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Doctoral Thesis

Neural Correlates of Retrieval of Declarative Memories Modulated by the Reconsolidation Process

By

Germán Adolfo Campos Arteaga

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"Certain things, they should stay the way they are. You ought to be able to stick them in one of those big glass cases and just leave them alone."

J.D. Salinger, The Catcher in the Rye

Dedicated to Amelia Barrera (1927-2018)

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Abbreviations

AtoM	Attentional to Memory
DM	Difference due to memory
EEG	Electroencephalography
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
HFS	High-frequency stimulation
INT	Interference group
LC-NA	Locus coeruleus - noradrenaline
LTM	Long-term memory
LTP	Long-term potentiation
MMN	Mismatch negativity
NMDA	N-methyl-D-aspartate
NO-REACT/NO-INT	No-reactivation/no-interference group
PONE	Pupil old/new effect
PTSD	Post-traumatic stress disorder
REACT	Reactivation group
REACT/INT	Reactivation/interference group
RNA	Ribonucleic acid
ROI	Region of interest
RSVP	Rapid serial visual presentation
rTMS	Repetitive transcranial magnetic stimulation
STM	Short-term memory

1. ABSTRACT

Consolidated memories can return to a labile state if they are reactivated by unpredictable reminders. To persist, active memories must be re-stabilized through a process known as reconsolidation. Although there is consistent behavioral evidence about this process in humans, the retrieval process of reconsolidated memories remains poorly understood. In this context, one fundamental question is whether the same or different neurophysiological mechanisms are involved in retrieval of consolidated and reconsolidated memories. Because it has been demonstrated that the exposure to the reconsolidation process may restructure and strengthen memories, we hypothesized distinct neurophysiological patterns reflecting enhanced recollective processes during retrieval of reconsolidated memories. Moreover, we hypothesized that the administration of an amnesic agent during reconsolidation, such as a new learning, can reverse these neurophysiological changes. To test it, consolidated and reconsolidated declarative memories (and memories whose reconsolidation process was interfered) (i.e., picture-word pairs) were evaluated in humans in an old/new associative recall task while the brain activity and the pupillary response were recorded using electroencephalography and eyetracking. Our results showed that retrieval of reconsolidated memories elicits specific patterns of brain activation, characterized by an earlier peak latency of the parietal ERP old/new effect compared to memories that were consolidated or whose reconsolidation process was disrupted by a new learning. Moreover, our results demonstrated that only retrieval of

reconsolidated memories is associated to a late reversed mid-frontal effect. Complementarily, reactivated memories showed an earlier peak latency of the pupil old/new effect compared to non-reactivated memories. Based on these results, we argue that partially distinct brain mechanisms – presumably associated to enhanced recollective processes - support retrieval of reconsolidated declarative memories.

2. INTRODUCTION

One of the most amazing and intriguing function of the brain is the ability that allow us to learn information from experiences that can be retrieved later (Nyhus and Curran, 2010). This ability gives animals a flexible adaptation to changing environments, improving the likelihood of survival and reproduction (Dudai, 2009; Kindt, 2014). In humans, learning and memory are the basis for the construction of a personal sense of identity that define us as individual subjects (Blagov and Singer, 2004; Eustache et al., 2016).

How memory changes over time is a fundamental question for the neuroscience of memory. Answering this question has important implications not only for the basic understanding of memory but also for the development of new applications in the clinical and educational fields. For instance, knowing how memories change could allow the design of novel techniques to modulate existing memories in patients with memory disorders (Schwabe et al., 2014a; Sandrini et al., 2015) as well as the implementation of new procedures to improve learning in educational contexts (Karpicke and Roediger, 2008a). One significant step towards a better understanding of the dynamic nature of memory was the discovery that once a memory is stored in the brain, it does not remain permanently fixed or unmodifiable. In fact, it has been demonstrated that previously consolidated memories can return to an unstable state if they are reactivated under specific circumstances. In order to persist,

these memories must be re-stabilized through a process known as memory reconsolidation (Nader et al., 2000b; Nader and Hardt, 2009). During this process, reactivated memories may become vulnerable to interference by amnesic agents, such as pharmacological (Schwabe et al., 2012) and behavioral manipulations (Walker et al., 2003a; Forcato et al., 2007; Hupbach et al., 2007), giving us a unique opportunity to strengthen, disrupt or update memories (Sandrini et al., 2015). However, despite the consistent behavioral evidence of human reconsolidation, little is known about the neural processes by which these memories, that were successfully reconsolidated or whose reconsolidation process was altered, are retrieved in the future. In this context, the main purpose of the current doctoral thesis was to investigate the neurophysiological correlates (i.e., electrophysiological and pupillary activity) underlying retrieval of declarative memories that were successfully reconsolidated or disrupted during the reconsolidation process.

Taking into account the evidence that the reconsolidation process allows restructuring of memories through modification of their strength and content (Forcato et al., 2011; Dudai, 2012; Sandrini et al., 2015), it seems plausible that retrieval of consolidated, reconsolidated and disrupted memories during reconsolidation is supported, at least partially, by distinct brain mechanisms. Therefore, we hypothesized that consolidated, reconsolidated and disrupted memories elicit differential neurophysiological patterns during retrieval. Specifically, we expected patterns of neural activity reflecting enhanced recollective processes during retrieval of reconsolidated memories. To test it, we implemented an adapted version of the three-day protocol used by Forcato et al. (2016). Memory performance was evaluated in an associative recall old/new task (Donaldson and Rugg, 1999) in which participants had to classify pictures as “old” or “new” (previously studied or not) and to recall a word associated to old items. In order to examine the neurophysiological correlates of retrieval, we measured event-related potentials (ERPs) and pupillary responses using electroencephalography (EEG) and

eyetracking, respectively. We mainly focused on two biological markers associated with memory retrieval: the left parietal ERP old/new effect (Donaldson and Rugg, 1998, 1999; Wilding, 2000; Rugg and Curran, 2007; Wilding and Evans, 2012) and the pupil old/new effect (Vo et al., 2008; Heaver and Hutton, 2011; Otero et al., 2011; Montefinese et al., 2013; Kafkas and Montaldi, 2015). The left parietal old/new effect, that has been observed in different retrieval tasks such as source retrieval, cued recall and old/new recognition, refers to the positive difference in neural activity between the correct classification of old and new items (Paller and Kutas, 1992; Wilding and Rugg, 1997; Donaldson and Rugg, 1999). This effect has a left parietal maximum around 500-800 ms post-stimulus and it has been traditionally linked to conscious recollection and, more specifically, to the amount of retrieved information during the task (Vilberg et al., 2006; Rugg and Curran, 2007). On the other hand, the pupil old/new effect refers to the greater pupil size in response to old compared to new items (Vo et al., 2008; Heaver and Hutton, 2011; Otero et al., 2011; Montefinese et al., 2013; Kafkas and Montaldi, 2015). Although the interpretation of this effect remains unclear, it has been suggested that it is related to recollective processes, similar to the left parietal old/new effect (Vo et al., 2008; Otero et al., 2011; Brocher and Graf, 2016).

Our results show that retrieval of consolidated and reconsolidated memories elicits different patterns of brain activity and pupillary response. This finding confirms our assumption that reconsolidation has an important impact in how memories are retrieved in the future, showing that retrieval of reconsolidated memories is partially supported by specific brain mechanisms. We believe that the current study is an important step towards a better understanding of the brain mechanisms underlying retrieval of reconsolidated declarative memories.

3. BACKGROUND

3.1 Learning and memory: An overview

Learning is defined as the biological process by which we can acquire information about the reality, while memory is the process of storing and reconstructing that knowledge over time (Kandel et al., 2000; Kandel et al., 2014). Both capabilities allow an animal to adjust its behavior to a demanding and changing environment, increasing the likelihood of survival (Dukas, 2008).

Memory is a complex process that can be classified in different ways, depending on the criterion used. First, according to its persistence, memory can be classified as short-term memory (STM) or long-term memory (LTM) (Kandel et al., 2000; Kandel et al., 2014). The STM, that last seconds to few minutes, facilitates the maintenance of transitional representations for immediate task resolution (Davis and Squire, 1984; Bermúdez-Rattoni, 2007; Kandel, 2009). On the other hand, LTM allows relatively permanent storage of information for hours, days and even lifetime (McGaugh, 1966; Davis and Squire, 1984; McGaugh, 2000; Purves et al., 2008). Second, considering the content, memories can be classified into implicit and explicit memories. Implicit memories refer to those memories that – once acquired – cannot be easily verbalized and are highly independent of conscious processing, such as playing the piano and riding a bike (Graf and Schacter, 1985; Kandel, 2009; Kandel et al., 2014; Byrne, 2017). In contrast, explicit or declarative memories are those that can be consciously retrieved and

reported through language (Squire and Zola, 1996; Eichenbaum, 1997; Tulving and Markowitsch, 1998; Eichenbaum, 2000). This last category includes episodic memories, that are established through personal and autobiographical experiences, and semantic memories, related to a general knowledge of words and concepts (Squire and Kandel, 2003; Kandel, 2009; Byrne, 2017). One fundamental discovery in the neuroscience of memory was that explicit (declarative) and implicit (non-declarative) memories depends on distinct brain regions. Specifically, declarative memories mainly depend on the medial temporal lobe (that includes areas such as the hippocampus and the amygdala), while implicit memories are associated to the normal functioning of the striatum, amygdala, cerebellum and reflex pathways (Kandel et al., 2000).

Memory can be also understood as a process consisting of different stages or phases. First, the acquisition phase is characterized by the encoding of information from the environment (Kandel et al., 2014; Axmacher and Rasch, 2017). Second, the consolidation phase is the biological process by which the acquired information is stabilized in different brain structures (McGaugh and Roozendaal, 2009; Nader and Hardt, 2009; Dudai, 2012). Finally, retrieval is the process by which consolidated memories are reconstructed and remembered over time (Gazzaniga and Heatherton, 2002; Kandel et al., 2014).

3.2 The Standard Consolidation Theory: when memories are "fixed"

According to the Standard Consolidation Theory (Glickman, 1961; McGaugh, 2000), immediately after the acquisition of new information, a first fragile, labile and unstable hippocampal-dependent memory must go through an active biological process (that involves RNA and protein synthesis, metabolic and morphological changes in neurons) to become persistent in cortical regions

(Squire, 1992; McGaugh, 2000; Kandel, 2001; Dudai, 2004). This process occurs following learning and can last hours, days or even months (McGaugh, 1966; Albright et al., 2000).

The consolidation process involves two levels. The first one, called synaptic or cellular consolidation, is a time-dependent process that implicates a cascade of neurochemical processes and changes in the efficacy of synaptic transmission between neurons in brain areas related to memory, such as the hippocampus and the amygdala. It has been suggested that this process begins in the first minutes after encoding of new information and can last minutes to hours (Kandel, 2001; Dudai, 2004; Dudai and Morris, 2013). Traditionally, the synaptic consolidation has been studied through the induction of long-term potentiation (LTP) by temporal and spatial coincidence between the presynaptic and postsynaptic activity in hippocampal slices (Bliss and Lomo, 1973). In these studies, a high-frequency stimulation (HFS) of axons of the perforant pathway of the rabbit causes a long-term modification of synaptic strength (measured as changes in the magnitude of excitatory postsynaptic potentials), supporting the idea proposed by Donald Hebb that synaptic plasticity could play a role in memory processes (Bliss and Lomo, 1973; Byrne, 2017). The second level of the consolidation process, called system consolidation, implies a large-scale reorganization of neuronal circuits and brain structures that are involved in information storage (Born and Wilhelm, 2012; Dudai, 2012). In this context, it has been suggested that initially hippocampal-dependent memories are finally reorganized over distributed brain circuits in cortical regions (Squire et al., 2004; Dudai, 2012).

Operationally, a memory is considered consolidated if it is immune to disruption by pharmacological or behavioral treatments (McGaugh, 1966), such as the administration of protein synthesis inhibitor, electric shock or a new learning (Flexner et al., 1965; Misanin et al., 1968; Gordon and Spear, 1973). In other words, it is traditionally considered that a memory that can be modified by any of these and other procedures is still in a labile state and, therefore, not consolidated. This standard

is also used to define if a memory is reconsolidated, as it will be explained in the next section (Forcato et al., 2016).

A critical aspect of the Standard Consolidation Theory is that assumes that a consolidated memory is "fixed" and, therefore, without any possibility of modification. Accordingly, the remembering act is considered just a passive read-out of a memory trace and not a process by which the memory could be changed (McGaugh, 2000; Alberini and LeDoux, 2013). Contrary to this idea, today we have extensive evidence that proves the dynamic nature and malleability of memory. For instance, cognitive psychology has shown that an existing memory can be changed by the subsequent integration of new information (Loftus and Hoffman, 1989; Loftus, 2005). On the other hand, in the field of neuroscience, it has been demonstrated that the maintenance of an existing memory depends on a continuous biological activity (such as the expression of the kinase M-zeta protein) even after the memory trace is stabilized (Shema et al., 2007; Sacktor, 2011, 2012). A third line of research, in which we will focus, has shown that memories can return to a labile state if they are reactivated under specific circumstances. In order to persist, these memories must go through a new stabilization process functionally similar to the consolidation process. During this phase, known as reconsolidation, memory is vulnerable to pharmacological and behavioral treatments, allowing memory change (Nader et al., 2000b; Nader et al., 2000a). Taken together, these studies demonstrate the dynamic nature of memory.

3.3 The Reconsolidation Theory: an opportunity for memory change

Despite the fact that there was early evidence about the malleability of memory in the field of neuroscience (Sara, 2000), one particular study revitalized the interest in the dynamic nature of memory. Using a fear conditioning paradigm in rats, Nader et al., (2000) (Nader et al., 2000b)

demonstrated that the local administration of a synthesis protein inhibitor (anysomycin) in the amygdala immediately after memory reactivation, could disrupt the existing fear memory. Importantly, in the absence of memory reactivation, the amnesic effect was not observed. Thus, it was concluded that an emotional memory can be labilized by a cue reminder and subsequently interfered by a pharmacological agent during the reconsolidation process (see Figure 1).

The current assumption is that memory reconsolidation is a fundamental memory process. By now, it has been demonstrated in different species, such as nematode, fish, rat, crab, human and others (Nader et al., 2000b; Pedreira et al., 2002; Walker et al., 2003a; Eisenberg and Dudai, 2004; Rose and Rankin, 2006) and it has been observed in emotional, spatial, motor and declarative memories (Nader et al., 2000b; Walker et al., 2003a; Morris et al., 2006; Forcato et al., 2007; Hupbach et al., 2007). Although consolidation and reconsolidation processes share some biological mechanisms (e.g., protein synthesis) (Tronson and Taylor, 2007), also have distinct underlying molecular mechanisms (Lee et al., 2004). In this context, it remains unclear if reconsolidation is an independent process or a recapitulation of the consolidation process. This last proposal, known as lingering consolidation, interprets reconsolidation as a continuous consolidation process that will occur until a memory is fully stabilized (Alberini, 2005).

3.3.1 The dynamic nature of memory

Although the idea of the dynamic nature of memory is present for a long time in cognitive psychology (Loftus et al., 1978), only recently the notion that memories can be changed and rewritten has been adopted by the cognitive neuroscience (Nader et al., 2000; Alberini and Ledoux, 2013a). At present, this line of research has had a great development due to the implications in the clinical and

educational areas. For instance, it has been proposed that reconsolidation gives a unique opportunity to modulate memories in psychiatric disorders (such as Alzheimer Disease or Post-Traumatic Stress Disorder) (Schwabe et al., 2014) and improve learning in educational contexts (Karpicke and Roediger, 2008).

In this context, reconsolidation has been studied mainly through its modulation. By now, there is a large body of evidence indicating that previously stabilized memories can be disrupted or improved after their reactivation (Walker et al., 2003a; Forcato et al., 2007; Hupbach et al., 2007; Forcato et al., 2014). Since the main objective of the present thesis is to study the neurophysiological correlates of retrieval of reconsolidated memories, in the next section we will review both the impairment and the strengthening of memory as consequence of reconsolidation, with focus on humans.

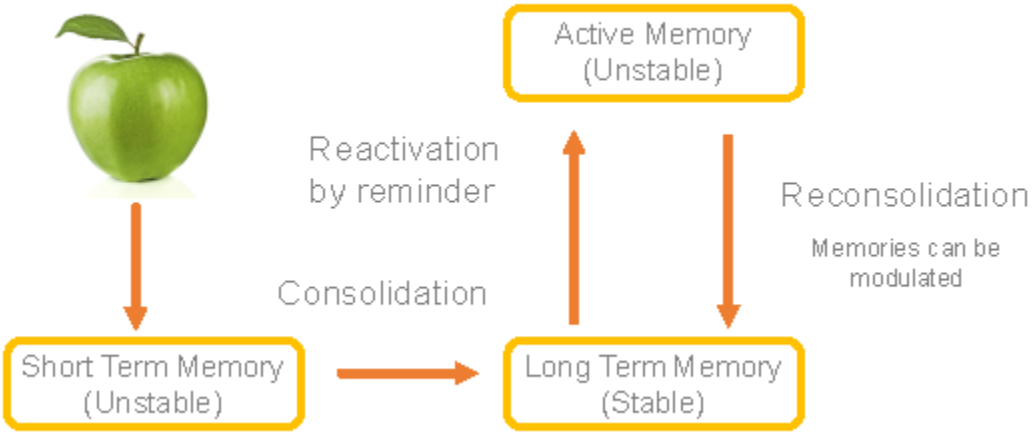

Figure 1. The Reconsolidation Theory: when a new information is encoded, a new fragile and unstable memory trace is created. In order to persist, this memory must go through a biological process of stabilization, called consolidation. If this memory is reactivated by reminder cues, it can return to an unstable state from which it must be re-stabilized. During this process, known as reconsolidation, the memory is vulnerable to amnesic agents like pharmacological and behavioral treatments, allowing memory modulation. Adapted from (Takashima, 2012).

3.3.2 Disrupting memories by interfering reconsolidation

In humans, memory modification has been studied through the interference of the reconsolidation process after memory reactivation (Forcato et al., 2007; Hupbach et al., 2007; Agren, 2014). In this context, typical amnesic treatments used to disrupt the initial consolidation, such as the administration of drugs (Lonergan et al., 2013; Thomas et al., 2017) and behavioral procedures such as the learning of new information (Walker et al., 2003a; Forcato et al., 2007), have been studied in the context of the reconsolidation process.

