', window, white, indicatorRect);
597
598         % Flip to backscreen
599         vbl = Screen('Flip', window, vbl + (isiFrames(randi([1,2])) - 0.5) ...
600             * ifi);
601
602         % Draw image Texture on the backscreen
603         Screen('DrawTextures', window, imageTexture, [], destinationRect);
604
605         % Draw Old/New prompts in backscreen
606         Screen('DrawTextures', window, [arrowRight,arrowLeft,...
607             [], [destinationRight;destinationLeft]');
608
609         Screen('DrawText',window, messages{12}, rememberCoord_x ,...
610             topTextCoord_y , white);
611         Screen('DrawText',window, messages{9}, newTextCoord_x,...
612             topTextCoord_y, white);
613
614         % Flip to answer screen
615         vbl = Screen('Flip', window, vbl + (stimulusFrames - 0.5) * ifi);
616
617         KbQueueFlush()
618
619         if p.Results.selfpaced

```



```

620         while true % While answer isn't given
621             [pressed, firstPress]=KbQueueCheck();
622             [¬,idx]=max(firstPress);
623             if pressed
624                 try
625                     Targets(counter).response = keymap.retrieval(idx);
626                     break;
627                 catch
628                     if firstPress(escapeKey)
629                         exitLoop = true;
630                         break;
631                     end
632                 end
633             end
634         end
635     else
636         % Implement timeout loop
637         while (GetSecs - vbl) ≤ answerDuration
638             % Check what key was pressed during the test
639             [pressed, firstPress]=KbQueueCheck();
640             [¬,idx]=max(firstPress);
641             if pressed
642                 try
643                     Targets(counter).response = keymap.retrieval(idx);
644                     break;
645                 catch
646                     if firstPress(escapeKey)
647                         exitLoop = true;
648                         break;
649                     end
650                 end
651             end
652         end
653     end
654
655     KbQueueFlush()
656     % Flip to fixation cross (Or dark screen)
657
658     if p.Results.useConfidenceRating && pressed
659         Screen('DrawTextures', window, [arrowRight,arrowLeft,...
660             arrowDown],[], ...
661             [destinationRightCentered;destinationLeftCentered;...
662             destinationCenterCentered]');
663
664         Screen('DrawText',window, messages{13}, conf_1_Coord_x ,...
665             topTextCoord_y - imageHeight*11/16, white);
666         Screen('DrawText',window, messages{14}, conf_2_Coord_x, ...
667             botTextCoord_y - imageHeight*11/16, white);
668         Screen('DrawText',window, messages{15}, conf_3_Coord_x,...

```

```

668         topTextCoord_y = imageHeight*11/16, white);
669
670     % Flip to answer screen
671     vbl = Screen('Flip', window);
672
673     KbQueueFlush()
674
675     if p.Results.selfpaced
676         while true % While answer isn't given
677             [pressed, firstPress]=KbQueueCheck();
678             [¬,idx]=max(firstPress);
679             if pressed
680                 try
681                     Targets(counter).confidence_rating = ...
682                         keymap.confidence(idx);
683                     break;
684                 catch
685                     if firstPress(escapeKey)
686                         exitLoop = true;
687                         break;
688                     end
689                 end
690             end
691         else
692             % Implement timeout loop
693             while (GetSecs - vbl) ≤ answerDuration
694                 % Check what key was pressed during the test
695                 [pressed, firstPress]=KbQueueCheck();
696                 [¬,idx]=max(firstPress);
697                 if pressed
698                     try
699                         Targets(counter).confidence_rating = ...
700                             keymap.confidence(idx);
701                         break;
702                     catch
703                         if firstPress(escapeKey)
704                             exitLoop = true;
705                             break;
706                         end
707                     end
708                 end
709             end
710         end
711     end
712
713     if counter ≠ 2*params.numImages
714         % Draw the fixation cross in white
715         Screen('DrawLines', window, allCoords,...

```

```

715         lineWidthPix, white, [xCenter yCenter], 2);
716     end
717
718     vbl = Screen('Flip', window); % Right after answer is given
719 end
720
721 %% Break Between Blocks
722
723 % Stop Stream
724 if useBrainflow
725     board_shim.stop_stream();
726 end
727
728 % Save images shown and responses given during this block
729 encodingTargets = [encodingResponse, num2cell(idxOldImages)];
730
731 if ~isempty(params.training) && p.Results.session == 1
732     subjectFilename = ['answers_Training_', ...
733         num2str(block), '.mat'];
734 else
735     subjectFilename = ['answers_S', sessionString, ...
736         '_', num2str(block), '.mat'];
737 end
738 save(fullfile(subjectPath, subjectFilename), ...
739     'startTime', 'retrievalTime', 'Targets', 'encodingTargets');
740
741 clear idxOldImages encodingResponse encodingTargets...
742     encodingAndRetrievalTime startTime retrievalTime Targets
743
744 if block ≠ params.numBlocks
745     % Draw text and flip to break screen
746     DrawFormattedText(window, messages{10}, 'center', 'center', white);
747     vbl = Screen('Flip', window);
748
749     % Wait a minute or move on when key is pressed
750     KbQueueWait([], 0, vbl + (pauseFrames*2 - 0.5) * ifi);
751 end
752
753 end
754 %% Terminate correctly
755 % Release stream and keyboard queue, Clear the screen
756
757 % Release Board
758 if useBrainflow
759     board_shim.release_session();
760 end
761
762 % Release Keyboard Queue
763 KbQueueRelease();

```

