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**The impact of selective attention on information maintenance
in visual short term memory: a neurofunctional investigation**

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Abstract

Two of the most important constructs of cognitive psychology are attention and memory. These are pillars of our cognition, allowing for the selection, encoding and storing of information in order to reach our goals. Attention and memory are nevertheless very broad concepts, both emerging from the interaction of different cognitive mechanisms. In the present work, emphasis has been placed on selective attention and visual short term memory as two main computational stages of information. Furthermore, selective attention both in the temporal and spatial domains was investigated with a special focus on how differently these domains impact the successful maintenance of visual information in short term memory. Close attention was paid to the neural activity underlying the processes mentioned above. Therefore, high-density electroencephalogram (HD-EEG) was used to provide an optimal compromise between temporal and spatial resolution. The first two chapters of this thesis provide a brief introduction of the concept of visual short term memory (VSTM) and selective attention. Next, the relationship between these two mental processes is examined by discussing some of the most relevant empirical studies on this topic. In the central chapters, it is presented new experimental evidence from two different studies. In the first study, the focus is on the effect of temporal orienting of attention (TO) on memory, targeting the encoding (Experiment 1a) and maintenance (Experiment 1b) of information as two distinct computational steps of VSTM. In the second study, it is further explored the neural patterns underlying the VSTM network identified in the first study, deepening the functional role and the relations of the relative nodes of this circuit with regard to the maintenance of visual information. The final part of the present work is dedicated to discussing the theoretical implication of the empirical

findings as well as to identifying new experimental routes to pursue with the aim of extending upon the presented results.

Chapter 1 – Theoretical background

1.1 A general overview of visual short-term memory

Visual short-term memory (VSTM) allows the storage and time-limited maintenance of visual information in the form of internal representations that persist beyond the original sensory input so that other cognitive processes can operate over the maintained information (Baddeley, 1992). In this regard, a relevant point is how a memory item or storage unit is defined. A first hypothesis could be that VSTM capacity might be limited over simple features such as color or line orientation. However, this hypothesis has been rejected based on the results of Luck & Vogel (1997), who showed that objects defined by a conjunction of multiple features are remembered as much as simple-feature objects. In the light of this evidence, it has been proposed that a memory item might be defined as a single unit chunk of multiple features (an integrated object) that relies on attention to bind features together (Duncan, 1984; Treisman & Gelade, 1980). A fundamental feature characterising VSTM is its limited capacity of seven items when studied with sequentially presented material (Miller, 1956), while for simultaneously presented stimuli, its capacity is limited to four items (Luck & Vogel, 1997; Cowan, 2010; Adam, Vogel, & Awh, 2017). Scientific literature presents two different models of the memory storage structure: one as discrete and the other as continuous. According to the ‘slot model’, a discrete model of memory storage, VSTM is able to store a number of representations in discrete slots, so that the resolution of the representation within each slot does not decrease as the memory load increases. On the other hand, the continuous model allocates resources in a way that the resolution of the storage of each memoranda (memory item) decreases as the overall load increases. While this model has potential merit in explaining why VSTM

capacity is reduced when more complex features need to be stored (Alvarez & Cavanagh, 2004), it nevertheless has not been supported in psychophysical measurements defined by mathematical models (Zhang & Luck, 2008). In fact, to better characterize the nature of the limited capacity both the number of elements and the resolution of the representation should be kept in the model and be considered as separate factors (Awh, Barton, & Vogel, 2014).

VSTM efficiency does not rely only on storage and information maintenance processes, but it is fundamental to take into account also the regulatory mechanisms operating on the gating and maintenance of task-relevant information. Moreover, considering the high capacity of early visual processes and the limited storage capacity of VSTM, most of the models theorized a critical role of selective attention (Duncan & Humphreys, 1989). Cowan (1995) proposed a theoretical model in which the contents of VSTM are ‘activated representations’ of the information within the long-term memory that are currently in the focus of attention. In this scenario, selective attention and VSTM has been maintained as being tightly related each other, as suggested by numerous studies (Nobre, 2001, Astle & Scerif, 2011; Murray, Nobre, Clark, Cravo, & Stokes, 2013). VSTM can be considered a multi-component rather than unitary process, separable into different steps as encoding, maintenance and retrieval of sensory inputs (Jolicoeur & Dell’Acqua, 1998). Selective attention interacts with VSTM throughout each of these steps (Gazzaley & Nobre, 2012). Before examining the specific mechanisms underlying the interaction between VSTM and selective attention, it is worthwhile to briefly introduce this function with reference to the computational components and neural networks that sustain it.

1.2 Selective attention and its neural signature

Attention can be defined in several ways, but one of the most common conceptual core definitions indicates that attention is the result of mental effort and selective processing (Posner & Boies, 1971). The ‘mental effort’ account comes from the assumption that the processing capacity of attention is limited (Kahneman, 1973). According to Kahneman’s model, attention limits are derived from biological constraints on the system to process multiple elements simultaneously. From this perspective, information are therefore processed sequentially through a sensory channel which blocks the processing of information exceeding the elaboration capacity (Kahneman, 1973). In a scene in daily life, there could be several elements of interest for broadcasting potential action. Besides considering the limits in the capacity to elaborate stimuli coming from different sources (divided attention), it might be very important to select a portion of the available information. In fact, object identification in the environment plays a fundamental adaptive role, specially for acting in a goal-directed manner. This process of selecting part of the information by enhancing the elaboration of the target and/or suppressing irrelevant information is traditionally defined as ‘selective attention’ (Johston and Dark, 1986).

The study of selective attention started with the research of Cherry (1953) about a phenomenon defined as the ‘cocktail party effect’, in which it is possible to be focused on a single conversation despite possible interference from surrounding conversations. Basically, the theoretical question is how the attentional system is able to select and analyze information (‘attended message’) coming from a specific source, filtering out any other distracting information (‘unattended message’). In studies investigating selective attention, two types of experimental paradigms have been generally used, namely ‘selective’ and ‘filtering’ paradigms. A classic example of a selective paradigm is the

visual search task, in which participants have to notify the absence or presence of a target among other stimuli (distractors). In contrast, filtering paradigms are based on rapid and sequential presentation of task relevant (to-be-identified) and irrelevant stimuli differing in some perceptual features. From a cognitive viewpoint, a relevant issue characterising selective attention investigation is related to the nature of the mechanism of selection. In fact, this can be conceived as an early computational step taking place before any other information processing or, by contrast, as a late computational step occurring after an initial amount of mental elaboration took place. Classic examples of early selection paradigms are the 'filter model of attention' (Broadbent, 1958) and the 'attenuation model' (Treisman, 1964). Broadbent's model proposes that the sensory system elaborates simultaneously all the perceptual features of the stimuli without any information selection. After this step, the information is transferred to the capacity-limited perceptual system where high-level processing (e.g., meaning extraction) is computed. In this framework, attention acts as a filter whose functional locus may operate at an early computational stage between the sensory and the perceptual systems, narrowing the amount of information that will be analysed by the latter. As a consequence, only attended stimuli will pass through the filter and reach the second stage of elaboration. By contrast, in Treisman's attenuation model, the attentional filter weakens any unattended information instead of completely filtering it out, explaining how sometimes unattended stimuli are processed. Thus, only stimuli exceeding a sensory threshold will undergo complete elaboration, while generally unattended stimuli lacking a sufficiently low threshold to be fully analysed will be processed at a perceptual rather than semantic level. Concerning the late selection theories, a classical model has been proposed by Deutsch and Deutsch (1963). Their model does not take into account the existence of a filter, since

it assumes that all the information is automatically processed. Selective attention is operating in the later stage controlling the access of the information to working memory. In order to select an item of information, attention should be oriented toward the target locus, allowing the target to be detected.

Besides these pioneering attentional models, in the following years new theoretical accounts of attention have been suggested. Among these, the mechanism of attentional orienting has been defined by Posner (1980) as the aligning of attention to an external sensory input or an internal structure stored in memory. On the other hand, the detection of the stimulus was considered by Posner (1980) as being aware or conscious of a stimulus. In this model, stimulus detection occurs when a sensory signal has reached a level of neural activation allowing the subject to consciously report its presence. In this light, attentional orienting and detection can be conceived as two independent but interactive processes. Posner (1980) further showed that previous knowledge about where in space a stimulus will occur affects the behavioural performance. Experimentally, this has been demonstrated by providing participants with a cue signaling information about the future locus of target presentation (i.e., right or left). The validity of this predictive information allows faster detection responses, compared to a neutral cue.

Another crucial aspect of attentional orienting is that it can be guided by either top-down (endogenous) or bottom-up (exogenous) processes (Posner, 1990). These two different predictive modalities seem to be both separable and interacting at the neural level. In their famous review, Corbetta & Shulman (2002) presented evidence of two distinct and functionally connected neural networks, one for top-down selection and the other for stimulus-driven orienting.

The goal-directed stimulus network, known as the ‘dorsal frontoparietal network’, is more related to activity in parietal cortices including the intraparietal sulcus (IPS) and the inferior parietal lobule, together with the frontal area, and more expressed in the frontal eye fields (FEF). The second system, mainly lateralized to the right hemisphere, is more related to stimulus-driven attentional orienting that acts as an alerting system. When a behaviourally-relevant stimulus appears outside the participant’s attentional focus, the dorsal frontoparietal stream is interrupted in order to shift the attentional focus toward the goal-relevant spatial localization where the stimulus actually appeared. The network related to this function includes the temporalparietal junction (TPJ) and the ventral frontal cortex (VFC), also known as two nodes of the right ventral frontoparietal network. Although these two networks are engaged in different cognitive processes, they have been proposed to interact and work in conjunction. One possibility is that the alerting system (ventral frontoparietal) detects behaviourally-relevant stimuli in the environment but is equipped with a high resolution spatial location. Once the stimulus is detected, its localization in space depends on the IPS-FEF network. Another hypothesis is that the attentional ventral network works as circuit breaker of current attentional set in the dorsal network, when a relevant stimulus is detected.

Since initial investigations, scientific knowledge regarding the cognitive and neural mechanisms of selective attention and spatial orienting has grown substantially. From a functional perspective, it is possible to infer that one of the main functions of attentional orienting is to prioritize relevant stimuli that may require an action to regulate our behaviour proactively (Nobre, 2001). This implies the existence of a pool of feedforward regulatory processes operating to efficiently mobilize and allocate cognitive and motor resources for stimuli elaboration and action implementation. Analogous to spatial

orienting, it might be assumed that in order to extract relevant information from the environment, it is evolutionarily fundamental to orienting resources also in the temporal dimension. The orienting of attention in time has been defined as temporal orienting (TO) (Coull & Nobre, 1998). In the next section the neurocognitive mechanisms of the temporal orienting will be introduced.

1.3 Selective attention in the time domain: Temporal orienting

Every day we are surrounded by a multitude of sensory stimuli that occur in a spatially distributed and temporally dynamic world. As mentioned previously, the process of selective attention allows the limited resources of the cognitive system to filter out any irrelevant information, focusing only on the task-relevant information. However, selective attention is not limited to the *hic et nunc* of cognition, simply selecting relevant information ‘on-line’ from one moment to the next. Rather, it can be cast into the future. This capability allows the cognitive system to build up an expectation of when a stimulus will appear. The functional consequence of the possibility to generate expectancy is to allow attentional resources to be directed with anticipation not only in space but also in the temporal window when a particular stimulus is most likely to appear. The mechanism at the basis of this attentional phenomenon is the human capacity to establish temporal expectancy for future events on the basis of environmentally available information. This includes either exogenous or endogenous sources of predictability. In their pioneering study, Niemi and Näätänen (1981) showed that by simply keeping constant, or at least predictable, the interval between a warning and a target stimuli (also known as the ‘foreperiod’ interval) across trials, it was possible to establish an exogenous temporal

expectancy, resulting in an increase of the response speed at the target onset. The following studies further showed that temporal expectancy is also established by endogenous mechanisms. This was first showed by Coull & Nobre (1998), who adapted the famous spatial cueing task by Posner (1980) for investigating the top-down modulatory effects (and the relative neural bases) of temporal orienting on target detection. The hypothesis driving this study was that people could be explicitly cued to direct their attention over discrete temporal intervals to enhance motor preparation. To this purpose, they used a symbolic, informative cue predicting the temporal onset of the target, which could appear after a short (300 ms) or long (1500 ms) interval from it. Additionally, the target could appear in the right or left hemifield. The results showed that participants had a behavioural benefit, expressed as faster target detection for valid rather than invalid trials, for both the spatial and temporal dimensions. Interestingly, the validity cost (i.e., the difference between valid vs. invalid trials) was smaller for long than short trials. This asymmetrical effect for the temporal dimension was never observed for spatial orienting, providing a new challenge for researcher to investigate. The general interpretation of this asymmetry is that the conditional probability of target onset as a function of time elapsing provides an additional prediction source about the timing of target onset. If the target does not occur at the shortest foreperiod, the probability that it will be delivered in the next useful interval increases over time. Thus, the *a priori* expectancy endogenously generated on the basis of the cue progressively vanishes as the foreperiod interval elapses (Coull, Frith, Büchel, & Nobre, 2000; Griffin, Miniussi & Nobre, 2001). In sum, whatever the exact nature of the mechanisms underlying TO, there is consensus that this phenomenon is based on the complex interaction of distinct sources

of expectation that may nevertheless operate in a similar although non-identical fashion that spatial orienting of attention.