Regarding the pharmacological treatments to interfere reconsolidation, some agents such as propranolol (a beta-adrenergic antagonist) have been used to modulate emotional memories (Muravieva and Alberini, 2010; Schwabe et al., 2012; Schwabe et al., 2013). For instance, Brunet et al. (2008) studied reconsolidation of emotional memories in patients suffering chronic post-traumatic stress disorder (PTSD), an anxiety disorder characterized by intrusive, intense and dysfunctional memories caused by extreme negative emotional experiences (Pitman et al., 2011). For this purpose, in a first session, patients had to write their traumatic memories in order to reactivate them. Immediately after, half of the patients received two doses of propranolol (40 mg and 60 mg for short- and long-lasting effects, respectively), while the other half of participants received just a placebo. A week later, physiological responses were evaluated while participants listened to a recording of what they wrote in session 1. The results showed that the propranolol group had less physiological activation (a correlate of emotional memory) compared to the placebo group (Brunet et al., 2008). Although this pharmacological procedure seems promising for the treatment of PTSD, other studies have shown limited effects of propranolol on memory reconsolidation (Wood et al., 2015). In this context, more research is needed to demonstrate the efficacy of this treatment in the clinical practice.

Memories can also be disrupted by a behavioral treatment. Specifically, the exposure to a new learning after memory reactivation may interfere the re-stabilization of the reactivated memory. This phenomenon has been studied in different types of memory in humans. For instance, to study the effect of a new learning in a motor procedural memory, Walker et al., (2003), implemented a traditional three-day reconsolidation protocol. On day 1, participants were instructed to learn a sequence of finger movements (for example, 3-2-4-1-3). On day 2, a group of participants retrieved the sequence and immediately after they were exposed to a new learning task (new sequence of finger movements). On day 3, the motor memory was evaluated. Subjects who reactivated the original motor memory before the new learning in session 2, performed worse retrieving the first sequence of finger movements compared to the level reached on session 1 and compared to the group of participants that did not reactivate the motor memory before the new learning (Walker et al., 2003). This effect has been also reported in declarative memories. For example, Hupbach et al., (2007), using a similar paradigm to Walker et al., (2003), studied the effects of new learning on the reconsolidation of declarative memories. In session 1, subjects had to learn a list of 20 everyday objects. In session 2, a group was instructed to describe the session 1 in order to reactivate the declarative memory, while another group of participants did not receive this instruction. After that, both groups learned a new list of objects. In the third session, memory was evaluated. The results showed that the reactivation/new-learning group made more mistakes at the moment of retrieval compared to the no-reactivation/new-learning group (Hupbach et al., 2007). Similar results were obtained in a paired-associate learning task (Forcato et al., 2007; Forcato et al., 2016).

3.3.3 Memory strengthening by reconsolidation

Although memories may become vulnerable to disruption after reactivation by reminder cues, there is an equivalent opportunity to improve memories during reconsolidation. In fact, memory strengthening has been proposed as one of the most important biological function of the reconsolidation process (Forcato et al., 2013, 2014).

In this context, memory strengthening as consequence of the reconsolidation process can be defined as the memory enhancement as result of any treatment that positively affect the re-stabilization of a reactivated memory (Forcato et al., 2014). This phenomenon has been studied in animals and humans primarily through the exposure to successive memory reactivations that do not involve a direct and explicit reinforcement of the learned information (Lee, 2008; Forcato et al., 2014). Below, we will refer to studies that have developed this line of research. Due to the scarce literature concerning memory strengthening by reconsolidation in humans, the main findings in animal model will be also included.

In animal model, it has been shown that a contextual fear memory can be enhanced through an additional training after memory reactivation in rats (Lee, 2008). Accordingly, Inda et al., (2011), using an inhibitory avoidance paradigm, showed that brief successive reactivations (i.e., exposures to the training context) may improve memory and prevent forgetfulness. However, this study also showed that this effect depends mainly on the time interval between learning and the subsequent reactivations. Thus, reactivations after two weeks could not trigger memory labilization while reactivation after four weeks produced memory extinction. In summary, successive reactivations strengthen recent memories and produce extinction in remote memories (Inda et al., 2011).

In human model, it has been found similar results. For instance, Forcato et al., (2013), using a paired associate paradigm, studied the effect of repeated reactivations on memory reconsolidation. For this purpose, a three-day protocol was used. During day 1, participants learned a list of associated nonsense syllables. During day 2, successive reactivations were performed by the presentation of contextual elements and a cue-syllable. Memory performance was assessed on day 3. The results indicated that at least two successive reactivations may strengthen a declarative memory (Forcato et al., 2011). Importantly, in a subsequent study, the authors demonstrated that memories that were improved as result of successive reactivations were more resistant to the interference by a new learning (Forcato et al., 2013).

Additionally, some studies have demonstrated that specific pharmacological agents may enhance memory altering the reconsolidation process. For instance, the administration of 0.25 mg of clonazepam (commonly used as anxiolytic) after memory reactivation, improves a declarative memory (Rodriguez et al., 2013). Similar results were obtained using the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine and glucose in emotional and declarative memories, respectively (Coccoz et al., 2013; Corlett et al., 2013). Moreover, it has been demonstrated that the exposure to a mild stressor (i.e., put an arm in cold water for 1 minute) may alter memory reconsolidation and improve memories, presumably through the cortisol effect on glucocorticoids receptors in critical brain areas related to memory such as the hippocampus (Coccoz et al., 2011; Coccoz et al., 2013).

In summary, there is consistent behavioral evidence for the modulation of existing memories during reconsolidation, in animals and humans. This knowledge could have important implications for the development of new procedures to treat memory disorders in the clinical field or to improve learning in educational settings (Schiller et al., 2010).

3.3.4 Reconsolidation in the human brain

Despite the robust behavioral and pharmacological evidence for human reconsolidation (Walker et al., 2003a; Forcato et al., 2007; Hupbach et al., 2007), little is actually known about the brain mechanisms underlying this process. In the following, we will review the main findings to date.

First, functional magnetic resonance imaging (fMRI) studies have sought to determine primarily which brain areas are modulated during retrieval of memories that have been modified through the reconsolidation process (Agren et al., 2012; Schwabe et al., 2012; Schiller et al., 2013). For instance, to study how disruption of norepinephrine signaling by propranolol affects reconsolidation of neutral and emotional memories, Schwabe et al., (2012), conducted a neuroimaging study in which participants had to learn a set of neutral and emotional pictures. In the second session, subjects were given a placebo or propranolol before the reactivation of the learned material. Finally, the memory was evaluated in the third day. Behaviorally, the results indicated that the administration of propranolol before memory reactivation negatively affects the reconsolidation of an emotional memory. Interestingly, the behavioral expression was associated with a stronger activation of the hippocampus and amygdala. The authors interpreted the altered activation of these brain areas as consequence of a greater effort exerted by participants to recognize the studied material during testing (Schwabe et al., 2012). In another study, Agren et al., (2012) examined the neural correlates of extinction after conditioned fear memory reactivation. At a behavioral level, the results showed that a post-reactivation extinction session prevented reinstallment of a conditioned fear memory by a recovery treatment. Accordingly, the extinction procedure outside the temporal window in which reconsolidation occurred did not prevent the return of fear, which was associated with a stronger activity of the amygdala, the dorsal anterior cingulate cortex and insula, brain areas related to fear expression (Agren et al., 2012). In addition, a subsequent study showed a decreased activity of the ventromedial cortex and ventromedial

cortex–amygdala coupling in response to retrieval of memories exposed to extinction procedure after memory reactivation (Schiller et al., 2013).

Another neuroimaging study by Forcato et al., (2016), focused on the neural activity associated to different type of reminders during memory reactivation. Specifically, they sought to determine whether the unpredictability of the reminder is a necessary condition to trigger the labilization-reconsolidation process. To test this idea, the authors implemented a three-day protocol. On day 1, subjects were instructed to learn picture-word pairs (for example, picture of clouds associated to the word “Paloma”, pigeon in spanish). On day 2, they received different type of reminders followed or not by an interference task (i.e., a new learning) immediately after memory reactivation. Finally, on day 3, memory was evaluated. The results showed that an unpredictable reminder is more effective than a predictable one to trigger the labilization-reconsolidation process during memory reactivation on day 2, leading to strengthened memories on day 3. Moreover, the exposure to the behavioral interference after memory reactivation by unpredictable reminders partially prevented the memory improvement observed in the first group. Importantly, the neural response to the presentation of unpredictable cues during memory reactivation, as revealed by fMRI, was associated with a larger left hippocampal activation compared to the presentation of predictable cues. These results corroborated previous findings that have shown that a proper reminder structure – that incorporates the detection of a prediction error due to a mismatch in the expectations - is crucial to destabilize a consolidated memory, triggering the reconsolidation process (Pedreira et al., 2004; Forcato et al., 2009; Sevenster et al., 2014). Also, they confirmed that memory can be disrupted by an amnesic agent, such as a new learning, during the reconsolidation process (Walker et al., 2003a; Forcato et al., 2007; Hupbach et al., 2007), as was described earlier. Finally, it demonstrated that a proper reminder structure may trigger the

reconsolidation process by engaging specific brain mechanisms during memory reactivation (Forcato et al., 2016).

In contrast, to the best of our knowledge, there is only one research that have used electroencephalography (EEG) to investigate the neural correlates underlying retrieval of consolidated memories that were reactivated. For this purpose, Wirkner et al., (2015), using a three-day protocol, analyzed event-related potentials (ERPs) related to the retrieval of neutral and emotional memories that were modulated after memory reactivation. During the first session, subjects were instructed to see and learn neutral and emotional images. In session 2, two groups reactivated their memories through a method called Rapid Serial Visual Presentation (RSVP) in which each image was presented very briefly to prevent a high level of cognitive processing of the item. During the same session, a group of participants also memorized a new set of images after the RSVP procedure. In session 3, memory was evaluated. The results indicated that memories that were interfered by a new learning after memory reactivation were associated with a smaller modulation of the “left parietal old/new effect”, an electrophysiological component associated with memory retrieval (evoked potentials related to memory will be explained in more details in the next section) (Rugg and Curran, 2007). However, this study failed to replicate the reconsolidation evidence by not using an appropriate reminder structure that considered the unpredictability (prediction error due to a mismatch in expectations) as a crucial element to trigger the labilization-reconsolidation process (Pedreira et al., 2004; Diaz-Mataix et al., 2013; Forcato et al., 2016). In this sense, this study by Wirkner et al., (2015), cannot be considered the first study to determine the electrophysiological correlates of retrieval of reconsolidated memories.

Finally, invasive and non-invasive techniques have been used to determine the role of different brain areas in human memory reconsolidation. For example, Kroes et al., (2014), examined the effects of electroconvulsive therapy applied to frontotemporal regions on reconsolidation of emotional

episodic memories. The results showed that electroconvulsive stimulation only affects reactivated emotional memories, suggesting a specific role of frontotemporal regions in reconsolidation of this kind of memory (Kroes et al., 2014). In addition, Sandrini et al., (2013), using repetitive transcranial magnetic stimulation (rTMS) applied over right lateral prefrontal cortex, demonstrated the participation of the prefrontal cortex in strengthening of declarative memories as consequence of reconsolidation (Sandrini et al., 2013).

In summary, despite the consistent behavioral findings about human reconsolidation, only few published studies to date have provided knowledge concerning the neural correlates of the reconsolidation process. To date, these studies have focused on determining those brain areas recruited during reconsolidation and the subsequent retrieval of the reconsolidated memory. Unfortunately, the neurodynamic underlying retrieval of declarative memories that have been modulated by reconsolidation remains poorly understood. Accordingly, our proposal is to determine the neural signature of retrieval of declarative memories that were modulated by reconsolidation. Since this work considers the analysis of evoked potentials and pupillary responses associated to memory retrieval, in the following section we will review these neurophysiological correlates of memory.

3.4 Event Related Potentials (ERPs) associated to memory: The parietal old/new effect

3.4.1 General aspects of ERPs

Electroencephalography (EEG) is extensively used in cognitive neuroscience to study the relationship between behavior and neural activity (Swartz and Goldensohn, 1998). It is considered a non-invasive technique used to measure the electrical activity of the brain (Berger, 1929; Berger, 1969; Luck, 2014). Specifically, the EEG measures the electrical activity elicited mostly by large populations of synchronized pyramidal neurons from the cortex (Basar and Guntekin, 2008). These cells, whose dendritic dipoles are aligned, may produce electrical potentials that can be recorded from the scalp (Binder et al., 2009). Today, the general pattern of electrical activity of large neuronal assemblies are analyzed in different tasks to study cognitive functions such as attention, memory and language (Hillyard and Anllo-Vento, 1998; Friedman and Johnson, 2000; Kutas and Federmeier, 2011).

In order to study the brain activity associated to specific stimuli (e.g., the presentation of a picture or a sound), ERPs are measured. We can define ERPs as changes in EEG signals that are associated with a particular type of neural or psychological event or process (Luck et al., 2011). It is calculated averaging segments of EEG (known as “epochs”) that are time-locked to a specific stimulus. This procedure allows to reduce the randomly noise distributed across epochs and detect more clearly the signal associated with the stimulus of interest (Luck, 2014). In this context, to attenuate noise and obtain a good signal-to-noise ratio, it is usually necessary a high number of presentations (Luck, 2005). The result can be observed as positive and negative deflections of the voltage (peaks and troughs) in the waveforms that occur at different post-stimulus time points (Luck, 2014). For example, the effect known as mismatch negativity (MMN) is a negative-going potential that occurs between 150 – 250 ms

after the presentation of a different auditory stimulus interspersed among more frequent stimuli (Sams et al., 1985; Winkler et al., 1990).

The ERP technique has important advantages. First, it provides measures of the electrical activity of the brain with a high temporal resolution (in order of milliseconds), allowing to study the temporal dynamic of cognitive processes. Second, it is non-invasive, which is particularly important in research with humans. Third, its implementation and use is relatively inexpensive compared to other techniques such as fMRI (Freeman and Quiroga, 2012; Byrne et al., 2014; Luck, 2014).

In this context, ERPs studies have provided important insights into the neurodynamic of memory processes such as encoding and retrieval (Friedman and Johnson, 2000; Luck, 2014). For instance, several studies have described the ERPs associated with the successful encoding of new information. In these studies, participants are instructed to learn different type of items presented on a screen while their brain activity is recorded by means of electroencephalography. Subsequently, their memory is tested for each studied item. The evidence indicates that those correctly recognized items elicit a different pattern of brain activity during encoding compared to those items that were forgotten (effect known as “Dm, difference due to memory” “or subsequent memory effect”). In other words, ERPs recorded at the time of encoding can predict if the studied item will be recalled in the future (Paller et al., 1987; Paller and Wagner, 2002; Luck, 2014). In the next section, we will focus only in ERPs that have been associated with memory retrieval, the central topic of this thesis.

3.4.2 ERPs and memory retrieval

Recognition memory is the judgment that determines if a stimulus has been experienced before. In research, it can be tested by presenting studied items to participants and asking them if they recognize them as being studied in the context of the experiment (Mandler, 1980; Byrne, 2017).

According to Yonelinas' dual-process account of recognition, it has been proposed that this ability is based on two independent subprocesses: familiarity and recollection. Familiarity refers to the subjective, nonspecific and decontextualized sense of having experienced a stimulus without the possibility of recall additional information about its origin or learning context (Yonelinas and Levy, 2002). In contrast, recollection is associated with a conscious, detailed and contextualized retrieval of previously learned information (for example, the place where a stimulus was experienced) (Mandler, 1980; Yonelinas and Levy, 2002; Yonelinas et al., 2005; MacKenzie and Donaldson, 2007; Rugg and Curran, 2007).

Accordingly, in ERPs studies in which recognition memory is evaluated, it is called "old/new effect" to the difference in neural activity between the successful classification of previously studied ("old") and non-studied ("new") material (Wilding et al., 1995; Friedman and Johnson, 2000; Wilding, 2000; Rugg and Curran, 2007). Broadly, this effect is characterized by a typically more positive-going waveform when a stimulus is correctly classified as old than new. This effect, depending on the requirements of the task and paradigm, can be observed in different temporal windows and topographical distributions from approximately 300 ms after the stimulus presentation (Friedman and Johnson, 2000). Specifically, familiarity has been associated with a mid-frontal component (also known as FN400). This effect occurs between 300-500 ms after the stimulus onset and it is modulated by similarity of the presented item to the original one (Rugg and Curran, 2007). For instance, in a study by Curran et al., (2000), participants had to distinguish between previously studied words (e.g., cat),

modified studied words (e.g., cats, in plural) and new words (e.g., dog). In this case, the mid-frontal effect only appeared when original and similar-to-original words were presented (Curran, 2000).

In contrast, recollection is associated to a positive difference (old-new) in the left parietal region in approximately 400-800 or 500-800 ms after the stimulus presentation (Curran, 2000; Ally and Budson, 2007; Rugg and Curran, 2007; Ally et al., 2008). Importantly, this effect has been observed in different tasks and paradigms, such as old/new recognition, associative recall, associative recognition and source judgment retrieval (Wilding and Rugg, 1996; Allan and Rugg, 1997; Donaldson and Rugg, 1999) and it has been associated to recollection partially because it is elicited when participants correctly judge the context in which the specific stimulus was studied (a fundamental aspect of the recollection process according to dual-process models) (Parker et al., 2005; Rugg and Curran, 2007; Luck, 2014). Accordingly, this effect also appears in memory tasks in which participants are instructed to retrieve associated information of studied items. In these studies, recollection is defined as the ability to retrieve additional information of a specific stimulus. For instance, Donaldson and Rugg (1999), instructed participants to learn pairs of words. Some minutes later, subjects had to complete the pairs after the first element of the pair was presented on the screen. In line with previous findings, the left parietal old/new effect was larger for those items for which the associated information was recalled in comparison to new items or responses in which the participant could not recall the associated information (Donaldson and Rugg, 1999; Parker et al., 2005). Finally, it has been demonstrated that the left parietal ERP old/new effect is reduced in participants whose recollection is impaired in behavioral tasks as result of pathological conditions (such as brain damage) or as consequence of the administration of pharmacological agents (Luck, 2014).