```

764
765 % Clear the screen.
766 sca;
767 end

1 function [exitCode, msg] = createExperiment(experimentID, experimentType)
2 % Creates a new experiment directory and sets key parameters
3 %
4 % @file createExperiment.m
5 %
6 % Creates the necessary partition to store all information related to the
7 % experiment being conducted. Information for the experiments is store in a
8 % file called params.mat. This file includes the language of the prompts,
9 % the number of sessions, blocks and repetitions and more, depending on the
10 % type of experiment. Experiment files are created in a folder named data
11 % in the current directory.
12 %
13 % SYNTAX:
14 %   exitCode = createExperiment(experimentID, ...)
15 %   [exitCode, msg] = createExperiment(experimentID, [])
16 %   [exitCode, msg] = createExperiment(experimentID, experimentType)
17 %
18 % INPUT:
19 %       experimentID:      identificator given to the experimental
20 %                          procedure, as well as the folder containing
21 %                          both all parameters unique to this group of
22 %                          experiments and collected data. (char)
23 %
24 %       experimentType:    type of experiment (char)
25 % OUTPUT:
26 %       exitCode:          exit code returned to the main script
27 %       msg:              message to be displayed to user
28 %
29 % Ana S S Cardoso, BRAIN group, INESC-TEC Porto, Jun/2021
30 % ...
31
32 %% Create experiment folder
33 % Create folder to store data pertaining to the created experiment,
34 % including subject folders.
35
36 path = fullfile('.\data',experimentID);
37
38 mkdir(path);
39 paramsFile = fullfile(path, 'params.mat'); % "create" file with experiment
40 % parameters
41 %% Get and save experiment parameters
42 % Requests user input depending on the type of experiment being created and

```

```

43 % saves the chosen parameters in the respective params.mat file
44
45 %% Configure generic parameters - Request user input and validate it
46
47 [general,training,exitCode] = InputDialogue();
48
49 % if the user selects 'Cancel' from the input dialogue the function
50 % returns exit code 1
51 if exitCode == 1
52     msg = 'Exit Code %d - Canceled. \nExiting...';
53     return
54 end
55
56 numSessions = general(1);
57 numBlocks = general(2);
58 numImages = general(3);
59
60 %% Select image categories for the experiment
61
62 % Get images directories
63 imageFolders = dir(fullfile('.\resources','68-scenes','*-68'));
64 imageFolders = {imageFolders.name};
65
66 % Pick some categories at random
67 idxFolders = Shuffle(1:numel(imageFolders));
68 idxFolders = idxFolders(1:2*numBlocks*numSessions);
69 imageFolders = (imageFolders(idxFolders));
70
71 % Implemented a switch case so it may be expanded to other
72 % experiments that might require different parameters.
73 switch experimentType
74     case 'Memory'
75         % Save parameters in the params.mat file
76         save(paramsFile,'numSessions',...
77             'numBlocks','numImages','training','imageFolders');
78
79         % Return success exit code
80         exitCode = 0;
81         msg = 'Success';
82 end

1 function [imageStruct, imageCategories] = getSessionTargets(experimentID, ...
2     subjectPath, language, session)
3 %
4 % @file getSessionTargets.m
5 %
6 % This function generates a randomized list of available categories. These

```

```

7 % will be used during the current session. Additionally, the function also
8 % returns a struct containing metadata related to every image loaded during
9 % the current session.
10 %
11 % SYNTAX:
12 %     [imageStruct, imageCategories] = getSessionTargets(experimentID, ...
13 % subjectPath, session)
14 %
15 %
16 % INPUT:
17 %     experimentID:   identificator given to the experimental
18 %                   procedure, as well as the folder containing both
19 %                   all parameters unique to this group of experiments
20 %                   and collected data. (char)
21 %
22 %     subjectPath:    path to the folder containing all files pertaining
23 %                   to a subject (char)
24 %
25 %     language:       language identifier for the language requested by
26 %                   the user(char)
27 %
28 %     session:        number of the session. Each session is
29 %                   composed by multiple blocks that contain a an
30 %                   encoding, distractor and retrieval phase. (int)
31 % OUTPUT:
32 %     imageStruct:     struct array containing metadata related to every
33 %                   image that will be presented during a given
34 %                   session. This includes the names of the image
35 %                   files, relative folder paths and the image's
36 %                   category (struct)
37 %
38 %     imageCategories: the categories that will be used for the
39 %                   current session (cell)
40 %
41 % Ana S S Cardoso, BRAIN group, INESC-TEC Porto, Jun/2021
42 % ...

```

```

43
44 %% Load struct array and categories generated for this subject
45 % Try to load the image struct array the category order generated for this
46 % subject. If the file cannot be found/cannot be read throw an error.
47 try
48     load(fullfile(subjectPath, 'cathistory.mat'), 'allImagePath', ...
49           'allImageCategories', 'idxCategories');
50 catch
51     %% Load experiment parameters and category names
52     % Loads experiment parameters from the params.mat file and image
53     % category names listed within the categories.xlsx file.
54

```