Besides the understanding of the computational machinery underlying TO, in recent decades it has consistently been shown that TO can operate at multiple cognitive levels. In this regard, behavioural experiments using perceptually demanding tasks demonstrated that the effect of TO is not limited to biasing motor preparation but rather can be extended to other functions such as perceptual processing. When perceptually demanding tasks are used, such as a 'feature detection' task involving spatial uncertainty (Griffin et al., 2001), or a discrimination task involving object uncertainty (Lange et al., 2003; Correa, Lupiáñez, Madrid, & Tudela, 2006), the effects of temporal attention are also observed at the perceptual level. Taken together, the present results suggest that temporal orienting enhances the speed of target detection by facilitating both stimuli perception and motor preparation for predictable compared to unpredictable stimuli.

The complex nature of TO has been further demonstrated by experimentally manipulating the cognitive load concurrently with an ongoing orienting task. Capizzi and colleagues (Capizzi, Sanabria & Correa, 2012, Capizzi, Correa & Sanabria, 2013) exploited a dual task paradigm to demonstrate that the exogenous TO effects survive the presence of an additional working memory task, while endogenously driven TO did not survive this interference. Moreover, the benefit of endogenously driven TO was reduced as a function of the competition for executive resources required by both working memory and temporal preparation tasks. These findings provide robust experimental evidence showing that TO is based upon both automatic and voluntary mechanisms, which can nevertheless interfere with each other. As an additional index of the complexity of the relationship between TO and cognitive control, Correa and colleagues (2010) found that explicit

temporal cues facilitate the resolution of perceptual conflict by reducing the spatial Stroop effect but reduce behavioural performance in the Simon and flanker tasks. These findings suggest that the impact of TO on executive control depends on where the conflict is located, that is, whether at the stimulus or at the response selection stage (Correa, Triviño, Pérez-Dueñas, Acosta, & Lupiáñez, 2010). Taken together, the current evidence suggests that TO is a complex and multi-component attentional phenomenon, depending on the time interval length, the recruitment of exogenous or endogenous mechanisms, the type of the task and the presence of interference coming from other cognitive processes sharing system resources. To shed light on the functional mechanisms underlying TO, research over the past twenty years has sought to use neuroimaging techniques to unveil the neural correlates of this complex attentional phenomenon. In particular, the study of event-related electrophysiological (ERP) activity has provided a useful tool to depict the timing of the cognitive mechanisms of TO. Several of these studies will be described in the following paragraph.

1.3.1 Neural mechanisms of temporal orienting

The first ERP study investigating the timing of brain activity underlying the orienting of attention in time was carried out by Miniussi and colleagues (Miniussi, Wilding, Coull & Nobre, 1999). They adapted the same experimental task previously employed by Coull and Nobre (1998) to elicit specific markers of both anticipatory activity induced by temporal expectation as well as post-target activity. Relative to the first aim, the contingent negative variation (CNV) was indicated as a reliable index of anticipation. The CNV was first identified by Walter and colleagues (1964) as a negative variation arising

between a first warning stimulus and a second imperative stimulus. In their seminal paper, Walter et al. (1964) examined the dependence of the CNV on the contingency between the two stimuli. By assessing the CNV, Miniussi and colleagues (Miniussi et al., 1999) showed that the expectation of the target onset after a cue predicting short rather than long intervals induced a larger CNV amplitude over the central electrodes. Moreover, they observed that the spatial distribution of the CNV shifted from the posterior electrodes to the central ones. This spatial effect was interpreted to suggest an early engagement of the posterior regions in the endogenous generation of temporal expectancy. Additionally, the anterior shift was potentially related to motor preparation following the initial attentional orienting. Importantly, the anatomical source of this CNV modulation was localized to the supplementary motor area (SMA) (Nobre, 2001), a region also linked to motor preparation as well as timing (Macar, Vidal, & Casini, 1999; Macar, Coull, & Vidal, 2006; Mento, 2013). These results suggest that TO speeds up the behaviour response by both orienting attention and biasing the preparation of a motor response at the expected time. These findings were further corroborated by additional studies (Griffin et al., 2002).

The importance of the CNV as a marker of TO is demonstrated by the fact that it has been shown to be sensitive not only to subjective expectation induced by symbolic cues but also that it is modulated by implicit expectation. An experimental phenomenon that well-describes this is sequential effects (SEs). SEs are adjustments in participants' behavioral performance as a function of sequential changes (i.e., trial-by-trial) in the temporal structure of a repetitive stream of events, such as the foreperiod (FP) interval between successive stimuli delivered in a trial. In the experimental context of the variable FP paradigm, SEs refers to the fact that the reaction time (RT) to an imperative stimulus depends not only on the current FP (FP_n) but also on the FP of the immediately preceding

trial (FP_{n-1}). For example, a short FP_{n-1} will lead to the automatic prediction of a short waiting time in the following FP_n trial, resulting in a clear behavioral advantage (i.e., RT decreasing). Analogously, the CNV amplitude in a short foreperiod at the n-th trial is higher when the n-1 trial presents a short interval (Los & Heslenfeld, 2005). These findings that both temporal cueing and SE modulate CNV amplitude suggest a possibility of a shared basis for endogenous and exogenous forms of temporal expectancy. However, the fact that an informative cue did not override the influence of sequential effects on CNV may suggest that exogenous and endogenous processes are independent. However, the experimental evidence regarding the dissociation or the interaction of brain areas between exogenous and endogenous TO are not so neat. As originally shown by Coull & Nobre (1998), the TO elicited on an endogenous basis produces parietal activity preferentially lateralized in the left hemisphere, together with the left ventral premotor cortex (vPMC). On the other hand, the bottom-up exogenous TO effects are accompanied by an increase in activation of the visual cortex. Critically, Mento (2017) was the first to target the activity at cue presentation, reporting electrophysiological evidence that voluntary (i.e., endogenous) and automatic (i.e., exogenous) TO are two dissociable processes that can be distinguished already at the expectancy generation stage. Specifically, his results indicated that the P3a and P3b ERP components, elicited at the cue onset, are two distinct ERP markers exhibiting different spatiotemporal features and reflecting automatic and voluntarily-driven TO, respectively. Source reconstruction of these two distinct potentials highlighted two separate underlying networks. Notably, the voluntary P3b was supported by a left sensorimotor network, while the automatic P3a was generated by a more distributed frontoparietal circuit. Remarkably, the neural patterns reported in this study overlapped previous fMRI neuroimaging evidence (Coull

et al., 2000). Moreover, Mento (2017) reported the presence of an automatic CNV modulation in both cued and uncued blocks. This suggests that the capacity to implement expectancy in time itself does not depend on the voluntary or automatic nature of attentional mechanisms engaged by the task. In other words, both endogenous (i.e., cue validity) and exogenous (i.e., sequential effects) can similarly affect motor preparation toward impending stimuli, although these two cognitive mechanisms seem to engage separate networks. This different pattern may indicate that the implementation of temporal expectancy into motor preparation may be subserved by different cortical circuits based on the voluntary or automatic nature of this process.

In addition to unravelling the timing of the anticipatory mechanisms of TO, the ERP investigation shed light on the effect of TO on the processing of task-relevant stimuli. In this regard, an important question is whether the behavioural benefit conferred by TO is due to an early or late functional effect. In the first case it is assumed that TO may operate by biasing perceptual acuity so that stimuli presented at the predicted moment will be better computed, which may possibly result in a cascade of later computational effects. By contrast, it may be assumed that the functional locus of TO takes place at a later stage, affecting response preparation, selection and/or execution. To disentangle the timing of TO effects, Miniussi et al. (1999) showed that TO decreases the amplitude of the N2 at target onset while increasing the amplitude of the P3, causing it to peak earlier for predicted rather than unpredicted stimuli. A possible interpretation is that the N2 reduction is related to response inhibition, while the effect on the P3 potential is possibly due to a modulation of decision-making and response preparation processes. Notably, no early effects on the P1 component were found. Accordingly, the authors proposed that the TO operates at a late computational stage. However, subsequent studies clearly

showed that, by using perceptually demanding tasks, TO is able to act on early components of a visual evoked potential, increasing the amplitude of the N1 (Griffin et al., 2002; Correa & Nobre, 2008). These findings demonstrate that TO is a complex mechanism which may influence both early (i.e., stimulus perception) and late (i.e., response preparation) processes according to task demand.

To sum up, the evidence presented here suggests a complex picture of the nature of the processes of TO, which only partially shares common features with spatial orienting. To better understand the complexity of TO, it should be inserted into a larger theoretical framework. In fact, the capability to anticipate events in time should not be limited to an increase in the stimulus elaboration speed. At the most basic level, the possibility to anticipate the occurrence of events can be translated into the opportunity to optimize allocation of cognitive resources to stimulus elaboration, for example, by implementing a strategy. Notably, the strategy implemented may depend on the salience or the *a priori* knowledge of the expected stimuli. Therefore, the TO can be conceptualized as the ability of the cognitive system to integrate both internal and external sources of temporal predictability to maximize the success of the behavioural outcome. As a consequence, this function may interact with both low- and high-level cognitive processes, improving the efficiency of the information encoding and maintenance over time. However, while the interaction between TO and motor or perceptual processes have been relatively well elucidated, few studies have investigated the interplay between TO and memory processes. Nevertheless, this topic is highly relevant for cognitive psychology and neuroscience. In the following chapter the relationship between selective attention and memory will be examined.

1.4 The functional mechanisms of selective attention on early perceptual processes

As described above, early investigation into selective attention focused on identifying the specific stage of information processing that attentional orienting acted upon—that is, understanding the functional locus of selective attention. An initial hypothesis theorized in the ‘early selection’ model (Broadbent, 1957) proposed that selective attention acts at an early processing stage, filtering out irrelevant sensory information prior to identification and encoding of the stimulus. By contrast, late-selection models (Deutsch and Deutsch, 1963) suggested that all the sensory information was encoded, but selective attention acts as a filter allowing only a portion of the sensory information access to successive stages of elaboration. These two seminal models have originally heavily influenced the scientific investigation of attention, but currently it is clear that this dichotomy is an oversimplification of more complex phenomena. It is evident now that selective attention operates both at early and late stages of processing. Van Voorhis & Hillyard (1977) provided one of the first indications of selective attention in early processing, showing that event-related potentials (ERPs) coming from visual cortex were amplified for attentionally attended visual stimuli at around 100 ms from stimulus onset. Single-unit recording studies in primates provided additional critical information, broadening the understanding of how attention impacts visual neuron responses. When attention is directed to a location inside the receptive fields (RFs), the neuron’s contrast-response threshold is reduced, enabling a response to stimuli that would have not elicited neural activation, allowing possible stimulus encoding. For stimuli presented at contrast levels that exceed the neuron’s threshold for saturation, attention has little or no effect on the neuronal firing rate. However, attention has different effects when it is directed to one

of two stimuli appearing simultaneously inside the receptive field. Both increases and decreases in firing rates are observed, depending on the neuron's selectivity for the two stimuli (Reynolds & Chelazzi, 2004). Attentional-dependent modulation of sensory processes is not an intrinsic characteristic of the visual cortex but occurs as a result of long-range connections from other areas, specifically regions subtending to the cognitive control as the prefrontal cortex (PFC) (Curtis & D'Esposito, 2003) and the lateral intraparietal (LIP) area (Reynolds & Chelazzi, 2004).

These findings support the account that attention enhances sensory stimuli elaboration in a top-down manner. Nevertheless, some critical questions still remain unaddressed. Among these, does the enhancement of early sensory processes influence information encoding and consequent VSTM performance? Several pioneering experimental tasks designed to investigate the relationship between spatial selective attention and memory provided some important answers to this question. The most well-known task is the cue report or partial report task (Sperling, 1960). In this task, a visuospatial cue can precede (pre-cues) or follow (retro-cue) a complex array of items to be encoded and stored in VSTM. Several studies adopting this paradigm have shown that selective attention oriented proactively or retroactively is able to influence what information will be encoded and stored in. Specifically, the spatial information vehiculated by the pre-cue allows prioritization of a portion of the available sensory information by a feedforward mechanism while retro-cues operate by facilitating the retrieval of a portion of the information representation temporally available in memory via a retroactive mechanism (Dell'Acqua, Sessa, Toffanin, Luria, & Jolicœur, 2010; Kuo et al., 2012; Lepsien, Thornton, & Nobre, 2011, Murray, Nobre, & Stokes, 2011, Lepsien et al., 2011; Shimi, Nobre, Astle, & Scerif, 2014; Shimi & Scerif, 2017)

A functional investigation of the effect of selective attention on VSTM has been carried out in neuroimaging studies. In this regard, fMRI studies investigating the role of top-down modulation of selective attention on VSTM encoding provided consistent evidence for a crucial role of the PFC both in processing relevant stimuli and in filtering out distractors (Gazzaley & Nobre, 2012). Functional connectivity studies further showed that a specific region within the PFC, namely the left middle frontal gyrus (l-MFG), showed higher coactivation with posterior brain areas devoted to visual processing when the stimuli were remembered relative to when the stimuli were ignored during the encoding phase of a delayed-response task (Gazzaley et al., 2007). Remarkably, the strength of this connectivity correlated with the magnitude of attentional enhancement for relevant stimuli, corroborating a previously-hypothesized role for brain regions that subserve cognitive control in the up- or down-regulation of visual cortex areas. Interestingly, another study revealed that visual cortices processing relevant information were functionally connected with prefrontal (MFG, inferior frontal junction (IFJ)) and parietal (intraparietal sulcus) areas, while visual areas were connected with the ‘default network’ while processing irrelevant stimuli (Chadick & Gazzaley, 2011). These studies identified a crucial functional locus for the selective attention modulation of VSTM maintenance, raising ‘*the possibility that limitations in attentional allocation by the PFC may serve as a limiting factor in the amount of information we can encode*’ (Gazzaley & Nobre, 2012, pp.131). Finally, to demonstrate a causal role for PFC top-down attentional effects in VSTM, a study used repetitive transcranial magnetic stimulation (rTMS) over the right IFJ, showing both a reduction of the P1 ERP component and a reduction of memory performance (Zanto, Rubens, Thangavel, & Gazzaley, 2011). Taken together, this evidence emphasizes the PFC-mediated role of top-down attentional modulation in

the early information processing stage in VSTM encoding, relating it with memory performance.