Until now, it has been shown that the magnitude of the left parietal old/new effect is modulated by different factors. First, the size of the effect depends on the amount of information

retrieved by participants. For example, Vilberg et al., (2006), using a modified Remember/Known task, evaluated the magnitude of the left parietal old/new effect associated to memory quality. During the practice session, participants had to learn picture pairs. Afterwards, during the test session, they had to provide an answer evaluating their subjective report of the amount of information retrieved during this task (e.g., they gave answer 1 to report that they recalled minor aspects about the study event related to the presented picture or answer 2 to report that they could recognize the presented picture and recall its associated image). This effect, sensitive to the amount of pictorial information, is also modulated by the amount of verbal information (Vilberg et al., 2006; Vilberg and Rugg, 2009). Accordingly, in source judgment tasks, the magnitude of the left parietal old/new effect varies according with the number of correct contextual judgments that are made by participants, with a larger old/new effect associated to responses that include contextual information. For example, Wilding and Rugg (1996), instructed participants to judge words as been studied or not. Additionally, after the old/new judgment, they had to indicate in which of two voices (male/female) the word was read during the study phase (Wilding and Rugg, 1996). In the same line, it has been shown that the magnitude of the left parietal old/new effect is also modulated by the recall of the modality (auditorily/visually) in which the items were initially presented during the study phase (Wilding et al., 1995). This phenomenon has been also observed in associative recall tasks. For example, in a study by Rugg et al., (1996), participants were instructed to learn pairs of words by integrating them into a single sentence. During the test phase, studied and non-studied words were presented, and the subjects were instructed to classify the words as old or new. For those old responses, they had to indicate the associated word. The results indicated that the left parietal old/new effect only was presented for those responses in which the associated word could be recalled (Rugg et al., 1996). Thus, it has been proposed that – in associative recall tasks – the old/new effect reflects the likelihood of recollection. In associative recognition tasks, a larger magnitude of the old/new effect has been found in tasks in which participants

have to judge word pairs as old, new or rearranged. These studies have shown that old pairs elicit a larger left parietal old/new effect compared to rearranged ones (Donaldson and Rugg, 1998, 1999; Parker et al., 2005). Finally, another factor that modulates the magnitude of the old/new effect is the level-of-processing at encoding. In this context, it has been demonstrated that words learned with a deep strategy elicit a greater parietal old/new effect during retrieval in comparison to words learned using a shallow strategy (Rugg et al., 1998b; Rugg and Curran, 2007). Taken together, these studies support the idea that the left parietal old/new effect is modulated by the amount of contextual and associated information retrieved during the task.

Until now, evidence from fMRI studies have added evidence to the idea that the left parietal old/new effect reflects neural activity of the lateral parietal cortex and cortico-hippocampal network, brain areas related to episodic memory retrieval (Wagner et al., 2005; Cabeza et al., 2008; Simons and Mayes, 2008; Vilberg and Rugg, 2009). Different interpretations have been proposed to explain the role of the parietal cortex in the left parietal old/new effect. Some authors have suggested that the left parietal old/new effect could reflect parietal activity that supports the reinstatement of memory (which in turn depends on hippocampal activity) (Rugg et al., 1998a). Other interpretation is that inferior regions of the left parietal cortex, that have been associated with successful recollection, support an "episodic buffer" that maintains the retrieved information over time and binds it into a unitary episodic representation (Baddeley, 2000; Vilberg and Rugg, 2008). Finally, it has been proposed that the parietal old/new effect could reflect an attentional shift as consequence of retrieval. This explanation is compatible with the known role of the parietal cortex in attentional processes (Kastner and Ungerleider, 2000; Cabeza, 2008; Cabeza et al., 2008).

In summary, the ERP research based on dual process models describes primarily two effects associated with recognition: familiarity and recollection. Both are linked to the successful recognition

of previously studied items, but only recollection is related to retrieval of contextual and associated information (Yonelinas and Jacoby, 1994; Yonelinas and Levy, 2002). To date, these memory processes and their ERP correlates have not been studied in advanced memory stages such as reconsolidation. Thus, further research in this area is needed.

3.5 Pupil size changes associated to memory retrieval: The pupil old/new effect

Pupil size, as a physiological reflex, is modulated by several factors and circumstances (Montefinese et al., 2018). It has been shown that reflects the balanced activity of the sympathetic and parasympathetic pathways (associated to dilation and constriction, respectively), which are modulated by brainstem centers (Loewenfeld and Lowenstein, 1993; Purves et al., 2014). Specifically, pupil dilation has been associated with the activity of the locus coeruleus-noradrenaline (LC-NA) system (Einhauser et al., 2008; Joshi et al., 2016). To our interest, it has been proposed that pupil dilations related to cognitive processing would be elicited by the increased activity of the LC-NA system as consequence of cognitive demands processed by the prefrontal cortex (Goldinger and Papesh, 2012; Montefinese et al., 2018). In this context, because it provides an index of cognitive processing, the pupillary response has been studied extensively in relation to different cognitive functions, such as emotional and language processing, mental arithmetic and decision making (Hess and Polt, 1960; Kahneman and Beatty, 1966; Wright and Kahneman, 1971; Ahern and Beatty, 1979; de Gee et al., 2014). To date, it has been established that pupil increases its diameter in response to a greater cognitive demand (Kahneman and Beatty, 1966; Verney et al., 2004). The present consensus suggests that this change in the size of the pupil is a summative index of brain activity, presumably reflecting cognitive processing, load and effort

(Kahneman and Beatty, 1966; Janisse, 1977; Siegle et al., 2003; Zekveld et al., 2014). In the last decade, pupil research has become increasingly popular in cognitive and neuroscience research mainly for two reasons. First, its high temporal resolution (similar to EEG) allows to study the temporal profile of cognitive processing. Second, its non-invasiveness gives to researchers a valuable tool to evaluate cognitive functions in humans (Granholm and Steinhauer, 2004).

Relevant to our work, there is a line of research that has associated changes in pupil diameter to memory processes (Bradshaw, 1967; Kahneman and Wright, 1971). In fact, similar to results found in ERP research, it has been demonstrated that variations in the pupil size can index encoding and retrieval of information (Vo et al., 2008; Kafkas and Montaldi, 2011, 2012). For example, Kahneman and Beatty (1966), using a short-term memory task, observed that pupil diameter increases in response to retrieval of digit strings that were studied before. They proposed that changes in pupil diameter is linked to working memory load and mental effort (Kahneman and Beatty, 1966). Similarly, in another study, Gardner et al., (1975), instructed participants to learn 7-digit numbers while pupil size was recorded during encoding, retention interval and recall. The results showed an increased pupil diameter during encoding and retrieval (Gardner et al., 1975). This effect has been also observed in recognition memory tasks. For example, Gardner et al., (1974), measured the pupil dilation related to the recognition of 3-letters nonsense words (consonant/vowel/consonant) that were or not presented previously. The results showed that pupil size dilates in response to the presentation of old words and contracts in response to new words (Gardner et al., 1974).

More recently, changes in pupil dilation have been explored in the context of recognition paradigms that use an old/new task very similar to those used in ERP research. Evidence has shown that pupil diameter dilates more when participants correctly recognize old items compared to the correct rejection of new stimulus. This old/new difference begins approximately at 500-700 ms after

the stimulus onset and can last seconds. Due to its similarity to the previously mentioned ERP old/new effect, this effect was called Pupil Old/New effect (PONE) (Vo et al., 2008; Heaver and Hutton, 2011; Otero et al., 2011; Papesh et al., 2012; Kafkas and Montaldi, 2015). Specifically, the first study that investigated this phenomenon in a recognition task and revitalized the interest in the relationship between pupil size and memory, found a greater pupillary response from approximately 500-700 ms until the end of the measured epoch (1800 ms) in response to the correct recognition of old items in comparison to the correct rejection of new ones. Interestingly, the pupil old/new effect was attenuated for emotional in comparison to neutral words. The authors suggested that this emotion-related modulation of the pupil old/new effect during retrieval was related to a reduced cognitive effort as consequence of a presumably better encoding of the emotional words during the study phase. This latter finding is the basis of the "cognitive load" interpretation of the pupil old/new effect (Vo et al., 2008).

Later studies sought to establish the factors that modulate the pupil old/new effect. One crucial finding was that the pupil old/new effect is independent of conscious control, emerging even in tasks in which participants were instructed to deliberately give wrong answers (i.e., to feign amnesia or report all the items as new) (Heaver and Hutton, 2011). Also, it was demonstrated that the magnitude of the effect is modulated by the depth-of processing during encoding, showing a greater pupil old/new effect items that were encoded using a deep compared to a shallow orienting strategy (Otero et al., 2011). This finding supports the idea that, contrary to the "cognitive load" interpretation explained above (Vo et al., 2008), changes in pupil size can reflect the strength of the memory trace and not necessary the cognitive effort associated to its retrieval ("strength-of-memory" account) (Otero et al., 2011). Another factor that modulates the pupil old/new effect is the retrieval of contextual information, as shown by studies that use known/remembered tasks. In these studies, the effect is attenuated in

known items (associated to familiarity) in comparison to remembered ones (associated to recollection) (Otero et al., 2011; Kafkas and Montaldi, 2012). Similar results have been provided by Kafkas and Montaldi (2015), showing that the pupil dilation is maximal in recollected items and minimal in novel stimuli (familiar items showed a pupil dilation between both) (Kafkas and Montaldi, 2015). Finally, some studies have demonstrated that the correct recognition and rejections of items is not sufficient for the emergence of the pupil old/new effect (Otero et al., 2011; Montefinese et al., 2013; Kafkas and Montaldi, 2015). For instance, Montefinese et al., (2013), observed in a recognition memory task that this effect not only appears when participants provide veridical old responses, but also when a novel item is considered as old. In this context, they authors coined the notion of a "subjective" pupil old/new effect to describe the greater pupil dilation associated to subjectively old responses in comparison to pupil dilation associated to correct rejections (Montefinese et al., 2013).

Taken together, although the specific role of the pupil old/new effect remains unclear, it can be considered a valid marker reflecting mnemonic processes, such as encoding and retrieval. However, until now, there are not reports about the pupil old/new effect elicited by retrieval of memories in advanced stages of memory, such as reconsolidation. In this context, we sought to describe the pupillary response elicited by retrieval of memories that were successfully reconsolidated or whose reconsolidation process was interfered by an amnesic agent.

3.6 Conclusions

Memories are not necessarily stored in a fixed state in the brain. They can be changed (improved, disrupted or upgraded) if they are reactivated under specific circumstances, through a process known as reconsolidation. Specifically, in humans, it has been demonstrated that the

reconsolidation process may modify declarative memories, a kind of memory that can be consciously retrieved and verbalized. However, we do not clearly know how memories that were reconsolidated or whose reconsolidation process was disrupted, are retrieved in the future. In this context, our main proposal in this thesis was to study the neurophysiological correlates (i.e., ERP and pupillary response) of retrieval of memories that were successfully reconsolidated or whose reconsolidation process was interfered. A better understanding of the neural correlates of retrieval of reconsolidated memories could help to determine the relationship, similarities and differences between consolidation and reconsolidation. In addition, it could contribute to develop diagnostic tools and new therapeutic techniques to evaluate and treat memory disorders in psychiatric population, such as PTSD and dementias. Also, it could be useful for the development of new procedures to improve learning process in educational contexts.

4. HYPOTHESES AND OBJECTIVES

4.1 Hypotheses

4.1.1 General Hypothesis

The labilization-reconsolidation process triggered by unpredictable reminders will affect the subsequent retrieval of declarative memories by enhancing recollective processes.

4.1.2 Specific Hypothesis

1) The labilization-reconsolidation process triggered by unpredictable reminders will strengthen declarative memories, which will be associated to a larger and earlier parietal ERP and pupil old/new effects.
2) The exposure to an amnesic agent (i.e., new learning) during the reconsolidation process will prevent the behavioral and neurophysiological changes associated to retrieval of strengthened memories as consequence of reconsolidation.

4.2 Objectives

4.2.1 General Objective

To investigate the neurophysiological correlates (i.e., electrophysiological and pupillary activity) of retrieval of declarative memories that were successfully consolidated, reconsolidated or whose reconsolidation process was interfered by an amnesic agent (i.e., new learning), in humans.

4.2.2 Specific Objectives

1) To implement an experimental paradigm that allows learning, consolidation, reconsolidation and retrieval of declarative memories.
2) At a behavioral level, to evaluate the effect of consolidation, reconsolidation and disruption of reconsolidation on the subsequent retrieval of declarative memories.
3) At a neurophysiological level, to evaluate and compare the ERP and pupil old/new effect elicited by retrieval of declarative memories that were consolidated, reconsolidated or whose reconsolidation process was interfered by an amnesic agent (i.e., new learning).

5. PARTICIPANTS AND METHODS

5.1 Subjects

A sample of 92 volunteers (24 males, 68 females, mean age = 21.4 years [S.D=2.35]) participated in the experiment. All participants were recruited from the student population of the Pontificia Universidad Católica de Chile.

All volunteers were native spanish speakers, had normal or corrected-to-normal vision and no reported history of psychiatric or neurological disorders. Additionally, participants were instructed to refrain from caffeine, alcohol and taking naps during the experimental days.

EEG data from 22 participants and pupillary data from 24 participants were excluded from further analysis due to technical reasons (i.e., poor signal quality or excessive artifacts in EEG or pupillary recording) or because they did not reach the minimum score at the training session (70% of performance, see Memory Task), leaving a final sample of 70 participants for EEG analyses (16 males, 54 females, mean age = 21.3 years [S.D=2.45]) and 68 for pupillary analyses (16 males, 52 females, mean age = 20.9 years [SD=2.08]). Because the final selection of participants differed for EEG and pupil recordings, different datasets of participants were used for EEG and pupil analyses.

This study was approved by the Ethics Committee of the Pontificia Universidad Católica de Chile and all participants gave informed, written consent before taking part in this investigation.

5.2 Experimental Design

5.2.1 Stimuli

Stimuli were 120 pictures of everyday objects and situations (48 for old and 24 for new conditions; and 48 for interference by new learning). From this pool of pictures, 72 were used in a previous study of memory reconsolidation (Forcato et al., 2016) and 48 were added to guarantee a sufficient number of trials for reliable ERP and pupil analyses. Each picture of the old condition or the interference list (see Experimental design) was paired with a three-syllable spanish word, not directly related. All the words were nouns and were composed by six letters. The stimuli were presented using Psychopy (Peirce, 2007) on a Tobii Pro TX300 monitor (Tobii Technology, Inc., Sweden). All the pictures were equated in contrast and luminance and were presented in the center of the screen, in grayscale with a gray background, within a rectangular area of approximately 9 cms (h) x 13 (w) cms and at a viewing distance of 65 cms, providing a visual angle of approximately 7° (h) x 11° (w). All the words and syllables were presented in uppercase and in black over a white rectangle superimposed on its associated picture. Additionally, a white central fixation cross was displayed during intertrial intervals to avoid unnecessary eye movements that could affect electroencephalographic and pupillary recordings.

5.2.2 Experimental task

Here we used a modified version of the three-day paradigm as described by Forcato et al. (2016). Sessions took place within a week and they were separated by 48 hours (monday, wednesday and friday) (See Figure 2).

5.2.3 Procedure

Session 1: Training

At the beginning of session 1, participants were instructed to learn 48 picture-word pairs (e.g., a picture of clouds and the word “PALOMA”, pigeon in spanish). Each trial started with the presentation of a fixation cross for 3 seconds. Then, each picture was shown for another 3 seconds. Immediately after, the associated word was superimposed onto the upper part of the picture for 1 second. This procedure was repeated until the 48 pairs were presented.

Five minutes later, learning was evaluated. Test trials began with the presentation of a fixation cross for 3 seconds. Then, each picture was presented alone for 3 seconds followed by the presentation of the picture and only the first syllable of the associated word, for 1 second (e.g., the picture of the clouds and the syllable “PA”). Afterwards, and every time an image of a microphone appeared, participants had 2 seconds to say aloud the associated word of the respective picture. Then, the picture and the associated word were presented for 1 second. This procedure was repeated for the total of picture-word pairs.

Session 2: Memory Reactivation and/or Interference

In the second experimental session, forty-eight hours later, memory was reactivated in order to trigger the labilization-reconsolidation process. As was described earlier, a proper reminder structure is crucial to destabilize a consolidated memory and trigger the reconsolidation process. In this context, previous findings have demonstrated that the detection of a prediction error due to a mismatch in the expectations (a discrepancy between what is expected and what actually happens) is necessary for the destabilization of an existing memory (Pedreira et al., 2004; Fernandez et al., 2016; Forcato et al., 2016).

Accordingly, here only unpredictable cues were used, and the prediction error was incorporated in the reminder structure as an interruption of the task that occurred before the participant could answer in each trial. This session was composed of two blocks: the memory reactivation and/or the subsequent interfering task.

During the reactivation procedure, participants were instructed to say the associated word aloud when a microphone image appeared on the screen. Each trial began with a fixation cross in the center of the screen for 3 seconds. Then, a studied picture was presented for 3 seconds followed by the simultaneous presentation of the picture and the first syllable of the associated word, for 1 second. Afterward, the experiment was interrupted with the text "INTERRUPCIÓN" ("interruption") for 2 seconds, followed by the text "RETOMA" ("continue") for another 3 seconds, indicating that the task continues in the next trial. This procedure was repeated for all the 48 picture-word pairs. Because no microphone images were presented during this block, participants could not provide an answer during the trials. Importantly, subjects were instructed to pay attention to the computer screen until all images and texts were presented.

To target the reconsolidation process (Forcato et al., 2007; Hupbach et al., 2007), some participants performed an interfering task five minutes after memory reactivation (see Experimental Groups). In this task, using the same procedure as that used in the training session, participants were asked to learn a new list of 48 picture-word pairs. Five minutes later, learning was evaluated. This procedure allowed us to investigate the retrieval of declarative memories whose reconsolidation process was disrupted, preventing its subsequent effects on memory.

Session 3: Memory Testing

Forty-eight hours after memory reactivation, memory was evaluated in an associative recall old/new task (Donaldson and Rugg, 1999) while brain activity and pupillary responses were simultaneously recorded by means of EEG and eyetracker, respectively. At the beginning of each trial, a fixation cross appeared in the center of the screen for a randomly selected duration of 2, 3 or 4 seconds. Pictures studied on session 1 (list 1, old pictures) and an additional set of 24 non-studied pictures were randomly shown one at a time for 4 seconds each, followed by a microphone image for another 3 seconds. Participants were instructed to say aloud, during the presentation of the microphone image, "VISTA" ("seen" in spanish) when an item was recognized as old or "NO VISTA" ("not seen") when an item was recognized as new. Additionally, for pictures recognized as old, the participant had to say the associated word aloud or "No sé" ("I don't know"), in case it was not possible to recall it. To obtain a sufficient number of trials in each condition for ERP and pupil old/new effect analyses, the test task was repeated 3 times in 3 independent blocks, separated by five minutes.