```

55     % Load experiment parameters
56     params = load(fullfile('.',data',experimentID,'params.mat'));
57
58     % Read file with category names in multiple languages
59     fileName = fullfile('.',resources','text','categories.xlsx');
60
61     % The first column in the categories.xlsx file corresponds to the name of
62     % the folder that contains the images for a certain category. All other
63     % columns contain a translation of each category.
64     try
65         categoryNames = readcell(fileName);
66     catch
67         [~, categoryNames, ~] = xlsread(fileName);
68     end
69
70     % Find what row corresponds to the language specified by the experiment
71     headers = categoryNames(1,:);
72     idxLanguage = find(ismember(headers,language));
73
74     categoryNames = categoryNames(2:end,:); % Exclude the headers
75
76     %% Get image information and store it in a struct array
77     % Create a structure list containing the directories for all image
78     % folders. Create a cell array containing all available categories.
79
80     % Get image directories of the requested categories
81     folderPaths = ...
            fullfile('.',resources','68-scenes',params.imageFolders,'*.jpg');
82
83     % allImagePath will be a struct array. Each entry corresponds to an image.
84     allImagePath = [];
85
86     % For each folder/category create a structure list containing the name of
87     % the file, the path and the category it belongs to.
88     for i = 1:numel(folderPaths)
89         imagePath = dir(folderPaths{i});
90
91         % Find what row from the formatted category names corresponds to the
92         % current category folder
93         idx = ismember(categoryNames(:,1),params.imageFolders{i});
94
95         % For each entry, add a "category" field to the struct.
96         [imagePath(:).category] = deal(categoryNames{idx,idxLanguage});
97
98         if ~isfield(imagePath, 'folder') % add folder field (Backwards ...
            compatibility)
99             temp = folderPaths{i};
100             [imagePath(:).folder] = deal(temp(1:end-5));
101         end

```

```

102
103     allImagePath = [allImagePath; imagePath];
104 end
105
106 % Remove unnecessary fields
107 allImagePath = rmfield(allImagePath, {'bytes'; 'isdir'; ...
108     'datenum'; 'date'});
109
110 % Get cell array including all category names
111 allImageCategories = unique({allImagePath.category});
112
113 %% Randomize categories
114 % Get a random order of categories to be used in this experiment
115
116 % Pick some categories at random
117 idxCategories = Shuffle(1:numel(allImageCategories));
118 idxCategories = mat2cell(idxCategories, 1, ...
119     repelem(2*params.numBlocks, params.numSessions));
120
121 % Store the categories and the image struct array in a .mat file
122 save(fullfile(subjectPath, 'cathistory.mat'), 'allImagePath', ...
123     'allImageCategories', 'idxCategories');
124 end
125 %% Obtain category order and image struct array
126 % Prepare only the portion of the image struct array that will be used for
127 % this session using the previously generated shuffled category order
128
129 % categories that will be used in this session
130 imageCategories = (allImageCategories(idxCategories{session}));
131
132 % only keep images belonging to the categories that will be used in this
133 % session
134 idxImage = ismember({allImagePath.category}, imageCategories);
135 imageStruct = allImagePath(idxImage);
136
137 % reshape array into category pairs
138 imageCategories = reshape(imageCategories, [], 2);
139 end

```



```

1 function [allTargets, allImages, idxOldImages] = ...
2     prepareTargets(imageStruct, categories, numOfTypeTargets, subjectID)
3 % Prepares images to be shown during a given block.
4 %
5 % @file prepareTargets.m
6 %
7 % This function takes the struct generated by getSessionTargets and loads
8 % the images needed for the experiment. Each image is labeled according to
9 % whether it will be encountered during encoding or not. Additionally, this

```



```

9 % function returns two shuffled image vectors. The first one contains all
10 % images, following the order they will be presented in during retrieval.
11 % The second vector is a shuffled vector of "old" targets, meaning targets
12 % presented during encoding.
13 %
14 % SYNTAX:
15 %     [allTargets, allImages, oldImages] = prepareTargets(imageStruct, ...
16 % categories, numOfTargets)
17 %
18 %
19 % INPUT:
20 %     imageStruct:    struct array containing data related to every image
21 %                    that will be presented during a given session. This
22 %                    includes the names of the image files, relative
23 %                    folder paths and the image's category (struct)
24 %
25 %     categories:     the two categories that will be used for the
26 %                    current block (cell)
27 %
28 %     numOfTargets:   number of targets to be studied during encoding
29 %                    (int)
30 %
31 %     subjectID:      identifier given to the subject (char)
32 %
33 % OUTPUT:
34 %     allTargets:     struct containing data related to every target that
35 %                    will be used during the current block. A subgroup
36 %                    of imageStruct. This variable includes a label that
37 %                    determines if an image will be presented during
38 %                    encoding or not (struct)
39 %
40 %     allImages:      cell array containing the images that will be
41 %                    shown during the retrieval phase
42 %
43 %     oldImages:      cell array containing the images that will be shown
44 %                    during the encoding phase
45 %
46 % Ana S S Cardoso, BRAIN group, INESC-TEC Porto, Jun/2021
47 % ...

```