1.5 Selective attention and VSTM maintenance

As demonstrated above, previous literature has shown that top-down modulation of selective attention may bias stimuli encoding into VSTM improving the memory performance. This further suggests that selective attention may also operate at later VSTM stages, such as the maintenance of information over time. An fMRI functional connectivity study showed that maintenance of items in VSTM involves the interaction between perceptual (occipito-parietal cortex) and control areas (PFC) (Gazzaley et al., 2007). Specifically, the occipito-parietal areas may be selectively engaged in the encoding of the relevant attributes of the stimulus while the latter may play an attention-directing role during the retention period. Neural findings also suggest that top-down modulation effects during VSTM maintenance are similar to those occurring during perception and encoding, but they also engage additional regulatory functions. For example, the activity of visual areas coding relevant versus irrelevant items are dynamically modulated by retro-cues directing attention to a given category of objects (Lepsien & Nobre, 2007). A similar activation pattern is also observed when asking participants to think back to a previously viewed item (Johnson, Mitchell, Raye, Esposito, & Johnson, 2007). Spatial retro-cues can also result in retinotopically specific modulation of visual activity during memory maintenance, in line with the hypothesis that attention in VSTM maintenance operates by refreshing the information representation in the current attentional focus during the retention (Sligte, Scholte, & Lamme, 2009).

The dorsolateral PFC (DLPFC) has been identified as one of the most probable area subtending the top-down modulation of attention during VSTM maintenance by Feredoes and colleagues (Feredoes, Heinen, Weiskopf, Ruff, & Driver, 2011). In their TMS-fMRI study, Feredoes and colleagues showed that DLPFC activity increased during retention in VSTM when distractors were presented. Thus, in this context DLPFC activation is an index of cognitive control preventing the detrimental effect of distractors on performance. Crucially, inhibition of DLPFC by TMS resulted in increased activation of posterior sensory brain areas when distractors were present.

These results provide strong evidence for the feedforward role of cognitive control on information storage, expressed by the influence of DLPFC over posterior target-representing regions. This role may consist of filtering out possible detrimental effects of distractors during VSTM maintenance, protecting task-relevant information.

Furthermore, selective attention is able to optimize VSTM maintenance by reducing the cognitive load through narrowing the representation of the information to-be-maintained. Electrophysiological evidence regarding this phenomena has been provided by Kuo et al. (2012), who demonstrated modulation of the contralateral delay activity (CDA). The CDA is a memory load sensitive ERP whose amplitude increases in relation to memory load augmentation and is associated with VSTM maintenance (Vogel & Machizawa, 2004). Kuo and colleagues observed that retro-cue-driven orienting to a part of the memory trace was associated with a reduction in the CDA amplitude, as an evidence of the attention-mediated reduction in the memory load (Kuo et al. 2012). The retro-cue-dependent decrease in the memory load is associated to a proportional reduction in PFC and PPC activity (Lepsien et al., 2011). However, it is important to consider that although selective attention has been shown to ameliorate memory performance, if the

representation of the memory trace is degraded, attentional refreshment via cue presentation may be not successful.

Considering the limit of the memory capacity, not all item representations can be maintained in an accessible way, particularly when capacity is exceeded. Shimi and Scerif (2017) proposed that when memory load is within capacity, the information is transferred to VSTM; however, when memory capacity is exceeded, part of the representation is degraded before it is entered into VSTM. In this case, providing attentional cues does not lead to performance improvements.

Shimi & Scherif (2017) further theorized a general model of the role of selective attention in VSTM, proposing two different but complementary functions. The first component is a more general *attentional scanning and reactivation mechanism*, which operates in a distributed mode and is responsible for information transfer across systems (iconic memory and VSTM) and for retaining information when no cues are available. Hypothetically, this mechanism might be related to the activation of posterior sensory areas. The second mechanism has been defined as more specialized in *visuo-spatial information refreshment* operating directly on the internal representations. Converging evidence supports a fundamental role for PFC over posterior sensory areas by biasing stimuli encoding and/or maintenance. Top-down modulatory function dynamically influences neuronal excitability both in the presence of stimuli (e.g., during encoding) and/or in the absence of external stimulation (e.g., memory maintenance of the mental representation). Therefore, one of the main candidates supporting the *visuo-spatial information refreshment* role is represented by the PFC and its connections to areas maintaining active the information representation.

The findings presented so far provide a complex picture in which top-down attention exerts an important functional role on the retention of information. This mechanism may operate in different ways: i) by enhancing the maintenance of attention over selected goal-relevant items compared to the irrelevant ones (Lepsien & Nobre, 2007); ii) by protecting the representation of the selected piece of information from decay or interference during maintenance (Shimi et al., 2014); and iii) by prioritizing a portion of the information trace, reducing the memory load (Kuo et al. 2012). Moreover, attention may also provide direct retrieval routes by prioritizing comparison of the selected items with the memory probe (Astle, Summerfield, Griffin, & Nobre, 2012).

Up until this point, the impact of selective attention on memory has been described considering only the spatial domain. However, the role of TO as a selective attentional mechanism in VSTM has been reported, though to a less extent. In the last twenty years, understanding of how temporal predictions of relevant events are extracted and can guide attentional control has become an active area of research, with considerable progress being made (Calderone, Lakatos, Butler, & Castellanos, 2014; Cravo, Rohenkohl, Wyart, & Nobre, 2013; Rohenkohl & Nobre, 2011). Nevertheless, there are few studies that examine how temporal predictions influence memory.

In a recent study, Cravo, Rohenkohl, Moreira Santos & Nobre (2017) found that detection and discrimination of targets appearing within previously learned contexts are enhanced when the timing of target appearance matches the learned temporal contingency. These stored temporal associations are projected dynamically to anticipate relevant items at the right moment to optimize performance. This study evidenced that selective attention conveyed by temporal expectation may result in better performance in long-term memory. However, some relevant unresolved questions still need to be clarified. For example, does

TO also influence short-term memory performance? If so, what mechanisms distinguish the effect of TO on short-term memory from its spatial counterpart?

Indeed, the investigation of TO-VSTM interaction allows the study of a broader and relevant theoretical issue: how the possibility to voluntarily implement a strategy to process and to react to forthcoming stimuli reflected in a more efficient behaviour? Providing an answer to this relevant question requires comprehension of the basic mechanisms of the relationship between TO and short-term memory, which still remains unclear.

In order to investigate the TO-VSTM relationship, a new experimental paradigm has been designed in this thesis work. The next chapters will be dedicated to: i) the explanation of the rationale behind the new designed task to investigate the effect of temporal orienting on the encoding and maintenance of information in VSTM; ii) deepening the understanding of the functional role of the brain regions involved in the VSTM maintenance network; iii) the exposition of the experimental methodology, the behavioural and electrophysiological (EEG) results. The final section will discuss the original contribution coming from the results in this thesis, elucidating the mechanisms of TO-VSTM interactions and the brain behaviour during the VSTM maintenance.

Chapter 2 - Experiment 1

2.1 Introduction

In the last two decades, an increasing body of work has focused on investigating the cognitive and neural basis of the endogenous mechanisms of temporal orienting in selective attention (Coull & Nobre, 1998). As previously described, the scientific community has converged on evidence that expectation induced by cues providing explicit and predictive information about the onset of a task-relevant stimulus produces an increase in response speed (Correa, Lupiáñez, Milliken, & Tudela, 2004) and perceptual accuracy (Correa, Lupiáñez, Madrid, & Tudela, 2006; Davranche, Nazarian, Vidal, & Coull, 2011) for predictable rather than unpredictable events. Taken together, these findings seem to suggest that TO may operate as a domain-general attentional mechanism biasing several cognitive functions. However, some studies indicated that the impact of temporal orienting on cognition might be more complex. In fact, previous evidence from studies using a detection task has clearly shown that only endogenous and not exogenous TO is disrupted in the presence of concurrent computational processing (i.e., dual-task paradigm) (Capizzi, Correa, & Sanabria, 2013; Capizzi, Sanabria, & Correa, 2012; Vallesi, Arbula, & Bernardis, 2014). As an additional index of the complexity of the relationship between TO and cognitive control, Correa and colleagues found that explicit temporal cues facilitate the resolution of perceptual conflict by reducing the spatial Stroop effect but reduce behavioural performance in Simon and flanker tasks. These findings suggest that TO may have an impact on executive control depending on where the conflict to be resolved is located, whether at a perceptual level or at the response selection stage (Correa, Triviño, Pérez-Dueñas, Acosta, & Lupiáñez,

2010). In light of these results, the investigation of the interplay between temporal orienting and VSTM assumes a two-fold important aim. First, it may help to extend previous knowledge about the attentional constraints on VSTM in the temporal dimension, with the purpose of gaining a deeper understanding of the nature of human memory systems. Second, it may shed light on the nature of temporal orienting as an important gating mechanism allowing target-relevant information to be further stored, maintained and retrieved for successful task performance. In the existing literature, only one study has examined the effect of temporal expectation on VSTM performance, namely Van Ede and colleagues (Ede, Niklaus, & Nobre, 2017). This group showed that internally guided temporal expectations are able to influence VSTM performance by fastening the access as well as improving the reproduction for memoranda probed in an expected moment in time. This finding suggests that attentional prioritization in working memory can be dynamically conveyed by temporal expectation.

However, this study did not provide participants with explicit information on the temporal structure of the trial, focusing instead on the implicit use of temporal information. In line with published studies in other domains (Correa et al., 2010), it may be speculated that the possibility to convey anticipatory resources proactively on the basis of explicit predictions may strategically optimize VSTM performance at multiple levels including preparation, encoding, maintenance and retrieval of information. Therefore, a new experimental paradigm was designed in this thesis work in order to: i) investigate the relationship between TO and VSTM performance, and ii) to understand at what information processing stage attentional orienting in TO acts on VSTM. EEG recording with a high density system (Geodesic, 128 channels) was utilised to investigate the spatiotemporal dynamic of the network involved, exploiting a good trade-off between

temporal and spatial resolution of the reconstructed source with 128 EEG sensors (Song et al., 2015; Lantz, De Peralta, Spinelli, Seeck, & Michel, 2003). Taking into consideration previous findings regarding the electrophysiological correlates of TO (described in the first chapter), two main ERP potentials were targeted: the CNV and the P3. However, considering the exploratory nature of the study and the scarce literature available on TO and VSTM, early potentials were also included in the analysis. The experimental procedure was divided in two parts to investigate the effects of induced top-down temporal expectancy on information encoding (Experiment 1a) and maintenance (Experiment 1b).

2.2 Method

2.2.1 Experiment 1a - Participants

A total of thirty healthy undergraduate students of Padova University (mean age = 24.13 years [SD = 2.7]; range, 22–32 years; 18 females) took part in Experiment 1. All participants provided written informed consent to participate in the study approved by the Research Ethics Committee of the School of Psychology, University of Padua (prot. N. 1807).

2.2.2 Stimuli and Experimental Paradigm

All stimuli were presented on a 19'' LCD monitor with a resolution of 1280 × 1024 pixels on a black background, with a distance of approximately 56 cm from the screen. A white fixation cross lasting 500 ms was presented at the beginning of each trial. After the fixation cross, a cue was centrally presented for 350 ms. The cue consisted of white contour shapes which could display either single animals (i.e., a tortoise or a hare) or an

unrecognizable combination of the two animals shapes (i.e., the presentation of both the tortoise and the hare overlapped and flipped upside down). After a variable inter-stimulus interval (ISI), the cue was followed by the presentation of a memory array. The ISI duration between the cue and the memory array could be predicted or not based on the symbolic nature of the cue, creating two kinds of experimental blocks thoroughly described below. The memory array consisted of the presentation of three cartoon characters whose spatial position on the screen corresponded to a triangle with each vertex equidistant from the centre of the visual field. The memory array set size ($n=3$) was kept constant. The items were presented in different colours (drawn from a set of seven colours: white, red, magenta, orange, yellow, green and blue) on a black background. Although the colours varied between trials, the layout of the three items remained constant. A total of 69 triplets corresponding to different colour combinations were randomly delivered. After a blank 1000-ms maintenance interval, a 500-ms memory probe consisting of the central presentation of a single character was displayed. The probe was presented in the memory array in 50% of trials. Each memory probe colour was randomly selected from one of the previously mentioned colours, with the constraints that all colours were equally represented and no more than three consecutive same colours could be delivered. Participants had to indicate by pressing one of two keys on a response box whether the probe colour matched one of the colours present in the memory array.

2.2.3 Cued Block (Experiment 1a)

In the cued block (Fig. 1a), participants received a visual cue providing temporal information about the onset of the memory array. Specifically, the display of the hare was always associated with a short (1000 ms) ISI duration, while the tortoise was associated with a long one (3000 ms). The trial types were defined as cued short (CS) for the short

ISI interval (1000 ms) and cued long (CL) for the long ISI interval (3000 ms). Additionally, trial types were equally distributed. The cue could be either left- or rightward oriented. The direction of cues was split equally across blocks and randomly delivered to counterbalance potential spatial orienting effects. This kind of experimental manipulation was derived from previous experimental tasks investigating the role of TO on motor preparation (Mento & Tarantino, 2015; Mento, Tarantino, Vallesi, & Bisiacchi, 2015; Mento & Vallesi, 2016; Mento, 2017) and purposely adapted here to investigate whether VSTM can benefit from a temporally predictive context. To maximize the likelihood of the TO effect, the association between the cued shape and the ISI was kept fixed and fully valid (100%) in both experiments.