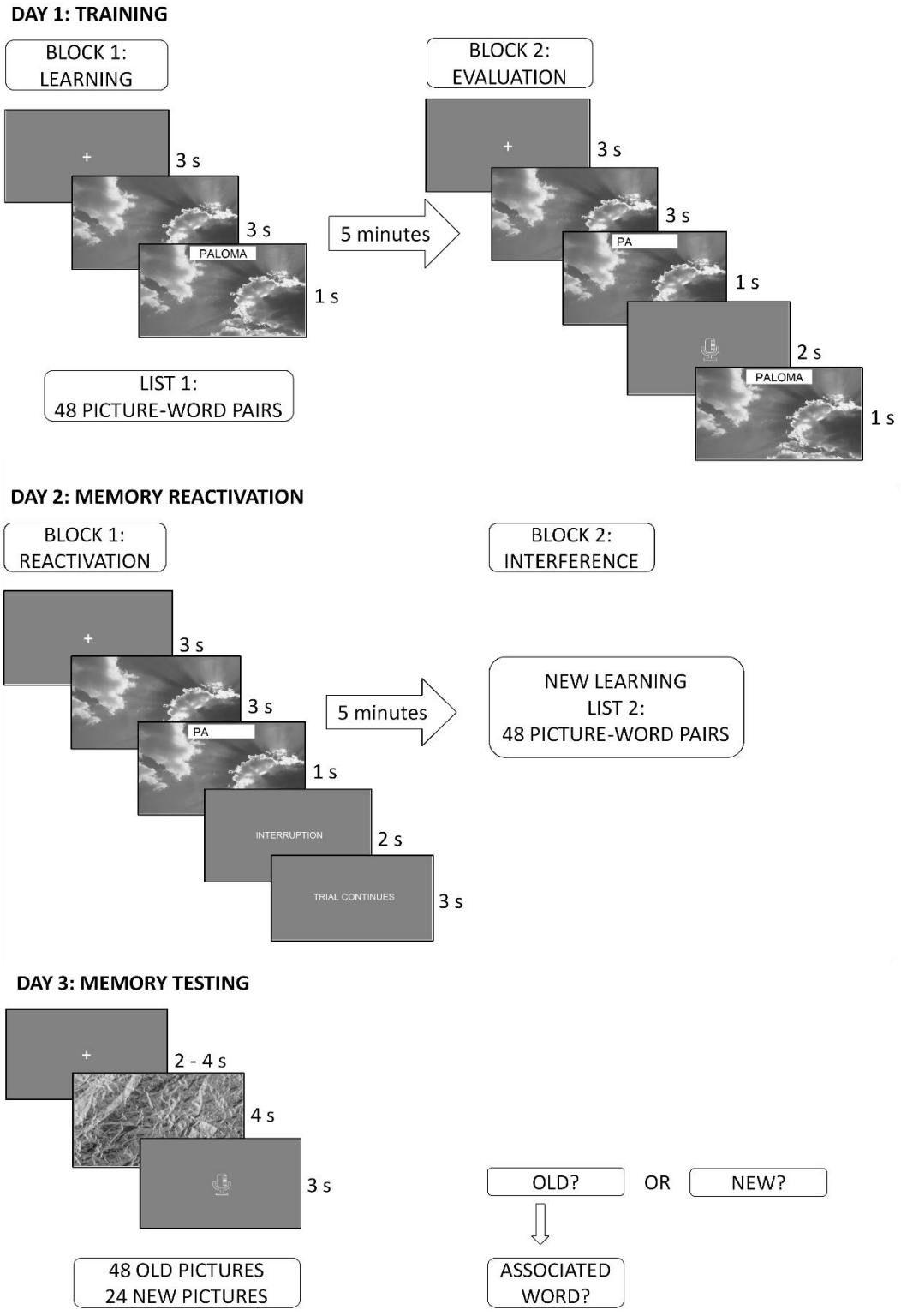

Figure 2. Experimental design (adapted from Forcato et al., 2016).

5.2.4 Experimental Groups

Participants were randomly assigned to one of the four following experimental groups: reactivation group, reactivation/interference group, interference group and no-reactivation/no-interference group. All groups were exposed to identical training and testing procedures in session 1 and session 3, respectively. During the second session, the reactivation group only underwent memory reactivation; the reactivation/interference group underwent memory reactivation followed by the interference task (new learning); the interference group was only exposed to the interference task; and the no-reactivation/no-interference group did not come back to the laboratory for the session 2 to prevent any kind of unintentional memory reactivation (See Table 1).

EXPERIMENTAL GROUPS	SESSION 1	SESSION 2	SESSION 3
REACT	TRAINING	REACTIVATION	TESTING
REACT/INT	TRAINING	REACTIVATION + INTERFERENCE	TESTING
INT	TRAINING	INTERFERENCE	TESTING
NO-REACT/NO-INT	TRAINING	-	TESTING

Table 1. Experimental Groups.

5.3 Data Acquisition

5.3.1 EEG Recording

A continuous EEG recording was acquired from 64 Ag-AgCl active electrodes - mounted in an elastic cap according to the extended International 10-20 System - using Biosemi ActiveTwo system

(Biosemi, Amsterdam, Netherlands). Additionally, left and right mastoids were recorded to be used as reference electrodes in offline analyses. During the recording, impedances were kept below 20kΩ. The continuous data was recorded at a sampling rate of 2048 hz and stored offline for later analysis.

5.3.2 Pupil Size Recording

A Tobii TX300 eye tracker system was used during session 3 to acquire the pupil size, with a sampling rate of 300 hz. The Tobii Studio software was used to record the pupillometry data and export it for later analyses. The system was calibrated before each test block using the Tobii Studio's 9-point automated calibration routine. The exported data were processed using custom MATLAB scripts.

5.4 Data recording and analysis

5.4.1 Behavioral Analysis

Learning in session 1 was measured by quantifying correct responses (correct recall of the associated word) and expressed as a percentage of the total number of picture-word pairs. Following Donaldson and Rugg (1999), to evaluate memory in session 3, we calculated the percentage of old responses with correct recall of its associated word, the percentage of old responses with no recall ('don't know' response) and the percentage of old responses with incorrect recall, for those items that were correctly recognized as old in the initial old/new judgment. Additionally, we calculated the recognition accuracy, measured as the difference between hits (correctly recognized old items) and false alarms (incorrectly classified new items). In all cases, memory evaluation considered the average scores from the three independent test blocks.

5.4.2 EEG analyses

For ERP analyses, only two response categories were considered: correct old responses (correct classification of old pictures and recall of their associated words) and correct new responses (correct classification of new pictures).

The data was preprocessed and analyzed with MATLAB (MathWorks, Inc., Natick, MA) using EEGLAB toolbox (version 14.1.1) (Delorme and Makeig, 2004) and ERPLAB (version 6.1.3) (Lopez-Calderon and Luck, 2014). For each subject, the three independent test blocks were imported and concatenated. Then, the data was resampled to 1024 hz, bandpass filtered using a Butterworth filter (half amplitude cutoffs at 0.1 and 100 hz, 12 dB/octave roll-off) and re-referenced to the average of the left and right mastoids. Continuous data was then epoched into 3000 ms segments (1000 ms before and 2000 ms after the picture onset). Segments of EEG were visually inspected to identify and remove bad channels and muscular activity artifacts. Additionally, blinks and eye movements artifacts were identified and manually removed using independent component analysis (ICA) (Jung et al., 2000b; Jung et al., 2000a; Delorme and Makeig, 2004). After ICA, removed channels were interpolated using spherical-spline interpolation, as implemented in EEGLAB.

To compute ERPs, the data was resampled to 512 hz and bandpass filtered using a Butterworth filter (half amplitude cutoffs at 0.1 and 30 hz, 12 dB/octave roll-off). Remaining artifacts were automatically rejected using the moving peak-to-peak algorithm (Lopez-Calderon and Luck, 2014) (with a voltage threshold of ±100 mV, moving windows full width of 200 ms and window step of 50 ms) in epochs from -200 to 2000 ms relative to the picture onset. The pre-stimulus window of 200 ms was used to correct for baseline activity in each trial. Then, the ERP old/new effect was calculated as the difference between ERPs elicited by the correct classification of old items (and the recall of their associated words) and new items. For tmax permutation analyses (Groppe et al., 2011a, b) (see

Statistical Analyses section), the data was downsampled to 128 hz to decrease the number of comparisons and increase statistical power (Luck, 2014). Following an examination of the permutation results, the difference score (old minus new) of the peak latencies, peak amplitudes (200-800 ms time window) and mean amplitudes (450-800 ms time window) relative to the 200 ms pre-stimulus baseline, were independently computed for two regions of interest (ROIs): left parietal (CP1, CP3, CP5, P1, P3, P5) and right parietal (CP2, CP4, CP6, P2, P4, P6).

5.4.3 Pupil Size Analyses

For pupil diameter analyses, pupil size of the right eye was chosen. Participants with excessive missing data due to head movements, pupil signal loss and blinks during the total recording time were excluded from analysis. Specifically, trials containing less than 50% of valid pupil recordings were excluded and, if 50% of all trials for each condition were missing after the former correction, the participant was no longer considered in further analyses. Then, missing data were linearly interpolated, signals were low-pass filtered at 3 hz and data was epoched from -1000 to 4000 ms relative to the image onset (time interval from -1000 to 0 ms was used as baseline), only considering correct old (old response + recall of the associated word) and new responses. Afterwards, maximal pupil dilation from baseline was independently calculated for each trial (Wainstein et al., 2017) and the difference between the post-stimulus and baseline values were computed. For each subject, the pupil old/new effect was calculated subtracting the mean maximal pupil diameter associated to correct old responses from the mean maximal pupil diameter associated to correct new responses. As a complementary measure, the mean pupil diameter was computed in the 1500-2500 ms time window for correct old and new responses and the pupil old/new effect was calculated as the difference. Finally, for each participant, the old-new average effect was calculated, from which we extracted the peak latency (500 – 3300 ms

time window) of the pupil. To find the maximum in this case, we looked for the local maximum (i.e., the point within the curve in which the derivative is 0, being positive in the left side of the point and negative in the right side).

5.5 Statistical analyses

5.5.1 Behavioral statistical analyses

Behavioral data for the ERP and pupil datasets were analyzed with non-parametric Kruskal-Wallis test, followed by planned comparisons (four contrasts of interest: reactivation vs reactivation/interference, reactivation vs no-reactivation/no-interference, reactivation/interference vs interference, no-reactivation/no-interference vs interference, corrected by post-hoc Dunn's comparisons). All p-values reported were two-tailed and were considered significant if they were less than 0.05.

5.5.2 EEG statistical analyses

Differences between ERPs elicited by old and new categories were detected using a two-tailed permutation test based on the tmax statistic (Blair and Karniski, 1993). This statistical test was used to avoid the traditional methods to correct for multiple comparisons that inflate type error II as consequence of its very strict criterions (for example, the Bonferroni method, based on the assumption that each t test is independent, which is not the case for EEG and pupil data). One critical advantage of the tmax procedure is that uses the characteristics of the actual data to evaluate statistical significance. Specifically, the tmax permutation test permutes the labels of the samples in order to estimate the null

distribution of the tmax values (i.e., the largest t value computed across all electrodes and time points in each iteration). To asses statistical significance, the real t values from the recorded data are calculated for each electrode/time bin and compared to the extreme values of the estimated distribution of tmax values. If the value is higher or lower (in a two-tailed permutation test) than the threshold established by the null distribution of tmax values, that point is statistically significant. It is considered that the permutation approach gives strong confidence about the statistical significance in every evaluated point or time window (Luck, 2014).

We performed the tmax permutation procedure on mean difference wave amplitudes considering five time windows (300-390, 400-490, 500-590, 600-690 and 700-790 ms), including 25 representative electrodes from occipital, parietal and mid-frontal areas (O1, Oz, O2, PO7, POz, PO3, P7, P3, Pz, P4, P8, TP7, CP3, CPz, CP4, TP8, AF3, AFz, AF4, F3, Fz, F4, FC3, FCz and FC4), with a family-wise alpha level of 0.01 and 100.000 permutations, as implemented in the Mass Univariate ERP Toolbox for MATLAB (Groppe et al., 2011a, b).

To investigate differences between groups in the mean amplitude (450-800 ms time window), peak latency and peak amplitude (200-800 ms time window) of the old/new effect, a one-way ANOVA was performed on the difference scores between old and new items (old minus new) in planned comparisons (same contrasts of interest considered in behavioral analyses, Bonferroni-corrected). All p-values were considered significant if they were less than 0.05.

5.5.3 Pupil size statistical analyses

To estimate reliable differences in pupil size between old and new responses in each group (pupil old/new effect), we performed a permutation test over consecutive time windows of 100 ms

each (family-wise alpha level of 0.01 and 10.000 random permutations). Following the observation of the permutation results, two-tailed independent t-tests were computed for the maximal and mean pupil diameter elicited by correct old and new responses, for each group. Subsequently, a one-way ANOVA was used to compare the difference scores of the maximal and mean pupil diameter between groups and a two-way ANOVA (with reactivation and interference as the between-subjects factors) to compare the peak latency of the pupil old/new effect between groups.

Because the final selection of participants differed for EEG and pupil datasets after the preprocessing stage, independent datasets were used for EEG and pupil size analyses. T-tests, Kruskal-Wallis and ANOVA analyses were performed using Prism software (version 7, GraphPad Software, San Diego, CA) and MATLAB.

6. RESULTS

6.1 Behavioral Results

6.1.1 The EEG dataset of participants showed no group differences in learning (session 1, training). In contrast, the reactivation group showed an overall better performance in the memory evaluation compared to the reactivation/interference and no-reactivation/no-interference groups (session 3, testing).

For the EEG dataset of participants, no significant differences among groups were found in session 1 (training) (mean percent of correct responses ± S.D., reactivation group: 87.75 ± 6.944; reactivation/interference group: 83.56 ± 7.177; interference group: 88.89 ± 8.634; no-reactivation/no-interference group: 84.68 ± 7.101; Kruskal-Wallis test, $p=0.1155$). This means that no group differences were detected in the learning rate during the study phase and, therefore, differences in memory (as evaluated in session 3) could not be explained by an initial difference in learning.

In session 3 (testing session), for those old items that were correctly recognized, we found significant differences between groups in the percentage of old responses with correct recall (mean ±

S.D., reactivation group: 92.9 ± 5.703; reactivation/interference group: 83.78 ± 10.07; interference group: 73.29 ± 16.73; no-reactivation/no-interference group: 72.95 ± 15.4, Kruskal-Wallis test, $p<0.0001$). Post-hoc analyses revealed that the percentage of old responses with correct recall was significantly higher in the reactivation group than the reactivation/interference and the no-reactivation/no-interference groups ($p=0.0463$ and $p<0.0001$ respectively, Dunn's post-hoc test). Moreover, we detected significant group differences in the percentage of old responses with no recall ('don't know' answers) (mean ± S.D., reactivation group: 5.195 ± 4.284; reactivation/interference group: 13.15 ± 8.771; interference group: 21.16 ± 14.16; no-reactivation/no-interference group: 22.31 ± 13.97; Kruskal-Wallis test, $p<0.0001$), showing the reactivation group a lower percentage of old responses with no recall compared to the reactivation/interference and no-reactivation/no-interference groups ($p=0.0408$ and $p<0.0001$ respectively, Dunn's post-hoc test). Also, there were significant group differences in the percentage of correct old responses with incorrect recall (mean ± S.D., reactivation group: 1.902 ± 2.016; reactivation/interference group: 3.067 ± 3.133; interference group: 5.554 ± 4.819; no-reactivation/no-interference group: 4.744 ± 3.659; Kruskal-Wallis test, $p=0.0121$). Post-hoc comparisons indicated that the percentage of correct old responses with incorrect recall was lower in the reactivation group compared to the no-reactivation/no-interference group ($p=0.0458$, Dunn's post-hoc test). Finally, significant group differences were detected in the recognition accuracy (mean percent of (p_hits – p_false alarms) ± S.D., reactivation group: 99.23 ± 1.008; reactivation/interference group: 97.72 ± 2.973; interference group: 97.34 ± 3.118; no-reactivation/no-interference group: 94.73 ± 3.331; Kruskal-Wallis test, $p=0.0003$). Specifically, the recognition accuracy was higher in the reactivation group compared to the no-reactivation/no-interference group ($p<0.0001$, Dunn's post-hoc test). However, no differences were detected between the reactivation and reactivation/interference groups ($p=0.6588$), indicating that the differences between these groups are

not related to the initial old/new judgment but to the later recall of the associated word (see Figure 3 and Table 2).

In summary, the reactivation group (in which memory were successfully reconsolidated) showed an overall better performance compared to the reactivation/interference and no-reactivation/no-interference groups in the memory task in session 3. This result cannot be explained by differences in the initial learning in session 1.