```

48
49 %% Prepare image struct array for the current block
50 maxNumOfTargets = 60;
51
52 % Get targets that belong to this block's categories
53 idxCategoryOne = find(ismember({imageStruct.category},categories{1}), ...
54     maxNumOfTargets);
55 idxCategoryTwo = find(ismember({imageStruct.category},categories{2}), ...
56     maxNumOfTargets);

```

```

57
58 allTargets = imageStruct([idxCategoryOne,idxCategoryTwo]);
59
60 % Attribute labels according to subject number
61 idx = false(1,maxNumOfTargets*2);
62 idx([1:maxNumOfTargets/2,maxNumOfTargets+1:maxNumOfTargets+maxNumOfTargets/2]) ...
    = true;
63 if strcmp(subjectID(end-1),'B')
64     idx = ~idx;
65 end
66 [allTargets(idx).label] = deal('New');
67 [allTargets(~idx).label] = deal('Old');
68
69 allTargets = allTargets([1:numOfTargets/2, ...
70     maxNumOfTargets/2+1:maxNumOfTargets/2+numOfTargets/2,...
71     maxNumOfTargets+1:maxNumOfTargets+numOfTargets/2,...
72     maxNumOfTargets*3/2+1:maxNumOfTargets*3/2+numOfTargets/2]);
73
74 % Shuffle images so they are presented in random order during
75 % retrieval
76 idxImages = Shuffle(1:numel(allTargets));
77 allTargets = allTargets(idxImages);
78
79 %% Read Images
80
81 allImages = cell(1,numel(allTargets));
82
83 % Read images and save them in a cell array
84 for i=1:numel(allTargets)
85     im = imread(fullfile(allTargets(i).folder,allTargets(i).name));
86     allImages{i} = im2double(im);
87 end
88
89 % Create a second cell array with images for encoding
90 idxOldImages = find(strcmp({allTargets.label},'Old'));
91
92 % Shuffle array of images for encoding so they're presented in a different
93 % order to that of the encoding phase
94 idxShuffle = Shuffle(1:numel(idxOldImages));
95 idxOldImages = idxOldImages(idxShuffle);
96 end

```

```

1 function [pixelHeight] = calculateImageSize(screenNumber,distanceFromScreen)
2 % Calculate height of visual stimuli
3 %
4 % @file calculateImageSize.m
5 %
6 % Calculates the height of an image so subjects at a given distance may be

```

```

7 % able to percieve it in its entirety at a single glance.
8 %
9 % INPUT:
10 % screenNumber:          The ID number of the screen, given by
11 %                      PsychToolBox's Screen('Screens') function (int)
12 %
13 % distanceFromScreen (m):  The distance between the subject and the
14 %                      monitor (double)
15 %
16 % OUTPUT:
17 % pixelHeight (px):  Height at which the image should be displayed
18 %
19 % Ana S S Cardoso, BRAIN group, INESC-TEC Porto, Jun/2021
20 % ...
    -----
21
22 % Get the size and resolution of the screen being used
23 [w, screenHeight]=Screen('DisplaySize', screenNumber); % height in millimeters
24 resolution = Screen('Resolution', screenNumber);      % struct with ...
    height in pixels
25
26 % Find the appropriate height for the image
27 % (Assuming paracentral vision of 7.5°)
28 height = distanceFromScreen * 7.5 * (pi/180) * 1e3; % Obtain height in ...
    millimeters
29
30 % Convert height to pixels
31 pixelHeight = round(resolution.height*height/screenHeight);
32 end

1 function [equation, isCorrect] = getEquation(n)
2 % Generates a random equation with n+1 operands.
3 %
4 % @file getEquation.m
5 %
6 % This function generates a char vector of a simple equation using the
7 % operators '+' and '-'. The numerical expression may be true or false.
8 %
9 % SYNTAX:
10 %     getEquation(n)
11 %     [equation, isCorrect] = getEquation(n)
12 %
13 % INPUT:
14 %     n:          number of operations to use (int).
15 %
16 % OUTPUT:
17 %     equation:    the generated numerical expression (char).
18 %

```

```

19 %      isCorrect:  indicates wether the numerical expression is true or
20 %                  false (bool)
21 %
22
23 %% List operators and randomly select n operations and n+1 operands
24
25 allOperators={'+' '-'};    % operators
26
27 operator=allOperators(randi(numel(allOperators),1,n));
28 operands=randi(10,1,n+1);
29
30 result = operands(1);
31 isCorrect = randi([0,1],1,1);
32
33 %% Calculate result
34
35 for i = 1:n
36     if strcmp(operator{i},'+')
37         result = result + operands(i+1);
38     else
39         result = result - operands(i+1);
40     end
41 end
42
43 %% IF FALSE - Generate false result
44
45 randomResult = result;
46 if ~isCorrect
47     while result == randomResult
48         randomResult = randi(20,1,1);
49     end
50     result = randomResult;
51 end
52
53 %% Construct char vector
54
55 equation = [];
56 for i = 1:n
57     equation = [equation,num2str(operands(i)),operator{i}];
58 end
59 equation = [equation,num2str(operands(n+1)),'=',num2str(result)];
60 end