2.2.4 Uncued block

In the uncued block (Fig. 1b), the cue was neutral since it did not provide predictive information about the temporal onset of memory arrays. In this case, the cue consisted of merging both the hare and the tortoise contour lines into a unique shape that was presented 180° flipped upside down to make them unrecognizable while at the same time controlling the amount of sensory stimulation in the uncued blocks. The physical features of the cue (i.e., contrast and luminosity) were balanced between blocks. Even in this case, the cue could be either leftward or rightward oriented with the same probability (50%). Crucially, in the uncued blocks the cue simply acted as a warning signal about the forthcoming memory array. However, in the cued blocks, the ISI was manipulated to create temporally equivalent conditions, leading to an uncued short (US) and an uncued long (UL) trial type of 1000 and 3000 ms, respectively.

Experiment 1a

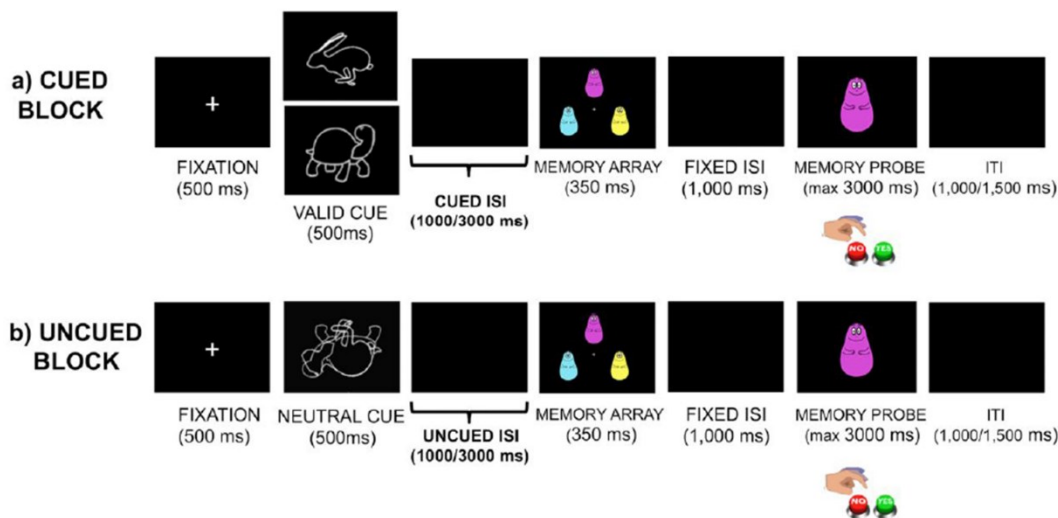


Fig.1. Experiment 1a structure. A) Trial structure of the cued block. After the fixation cross a 100% valid cue was displayed for 500 ms indicating the time onset of the memory array after 1000 ms (hare) or 3000 ms (turtle). The presentation of the memory array (350 ms) was followed by a fixed ISI (1000 ms) and the presentation of the memory probe. At the probe onset participants were required to answer whether the probe was present or not in the memory array. B) Trial structure of the uncued block. The structure was kept identical to the cued block, with the only difference that a neutral cue, not indicating memory array onset, was provided.

2.3 Experiment 1b

2.3.1 Participants

Participants for Experiment 1b were all undergraduate students enrolled at both the University of Padova (mean age, 25.83 years; SD, 3.5; range, 21–36 years; 9 females N=18) and at the University of Oxford (mean age, 24.39 years; SD, 4.7; range, 19–35 years; 9 females; N=18). The two samples were comparable since the participants from both samples performed the exact same experimental task, stimuli were presented with the same monitor parameters (i.e., refreshing rate, resolution, luminance) and their EEG

activity was recorded by using two settings featuring identical technical parameters including the physical devices (i.e., electrode net and amplifier) and parameters (i.e., sampling rate, filters, etc.) employed to physically acquire and store the EEG. Both behavioural and EEG data were preliminarily analysed separately. Since exploratory analyses did not show significant differences between groups relative to age ($t(17) = 1.01$; $p > .3$) and gender ratio ($\chi^2(17) = 1$; $p > .9$), both the Padua and Oxford samples were collapsed into a unique group in order to improve statistical power. The final sample included thirty-six participants (mean age, 25.1 years; SD, 4.2; range, 19–36 years; 18 females). All participants provided written informed consent to participate. The study protocol was approved by the Research Ethics Committee of the School of Psychology, University of Padua (prot. N. 1807) and by the University of Oxford Central University Research Ethics Committee (CUREC).

2.3.2 Stimuli and experimental paradigm

In Experiment 1b, an experimental apparatus identical to the one used in Experiment 1a was employed. The sequence of events within each single trial and the task demands were also matched to Experiment 1a. Additionally, the same experimental design including cued (Fig. 2a) and uncued (Fig. 2b) blocks as in Experiment 1a was used. However, in Experiment 1b, the cue predicted the duration of the memory maintenance interval because it could provide valid or neutral information about the temporal onset of the memory probe. Specifically – and consistent with Experiment 1a – the picture of the hare was always (100% validity) associated with a cued short (CS) maintenance interval (1000 ms), while the picture of the tortoise always predicted a cued long (CL) maintenance interval (3000 ms). Also in Experiment 1b, temporally matched uncued trials (uncued short (US) and long (UL)) were delivered. The experimental stimuli, paradigm, procedure

and design were accurately matched between Experiment 1a and Experiment 1b, with the only difference that in the first case participants were cued about how long they would have to wait before being presented with the memory array, while in the second case the cue informed them about how long they would have to maintain the stored information in VSTM before matching it with the information in the memory test. This different experimental manipulation was designed to investigate the effect of TO on either the encoding (Experiment 1a) or the maintenance (Experiment 1b) of information in VSTM.

Experiment 1b

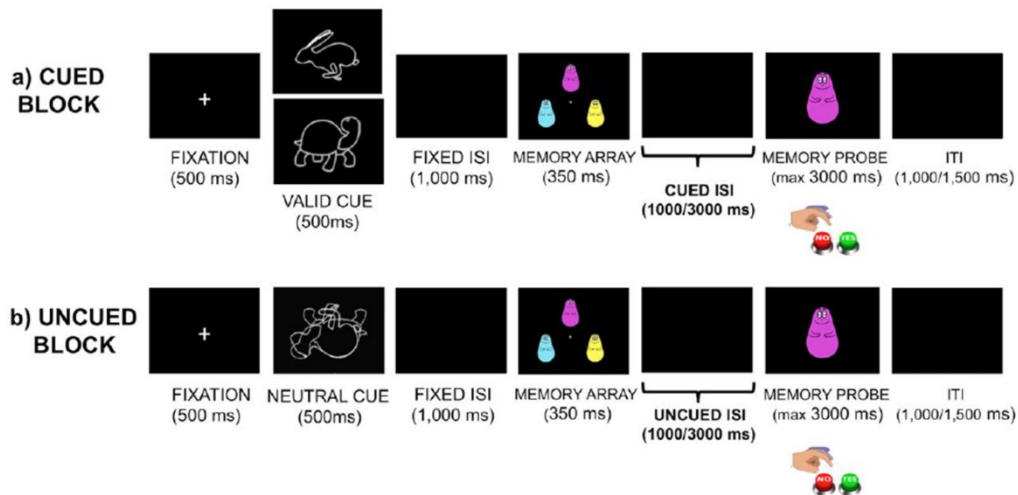


Fig.2. Experiment 1b structure. Trial structure of Experiment 1b. A) Trial structure of the cued block. After the fixation cross (500 ms) a 100% valid cue was displayed for 500 ms indicating the time interval between the memory array and the probe onset: 1000 ms (hare) or 3000 ms (turtle). After the cue presentation a black screen (ISI) was presented for 1000 ms. The presentation of the memory array (350 ms) was followed by the cued variable ISI: hare = 1000 ms, turtle = 3000 ms. At the probe onset participants were required to answer, in max 3000 ms, whether the probe was present or not in the memory array. B) Trial structure of the uncued block. The structure was kept identical to the cued block, with the only difference that a neutral cue, not indicating maintenance length (time interval between memory array and the probe onset), was provided.

2.4 Experimental design

In both Experiment 1a and Experiment 1b, the cued- and uncued-blocks were administered separately in a block-wise rather than inter-mixed manner to reduce the top-down control that is necessary to switch continuously from a predictive to a non-predictive setting and vice versa (Capizzi et al., 2012; Mento, 2017; Mento and Tarantino, 2015; Mento and Vallesi, 2016; Mento et al., 2015). Two temporal blocks and two neutral blocks were administered to each participant for a total of 240 trials (sixty trials per condition). Block order was counterbalanced between subjects to avoid order or sequential effects. Participants were also explicitly instructed at the beginning of each block whether or not they could predict in advance the temporal onset of the memory array (Experiment 1a) or memory probe (Experiment 1b). These manipulations resulted in a 2 (cue) \times 2 (ISI) factorial design that allowed an orthogonal comparison of performance across the experimental conditions. Specifically, the between-block contrasts (CS vs. US and CL vs. UL) allowed us to assess the effect of TO on VSTM in relation to either short or long ISIs. After signing the informed consent, each participant performed a short practice block (20 trials), which was repeated at the beginning of each block type and in both experiments 1a and 1b. After practice, the experimental trials were delivered.

2.5 EEG recording

The EEG signal was continuously recorded during the experiments with the Geodesic high-density EEG System (EGI GES-300) with a pre-cabled 128-channel HydroCel Geodesic Sensor Net (HCGSN-128) and an electrical reference to the vertex. The sampling rate

was 500 Hz. The impedance was kept below 60 k Ω for each sensor. EEG signal quality is assured at this impedance level thanks to EGI high-impedance electrodes and amplifier, which typically work between 50-100 k Ω .

2.6 Behavioural Analysis

For both Experiment 1a and Experiment 1b, mean reaction times (RTs) and accuracy were calculated for each experimental condition and participant. Specifically, D Prime (d') (Green & Swets, 1966) was computed separately for each condition as a more sensitive measure of performance. D' was calculated as the difference in z-scores for hits (correct 'match' detection) and false alarms (incorrect 'match' detection), such that: $d' = Z_{Hit} - Z_{FA}$. Identical analyses were performed on both RTs and d' for each experiment (1a,1b) in order to investigate the effect of TO on VSTM for both these measures. The analysis of RTs was performed considering only trials with correct responses.

2.7 EEG Analysis

All EEG recordings were processed offline using the MATLAB toolbox EEGLAB (Delorme & Makeig, 2004). The continuous data were first band-pass filtered between 0.1 and 30Hz and then segmented into epochs targeting different time windows for the two experiments. The aim of the study was to examine the effect of TO on different stimulus processing stages in VSTM, therefore the cue-, memory array- and memory test-locked ERP activity was investigated both in Experiment 1a and 1b. Specifically, in Experiment 1a the ERPs were extracted between -200 and 4500 ms from the onset of the cue, between -200 and 1000 ms from the onset of the memory array and between -200 and 1000 ms from the onset of the memory probe. In Experiment 1b the ERPs were extracted between

-200 and 1600 ms from the onset of the cue, between -200 and 4500 from the onset of the memory array and between -200 and 1000 ms from the onset of the memory probe. The epochs were visually inspected to interpolate isolated bad channels and remove rare artefacts. Signals from bad channels were reconstructed with the spherical spline interpolation method (Perrin, Pernier, Bertrand, & Echallier, 1989; Ferree, 2000). Artefact-reduced data were then subjected to Independent Component Analysis (Stone, 2002). All independent components were visually inspected, and those related to eye blinks or eye movements according to their morphology and scalp distribution were discarded. The remaining components were then projected back to the electrode space to obtain cleaner EEG epochs. The remaining epochs containing excessive noise or drift ($\pm 100 \mu\text{V}$ at any electrode) were further rejected. Data were then re-referenced to the average of all electrodes, and the signal was aligned to the baseline by subtracting the mean signal amplitude in the pre-stimulus interval. Subject average and grand average ERPs were generated for each electrode site and experimental condition. In Experiment 1a a mean of 50.5 ± 6 (SD), 52.3 ± 3 (SD) and 53.4 ± 2 (SD) artefact-free epochs were accepted for the epochs locked to the cue, the memory array and the memory probe, respectively. In Experiment 1b a mean of 48.8 ± 5 (SD), 51.1 ± 3 (SD) and 54.32 ± 3 (SD) artifact-free trials were accepted for the epochs locked to the cue, the memory array and the memory probe, respectively. A series of four-way ANOVAs with all conditions as repeated measures yielded no significant differences across accepted numbers of trials per condition in any type of epoch and in any of the two experiments. A whole-brain analysis approach was performed at all electrode sites using a paired two-tailed t-test ($\alpha = .05$) permutation approach to control the family-wise error rate (Groppe Urbach, & Kutas, 2011). A similar technique was employed in previous ERP studies (Duma, Mento,

Manari & Tressoldi, 2017; Mento, Astle, Scerif, 2018; Strauss et al., 2015; Capizzi, Ambrosini, Arbula, Mazzonetto & Vallesi, 2016). Monte-Carlo permutations (1000) with cluster-based correction over all 128 electrode locations were derived using the Fieldtrip functions (Oostenveld, Fries, Maris, & Schoffelen, 2011) accessible via Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011).