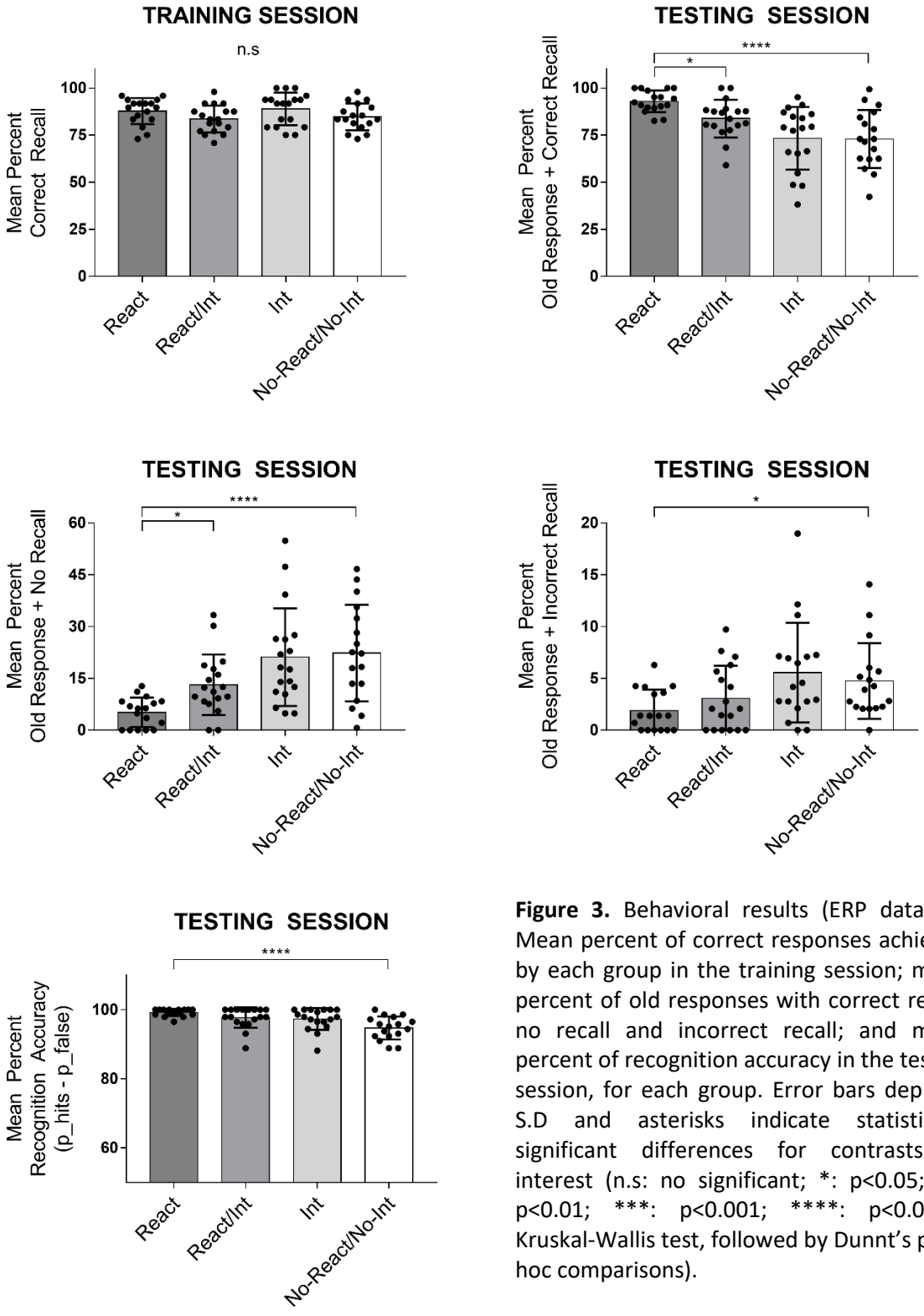

Figure 3. Behavioral results (ERP dataset). Mean percent of correct responses achieved by each group in the training session; mean percent of old responses with correct recall, no recall and incorrect recall; and mean percent of recognition accuracy in the testing session, for each group. Error bars depict ± S.D and asterisks indicate statistically significant differences for contrasts of interest (n.s: no significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; ****: $p<0.0001$, Kruskal-Wallis test, followed by Dunnt's post-hoc comparisons).

6.1.2 The pupil dataset of participants showed no group differences in learning (session 1, training). In contrast, the reactivation group showed an overall better performance in the memory evaluation compared to the reactivation/interference and no-reactivation/no-interference groups (session 3, testing). These results are in accordance to the findings observed in the ERP dataset.

A very similar pattern of behavioral results to that obtained in the ERP dataset of participants was observed in the pupil dataset. No significant differences in the percentage of correct responses were observed between groups in the training session (mean ± S.D., reactivation group: 86.67 ± 6.579; reactivation/interference group: 83.11 ± 7.574; interference group: 88.6 ± 8.139; no-reactivation/no-interference group: 83.33 ± 6.67; Kruskal-Wallis test, $p=0.0813$).

In session 3 (testing session), significant group differences were detected in the percentage of correct old responses with correct recall (mean ± S.D., reactivation group: 93.12 ± 5.142; reactivation/interference group: 84.08 ± 9.669; interference group: 73.04 ± 14.46; no-reactivation/no-interference group: 71.37 ± 13.69; Kruskal-Wallis test, $p=0.0003$), showing the reactivation group a higher percentage of old responses with correct recall compared to the reactivation/interference and no-reactivation/no-interference groups ($p=0.0441$ and $p<0.0001$ respectively, Dunn's post-hoc test). Differences between groups were also detected in the percentage of old responses with no recall (mean ± S.D., reactivation group: 5.147 ± 4.188; reactivation/interference group: 12.47 ± 8.818; interference group: 20.98 ± 11.76; no-reactivation/no-interference group: 23.32 ± 12.52; Kruskal-Wallis test, $p<0.0001$). Specifically, the reactivation group had a lower percentage of old responses with no recall

compared to the no-reactivation/no-interference group. No differences were observed between reactivation and reactivation/interference groups, although there was a trend towards significance ($p<0.0001$ and $p=0.0731$, Dunn's post-hoc test). Also, there were significant differences between groups in the percentage of old responses with incorrect recall (mean ± S.D., reactivation group: 1.737 ± 1.727; reactivation/interference group: 3.522 ± 3.643; interference group: 5.971 ± 4.793; no-reactivation/no-interference group: 5.317 ± 3.496; Kruskal-Wallis test, $p=0.0023$), showing the reactivation group a lower percentage compared to the no-reactivation/no-interference group ($p=0.0066$, Dunn's post-hoc test). Finally, differences in recognition accuracy between groups were detected (mean percent of (p_hits – p_false alarms) ± S.D., reactivation group: 99.08 ± 1.038; reactivation/interference group: 97.81 ± 2.939; interference group: 96.12 ± 4.763; no-reactivation/no-interference group: 95.22 ± 3.599; Kruskal-Wallis test, $p=0.0047$). Specifically, Dunn's post-hoc tests showed differences between reactivation and no-reactivation/no-interference groups but not between reactivation and reactivation/interference groups ($p=0.0033$ and $p>0.99$, respectively) (see Figure 3 and Table 2).

In summary, these findings mirrored the results obtained in the ERP dataset. Specifically, the reactivation group, whose memories were successfully reconsolidated, showed a better memory performance in session 3, compared to the reactivation/interference and no-reactivation/no-interference groups. These results cannot be explained by initial differences in learning.

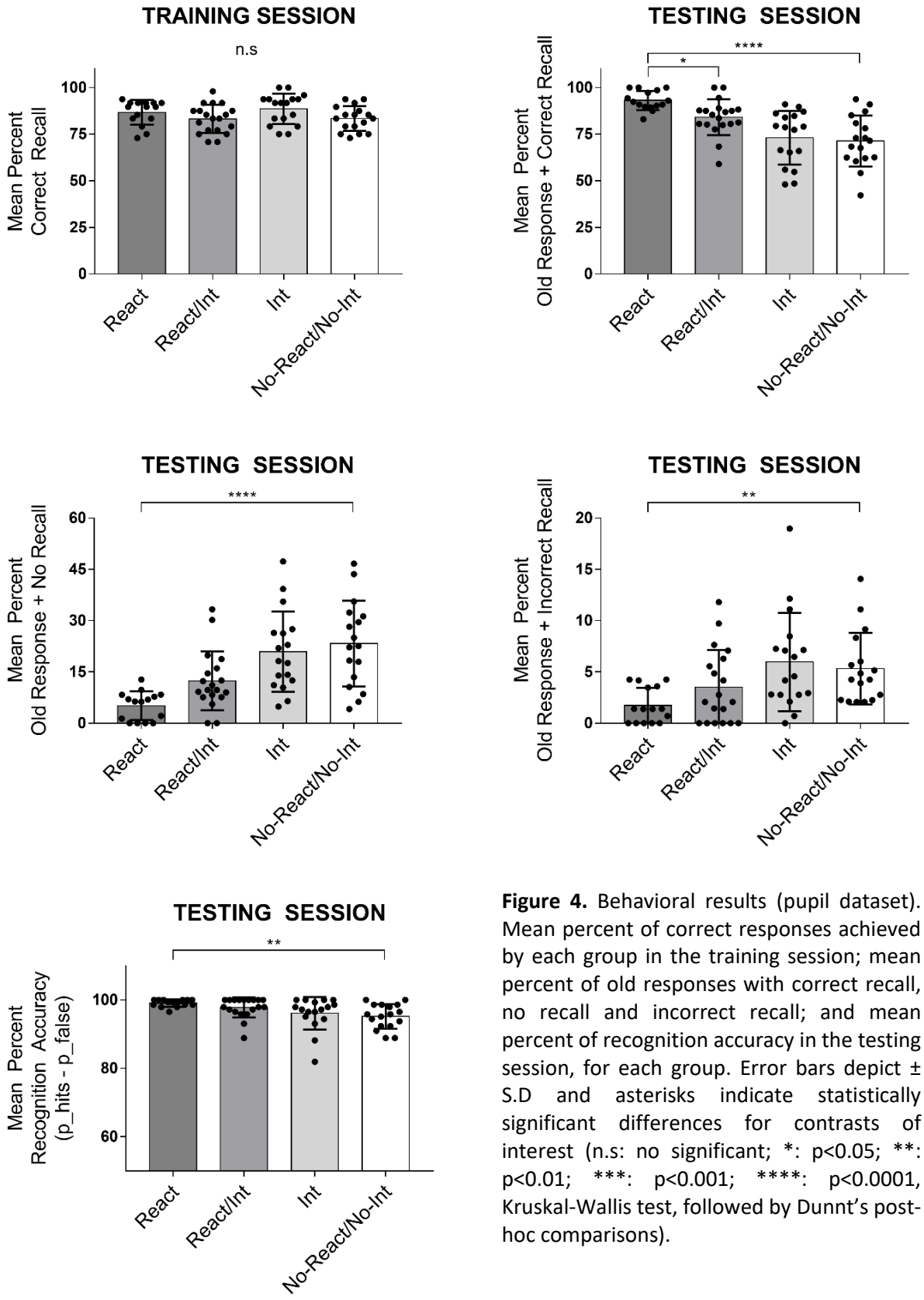

Figure 4. Behavioral results (pupil dataset). Mean percent of correct responses achieved by each group in the training session; mean percent of old responses with correct recall, no recall and incorrect recall; and mean percent of recognition accuracy in the testing session, for each group. Error bars depict ± S.D and asterisks indicate statistically significant differences for contrasts of interest (n.s: no significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; ****: $p<0.0001$, Kruskal-Wallis test, followed by Dunnt's post-hoc comparisons).

	Training	Old + Correct Recall	Old + No Recall	Old + Incorrect Recall	Recognition Accuracy (p_hits - p_fa)
Kruskal-Wallis Test					
ERP Dataset	n.s	p<0.0001 (****)	p<0.0001 (****)	p=0.0121 (*)	p=0.0003 (****)
Pupil Dataset	n.s	p<0.0001(****)	p<0.0001 (****)	p=0.0023 (**)	p=0.0047 (**)
Contrasts of Interest (Dunn's post-hoc test)					
React vs React/Int					
ERP Dataset	-	p=0.0463 (*)	p=0.0408 (*)	-	-
Pupil Dataset	-	p=0.0441 (*)	-	-	-
React Vs No-React/No-Int					
ERP Dataset	-	p<0.0001 (****)	p<0.0001 (****)	p=0.0458 (*)	p<0.0001 (****)
Pupil Dataset	-	p<0.0001 (****)	p<0.0001 (****)	p=0.0066 (**)	p=0.0033 (**)
React/Int vs Int					
ERP Dataset	-	-	-	-	-
Pupil Dataset	-	-	-	-	-
No-React/No-Int vs Int					
ERP Dataset	-	-	-	-	-
Pupil Dataset	-	-	-	-	-

Table 2. For the ERP and pupil datasets of participants, results of the Kruskal-Wallis tests and comparisons of interest (reactivation vs reactivation/interference, reactivation vs no-reactivation/no-interference, reactivation/interference vs interference and no-reactivation/no-interference vs interference, Dunn's test) for correct responses in session 1 (training) and old responses + correct recall, old responses + no recall, old responses + incorrect recall and recognition accuracy in session 3 (testing). Asterisks indicate statistically significant differences (n.s: no significant; *: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001).

6.2 Electrophysiological results

6.2.1 The parietal ERP old/new effect was detected in all groups. Retrieval of reconsolidated memories elicited a robust parietal old/new effect from the 400-490 ms until the 500-590 ms time window, followed by a reversed mid-frontal effect (new>old) in the 600-690 ms time window. In contrast, retrieval of consolidated memories or memories whose reconsolidation process was interfered by an amnesic agent (i.e., new learning), showed a parietal old/new effect predominantly in the 500-590 ms time window, not followed by the reversed mid-frontal old/new effect observed in retrieval of reconsolidated memories.

Tmax permutation tests showed differences between old and new categories in all groups. These results are illustrated in raster diagrams in Figure 6 and in topographical plots in Figure 7 (for representative plots of the parietal old/new effect, see Figure 5).

In the reactivation group, the permutation test revealed a positive difference between old and new categories over occipital, parieto-occipital, parietal and temporo-parietal regions in the 400-490 ms (PO7, O1, Oz, TP8, P8, PO8, O2) and in the 500-590 ms (P7, PO7, O1, POz, Oz, P8, PO8, O2) time windows. Additionally, a later reversed old/new effect was detected over mid-frontal electrodes (AF3, F3, FC3, AFz, Fz, FCz, AF4, F4, FC4, TP8) in the 600-690 ms time window.

In the reactivation/interference group, the tmax test revealed a positive effect over occipital electrodes in the 400-490 ms window (O1, Oz) and in occipital, parietal and parieto-occipital sensors (P7, P3, PO7, O1, Pz, POz, Oz, P8, PO8, O2) in the 500-590 ms time window.

In the interference group, a positive difference between old and new categories was observed in occipital (O1, Oz, O2) and left parietal electrodes (P7, P3, PO7) in the 500-590 ms time window. An old/new significant difference was also detected in the P7 electrode in the 400-490 ms time window.

Finally, in the no-reactivation/no-interference group, a positive effect was detected in centro-parietal, parietal, parieto-occipital and occipital electrodes (CP3, P7, P3, PO7, O1, CPz, Pz, POz, Oz, P8, P4, PO8, O2) in the 500-590 ms time window. This effect extended until the 600-690 ms time window in the P7 and Oz electrodes.

In summary, the tmax permutation tests revealed a consistent parietal old/new effect in all groups. However, retrieval of reconsolidated memories showed a distinct temporal and topographical profile compared to retrieval of memories that were consolidated or disrupted during reconsolidation.

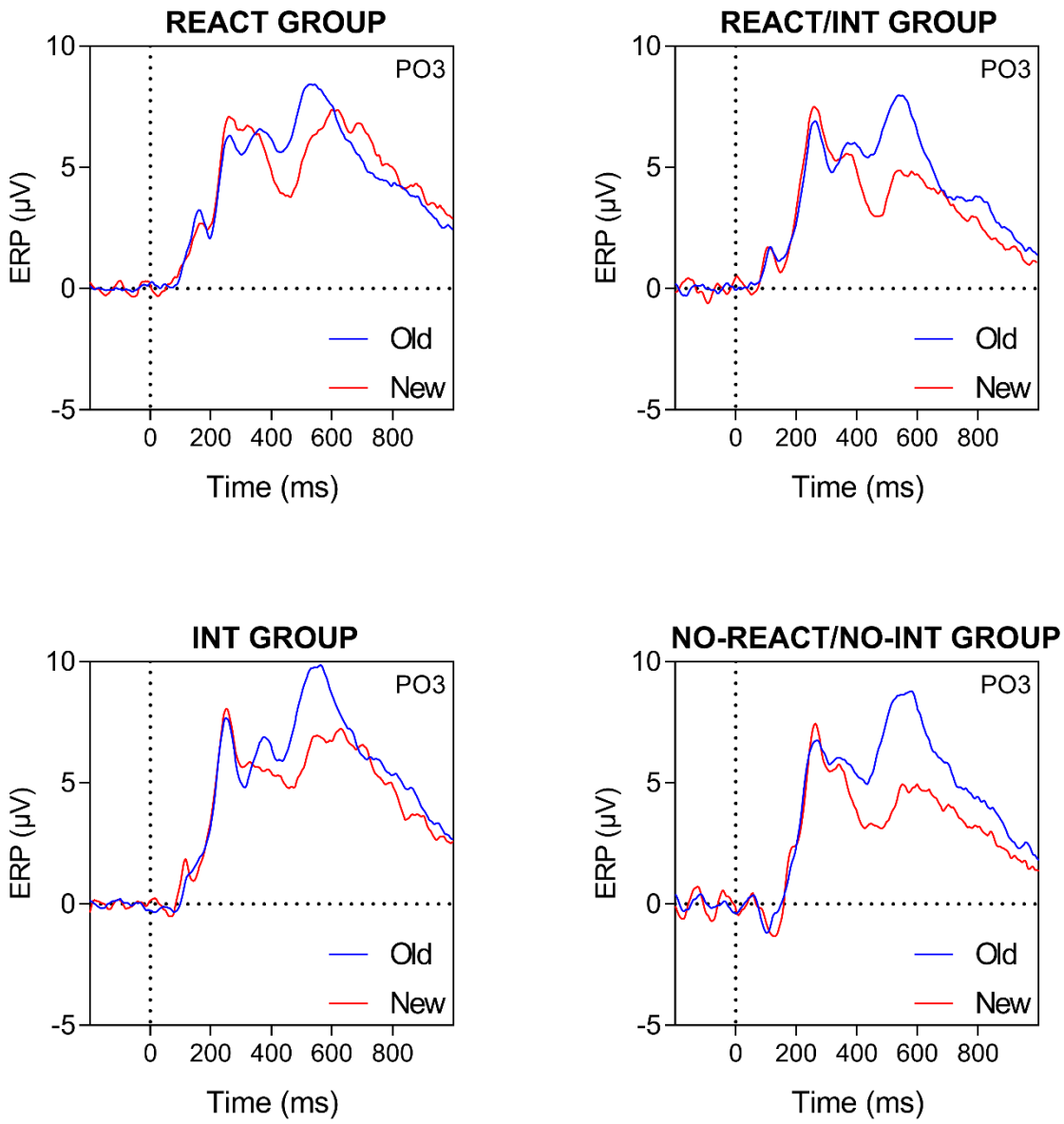

Figure 5. ERPs from a representative electrode (left parietal region, PO3) for correct responses. In blue, the potential elicited by the correct classification of an old picture and the recall of the associated word. In red, the potential elicited by the correct classification of a new picture.