1 function varargout = InputDialogue(varargin)
2 % INPUTDIALOGUE MATLAB code for InputDialogue.fig
3 %     INPUTDIALOGUE, by itself, creates a new INPUTDIALOGUE or raises the
4 %     existing singleton*.
5 %

```

```

6 %      OUTPUT:
7 %      varargout{1}: returns a matrix with the number of sessions, blocks
8 %      and stimuli to show at encoding specified by the user (double)
9 %
10 %      varargout{2}: returns a struct with the number of blocks (double)
11 %      and number of stimuli (double) to set for the training session
12 %
13 %      varargout{3}: returns an exit code (int)
14
15 % Begin initialization code - DO NOT EDIT
16 gui_Singleton = 1;
17 gui_State = struct('gui_Name',       mfilename, ...
18                   'gui_Singleton',  gui_Singleton, ...
19                   'gui_OpeningFcn', @InputDialogue_OpeningFcn, ...
20                   'gui_OutputFcn',  @InputDialogue_OutputFcn, ...
21                   'gui_LayoutFcn',  [], ...
22                   'gui_Callback',   []);
23 if nargin && ischar(varargin{1})
24     gui_State.gui_Callback = str2func(varargin{1});
25 end
26
27 if nargin
28     [varargout{1:nargout}] = gui_mainfcn(gui_State, varargin{:});
29 else
30     gui_mainfcn(gui_State, varargin{:});
31 end
32 % End initialization code - DO NOT EDIT
33
34
35 % --- Executes just before InputDialogue is made visible.
36 function InputDialogue_OpeningFcn(hObject, eventdata, handles, varargin)
37 % This function has no output args, see OutputFcn.
38 % hObject    handle to figure
39 % eventdata  reserved - to be defined in a future version of MATLAB
40 % handles    structure with handles and user data (see GUIDATA)
41 % varargin   command line arguments to InputDialogue (see VARARGIN)
42
43 % Choose default command line output for InputDialogue
44 handles.output = hObject;
45
46 set(findall(handles.tpanel, '-property', 'enable'), 'Enable', 'off');
47
48 % Update handles structure
49 guidata(hObject, handles);
50
51 % UIWAIT makes InputDialogue wait for user response (see UIRESUME)
52 uiwait(handles.figure1);
53
54 % --- Outputs from this function are returned to the command line.

```

```

55 function varargout = InputDialogue_OutputFcn(hObject, eventdata, handles)
56 % varargout    cell array for returning output args (see VARARGOUT);
57 % hObject      handle to figure
58 % eventdata    reserved - to be defined in a future version of MATLAB
59 % handles      structure with handles and user data (see GUIDATA)
60
61 % Get output from the handles structure
62 varargout{1} = handles.param;
63 varargout{2} = handles.training_param;
64 varargout{3} = handles.exitcode;
65
66 delete(handles.figure1);
67
68 % --- Executes on button press in okButton.
69 function okButton_Callback(hObject, eventdata, handles)
70 % hObject      handle to okButton (see GCBO)
71 % eventdata    reserved - to be defined in a future version of MATLAB
72 % handles      structure with handles and user data (see GUIDATA)
73
74 numSession = str2double(get(handles.inputSession, 'string'));
75 numBlock = str2double(get(handles.inputBlock, 'string'));
76 numStim = str2double(get(handles.inputStim, 'string'));
77
78 handles.training_param = [];
79
80 if get(handles.trainingOn, 'Value')
81     numSession = numSession + 1;
82     training.numBlocks = str2double(get(handles.inputTBlock, 'string'));
83     training.numStim = str2double(get(handles.inputTStim, 'string'));
84     handles.training_param = training;
85 end
86
87 handles.param = [numSession, numBlock, numStim];
88 handles.exitcode = 0;
89
90 guidata(hObject, handles)
91
92 uiresume(handles.figure1);
93
94 % --- Executes on button press in cancelButton.
95 function cancelButton_Callback(hObject, eventdata, handles)
96 % hObject      handle to cancelButton (see GCBO)
97 % eventdata    reserved - to be defined in a future version of MATLAB
98 % handles      structure with handles and user data (see GUIDATA)
99
100 function inputBlock_Callback(hObject, eventdata, handles)
101 % hObject      handle to inputBlock (see GCBO)
102 % eventdata    reserved - to be defined in a future version of MATLAB
103 % handles      structure with handles and user data (see GUIDATA)

```