2.8 Source modeling

2.8.1 Introduction to the brain source reconstruction

EEG provides a privileged window on the human brain thanks to its high temporal resolution. EEG electrodes record electrical activities that are generated several centimetres below the scalp and that go through different resistive layers before being measured (Nunez and Westdorp, 1994). These layers, especially the skull (Srinivasan et al. 1996), caused a blurring effect at the scalp level, therefore, the recorded brain activity from an electrode might be a sum of different underlying brain sources. Due to this volume-conduction-induced mixture, a given scalp topography could in principle have been generated by many different sources configuration. For this reason, the activity over certain electrodes cannot be unequivocally attributes to the sources of the underlying area (Michel et al. 2004). In the last two decades the literature focused a lot of efforts in the implementation of algorithms capable of estimating the location and distribution of the current sources responsible for the electromagnetic activity recorded on the scalp. This problem has been termed as brain source reconstruction. In order to solve this problem the first thing to do is to generate a model of the projection of the sources on the scalp, and this is defined as the forward-problem. The resolution of this problem generates what is

named as head model. Starting from the head model it is possible to solve the inverse-problem, namely to estimate from the scalp activity the brain region which are contributing the most to that electromagnetic scalp configuration (Michel et al. 2004). In literature are present numerous different forward and inverse solving algorithms, which will not be discussed in this thesis. It worths to mention that a critical issue to the spatial resolution of the EEG source reconstruction is the number of electrodes. Noteworthy, a study from Lantz and colleagues (Lantz, De Peralta, Spinelli, Seeck & Michel, 2003) showed a critical incread in the spatial resolution using a 123 channels array, instead of 63 or 32. For this reason in this thesis it was used a high-density EEG recording system as the Geodesic with 128 channel. Thanks to the development of forward and inverse solving methods, EEG found its application as a neuroimaging tools. For example, source reconstruction found a fruitful application in the localization of epileptogenic zones helping in clinical applications such as for surgery in patients with partial seizures (Sperli et al., 2006). Source reconstruction is currently applied also into basic research in order to identify, using the EEG, the brain area activated by specific tasks (De Cul, Baillet & Dehane, 2007; Wacogne et al., 2011; Mento, 2017). In the present experiment source reconstruction was applied to explore the brain areas involved in the interaction between TO and VSTM.

2.8.2 Brain source reconstruction in the Experiment 1a and 1b

Baseline-corrected epochs were imported in Brainstorm (Tadel et al., 2011) to model their cortical generators. ICBM152 was used as anatomical template to approximate the individual anatomy of each participant (Evans, Janke, Collins, & Baillet, 2012) which

was warped to the digitized EEG sensor positions of the GSN Hydrocel 128 E1, available in Brainstorm. An EEG head model was then derived using the three-layer boundary element method (BEM) from OpenMEEG, also via Brainstorm (Kybic, Clerc, Faugeras, Keriven, & Papadopoulo, 2005; Gramfort, Papadopoulo, Olivi, & Clerc, 2011). The source space was constrained to the cortex and modeled as a grid of 15002 orthogonal current dipole triplets. SLORETA was used as a source model, with Brainstorm's default parameter settings. The empirical noise covariance model was obtained from the average of baseline EEG signals. Lastly, the sources were projected to the standard anatomical template (MNI), and their activity was transformed in Z scores relative to the baseline.

2.9 Experiment 1a results

2.9.1 Behavioural results

The ANOVA revealed no main CUE or ISI effects on d' (CUE: $F = .108$; $p = .744$; ISI: $F = .208$; $p = .868$), but a significant CUE \times ISI interaction was observed ($F(1, 29) = 21.7$; $p < .001$; $\eta^2_p = 0.43$). Posthoc t-tests revealed that the CUE improved performance (higher d') in CS compared to US trials ($t(29) = 3.12$; $p = .004$; Cohen's $d = .572$) but resulted in lower accuracy (lower d') in CL compared to UL trials ($t(29) = -2.772$; $p = .010$; Cohen's $d = -.506$). Neither main nor interaction effects were found for RTs (CUE: $F = 3.64$; $p = .07$; ISI: $F = .871$; $p = .358$; CUE*ISI= $F = .046$; $p = .832$). The behavioural results are displayed in Fig. 3.

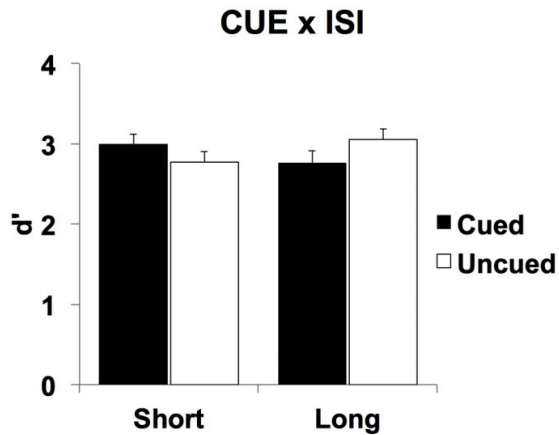
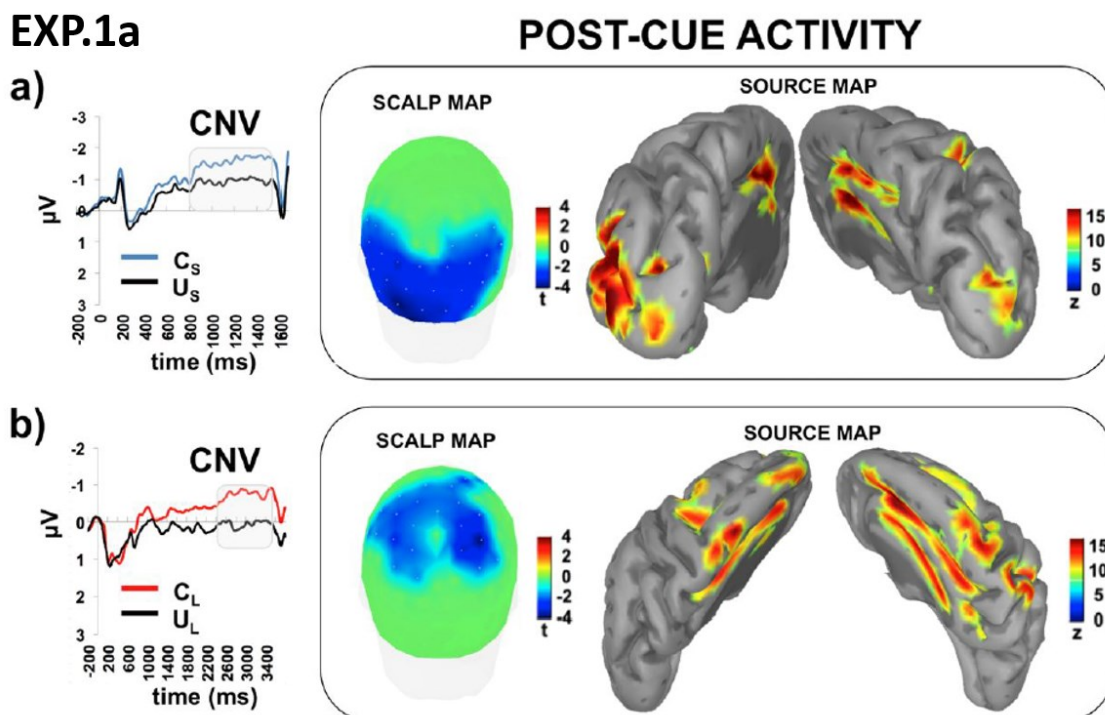


Fig.3. Behavioural results. Behavioural performance measured with the sensitivity index d' in Experiment 1a.

2.9.2 ERP results post-cue

A pair-wise cluster-based permutation analysis was performed over the time window between the cue and the memory array, revealed a modulation of a sustained CNV-like potential (referred to as CNV hereafter) (Fig. 4). Specifically, in the short ISI (1000ms) comparison, a significant modulation of the CNV between 800 and 1400 ms was observed, expressed as a negative cluster covering posterior scalp locations ($p = .018$; cluster statistic = -118; cluster size = 70). This modulation consisted of larger negative electrophysiological activity elicited by the temporal CS compared to the neutral US condition (Fig. 4a). The reconstruction of the cortical sources of the CS trials revealed that the observed CNV modulation (800-1400 ms) was supported by a network mainly involving the bilateral anterior cingulate cortex (ACC) together with the left inferior parietal cortex (l-IPC), the left inferior temporal gyrus (l-ITG) and the occipital cortex (bilaterally). Regarding the long ISI trials (CL), a larger CNV-like component was identified following temporal rather than neutral cues and extending between about 2200 and 3400 ms from cue onset. The cluster-based permutation identified that the cue-dependent CNV-like potential was expressed over a cluster of electrodes located in the

central scalp region ($p = .008$; cluster statistic = -53; cluster size = 46) (Fig. 4b). The different scalp distribution of the CNV-like effects was supported by engagement in the 2200-3400 ms time window of cortical areas only partially overlapping with those found in the short ISI comparison. Furthermore, source reconstruction identified the bilateral activation of ACC with an additional bilateral recruitment of frontal areas such as the Supplementary Motor Area (SMA) and the premotor areas (pre-MA), while no posterior



activation was identified.

Fig.4. Cued condition source reconstruction. a) The upper row left side reports the CNV modulation in the comparison Cued short (CS) vs. Uncued short (US) trials, derived from the identified significant posterior negative cluster. The source map represents the mean activity between (800-1400 ms) for the CS condition. b) The bottom row left side reports the CNV modulation in the comparison Cued long (CL) vs. Uncued long (UL) trials, derived from the identified significant central negative cluster. The source map represents the mean activity between 2200-3400 ms relative to the CL condition. Source activations are plotted as Z scores

and are adjusted using a threshold of 50% of the maximum amplitude and a size of at least 10 vertices.

2.9.3 ERP results post memory array

The ERP activity elicited by presentation of the memory array when it was temporally predicted by the short ISI cue showed larger scalp voltages for cued as compared to uncued memory arrays. As shown in Fig. 5a, the earlier effect was a modulation of the P1 component occurring between 80 and 120 ms ($p = .038$; cluster statistic = 51; cluster size = 44) identified in an occipital positive cluster, consistent with the brain source analysis that located this effect in the bilateral occipital cortex. This effect was followed by a modulation of the P3 component between 300 and 500 ms extending over occipitoparietal electrodes ($p = .003$; cluster statistic = 121; cluster size = 80), sustained by a more diffused activation over occipital and parietal cortical areas. Notably, following the positive components a negative sustained ERP activity pattern was observed spreading over fronto-central scalp sites and exhibiting a climbing trend lasting for the whole maintenance period. The morphology and scalp distribution was consistent with the negative slow wave (NSW) component previously reported in ERP studies on working memory (Drew, McCollough, & Vogel, 2006; Ruchkin, Johnson, Canoune, & Ritter, 1990, Mecklinger & Pfeifer, 1996). As shown in Fig. 5b, the NSW was larger (i.e., more negative) following the presentation of the memory array when its onset was temporally predicted by the cue as compared to when it was not within the interval 400-1400 ms ($p = .022$; cluster statistic = -56; cluster size = 44). This effect was supported by diffused cortical activity entailing occipital, temporal and parietal areas. Concerning the long ISI contrast, no statistically significant differences were found in the early or late ERP activity patterns following the memory array presentation.

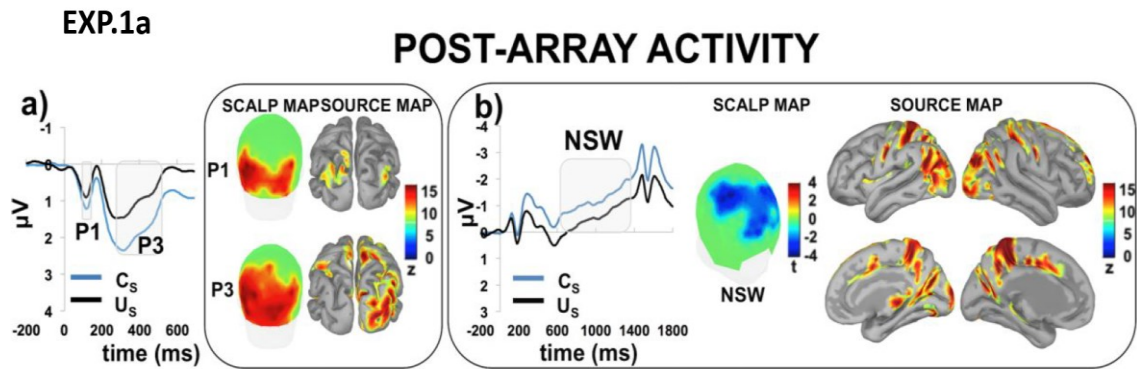


Fig.5 Post memory array activity. a) The figure on the left side shows the significant difference in the early (P1) and late (P3) potentials revealed by comparing the memory array-locked activity (CS vs. US), expressed on the posterior positive cluster (right side). The source-reconstructed maps represents the mean memory array-locked activity relative to the significant modulation of the P1 (80-120 ms) and P3 (300-500 ms). b) The left side of the panel shows the modulation of the NSW potential expressed in the comparison between CS vs. US trials in the occipital-parietal negative cluster. The right side of the panel b shows the source maps relative to the CS memory array-locked activation in the interval 600-1400 ms.

2.9.4 Post-probe activity

The effects of the cue also seemed to influence the probe-locked EEG activity, evident in two distinct temporal windows showing changes in amplitude due to the experimental manipulation. Specifically, the cue-driven modulation was exhibited over early (P1 between 80 and 120 ms over posterior electrodes [$p = .023$; cluster statistic = 58; cluster size = 52]) and late (P3 between 250 and 350 ms over posterior electrodes [$p = .013$; cluster statistic = 60; cluster size = 52]) ERP components. In all cases, the scalp voltage amplitude was larger when the memory probe was presented within cued rather than uncued trials in the short-ISI (1000 ms) condition only (Fig. 6).