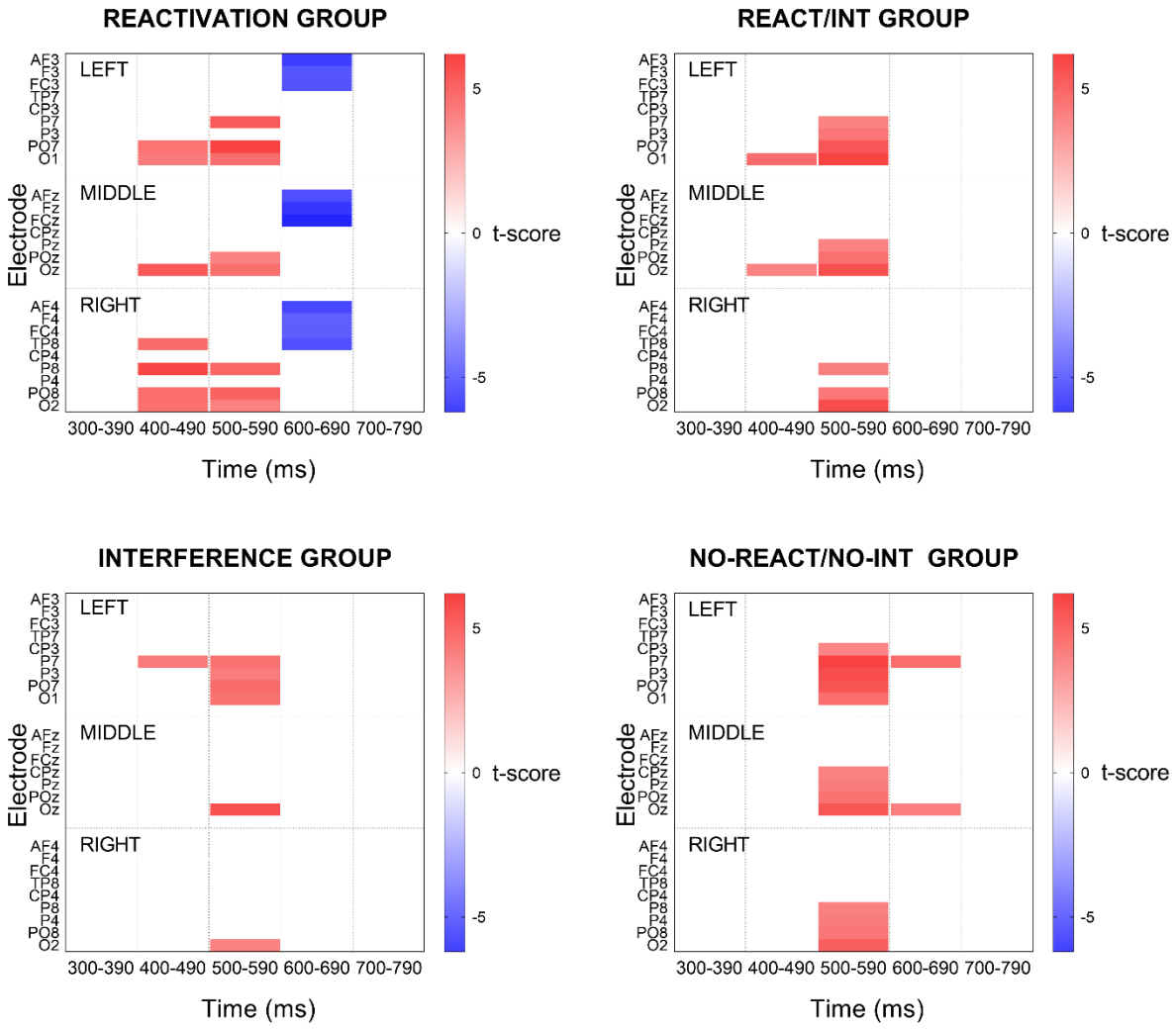

Figure 6. Raster diagrams illustrating the temporal-spatial distribution of the significant effects for each time-electrode bin, according to the tmax permutation test (in red, positive t values indicating positive differences, old>new; in blue, negative t values indicating negative differences, new>old).

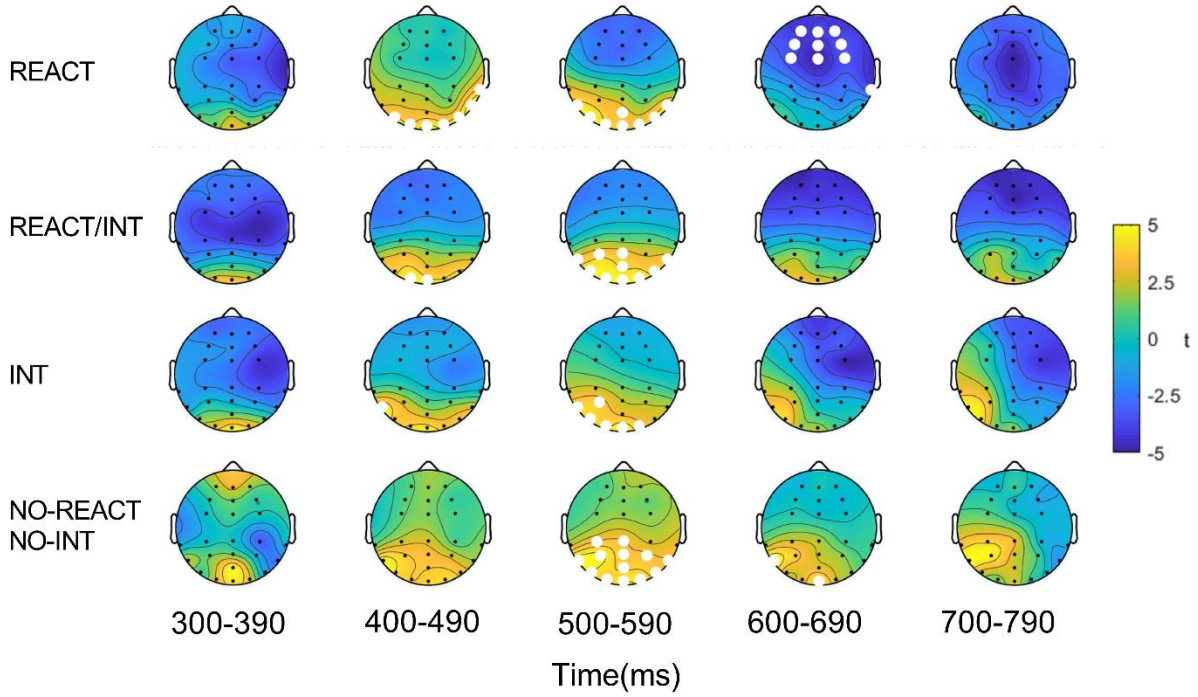

Figure 7. Topographical maps showing the scalp distributions of the significant differences (in white) between old and new responses (old responses with correct recall minus new responses) in five temporal windows (300-390, 400-490, 500-590, 600-690 and 700-790 ms), for each experimental group. Note that, in the case of the reactivation group (first row), a reversed old/new effect (new>old) was detected in the 600-690 ms time window.

6.2.2 Retrieval of reconsolidated memories showed an earlier peak latency of the parietal ERP old/new effect compared to retrieval of consolidated memories or memories whose reconsolidation process was disrupted (left parietal ROI). Moreover, retrieval of reconsolidated memories showed a smaller peak and mean amplitudes than retrieval of consolidated memories (left parietal ROI).

To evaluate group differences in the peak latency, peak amplitude and mean amplitude of the parietal old/new effect, differences scores (old minus new) were compared independently for left and right parietal ROIs. In the left parietal ROI (CP5, CP3, CP1, P5, P3, P1), significant differences between groups were observed in the peak latency (200-800 ms time window) (mean ± S.D., reactivation group: 447 ± 97.35; reactivation/interference group: 552.4 ± 126.7; interference group: 558.6 ± 78.64; no-reactivation/no-interference: 560 ± 127, one-way ANOVA, $F(3, 66) = 4.3$, $p=0.0076$). Specifically, the reactivation group showed an earlier peak latency of the parietal old/new effect compared to the reactivation/interference and the no-reactivation/no-interference groups ($p=0.0238$ and $p=0.015$, respectively, Bonferroni-corrected). Differences in the peak amplitude were also detected between groups in the left parietal ROI (mean μV ± S.D., reactivation group: 3.245 ± 2.163; reactivation/interference group: 3.589 ± 2.113; interference group: 4.847 ± 2.812; no-reactivation/no-interference: 5.576 ± 2.955, one-way ANOVA, $F(3, 66) = 3.2$, $p=0.0303$). Specifically, the reactivation group showed a smaller peak amplitude compared to the no-reactivation/no-interference group but no differences were observed between the reactivation and the reactivation/interference groups ($p=0.0451$ and $p>0.99$, respectively, Bonferroni-corrected). Significant differences were observed between groups in the mean amplitude (450-800 ms time window) (mean μV ± S.D., reactivation group:

0.1187 ± 1.49; reactivation/interference group: 0.6645 ± 1.986; interference group: 1.326 ± 2.419; no-reactivation/no-interference: 2.143 ± 2.364, one-way ANOVA, F (3, 66) = 2.951, p=0.0390). Specifically, the reactivation group showed a smaller mean amplitude of the parietal old/new effect compared to the no-reactivation/no-interference group in the left parietal ROI. No differences were detected between the reactivation and the reactivation/interference groups (p=0.0324 and p=0.8686, respectively, Bonferroni-corrected) (see Figure 8).

In the right parietal ROI (CP2, CP4, CP6, P2, P4, P6), no significant differences between groups were observed in the peak latency, peak amplitude and mean amplitude, although there was a trend towards significance in the peak amplitude (mean peak latency ± S.D., reactivation group: 458.6 ± 132; reactivation/interference group: 516.5 ± 112.9; interference group: 483 ± 139.5; no-reactivation/no-interference: 554.6 ± 118.3, one-way ANOVA, F (3, 66) = 1.868, p=0.1436; mean peak amplitude (μV) ± S.D., reactivation group: 3.153 ± 2.04; reactivation/interference group: 3.45 ± 1.996; interference group: 4.014 ± 2.572; no-reactivation/no-interference: 5.148 ± 2.691, one-way ANOVA, F (3, 66) = 2.4, p=0.0747; mean amplitude (μV) ± S.D., reactivation group: -0.5549 ± 1.778; reactivation/interference group: 0.4649 ± 2.05; interference group: 0.2301 ± 2.275; no-reactivation/no-interference: 1.215 ± 2.13, one-way ANOVA, F (3, 66) = 2.111, p=0.1073) (see Figure 8).

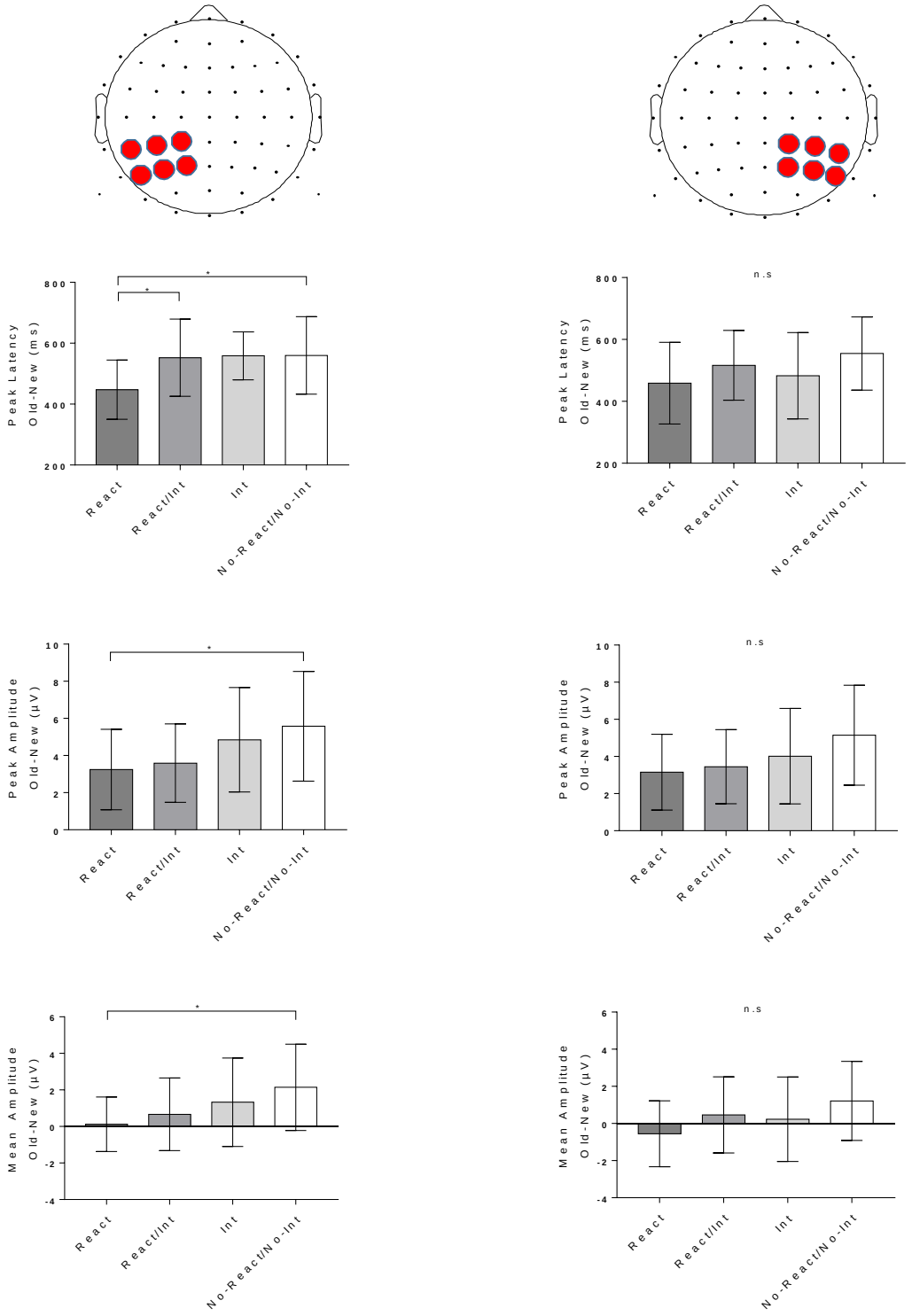

Figure 8. Peak latency, peak amplitude and mean amplitude of the parietal old/new effect (difference scores) for left and right ROIs (left ROI: CP5, CP3, CP1, P5, P3, P1; right ROI: CP6, CP4, CP2, P6, P4, P2), for each group. Error bars depict ± S.D. and asterisks indicate statistically significant differences for contrasts of interest (n.s: no significant; *: $p<0.05$).

6.3 Pupil size results

6.3.1 During retrieval, all groups showed a greater pupil dilation for correct old responses in comparison to correct new responses (pupil old/new effect). However, no group differences were detected in the magnitude of the effect.

Two-tailed independent t-tests showed that the maximal pupil dilation was greater for old than for new responses in all groups (mean ± S.D., reactivation group: old, 1.548 ± 0.3495, new, 1.121 ± 0.3967, $t=7.195$, $df=14$, $p<0.0001$; reactivation/interference group: old, 1.623 ± 0.3249, new, 1.083 ± 0.4037, $t=10.35$, $df=18$, $p<0.0001$; interference group: old, 1.446 ± 0.2832, new, 0.9737 ± 0.3395, $t=7.608$, $df=16$, $p<0.0001$; no-reactivation/no-interference group: old, 1.627 ± 0.3364, new, 1.105 ± 0.377, $t=8.759$, $df=16$, $p<0.0001$). Complementarily, two-tailed independent t-tests showed that the mean pupil diameter between 1500 and 2500 ms was greater for old than for new responses in all groups (mean ± S.D., reactivation group: old, 0.2496 ± 0.5591, new, -0.5368 ± 0.5902, $t=8.268$, $df=14$, $p<0.0001$; reactivation/interference group: old, 0.3836 ± 0.4293, new, -0.5105 ± 0.4949, $t=12.73$, $df=18$, $p<0.0001$; interference group: old, 0.0644 ± 0.4347, new, -0.7228 ± 0.4811, $t=8.646$, $df=16$, $p<0.0001$; no-reactivation/no-interference group: old, 0.33 ± 0.5031, new, -0.5717 ± 0.5174, $t=9.226$, $df=16$, $p<0.0001$) (see Figure 9). Finally, an independent permutation test for each group showed that the difference between old and new categories exceeded the critical t-value (old>new) in the 1000-1100 ms time window in the reactivation, interference and no-reactivation/no-interference groups and in the 700-800 ms time window in the reactivation/interference group (critical t-value, reactivation group: 1.8901; reactivation/interference group: 0.7571; interference: 1.5094; no-reactivation/no-interference: 1.7626, $p<0.01$). In all cases, the pupil old/new effect continued until the end of the 4000 ms epoch (see Figure 10).

To evaluate differences in the magnitude of the pupil old/new effect between groups, differences in the maximal and mean pupil dilation between old and new responses were directly compared between groups (see Pupil Recording and Analyses). No group differences were detected in the maximal and mean pupil diameter (mean ± S.D. for maximal pupil diameter, reactivation group: 0.4278 ± 0.2302; reactivation/interference group: 0.5392 ± 0.2272; interference group: 0.472 ± 0.2558; no-reactivation/no-interference: 0.5217 ± 0.2456, one-way ANOVA; $F(3, 64) = 0.7294$, $p=0.5382$); mean ± S.D. for mean pupil diameter, reactivation group: 0.7864 ± 0.3684; reactivation/interference group: 0.8941 ± 0.3061; interference group: 0.7872 ± 0.3754; no-reactivation/no-interference: 0.9017 ± 0.403, one-way ANOVA; $F(3, 64) = 0.5277$, $p=0.6648$).