```

104
105 % Hints: get(hObject,'String') returns contents of inputBlock as text
106 %         str2double(get(hObject,'String')) returns contents of inputBlock ...
           as a double
107 input = str2double(get(hObject,'String'));
108 if isnan(input)
109     set(hObject,'String','4');
110     warndlg('Input must be numerical');
111 end
112
113 % --- Executes during object creation, after setting all properties.
114 function inputBlock_CreateFcn(hObject, eventdata, handles)
115 % hObject    handle to inputBlock (see GCBO)
116 % eventdata  reserved - to be defined in a future version of MATLAB
117 % handles    empty - handles not created until after all CreateFcns called
118
119 % Hint: edit controls usually have a white background on Windows.
120 %         See ISPC and COMPUTER.
121
122 if ispc && isequal(get(hObject,'BackgroundColor'), ...
    get(0,'defaultUiControlBackgroundColor'))
123     set(hObject,'BackgroundColor','white');
124 end
125
126 function inputStim_Callback(hObject, eventdata, handles)
127 % hObject    handle to inputStim (see GCBO)
128 % eventdata  reserved - to be defined in a future version of MATLAB
129 % handles    structure with handles and user data (see GUIDATA)
130
131 % Hints: get(hObject,'String') returns contents of inputStim as text
132 %         str2double(get(hObject,'String')) returns contents of inputStim as ...
           a double
133
134 input = str2double(get(hObject,'String'));
135 if isnan(input)
136     set(hObject,'String','20');
137     warndlg('Input must be numerical');
138 elseif input > 60
139     set(hObject,'String','20');
140     warndlg('Must use LESS THAN 60 stimuli');
141 elseif mod(input,4) ~= 0
142     newInput=4*round(input/4);
143     set(hObject,'String',num2str(newInput));
144     warndlg('Must be a MULTIPLE OF 4');
145 end
146
147 % --- Executes during object creation, after setting all properties.
148 function inputStim_CreateFcn(hObject, eventdata, handles)
149 % hObject    handle to inputStim (see GCBO)

```

```

150 % eventdata reserved - to be defined in a future version of MATLAB
151 % handles empty - handles not created until after all CreateFcns called
152
153 % Hint: edit controls usually have a white background on Windows.
154 % See ISPC and COMPUTER.
155 if ispc && isequal(get(hObject,'BackgroundColor'), ...
    get(0,'defaultUiControlBackgroundColor'))
156     set(hObject,'BackgroundColor','white');
157 end
158
159 function inputSession_Callback(hObject, eventdata, handles)
160 % hObject handle to inputSession (see GCBO)
161 % eventdata reserved - to be defined in a future version of MATLAB
162 % handles structure with handles and user data (see GUIDATA)
163
164 % Hints: get(hObject,'String') returns contents of inputSession as text
165 % str2double(get(hObject,'String')) returns contents of inputSession ...
    as a double
166 input = str2double(get(hObject,'String'));
167 if isnan(input)
168     set(hObject,'String','3');
169     warndlg('Input must be numerical');
170 end
171
172
173 % --- Executes during object creation, after setting all properties.
174 function inputSession_CreateFcn(hObject, eventdata, handles)
175 % hObject handle to inputSession (see GCBO)
176 % eventdata reserved - to be defined in a future version of MATLAB
177 % handles empty - handles not created until after all CreateFcns called
178
179 % Hint: edit controls usually have a white background on Windows.
180 % See ISPC and COMPUTER.
181 if ispc && isequal(get(hObject,'BackgroundColor'), ...
    get(0,'defaultUiControlBackgroundColor'))
182     set(hObject,'BackgroundColor','white');
183 end
184
185 % --- Executes on button press in trainingOn.
186 function trainingOn_Callback(hObject, eventdata, handles)
187 % hObject handle to trainingOn (see GCBO)
188 % eventdata reserved - to be defined in a future version of MATLAB
189 % handles structure with handles and user data (see GUIDATA)
190
191 % Hint: get(hObject,'Value') returns toggle state of trainingOn
192
193 if get(hObject, 'Value')
194     set(findall(handles.tpanel, '-property', 'enable'), 'Enable', 'on');
195 else

```



```

196     set(findall(handles.tpanel, '-property', 'enable'), 'Enable', 'off');
197 end
198
199 function inputTBlock_Callback(hObject, eventdata, handles)
200 % hObject     handle to inputTBlock (see GCBO)
201 % eventdata   reserved - to be defined in a future version of MATLAB
202 % handles     structure with handles and user data (see GUIDATA)
203
204 % Hints: get(hObject,'String') returns contents of inputTBlock as text
205 %         str2double(get(hObject,'String')) returns contents of inputTBlock ...
           as a double
206 input = str2double(get(hObject,'String'));
207 if isnan(input)
208     set(hObject,'String','4');
209     warndlg('Input must be numerical');
210 end
211
212 % --- Executes during object creation, after setting all properties.
213 function inputTBlock_CreateFcn(hObject, eventdata, handles)
214 % hObject     handle to inputTBlock (see GCBO)
215 % eventdata   reserved - to be defined in a future version of MATLAB
216 % handles     empty - handles not created until after all CreateFcns called
217
218 % Hint: edit controls usually have a white background on Windows.
219 %         See ISPC and COMPUTER.
220 if ispc && isequal(get(hObject,'BackgroundColor'), ...
           get(0,'defaultUicontrolBackgroundColor'))
221     set(hObject,'BackgroundColor','white');
222 end
223
224 function inputTStim_Callback(hObject, eventdata, handles)
225 % hObject     handle to inputTStim (see GCBO)
226 % eventdata   reserved - to be defined in a future version of MATLAB
227 % handles     structure with handles and user data (see GUIDATA)
228
229 % Hints: get(hObject,'String') returns contents of inputTStim as text
230 %         str2double(get(hObject,'String')) returns contents of inputTStim ...
           as a double
231 input = str2double(get(hObject,'String'));
232 if isnan(input)
233     set(hObject,'String','20');
234     warndlg('Input must be numerical');
235 elseif input > 60
236     set(hObject,'String','20');
237     warndlg('Must use LESS THAN 60 stimuli');
238 elseif mod(input,4) ~= 0
239     newInput=4*round(input/4);
240     set(hObject,'String',num2str(newInput));
241     warndlg('Must be a MULTIPLE OF 4');

```