EXP.1a POST-PROBE ACTIVITY

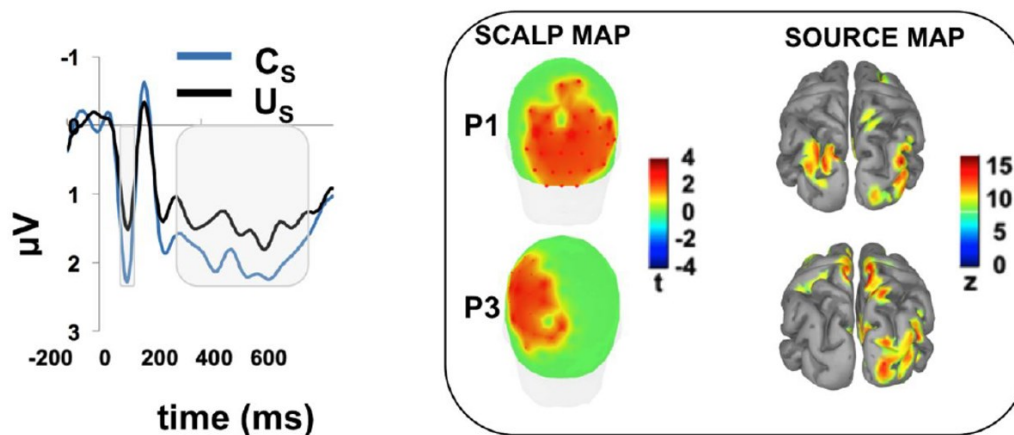


Fig.6. Probe-lock activity. The present figure shows the cue-dependent modulation of the early (P1 between 80-120 ms) and late (P3 between 250-350 ms) ERP components. Source maps represent the mean activity in the respective component time window.

2.10 Experiment 1b results

2.10.1 Behavioural results

The ANOVA performed on d' revealed no main CUE effect ($F = .006$; $p = .9$), but a significant main effect of ISI [$F(1,35) = 5.52$; $p = .025$; $\eta^2_p = 0.13$] and an interaction between CUE and ISI [$F(1,35) = 12.23$; $p = .001$; $\eta^2_p = .26$] were observed. Post-hoc t -tests revealed that the CUE improved performance (higher d') in CS compared to US trials ($t(35) = 2.167$; $p = .037$; Cohen's $d = .369$), but resulted in lower accuracy (lower d') in CL compared to UL trials ($t(35) = -2.734$; $p = .013$; Cohen's $d = -.437$). Neither main nor interaction effects were found for RTs (CUE: $F = .64$; $p = .42$; ISI: $F = .221$; $p = .641$; CUE*ISI: $F = 4.03$; $p = .052$). The behavioural results of the Experiment 1b are plotted in the Fig. 7.

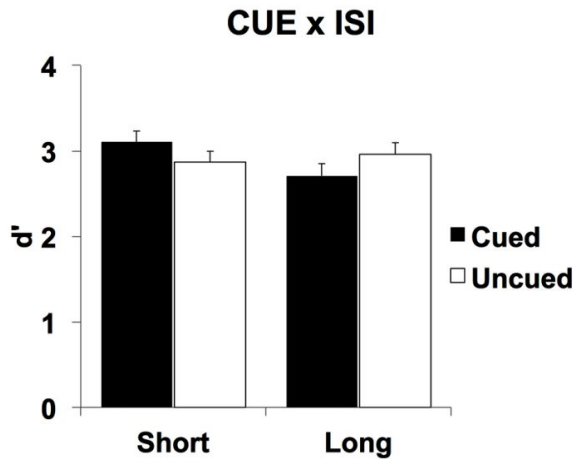


Fig.7. Behavioural results. Behavioural performance measured with the sensitivity index d' in Experiment 1b.

2.10.2 Post-cue ERP results

Similar to Experiment 1a, in Experiment 1b a significant modulation of the sustained CNV-like component was observed in the short ISI comparison, which was larger following the cued short rather than the neutral short trial ($p = .006$; cluster statistic = -68; cluster size = 48). Notably, this effect lasted between 1000 and 1400 ms from the onset of the cue and was expressed as a negative cluster encompassing a large number of electrodes over posterior scalp locations (Fig. 8). The reconstruction of the cortical sources revealed that this modulation was supported by a network mainly involving the bilateral ACC/SMA regions together with the bilateral superior parietal cortex (SPC), the ventral projection of the ITG and the occipital cortex. Regarding the long ISI contrast, no statistically significant differences were found in the early or late ERP activity patterns following the cue presentation.

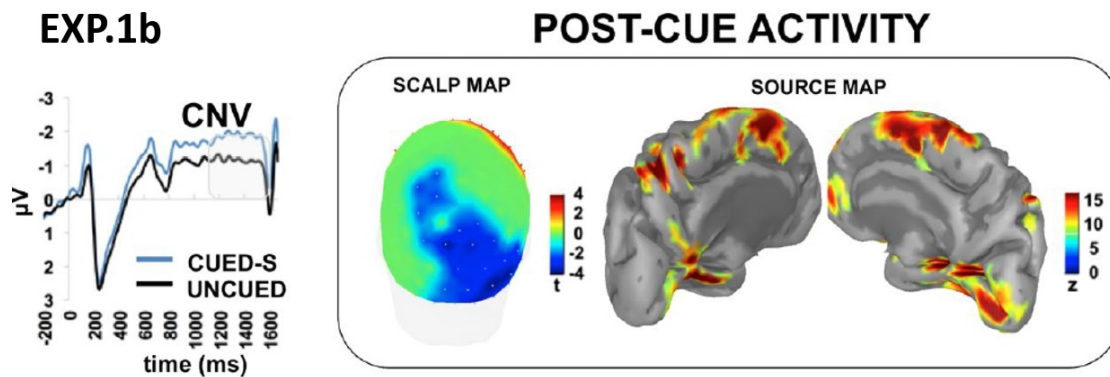


Fig.8. Cue-locked activity experiment 1b. CNV cue-dependent modulation of CS vs. US, expressed in a posterior negative cluster, is evident in the interval between cue presentation and memory array target presentation. The Z score source map represents the mean activity in the time window of the significant difference (1000-1400 ms).

2.10.3 Memory array-locked activity

The ERP activity elicited by the presentation of the memory array in Experiment 1b showed significant effects due to the experimental manipulation. Specifically, the posterior P3 component between 200 and 400 ms showed a larger scalp voltage in the cued rather than uncued short trials ($p = .025$; cluster statistic = 49; cluster size = 48) (Fig. 9a). This effect was due to a greater recruitment of the SPC, which was more activated in the right hemisphere in cued short trials. No significant later effects were found, since the NSW component occurring during memory array maintenance was not affected by experimental conditions. By contrast, in the long ISI comparison we did not find any P3 effect but observed significant modulation of the sustained ERP activity, which took place during maintenance. Remarkably, as shown in Fig. 9b, the NSW was larger (i.e., more negative) during the uncued maintenance interval (1300-3200) ($p = .002$; cluster statistic = -93; cluster size = 58). The cortical map reconstruction of this long-lasting effect

showed an involvement of the SMA in addition to a diffused recruitment of left frontal and temporal cortical areas.

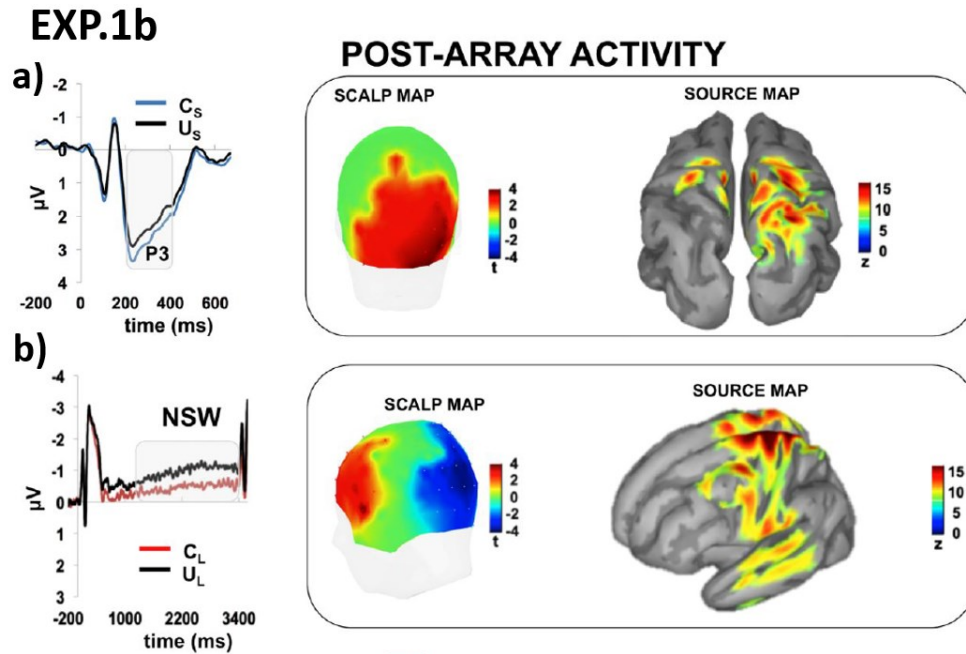
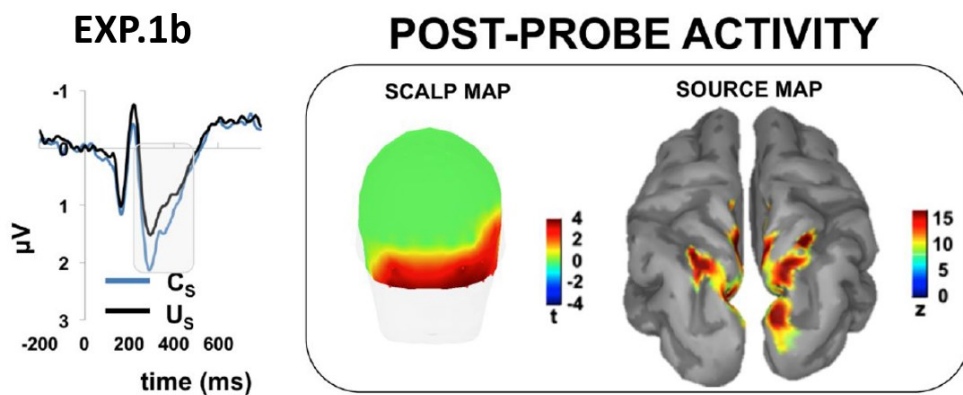


Fig.9. Maintenance activation. A) P3 modulation, expressed in the posterior positive cluster, during the maintenance interval in the temporal window between 200-400 ms, contrasting cued short vs. uncued short trials. The right side shows the corresponding mean activation source map. B) NSW modulation, expressed in the dipolar cluster, during the maintenance interval in the temporal window between 1500-3200 ms, when contrasting cued long vs. uncued long trials. The right side shows the corresponding mean activation source map.

2.10.4 Probe-locked activity

The results of this experiment show modulation of the P3 component between 250 and 350 ms over the posterior electrodes. Specifically, in the short maintenance condition (1000 ms) the cued trials elicited an increase in the P3, expressed in the posterior positive cluster ($p = .038$; cluster statistic = 40; cluster size = 34) (Fig.10), compared to the uncued trials. The underlying cortical activation is maximally expressed in the parietal areas



surrounding IPS (Fig.10).

Fig.10. Probe locked activity. This figure shows the P3 modulation between 250 and 350 ms, expressed in the posterior positive cluster, when contrasting cued vs. uncued trials in the short maintenance (1000 ms) condition. The right side displays the mean activity source map in the P3 significant time window (240-350 ms).