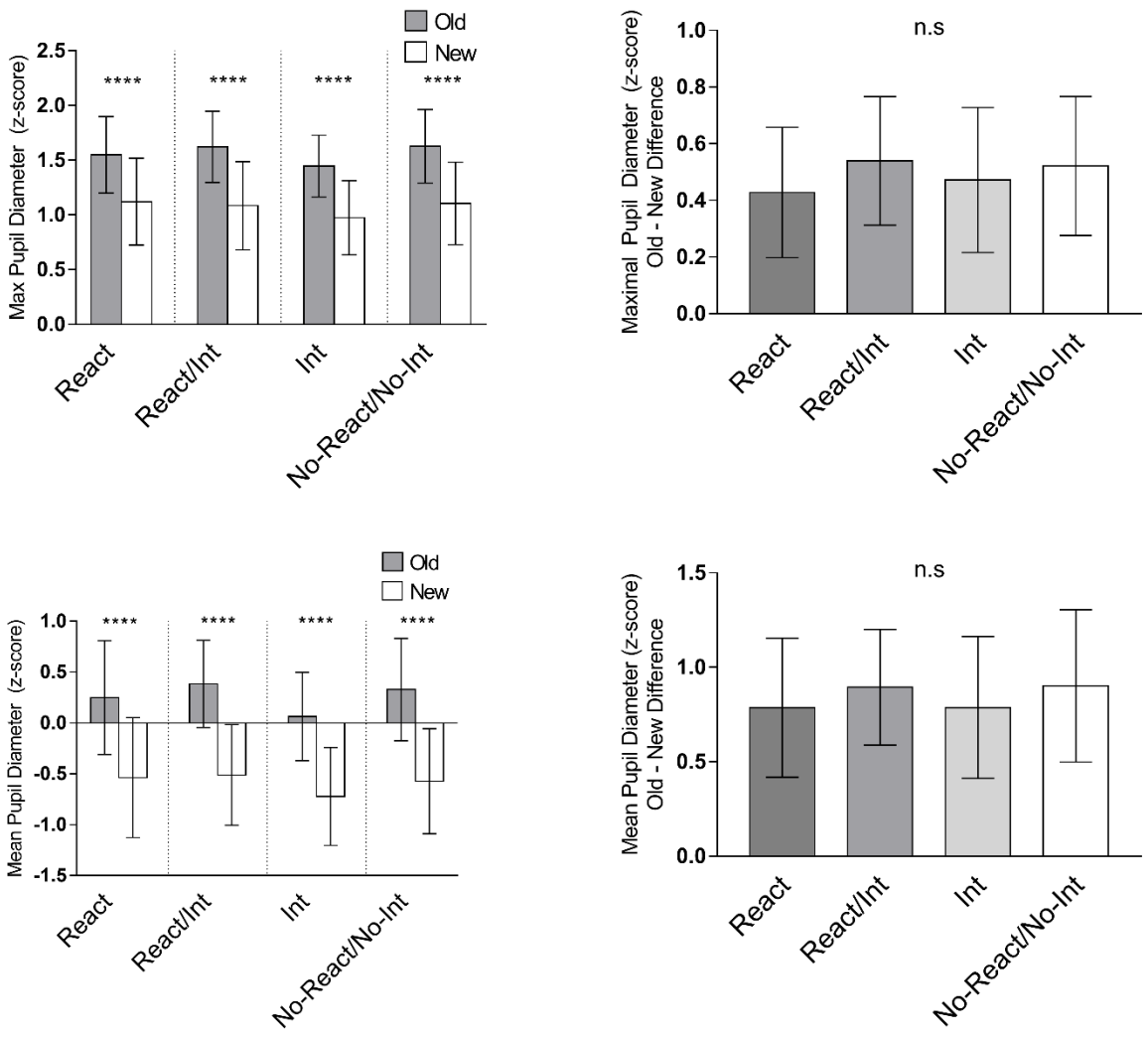

Figure 9. Left: maximal and mean pupil diameter (expressed in z-score) elicited by correct old and new responses, for each group. Right: maximal and mean pupil diameter old/new difference, for each group. Error bars depict ± S.D. and asterisks indicate statistically significant differences (n.s: no significant; ***: $p<0.001$, ****: $p<0.0001$).

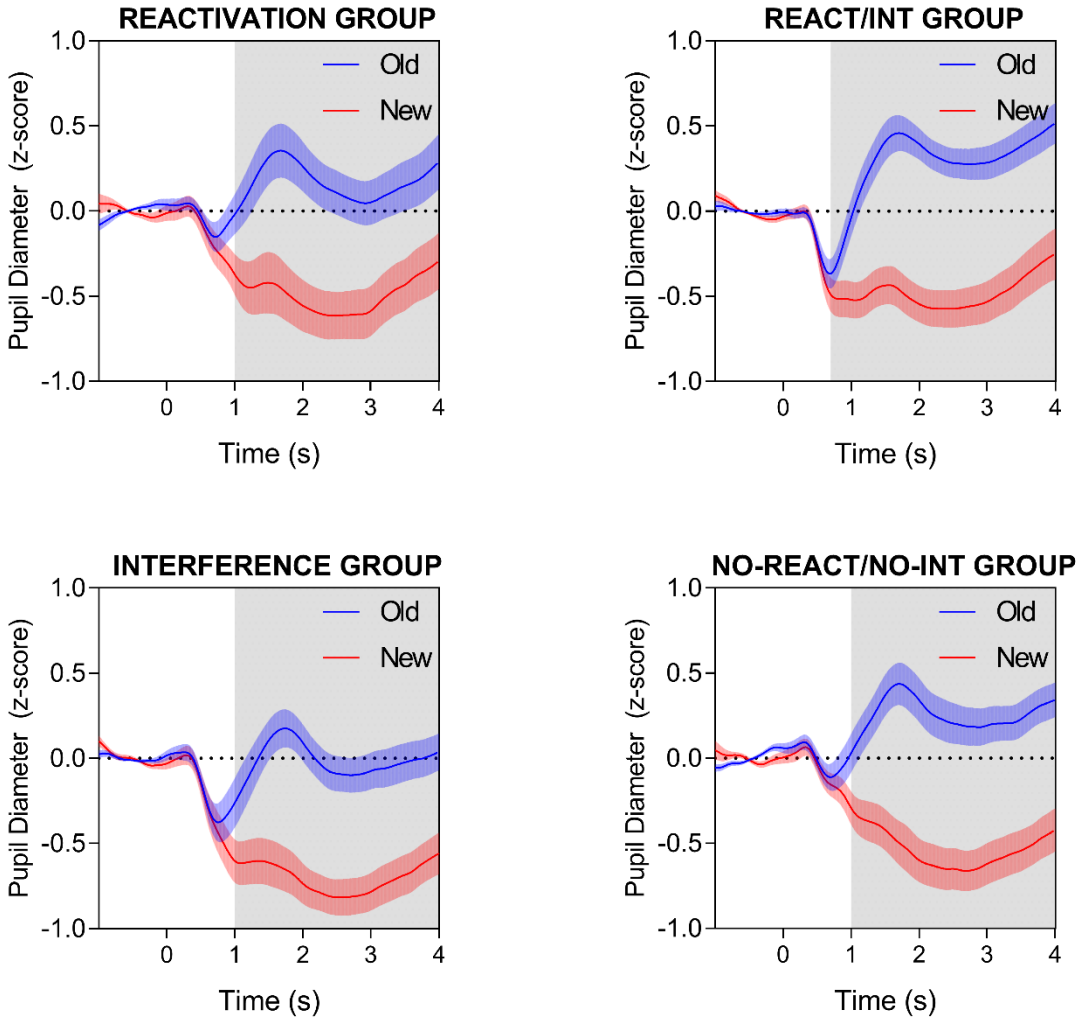

Figure 10. Pupil diameter elicited by correct answers (expressed in z-scores). In blue, the pupil diameter elicited by the correct classification of an old picture and the recall of the associated word. In red, the pupil diameter elicited by the correct classification of a new picture. The shaded area defines the temporal windows in which an independent permutation test detected positive significant differences between old and new categories in each group ($p<0.01$).

6.3.2 Retrieval of memories exposed to reactivation in session 2 showed an earlier peak latency compared to memories not exposed to reactivation.

Finally, a two-way ANOVA on the mean peak latency revealed a significant effect of reactivation ($F(1, 64) = 10.63$, $p=0.0018$). No main effect of interference and no interaction between reactivation and interference were detected ($F(1, 64) = 3.004$, $p=0.0879$; $F(1, 64) = 0.0006$, $p=0.9805$, respectively) (mean ± S.D., reactivation group: 1.7877 ± 0.9376; reactivation/interference group: 2.001 ± 0.9546; interference group: 2.4111 ± 1.1162; no-reactivation/no-interference: 2.1917 ± 1.021) (see Figure 11).

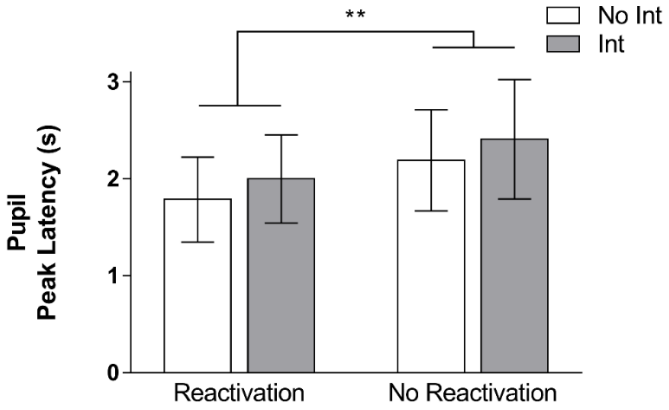

Figure 11. Latency of pupil old/new effect, for each group. On the left, groups that were exposed to memory reactivation during session 2 (reactivation and reactivation/interference groups). On the right, groups not exposed to memory reactivation (no-reactivation/no-interference and interference groups). A two-way ANOVA revealed a main effect of reactivation on the peak latency of the pupil old/new effect (**: $p<0.01$).

7. DISCUSSION

Reconsolidation refers to the process whereby a previously consolidated memory requires to be re-stabilized after its reactivation (Nader et al., 2000a). However, despite the behavioral and pharmacological evidence of reconsolidation in humans (Walker et al., 2003a; Forcato et al., 2007; Hupbach et al., 2007; Agren et al., 2012; Schwabe et al., 2012), little is actually known about the neurophysiological correlates of retrieval of reconsolidated memories.

The present study sought to identify the neural mechanisms underlying the retrieval of declarative memories modulated by reconsolidation. In order to accomplish this goal, ERPs and pupillary responses associated to retrieval of memories that were consolidated, reconsolidated or whose reconsolidation process was disrupted by a new learning, were measured in an associative recall old/new task. Our main hypothesis was that retrieval of successfully reconsolidated memories is associated with enhanced recollective processes. Operationally, our prediction was that retrieval of reconsolidated memories is associated with a larger and earlier ERP and pupil old/new effect. These modulations of neurophysiological markers of memory retrieval would be prevented in those memories whose reconsolidation process was interfered.

Based on the existing literature (Forcato et al., 2011; Forcato et al., 2014; Forcato et al., 2016), we predicted that the exposure to the reconsolidation process would improve memory performance. Moreover, we expected that the exposure to an amnesic agent would disrupt the re-stabilization

process of the reactivated memory, preventing the memory strengthening predicted for reconsolidated memories. In this context, our results confirmed our assumptions. In both ERP and pupil datasets of participants (see Table 2, Figure 3 and Figure 4), we found that the reactivation group performed better in the memory evaluation in session 3 compared to the reactivation/interference and the no-reactivation/no-interference groups, as was primarily expressed in a higher percentage of correct responses (correct recognition + recall of associated information) achieved by the reactivation group. This means that, of those items that were correctly recognized as old in the initial old/new judgment, the reactivation group could recall in a higher percentage the associated word. This result indicates that the exposure to the reconsolidation process enhances the access to the associated information, process related to recollection according to dual-process models (for details, see Background section) (Yonelinas and Levy, 2002). We also detected group differences in the recognition accuracy, showing the reactivation group a small but significantly difference in the percentage of recognition accuracy in comparison to the no-reactivation/no-interference group. In this context, these results indicate that reconsolidated memories were associated not only to a better recollection of associated information but also to a better recognition of pictures. Interestingly, no differences between the reactivation and the reactivation/interference groups were detected in recognition accuracy, indicating that the difference between these two groups was related only to recollection and not to recognition. In this sense, it is possible that the exposure to the reconsolidation process partially improved memories in the reactivation/interference group but not at the level reached by the reactivation group (as it can be seen as a trend in the behavioral results). Taken together, these results confirm previous evidence showing that an unpredictable reminder can trigger the labilization-reconsolidation process, which in turn can improve existing declarative memories (Forcato et al., 2014; Forcato et al., 2016). In this context, these findings support the idea that memory strengthening is one of the main roles of the

reconsolidation process (Lee, 2008; Forcato et al., 2011; Forcato et al., 2013; Exton-McGuinness et al., 2014; Forcato et al., 2014).

Our behavioral results also show that the post-reactivation behavioral interference partially prevented the memory improvement observed in the reactivation group, as was indicated by a lower percentage of correct responses in the reactivation/interference group compared to the reactivation group. The present result is in line with previous findings showing that behavioral interference, in the form of a new learning, can disrupt the reconsolidation of declarative memories (Walker et al., 2003a; Forcato et al., 2007; Hupbach et al., 2007; Forcato et al., 2013). One possible explanation for this effect is that, if new information is encoded after reactivation of an existing memory, the consolidation of the new material will temporally coincide with the reconsolidation of the previously reactivated memory, competing for limited resources and, as consequence, interfering the normal course of memory re-stabilization. Complementarily, as has been suggested in previous studies (Hupbach et al., 2007; Hupbach et al., 2009), it is possible that the original memory (items studied in session 1) is updated with the content of the interfering list (items studied in session 2). If this is the case, the new information is integrated into the first memory during the reconsolidation process. In our study, this could explain why participants of the reactivation/interference group showed a worse performance in the memory task in session 3. Contrary to the reactivation group (that was not exposed to interference), the reactivation/interference group probably had to manage more information during the memory task (i.e., accessing to a bigger pool of picture and words), negatively affecting its memory performance.

At an electrophysiological level, a positive parietal ERP old/new effect that peaked approximately 500 ms after the stimulus presentation was clearly evident in all the experimental groups (see Figure 5). This effect, traditionally known as “left parietal old/new effect”, is assumed to reflects recollective processes (see Background section for details) (Rugg et al., 1996; Donaldson and Rugg,

1999; Opitz and Cornell, 2006; Rugg and Curran, 2007; MacKenzie and Donaldson, 2009; Wilding and Evans, 2012). In this context, it can be suggested that retrieval of memories that were consolidated, reconsolidated or disrupted during reconsolidation share some neurophysiological mechanisms as was evidenced by the presence, in all the groups, of the left parietal old/new effect. In other words, we can assume that the left parietal old/new effect indexes memory retrieval regardless of whether the memory was previously modulated or not by reconsolidation. Our prediction was that, considering that the exposure to the reconsolidation process can strengthen declarative memories, retrieval of reconsolidated memories would be linked to modulations of the left parietal old/new effect reflecting enhanced recollective processes, such as an earlier and greater left parietal old/new effect. We also expected topographical group differences that could reflect distinct brain mechanisms underlying retrieval of consolidated and reconsolidated memories.

According to our assumption, the left parietal old/new effect was detected from the 400-500 ms time window in response to retrieval of memories that were reconsolidated, while memories that were just consolidated or disrupted during reconsolidation showed a left parietal old/new effect primarily starting from the 500-600 ms time window, as was evidenced by within-group permutation tests (see Figure 6 and 7). Concordant with this result, we found an earlier peak latency of the left parietal old/new effect (at 450 ms approximately) in reconsolidated memories in comparison to memories that were consolidated or whose reconsolidation process was interfered by a new learning (at 550 ms approximately) (see Figure 8). One possible explanation is that reconsolidation, allowing reactivated memories to be restructured and strengthened, facilitates memory accessibility for future recalls. Because, as it was mentioned previously, the left parietal old/new effect is considered an index of recollection (Wilding, 2000), it is possible that an earlier onset and peak latency associated to retrieval of reconsolidated memories reflects a more effective recollection process as a result of a

stronger memory trace. In consonance with this idea, previous studies have linked an earlier parietal old/new effect to an enhanced recollection. For instance, De Chastelaine et al., (2009), using a recognition memory task, demonstrated that improved memories as consequence of multiple study-test repetitions show an earlier parietally distributed old/new effect, suggesting an earlier recollection (De Chastelaine et al., 2009). Additionally, an earlier onset of the parietal old/new effect has been found when more details of items are retrieved or when the retrieved information is highly precise (Vilberg et al., 2006; Murray et al., 2015). In line with this idea, in our study it is possible that an earlier onset and peak of the left parietal old/new effect could reflect not only earlier but also enhanced retrieval processes that support the memory improvement observed in the behavioral results described above. More research is needed to validate the idea that an earlier onset and peak latency of the left parietal old/new effect reflect enhanced recollective processes as consequence of reconsolidation.

A second noteworthy finding was that the reactivation group, whose memories were successfully reconsolidated (and, as consequence, improved), was the only group that showed a significant reversed mid-frontal old/new effect following the parietal effect, in the 600-690 ms time window. Today, it is widely known that the prefrontal cortex plays a role not only in encoding but also in retrieval processes (Rudy, 2008). In general, it has been demonstrated that prefrontal cortex regions participate in retrieval of information stored in long-term memory (Dere et al., 2008; Eichenbaum, 2011; Byrne, 2017). Considering the topographical distribution and temporal course, we speculate that the observed effect is associated with control operations related to memory retrieval supported by the prefrontal cortex (Velanova et al., 2003). Specifically, it could be hypothesized that the reversed mid-frontal old/new effect reflects the neural activity associated to a possible retrieval inhibition after successful task completion by participants, making any later retrieval processing unnecessary. This interpretation agrees with previous studies about the reversed ERP old/new effect. Although the

functional role of this effect remains unclear, it has been discussed in the context of directed forgetting paradigms. For instance, Nowicka et al., (2009), observed a more negative going-effect in forgotten items that were initially instructed to be forgotten. The authors, based on these results, interpreted the reversed old/new effect as the neural correlate of an intentional and active inhibition of encoding, retrieval or both (Nowicka et al., 2009; Van Hooff et al., 2009). Therefore, it can be suggested that, in our case, this effect could reflect neural operations to prevent retrieval of additional information that is not necessary to complete the instructed task. An alternative explanation for this result is that the reversed mid-frontal old/new effect could be related to post-retrieval monitoring processes and evaluative operations over the retrieved information (Rugg et al., 1999; Rugg and Wilding, 2000). Future research will be needed to confirm or reject these interpretations.