```

242 end
243
244 % --- Executes during object creation, after setting all properties.
245 function inputTStim_CreateFcn(hObject, eventdata, handles)
246 % hObject    handle to inputTStim (see GCBO)
247 % eventdata  reserved - to be defined in a future version of MATLAB
248 % handles    empty - handles not created until after all CreateFcns called
249
250 % Hint: edit controls usually have a white background on Windows.
251 %       See ISPC and COMPUTER.
252 if ispc && isequal(get(hObject,'BackgroundColor'), ...
    get(0,'defaultUicontrolBackgroundColor'))
253     set(hObject,'BackgroundColor','white');
254 end
255
256 % --- Executes when user attempts to close figure1.
257 function figure1_CloseRequestFcn(hObject, eventdata, handles)
258 % hObject    handle to figure1 (see GCBO)
259 % eventdata  reserved - to be defined in a future version of MATLAB
260 % handles    structure with handles and user data (see GUIDATA)
261
262 % Hint: delete(hObject) closes the figure
263 handles.param = [];
264 handles.training_param = [];
265 handles.exitcode = 1;
266
267 guidata(hObject,handles)
268
269 if isequal(get(hObject,'waitstatus'), 'waiting')
270 % The GUI is still in UIWAIT, use UIRESUME
271 uiresume(hObject);
272 else
273 % The GUI is no longer waiting, just close it
274 delete(hObject);
275 end

```

Appendix B

Instructions

B.1 Procedure Instructions

B.1.1 Portuguese

Vamos utilizar um teste de reconhecimento de imagens para estudar a sua atividade cerebral durante a aquisição de novas memórias. Cada teste inclui três fases: estudo, distração e reconhecimento, por esta ordem.

Primeiro vai ver um conjunto de imagens de paisagens. Cada conjunto contém imagens de duas categorias semânticas diferentes (p.e., imagens de icebergs e campos de golfe). Não há imagens repetidas. Ser-lhe-á pedido que classifique rapidamente as imagens de acordo com a categoria a que pertencem. Dispõe de aproximadamente dois segundos e meio para o fazer. Entre imagens, vai aparecer uma cruz no ecrã, durante aproximadamente um segundo e meio. Iremos referir-nos a esta fase da experiência como a **fase de estudo**.

Após a fase de estudo, vai aparecer no ecrã uma igualdade simples, tal como $2+3-1=4$. Vai indicar se a igualdade é verdadeira ou falsa, utilizando as teclas. Depois de dar a sua resposta, aparecerá uma nova igualdade no ecrã. Tente classificar o maior número de igualdades que puder, dentro de 30 segundos.

Finalmente, na **fase de reconhecimento**, ser-lhe-á mostrada um novo conjunto de imagens. Este contém as imagens às quais foi exposto anteriormente, numa nova ordem, intercaladas com imagens totalmente novas que nunca viu antes. Ser-lhe-á pedido que identifique se as imagens são novas ou antigas, isto é, se se lembra de as ter visto na fase de estudo. Sempre que identifique uma imagem antiga, deve indicar qual o tipo de memória que o permitiu reconhecê-la.

Em resumo, ser-lhe-á apresentada um conjunto de imagens pertencentes a uma de duas categorias aleatórias. Após um período de distração, as imagens antigas serão apresentadas numa nova ordem, intercaladas com novas imagens. O seu principal objetivo é identificar as imagens que viu durante a fase de estudo e relatar o processo de memória que lhe permitiu identificá-las.

A Fase de Estudo

Durante a fase de estudo categorize rapidamente as imagens usando as setas corretas. Entre a apresentação dos estímulos, será apresentada uma cruz no ecrã. Olhe fixamente para a cruz.

A Fase de Reconhecimento

Cada imagem vai aparecer sozinha no centro do ecrã. Em primeiro lugar, vai analisar a imagem e pensar na sua resposta. Não se mova ou fale. Passados dois segundos vão aparecer indicadores debaixo da imagem. Deve explicar em voz alta se acha que já viu a imagem e porquê. Tem todo o tempo necessário para justificar a sua resposta. Depois clique no botão da resposta que quer dar.

B.1.2 English

We will use an image recognition test to study your brain activity during the acquisition of new memories. Each test includes three phases: study, distraction, and recognition, in that order.

First you will be presented a set of scene images. Each set contains images from two different semantic categories (e.g., images of icebergs and golf courses). There are no repeated images. You will be asked to quickly identify what category the images belong to. You have approximately two and a half seconds to do this. Between images, a fixation cross will appear on the screen for approximately one and a half seconds. We will refer to this phase of the experiment as the study phase.

After the study phase, a simple equation will appear on the screen, such as $2+3-1=4$. You will indicate whether the equation is true or false, using the keys. After you have given your answer, a new equation will appear on the screen. Try to judge as many equations as you can within 30 seconds.

Finally, in the recognition phase, you will be shown a new set of images. This contains the images you were exposed to before, in a new order, interspersed with completely new images that you have never seen before. You will be asked to identify whether the images are new or old, that is, whether you remember seeing them in the study phase or not. Whenever you identify an old image, you will also be asked to identify the type of memory that allowed you to recognize it.

In short, you will be presented with a set of images belonging to one of two randomly selected categories. After a distractor period, the old images will be presented in a new order, interspersed with new images. Your main goal is to identify the images you have seen during the study phase and report on the memory process that allowed you to identify them.