2.11 Discussion of the first experiment

The aim of this first study was to investigate the effects of temporal orienting (TO) of attention on visual short-term memory (VSTM), to shed light on the neurocognitive mechanisms involved in the interaction between these two fundamental processes. Indeed, while the effect of TO on motor speed and perceptual accuracy has been well-

elucidated both at the behavioural (Correa, 2010) and neural (Coull, 2010) level, little is known as to what extent the ability to encode, maintain and retrieve visual information from VSTM is affected by top-down attentional orienting in the temporal dimension. Therefore, considering the relevance of these two cognitive processes, understanding their relationship requires deeper investigation. To this purpose, a temporal cueing task was adapted from a previously employed task to measure simple RTs (Mento, 2017; Mento & Vallesi, 2016) in order to investigate the impact of top-down-driven attentional processes in temporal orienting during VSTM performance. The rationale of this study was to determine whether and to what extent proactive control triggered by temporal cueing could impact VSTM performance and at which processing stages this influence is mainly exerted. Specifically, in the context of the same memory task, the focus of Experiment 1a was to examine the effects of TO on the encoding phase, while the goal of Experiment 1b was to test the effects of TO on the maintenance phase. Behavioural results showed that VSTM performance improved in the temporally cued blocks compared to the uncued blocks when the cue signalled the onset of either the memory array (Experiment 1a) or the length of the maintenance period (Experiment 1b) after a short time interval (1 sec). By contrast, in both experiments performance was disrupted when the cue predicted a longer interval (3 sec), showing that the effect of TO on encoding and maintenance in VSTM depended on the temporal structure of the task. This finding suggests that VSTM performance advantage is not simply related to the opportunity to implement proactive stimuli elaboration strategies of the forthcoming stimuli. Rather, the effect of top-down temporal attention impacted memory processing differently as a function of task-specific characteristics. These findings suggest that TO of attention plays a complex role in cognitively demanding processes such as VSTM, in line with previous

results evidencing that temporal prediction modulates executive control through dissociable mechanisms (Correa et al., 2010; Korolczuk, Burle, & Coull, 2018). The analysis of neural activity associated with distinct VSTM stages was helpful to depict in detail the functional locus of TO effects on VSTM. In Experiment 1a, neural activity data showed a modulation of the ERP activity preceding the presentation of the memory array (i.e., the post-cue preparatory interval) based on the information driven by the cue value (informative vs. uninformative). Specifically, the amplitude of the CNV component during the interval between the cue and the memory array onset was larger following informative compared to neutral cues, both for the short (1000 ms) and the long (3000 ms) interval. This effect was localized over posterior scalp regions for short intervals and over central electrodes for long intervals. The source reconstruction of these effects revealed two partially distinct networks underlying the CNV modulation for the short- and long-ISI conditions. Specifically, for both short and long preparatory intervals, a large recruitment of the ventro-medial prefrontal regions, mainly including the bilateral anterior cingulate cortex (ACC) and, to a minor extent, the SMA, was observed. The engagement of the prefrontal cortex has been consistently reported by neuroimaging studies investigating the neural bases of TO; in particular, it has been suggested that the SMA and the ACC play a key role in temporal expectancy (Mento et al., 2013, 2015; Mento, 2017; Coull, Charras, Donadieu, Droit-Volet, & Vidal, 2015) and more generally in temporal processing (Macar et al., 1999; 2006; Schwartz & Kotz, 2013). In line with this evidence, the pre-activation of the ACC during either the short- or long-ISI conditions may be interpreted as reflecting the proactive control of attentional resources conveyed by the temporal information inherent to the cue. Interestingly, as mentioned above, the source reconstruction of the CNV modulation indicated differences between the two interval

conditions, such that an additional engagement of the occipito-temporal cortical regions was observed selectively in the case of the short anticipatory interval. The specific recruitment of posterior regions following cues indicating short-ISIs can be interpreted as a possible neurophysiological mechanism allowing participants to strategically pre-activate the cortical areas that will be engaged in the elaboration of the forthcoming stimuli. This observation is in line with the hypothesis that CNV activity could reflect not only temporal expectation and/or motor preparation but also a more general mechanism of optimization of resources allocation, aiming at optimizing the execution of a task (Mento, 2013). In support of this hypothesis, the memory array-locked P1 and P3 ERP components exhibited significantly larger activity in posterior electrodes in the cued compared to the uncued blocks selectively for the short-ISI condition. This whole pattern suggests that: i) resource optimization was more effective in the condition in which the cue indicated a short interval before the presentation of the memory array and ii) such optimization was in fact translated into more efficient processing (both early, e.g., P1 and late, e.g., P3) of the triplet of stimuli in the memory array. These findings converge to support the hypothesis that both the perceptual analysis and the memory encoding of information were enhanced by TO, although this advantage was observed only for short preparatory intervals. Furthermore, in the short-ISI trials the TO modulation was extended to the whole VSTM maintenance interval (i.e., the period between the memory array offset and the memory probe onset), as reflected in the increase of the NSW. The underlying generators of the NSW were identified in a distributed fronto-parietal network including the ACC together with cortical areas surrounding the intraparietal sulcus (IPS). Finally, larger P1 and P3 responses were observed in response to the presentation of the memory probe in the short-ISI conditions only, accompanied by distributed occipito-

parietal activation. By contrast, the CNV modulation during the preparatory interval following cues indicating long-ISI trials was not followed by further neural modulation. This evidence suggests that, in the case of long-ISI, the mechanism implemented in the preparatory interval did not facilitate the processing of the forthcoming stimulus, and as a consequence any modulation of neural activation is reported during the memory maintenance period. In sum, the results obtained from Experiment 1a are in line with the hypothesis that the opportunity to predict the onset of the memory array induces anticipatory neural enhancement of discrete cortical regions. Specifically, prefrontal areas were engaged regardless of the duration of the preparatory interval, while posterior areas were pre-activated only during short anticipatory intervals. Noteworthy, the pre-activation of this fronto-parietal circuit is not limited to an advantage in the encoding of information into VSTM; rather, it is translated into a top-down cascade of neural modulation that endured throughout the whole memory process, encompassing both memory maintenance and retrieval computational stages. One of the most relevant results is that the cue advantage is not prolonged into the stimulus encoding and maintenance. One explanation of this important finding will be proposed later, in light of the results of the Experiment 1b.

The findings in Experiment 1b evidenced a larger CNV activity following cues indicating short-ISI trials compared to neutral ones, similarly to Experiment 1a, even though no effects were observed following cues indicating long-ISI trials. This finding was surprising, since in Experiment 1b any possible cue-related neural modulation was expected during the maintenance interval rather than as early during the preparatory interval. A possible explanation for this early effect may be that although the specific temporal content of the cue was related to a later temporal window (i.e., VSTM

maintenance), participants began to strategically prepare for maintaining information in memory well before the actual onset of the memory array. This hypothesis is supported by the evidence that, in addition to a frontoparietal network similar to Experiment 1, the CNV was further supported by ventral temporo-occipital cortical activity, likely related to pre-activation of areas engaged in maintaining semantic information in VSTM. This neural modulation was further observed in relation to both memory encoding and retrieval. A larger P3 component originating from parietal areas surrounding IPS was elicited by either memory array or memory probe onsets when these were preceded by cues indicating a short maintenance interval. The results of Experiment 1b show, for the first time, that a temporal cue might be able to affect distinct information elaboration stages underlying VSTM, including preparatory processes (CNV), memory encoding (P3 at the memory array) and retrieval (P3 at the memory probe) of visual information. Remarkably, these ‘facilitation’ effects were observed only for the cue that indicated a short interval, showing a correspondence with the behavioural results. In light of these findings, it is possible to generate a hypothesis regarding the dissociation observed between short- and long-ISI trials. A first explanation may take into account the possible differences in terms of executive control demands in voluntary TO for short- vs. long-ISI trials, indicating that these resources are shared with the network responsible for the maintenance of information in VSTM. In fact, participants not only did not benefit from the information related to the long interval, but in these trials their performance was worse than when the cue was neutral. This pattern might suggest that the cognitive mechanism involved in TO for long intervals and VSTM may compete for partially overlapping resources/network, worsening behavioural performance. Furthermore, although within different research lines, both TO and VSTM studies independently identified the fronto-

parietal network as a core circuit for orienting attention in time (Coull, 2010; Mento et al., 2015; Mento, 2017) and maintaining information in memory (Astle et al., 2014, Curtis & D'Esposito, 2003). The task of the Experiment 1b allows for manipulating two distinct processes at the same time, setting and implementing proactive attentional control and protecting the representation of the selected items from decay or interference during the retention interval, resulting in increased cognitive effort that may be the cause of low performance. In other words, one explanation of the behavioural and neurophysiological results may be identified in the overlay between cognitive control, instantiated by endogenous TO, and VSTM mechanisms culminating in resources splitting due to the partially shared underlying neural pathways. However, further studies are needed to better disentangle the role of prefrontal and posterior areas in attentional and mnemonic processes. Furthermore, it is not possible to entirely exclude the possibility that both behavioral and neural differences for short and long cues may be due to the use of different mnemonic strategies. In fact, it is well-known that information decays as a function of time after encoding in short term memory (Phillips & Baddeley, 1971), therefore the two maintenance intervals may require different strategies to actively maintain the memory trace. Indeed, the possibility to prepare for a short maintenance interval may have induced participants to rely on a visual-based maintenance strategy, since short cues indicated that they did not have enough time to implement other types of strategies. This might be in line with the pre-activation observed in the short cue condition in posterior areas. By contrast, when the cue predicted a long maintenance interval, participants could potentially exploit collateral strategies like verbal rehearsal to improve maintenance of the memory trace; however, this strategy was not behaviourally advantageous for the present test stimuli. A possible clue might come from source reconstruction underlying

the NSW in Experiment 1b, which showed activation of left peri-sylvian areas during long-uncued intervals. Indeed, the recruitment of left peri-sylvian areas may underlie the possible use of verbal phonological loops during information maintenance for long intervals. The present study, divided in two experiments (1a and 1b), demonstrated overall a key finding, that is, that TO impacts VSTM performance, even though this effect is not always translated into an advantage. Furthermore, this effect depends on the characteristics of the task, particularly on the relative duration of the maintenance interval since this offers the possibility to implement strategic control. Another relevant result is that TO elicits activation of a frontoparietal network. This may be interpreted as possible pre-activation of those brain areas that will be successively engaged in maintenance of visual information.

The recruitment of a distributed fronto-parietal network supporting TO on short-retention items is in line with previous neuroimaging evidence (Curtis & D'Esposito, 2003). The results of the first study evidenced a recruitment of the cingulate cortex and the parietal cortex (IPS), the latter of which is well-known to be a fundamental node for visual information maintenance (Todd & Marois, 2004; Xu & Chun, 2006). However, the functional role of these nodes and their interaction still need to be clarified. Therefore, in light of these results, the engagement of frontal and parietal areas was targeted in a second experiment (Experiment 2), with the specific aim of investigating their functional roles during information maintenance in visual short term memory.

Chapter 3 - Experiment 2

3.1 Introduction

Our visual system allows us to perceive the surrounding visual world, yet our internal representation of the external world is sparse because we can only hold in mind a fraction of the visual scene. These mental representations are stored in visual short-term memory (VSTM). It has been consistently shown that humans have a limited capacity for VSTM, since information about only three or four items can be retained at one time (Luck and Vogel, 1997; Cowan, 2001). Maintenance of information in short term memory engages a distributed frontoparietal network, including posterior parietal cortex (PPC), intraparietal sulcus (IPS), and other prefrontal areas like DLPC and VLPFC. Evidence from neuroimaging studies shows that one of the main regions responsible for maintenance of visual information is the IPS. This region shows an almost linear increase in hemodynamic activity as the number of items encoded in VSTM is increased but levels off after individual memory capacity is reached (Brigadoi et al., 2016; Todd and Marois, 2004; Xu and Chun, 2006). However, while these results may suggest that the functional locus of VSTM maintenance is limited to IPS activity, other neuroimaging studies have shown that maintenance of visual information also involves frontal regions. Linden et al. (2003) reported the presence of a distributed circuit involving the IPS, frontal eye fields (FEF), the dorsolateral prefrontal cortex (DLPFC) and the pre-supplementary motor area (pre-SMA) during the VSTM retention period. In particular, they found a monotonic increase of activity over frontal areas (DLPFC and pre-SMA) that was related to the number of items to be encoded. Based on these findings, they theorized that the operations

performed by the DLPFC and pre-SMA could support an integrated representation of the encoded visual information, helping subjects maintain efficient performance in the highest load condition. Frontal engagement during the delay period (maintenance) has been also shown by Ester, Sprague, and Serences (2015). Based on the voxel-wise activation of ventral and dorsolateral prefrontal cortex during the delay period, they reconstructed high-fidelity representations of the memorized orientation of a visual stimulus. From a theoretical perspective, frontal activity in the visual working memory task has been usually interpreted as an element of general domain cognitive control, mainly related to Baddeley's executive central system (Baddeley, 1996), while posterior regions such as the IPS may be responsible for storage (Christophel, Hebart, & Haynes, 2012). Another fundamental hub of working memory (WM) has been identified in the anterior cingulate cortex (ACC). In line with previous studies claiming a core role for the ACC in cognitive control during complex tasks (Chein & Schneider, 2005; Kondo, Osaka, & Osaka, 2004; MacDonald, Cohen, Stenger, & Carter, 2000; Paus, 2001; Peterson et al., 1999), this structure may underlie executive processes necessary for maintenance of information into short-term storage. The ACC has been identified as a key generator of frontal midline theta (FMT; Gevins, Smith, McEvoy, and Yu, 1997), which shows a memory load-related power increase during a working memory (WM) task (Jense & Tesche, 2002). Functional connectivity studies also reported that memory load modulations could be related to the strength and pattern of the connectivity between ACC and at least two other main WM regions: the PFC and the posterior parietal cortex (PPC) (Bakshi, et al., 2011, Ma et al, 2012, Lenartowicz & McIntosh, 2005). Based on the results of the previous experiments (Chapter 2), the ACC seems to be also actively involved in the maintenance of visual information in the VSTM in conjunction with

parietal areas. While the role of posterior areas seems to be better delineated in literature, the actual functional role of the ACC in the VSTM and its relationship with posterior areas of maintenance networks still remains unclear. A first hypothesis is that it is limited to domain-general supervision, supporting cognitive control over the entire maintenance process. In support of this hypothesis, it is possible to predict that the ACC should exhibit sustained rather than phasic activation over the whole delay period. Alternatively, the ACC might be specifically involved in boosting information maintenance and/or in protecting the memory trace from decay. If this were the case, its engagement should result in a functional pattern characterized by a precise temporal dynamic. Since an information trace decays with time in short term memory (Phillips & Baddeley, 1971), ACC involvement should exhibit a phasic boost of activity over the late phase of information maintenance. Furthermore, in line with the hypothesis that ACC is a core node of the VSTM distributed brain network engaged during maintenance, its functional connectivity with other regions of the frontoparietal network should exhibit task demand-dependent modulation. The present experiment was aimed at clarifying the functional role of ACC as a core node of the frontoparietal network entailed in VSTM. More specifically, by using time-resolved ERP source imaging, the main aim was to investigate the spatiotemporal dynamics of ACC activation to shed light on how this structure interacts with the posterior parietal areas. To this purpose, EEG activity was recorded with a high-density system while participants performed a VSTM task. In this second study, the ERP component, referred to as the contralateral delay activity (CDA), was exploited to investigate the maintenance of visual information. This component was first described by Vogel & Machizawa, (2004), who reported increased negativity during a lateralized change-detection task at the posterior scalp regions contralateral to the visual hemifield

of the memoranda relative to the ipsilateral side. The CDA was obtained by subtracting the ipsilateral from the contralateral activity over occipital-parietal scalp sites. Importantly, the CDA shows a monotonical increase with the number of items to be held in memory, starting from about 300 ms from stimulus onset. However, the amplitude increase plateaus when individual VSTM capacity is reached. One of the main candidates of CDA generators is the IPS, which shows a similar activity pattern in relation to the memory load (Todd & Marois, 2004; Xu & Chun, 2006). In this experiment, it was expected to confirm the memory load-dependent modulation of electrophysiological activity, focusing on modulation of activity in both the parietal cortex (IPS) and the ACC. Secondly, if ACC and IPS are two nodes of a distributed network sustaining the maintenance of the memory trace, it is possible to hypothesize that the functional connectivity between the ACC and posterior parietal areas would be enhanced as a function of increased memory load. Oscillatory activity in one of the main communication mechanisms between brain regions (Thut, Miniussi & Gross, 2012). This theory is based on the fact that brain oscillations represent rhythmic modulations of local excitability. Brain communication relies on spikes from the sending reaching the receiving population at a certain phase. When sending and receiving neuronal populations exhibit phase-locked oscillations with a constant phase delay, that matches the conduction time from the sending to the receiving group, a communication is assumed (Fries, 2005). In order to investigate the strength of the phase synchrony between brain areas, in the present thesis it was used the measure named phase-locking value (PLV). PLV measures the phase covariance between two signals with a reasonable time-resolution (< 100 ms). Unlike the more traditional method of spectral coherence, PLV separates the phase and

amplitude components and can be directly interpreted in the framework of neural integration (Lachaux, Rodriguez, Martinerie, & Varela, 1999).