A third ERP-result of interest concerns the smaller magnitude of the parietal old/new effect observed in the reactivation group compared to the no-reactivation/no-interference group. This result apparently contradicts our initial expectation that retrieval of reconsolidated memories would be associated to a larger magnitude of the left parietal old/new effect compared to retrieval of consolidated memories or disrupted memories during reconsolidation. Previous studies have demonstrated that the magnitude of the left parietal old/new effect is modulated by several factors. Specifically, in associative recall tasks, this effect is modulated by recall of associated information during retrieval (for more details, see the Background section) (Rugg et al., 1996). Unexpectedly, our results showed a smaller old/new effect associated to retrieval of strengthened memories by reconsolidation in comparison to retrieval of consolidated memories (and no differences between retrieval of memories that were reconsolidated and memories that were disrupted were detected). One possible explanation is that memory strengthening as consequence of the reconsolidation process minimizes retrieval demands, being necessary less neural resources to complete the task. In this context, a smaller parietal

old/new effect may partially reflect a decreased cognitive effort to mobilize resources in order to classify old and new items and recall associated information (Rugg and Wilding, 2000). Because the magnitude of the old/new effect was evaluated using fixed traditional ROIs, another possible interpretation is that the smaller magnitude of the parietal effect associated to reconsolidated memories is the final effect of topographical dissociations that may reflect distinct brain mechanisms underlying memory retrieval of consolidated and reconsolidated memories. Indeed, a more lateral and limited topographical distribution of the parietal old/new effect was observed in memories improved by reconsolidation (see Figure 7). Evidence from event-related fMRI studies have shown that the activation of the left parietal cortex during successful retrieval tend to become more ventral depending on a better memory quality, operationally expressed by more recollected information and a higher confidence related to retrieval (Cabeza et al., 2008). Crucially, it has been suggested the engagement of specific regions of the parietal cortex in memory retrieval depending on memory strength. In this context, the Attentional to Memory (AtoM) Model proposes that retrieval associated to a greater amount of information and a high confidence depends mainly on bottom-up attentional mechanisms supported by the ventral parietal cortex. In this case, retrieval of information is initially triggered by the medial temporal lobe, being primarily spontaneous, automatic, involuntary and effortless. In contrast, memory retrieval that involves a poor recovery of information, a low confidence and an effortful and conscious memory search seems to depend on top-down attentional processes supported by the dorsal parietal cortex (Cabeza, 2008; Cabeza et al., 2008). Considering this evidence, it is possible to suggest that the observed modulation in the magnitude and topography of the left parietal old/new effect in reconsolidated memories reflects distinct brain mechanisms supporting retrieval depending on memory strength.

In the same line, differences between the brain activity associated to retrieval of consolidated and reconsolidated memories were found in other electrophysiological markers, such as the oscillatory old/new effect (not included in the main text since it does not address the initial question of the current thesis. However, preliminary results are provided in the Annexes section). Specifically, retrieval of reconsolidated memories was associated to a theta old/new effect (400-700 ms), while retrieval of consolidated memories to a reversed alpha old/new effect (700-1100 ms). In the existing literature, the presence of a theta old/new effect has been linked, in general, to a better memory quality. For instance, studies have linked a theta old/new effect to the recollection process more than familiarity (Nyhus and Curran, 2010). Moreover, it has been observed in retrieval of improved memories in pictorial old/new tasks (Osipova et al., 2006) and in strengthened memories as consequence of repetition (Van Strien et al. 2007). In contrast, a reversed alpha old/new effect has been related to higher processing demands (Van Strien et al., 2007; Sebastian et al., 2011). In this context, differences in the oscillatory old/new effect, in our case, could reflect distinct brain mechanisms associated to retrieval of consolidated and reconsolidated memories. Although a more detailed discussion of the oscillatory old/new effect is beyond the scope of this work, these preliminary results support our assumption that retrieval of memories that were reconsolidated partially depends on specific mechanisms.

In summary, our electrophysiological results showed that reconsolidated memories elicit distinct pattern of brain activation during retrieval as compared to consolidated memories and memories whose reconsolidation process was disrupted by an amnesic agent.

Complementarily, a larger maximal pupil dilation associated to old as opposed to new responses were found in all the experimental groups (see Figure 9 and 10). Our results not only confirm the pupil old/new effect previously described in recognition tasks (Vo et al., 2008; Kafkas and Montaldi, 2015; Brocher and Graf, 2017), but also expand the previous findings in two critical aspects. First, the

pupil old/new effect, in our case, was found in an associative recall task that required participants not only to recognize items as old or new but also to consciously recall associated information. Second, to our knowledge, this is the first study that describes the pupil old/new effect in memories that were reconsolidated. Thus, these findings add new knowledge to the existing literature.

Although no differences between groups were detected in the maximal pupil dilation (see figure 9), our analyses showed an earlier peak latency of the pupil old/new effect in those groups that were exposed to memory reactivation in comparison to non-reactivated groups (see Figure 11). Because the pupil old/new has been associated to recollection (Vo et al., 2008), we suggest that an earlier peak latency of this effect could reflect earlier and presumably more efficient recollective processes in those groups that were exposed to memory reactivation and, subsequently, to the reconsolidation process. This explanation is closely in line with our previous suggestion that the observed modulation of the parietal old/new effect reflects enhanced recollective processes. Interestingly, despite the observed trend, no statistical differences in the peak latency elicited by retrieval of memories that were successfully reconsolidated and memories that were interfered during reconsolidation were found. One possible explanation is that the behavioral interference (new learning) did not fully prevent the memory improvement observed in the reactivation group and, therefore, an earlier peak latency of the pupil old/new effect is partially reflecting improved memories in both reactivated groups in comparison to non-reactivated groups. Finally, the lack of group differences in the maximal pupil dilation could be explained by the fact that we only considered correct old and new responses in our analyses. Therefore, because only successful trials were selected, it is possible that the similar magnitude of the pupil old/new effect between groups reflects brain mechanisms underlying successful recollection in all groups, not indexing retrieval of different amounts of information. If this was the case, the paradigm used here was not suitable to detect group differences in the magnitude of

the effect. In this context, more research is needed to investigate the pupil old/new effect in the retrieval of consolidated and reconsolidated memories in associative recall old/new paradigm.

In summary, our results show that memory reactivation by unpredictable reminders can trigger the reconsolidation process, improving declarative memories. At an electrophysiological level, the left parietal old/new effect showed an earlier peak latency and a smaller magnitude in retrieval of reconsolidated memories in comparison to retrieval of consolidated memories. Furthermore, a late reversed mid-frontal effect only was detected during retrieval of memories that were exposed to the labilization-reconsolidation process. Complementarily, memories that were exposed to the labilization-reconsolidation process had an earlier peak latency of the pupil old/new effect than memories that were not. Taken together, the neurophysiological activity (i.e., electrophysiological and pupillary) underlying retrieval of consolidated and reconsolidated memories partially differs. Although the brain mechanisms by which declarative memories are improved by reconsolidation and subsequently recalled remain poorly understood, we propose a general explanation based on the existing literature (see Background section for details). During the memory reactivation by unpredictable reminders, the left hippocampus is activated as consequence of an error prediction (a mismatch between what is expected and what actually occurs). This signal prepares the system to restructure the content or strength of a reactivated memory, triggering the labilization-reconsolidation process (Forcato et al., 2016). During the subsequent hours, the reactivated memory is strengthened by biological processes that involve cellular and system changes in critical areas and networks for encoding and retrieval of explicit memories, such as the medial temporal lobe (i.e., the hippocampus and the hippocampal-cortical network). After the process is complete, the neural circuits supporting the specific memory are enhanced at synaptic (i.e., increased synaptic efficacy) and system levels (i.e., large-scale reorganization of neural circuits). Because the re-stabilization process presumably depends on limited resources (e.g.,

protein synthesis), any additional process such as the encoding of new information can interfere with the normal course of the re-stabilization of the previously reactivated memory. Accordingly, if new content is added to the reactivated memory, the resources for the encoding and consolidation of the new memory will compete with the resources allocated for the reconsolidation of the reactivated memory. In this context, retrieval of improved memories by reconsolidation is facilitated and less demanding, probably depending more on the participation of the ventral parietal cortex that supports bottom-up attentional strategies (related to a better memory quality) than consolidated memories that lacked an opportunity to be reactivated and enhanced. In this last case, the retrieval is an effortful, slow and demanding process that requires a conscious and voluntary memory search mediated by top-down attentional strategies that are supported by the dorsal parietal cortex. On the other hand, retrieval of memories whose reconsolidation process was disrupted would show similar neurophysiological activation patterns than retrieval of consolidated memories, suggesting that the re-stabilization of reactivated memories could not be fully completed. We can suggest that, at least in our case, the slower and more effortful retrieval process observed in disrupted memories is not only a consequence of a weak memory trace as a result of the passage of time (as in consolidated memories that have been not exposure to reactivation) but also due to the additional effort to manage the original memory updated with new content. This is not the case when the original memory is not reactivated before the exposure to the new learning. In this latter scenario, we can assume that two independent memories are created. Future research will be needed to confirm the validity of this general explanation of our findings.

8. CONCLUSIONS

On this work, we have shown that the exposure to the reconsolidation process can have a strong impact on how memories are retrieved. Specifically, our results show distinct patterns of electrophysiological and pupillary activity associated to retrieval of memories that were consolidated, reconsolidated or whose reconsolidation was disrupted by an amnesic agent. Thus, our results suggest that partially distinct brain mechanisms support the retrieval of memories that were exposed to the reconsolidation process. We argued that these changes may be associated with more effective, efficient and earlier recollective processes.

Answering the question about how memory changes has crucial implications for the development of new treatments of memory disorders in which memories are pathologically weakened or exacerbated (such as Alzheimer's disease and Post-traumatic stress disorder). Furthermore, knowing the neural correlates of consolidated and reconsolidated memories can ease the creation of new diagnostic tools to evaluate memory in normal and pathological populations. Finally, a better understanding of the reconsolidation process could allow the implementation of novel pedagogical techniques to improve learning and memory in the educational field. In all, this thesis explores the mysterious process by which memories are kept together like a collage of experiences that we called identity, while fluidly evolving during the changing course of life.

9. ANNEXES

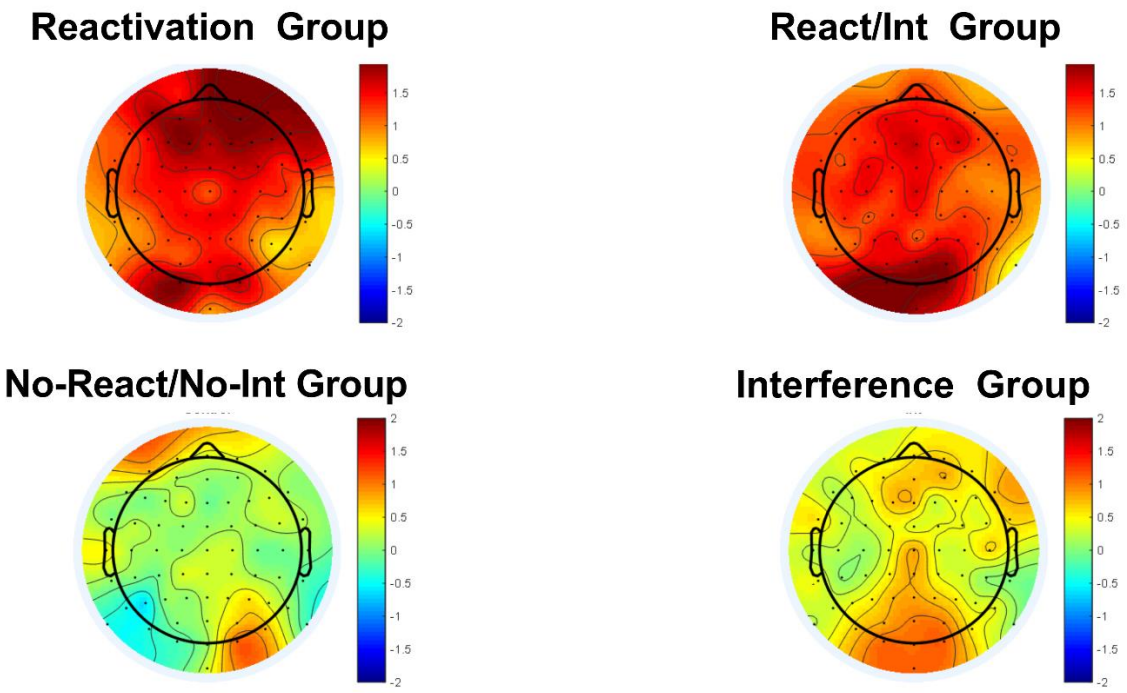

Figure 12. Topographic map of the difference in oscillatory power between correct old and new responses (oscillatory old/new effect) in theta frequency band (4-8 hz) in the time window of 400-700 ms following the stimulus onset (Preliminary results).

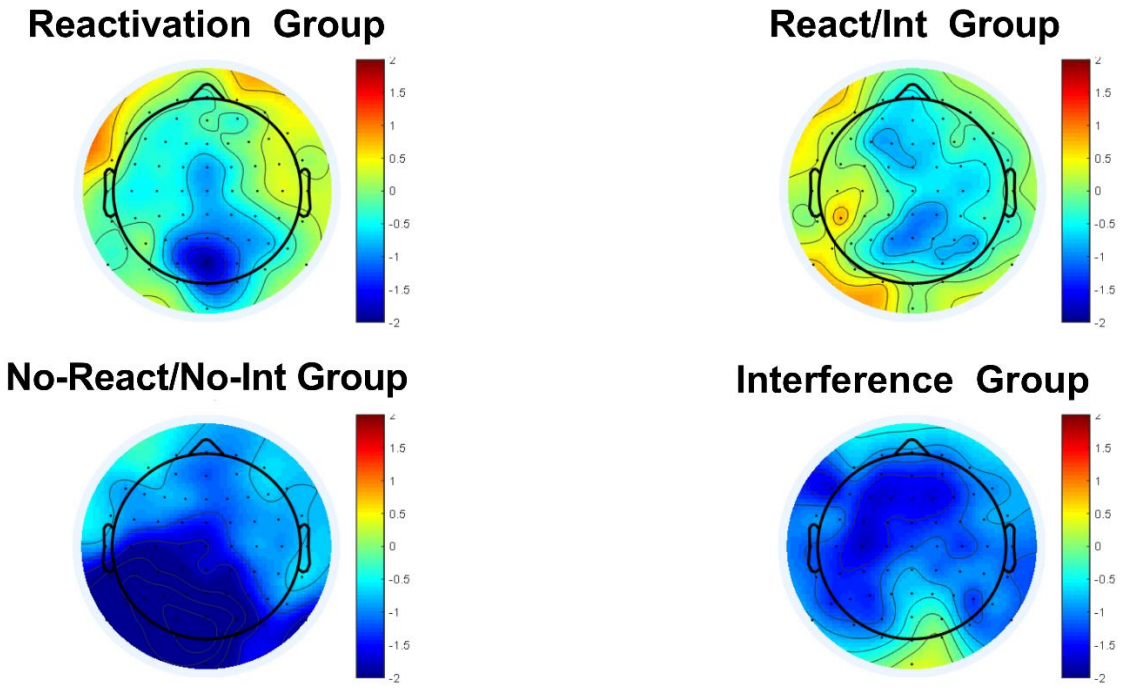

Figure 13. Topographic map of the difference in oscillatory power between correct old and new responses (oscillatory old/new effect) in alpha frequency band (8-12 hz) in the time window of 700-1100 ms following the stimulus onset (Preliminary results).

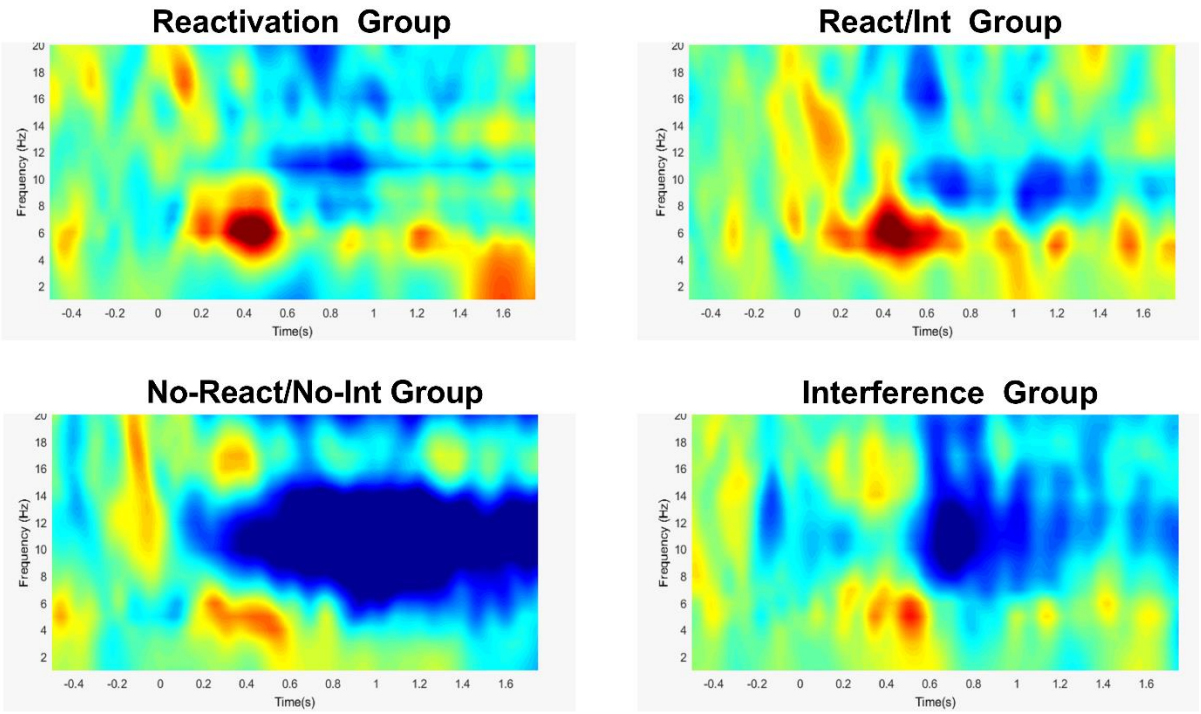

Figure 14. Averaged spectrograms of the difference in oscillatory power between correct old and new responses (oscillatory old/new effect), for a representative left parietal electrode (PO3) (Preliminary results).

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