Study phase

During the study phase you will be shown the images and asked to categorize them, using the designated arrow keys. In between images, a fixation cross will show upon the screen. We ask you to fix your eyes on it.

Recognition Phase

Images will show up individually in the middle of the screen. When an image appears, you are to analyze it and think about your response. Don't move or talk. After two seconds, response indicators will appear underneath the image. You are to explain aloud whether you have already seen the image and why you were able to recognize it. You have an unlimited amount of time to justify your judgement. Finally, press the key that corresponds to your answer.

B.2 Recollection and Familiarity Instructions**B.2.1 Portuguese**

Sempre que encontrar uma paisagem que viu durante a fase de estudo, vai ter que identificar o tipo de memória que usou. Para esta experiência, concentrar-nos-emos na memória de **recordação** e na memória de **familiaridade**.

Memória de recordação

Por vezes, ao encontrar uma imagem antiga, pode lembrar-se de pormenores do momento em que viu a imagem pela primeira vez. Ao recordar, lembra-se obrigatoriamente de pormenores adicionais que não estão explícitos na imagem, pelo não podem ser inferidos só a partir dela. O ato de recordar pode incluir reviver, ou imaginar, o momento em que viu a imagem durante a fase de estudo.

Pode, por exemplo, lembrar-se do que é que pensou quando viu a imagem pela primeira vez. Pode ainda lembrar-se que a imagem apareceu no início ou no fim da fase de estudo, ou lembrar-se de algo que tenha acontecido na sala quando a imagem apareceu.

Deve responder “Recordação”, quando lembrar-se de algo adicional que tenha acontecido quando viu a imagem durante a fase de estudo. Não tente “puxar muito pela cabeça”. A recordação deve ser espontânea e com pouco esforço.

Memória de familiaridade

As coisas são-nos familiares quando conseguimos reconhecê-las sem nos lembrarmos de qualquer informação adicional sobre quando as encontramos pela última vez. A familiaridade implica a ausência de recordação.

Como exemplo, considere que se depara com um sujeito na rua. Você pode ter a certeza que o conhece de algum lado, mas pode não se conseguir lembrar de nada sobre ele, onde o viu pela última vez ou de onde o conhece. Essa pessoa é-lhe familiar.

Quando tiver a sensação de que já viu uma determinada imagem, sem se lembrar de qualquer pormenor adicional sobre a fase de estudo, deve responder “Familiar”. Neste caso, não se lembra do que estava a pensar, nem se a imagem apareceu no início ou no fim da fase de estudo. Só tem a impressão de que se lembra de a ter visto.

Observações adicionais

Não confunda a distinção entre familiaridade e recordação com a sua sensação de certeza, ou a sensação de “força” da memória. Pode ter a certeza que já viu uma imagem, independentemente do tipo de memória que usou para a reconhecer. A familiaridade pode ser forte – quando tem a certeza que já viu aquela imagem– ou fraca – quando acha que já a viu, mas não tem a certeza.

B.2.2 English

Every time you encounter a scene that you were previously shown, you are expected to identify the type of memory supporting its recognition. For this experiment, we will focus on recollection memory and familiarity memory.

Recollection Memory

Sometimes, when you encounter an old image, you will be able to recall details about the moment you first saw it. When recollecting, you must necessarily be remembering additional details that aren't in front of you, so they cannot be inferred from the image alone. Recollection may include reliving, or imagining, the moment you saw the image during the study phase.

You can, for example, remember what you thought when you first saw the image. You can also remember that the image appeared at the beginning or end of the study phase or remember something that happened in the room when the image appeared.

In short, you should answer "Recollection" when you remember something additional that happened when you saw the image during the study phase. Don't think too hard. Recollection should be spontaneous and with little effort.

Familiarity Memory

Something is familiar when we can recognize it without remembering any additional information about when we last encountered it. Familiarity implies the absence of recollection.

As an example, consider that you come across someone on the street. You're sure you know them from somewhere, but you can't remember anything about them, like where you last saw them, or where you know them from. This person is simply familiar.

During the recognition phase, you may be struck with the feeling that you have already seen an image but cannot remember any details about what happened when you first saw it. You don't remember what you were thinking about, or whether the image appeared at the beginning or end of the study phase. You only have the impression that you remember seeing it. In this case, you should answer "Familiarity".

Additional observations

Don't confuse the distinction between familiarity and recollection with your sense of confidence, or the sense of memory "strength". You can be certain that you have seen an image, regardless of the type of memory you used to recognize it. Familiarity can be strong - when you are sure you have seen that image - or weak - when you think you have seen it but are not sure.

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