Finally, to better enucleate the contribution of each cortical region as being specifically associated to VSTM, it was evaluated both sensor- and source-level neural activity elicited by a memory-probe task already employed in a previous study (Brigadoi et al., 2017) and the activity generated by a control task. This task was purposely designed to match the VSTM task in both perceptual and motor demands but without involving memory load modulations. This comparison was planned to specifically address how frontoparietal areas are functionally shaped by VSTM demands, removing the effect of other confounds such as perceptual or motor processes.

3.2 Method

3.2.1 Participants

Data were collected from 30 healthy adult participants (mean age= 22.5 years [SD= 2]; range 20-25 years; 18 females). Only participants with at least 60% accuracy in the VSTM task were included in the analysis (4 participants excluded). Moreover, only participants with at least 30 valid epochs in each experimental condition were included in the analysis. Six participants were excluded because they did not reach the sufficient number of trials due to eye/muscular movements and/or equipment failure. The final sample included 20 participants (mean age = 22.15 years, [SD= 1.6], range 20-25, 8 males). All participants reported normal or corrected-to-normal vision and had no history of neurological and/or psychiatric disorders. All participants gave their informed consent before the experiment, which was approved by the local ethics committee (prot. N. 2071).

3.2.2 Stimuli and Procedure

Stimuli were presented on a 17-inch monitor at a resolution of $1,280 \times 1,024$ pixels. Participants were seated comfortably in a chair at a viewing distance of approximately 57 cm from the monitor. The experimental procedure consisted of two tasks, explained below. The experimental design was task-wise delivered, and task order was counterbalanced across participants. Before EEG data acquisition, participants were familiarized with the task with a practice session where they received feedback on their responses with a plus (correct) or minus (incorrect) sign displayed at fixation at the end of each trial. No feedback was provided during actual data acquisition. During practice, response accuracy was emphasized relative to response speed.

3.2.2.1 VSTM Task

In the VSTM task, participants performed the cued memory probe task illustrated in Figure 11. Each trial began with the presentation of a fixation point at the centre of the screen for 500 ms followed by a 400 ms arrow cue pointing to either the left or right side of the screen. The offset of the directional cue was followed by a blank interval of 200–600 ms (randomly jittered in 100-ms bins) and by the onset of a memory array composed of four, eight or ten colour patches, evenly distributed in the left/right visual hemifields, displayed for 300 ms on a black background (RGB 0 0 0). Two different geometrical shapes were used (squares or circles). A memory array could be composed either of the same geometrical shape in both hemifields or of a different shape for each hemifield: within the same hemifield all items were of the same geometrical shape. For the VSTM

task, the shape of the stimuli was task-irrelevant, since participants were asked to remember colours only. Two different shapes were used to equate the perceptual features across the VSTM task and the control task (explained in detail in the forthcoming section). The size of each colour patch was $1^\circ \times 1^\circ$ of visual angle. Colours were randomly chosen from a set of ten highly discriminable hues: yellow (RGB 230 235 5), blue (RGB 0 0 255), green (RGB 0 90 45), red (RGB 255 0 0), white (RGB 255 255 255), cyan (RGB 30 255 255), violet (RGB 255 0 255), light green (RGB 2 255 45), grey (RGB 125 125 125) and claret (153 0 48). Each colour appeared no more than once on either side of fixation. Stimuli could be displayed in random positions within two rectangles of $3.5^\circ \times 7^\circ$ visual angle placed symmetrically on the left or right side of fixation at a distance of 2.5° of visual angle. The distance between the upper left corners of two adjacent stimuli was constrained to be at least 1.5° . Participants were instructed to keep their gaze at fixation and to memorize the colours of the patches presented in the cued visual hemifield while ignoring those presented in the opposite hemifield. A single probe colour patch was then presented at fixation after a blank retention interval of 900 ms. Participants had to indicate whether the probe colour matched one of the to-be-memorized colours within 2000 ms by pressing one of two keys on a response box. Half of the participants used the left index finger to respond 'match' and the right index finger to respond 'no match,' whereas the other half of participants used the opposite response mapping. On half of the trials, the colour of the probe matched one of the colours displayed in the cued hemifield, whereas on the other half of trials the probe colour was randomly selected among the set of non-displayed colours. Following the response, an inter-trial interval of 700–1100 ms (randomly jittered in 100-ms bins) elapsed before the beginning of the next trial. The experimental session consisted of 3 blocks of 96 trials each, for a total of 288 trials. Each

participant was exposed to 96 trials per condition in a design generated by the orthogonal combination of memory load (2, 4, 5) and cued visual hemifield (left vs. right).

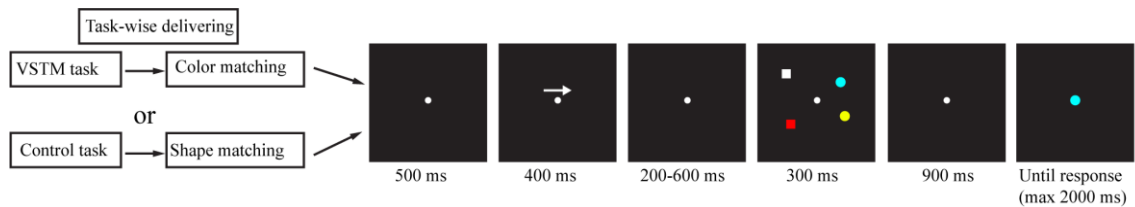


Fig.11. Experimental paradigm. In the VSTM task, participants were instructed to memorize the colours of either two, four or five coloured patches displayed in the cued visual hemifield (left or right). The probe array consisted of one centrally displayed coloured patch, which could be ('same') or not be ('different') of the same colour as one of the to-be-remembered coloured patches. In the control task, participants had to remember only the stimulus shape of the items in the cued hemifield.

3.2.2.2 Control task

The temporal and stimulus structure of the control task was identical to that of the WM task (Fig. 11), but the instructions were different. Participants were required to memorize only the shape of the stimuli displayed in the cued hemifield and to ignore those in the opposite one. Although the number of items displayed in each hemifield could be either 2, 4 or 5, the shape of all the items in the same visual hemifield was the same, thus implying that only one element had to be kept in memory regardless of the number in the visual array. Participants were requested to judge whether the probe shape matched the one presented in the cued hemifield by pressing one of two keys on a response box (counterbalanced across participants, same as the VSTM task). The number of trials was identical to the VSTM task.

3.2.3 EEG recording

The continuous EEG was recorded by using a Geodesic high-density EEG System (EGI GES-300) with a pre-cabled 128-channel HydroCel Geodesic Sensor Net (HCGSN-128) and electrical reference to the vertex. EEG data were recorded during the entire experiment. The sampling rate was 500 Hz. The impedance was kept below 60 k Ω for each sensor. In order to reduce signal contamination, participants were instructed to limit eye blinks and eye movements as much as possible during task trials.

3.2.4 Behavioural analysis

Psychophysical estimates of individual VWM capacity were derived using Cowan's equation (2001), $K = S \times (H - FA)$, where K is the number of colours stored in visual short-term memory, S is the number of colours displayed in the cued side of the memory array, H is the proportion of 'hits' (i.e., correct 'match' detections), and FA is the proportion of 'false alarms' (i.e., incorrect 'match' detections).

Table 1 reports the average 'hit' and 'false alarm' rates and the average accuracies for all set sizes and both tasks. The sensitivity index d' was also computed: $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$ (Green & Swets, 1966). Trials associated with an incorrect response were excluded from EEG analyses.

	WM task			Control task		
	Set Size 2	Set Size 4	Set Size 5	Set Size 2	Set Size 4	Set Size 5
Hit Rate	.90(.10)	.85(.10)	.72(.09)	.95(.05)	.95(.04)	.95(.03)
False Alarm	.08(.09)	.15(.10)	.19(.11)	.04(.04)	.04(.05)	.04(.06)
Mean Accuracy	.92(.09)	.78(.10)	.73(.11)	.96(.04)	.96(.03)	.96(.04)

Tab.1. Mean 'hit' and 'false alarm' rate and standard deviation (between brackets) for each sets size and task.

3.2.5 ERP analysis

The continuous EEG signal was bandpass filtered (0.1-45Hz) using a Hamming windowed sinc finite impulse response filter (filter order = 16500), down-sampled at 250 Hz, and epoched from 200 ms before memory array onset until 100 ms after probe onset, for a total epoch length of 1298 ms. Signal preprocessing was performed with EEGLAB (Delorme & Makeig, 2004).

Epochs were visually inspected for bad channels and artefacts. Data cleaning was performed with independent component analysis (Stone, 2002). The resulting independent components were visually inspected in topography and time-series, and those related to eye blinks, eye movements and muscle artefacts were discarded. The remaining components were then projected back to the electrode space to obtain cleaner EEG epochs. Epochs with excessive noise or signal drift ($\pm 100 \mu\text{V}$ at any electrode) were also rejected (mean number of rejected epochs: WM task [11.20]; control task [7.19]). Signals from bad channels were reconstructed with the spherical spline interpolation method (Perrin, Pernier, Bertrand, & Echallier, 1989; Ferree, 2000). The data were then re-referenced to the average of all electrodes, and baseline correction was applied by subtracting the mean signal amplitude in the pre-stimulus interval. Individual average and grand average ERPs were obtained for each electrode site and experimental condition of both tasks (mean number of averaged epochs for the VSTM task: 39.42, 35.08, 34.15 for the three set sizes, respectively; mean number of averaged epochs for the control task: 40.85, 40.75, 40.08 for the three set sizes, respectively).

In line with the analysis of the first experiment, the same whole-brain analysis approach was applied by using 1000 Monte-Carlo permutations with cluster-based correction over all 128 electrodes using Fieldtrip functions (Oostenveld et al, 2011) via Brainstorm (Tadel

et al. 2011). The permutation approach was applied over the whole memory maintenance window (300-1200 ms from memory array onset).

In line with previous literature (Brisson & Jolicoeur, 2007), one set of analyses was performed exclusively on lateral parieto-occipital electrodes (PO7, PO8) where CDA is typically maximal. The equivalent of PO7 and PO8 electrode locations were identified from the 128-channel Geodesic montage (PO7 = E65, PO8 = E90) (Luu & Ferree, 2005). ERP waveforms were re-arranged as contralateral and ipsilateral ERPs depending on electrode site and cued visual hemifield. For each condition and participant, the CDA was obtained by subtracting ERP waveforms at ipsilateral electrodes (PO7 for left cued hemifield, PO8 for right cued hemifield, respectively) from those at contralateral sites (PO8 for left cued hemifield, PO7 for right cued hemifield, respectively) (Lefebvre, Dell'Acqua, Roelfsema, & Jolicoeur, 2011).

Statistical analyses on the CDA component were conducted using a linear-mixed-model approach implemented in R, with the following dependent variables: i) the mean amplitude of the CDA over the entire maintenance time window (300-1200 ms), ii) the number of items (2, 4, 5), and both types of task (WM and control task) as factors. Linear Mixed Models were performed with the packages lme4 (Bates, Mächler, Bolker, & Walker, 2015) and lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017). In order to test the statistical significance of the predictors, the Car package was used (Fox & Weisberg, 2011). To contrast the levels of the factors, an *a priori* helmert contrast was applied from the package emmeans (Lenth, 2018), with FDR correction for multiple comparisons.

3.2.6 Source modelling

As in the first study, baseline-corrected epochs were imported in Brainstorm (Tadel et al., 2011) to model their cortical generators. The ICBM152 was used as anatomical template to approximate the individual anatomy of each participant (Evans, Janke, Collins, & Baillet, 2012) and warped to the digitized EEG sensor positions of the GSN Hydrocel 128 E1 available in Brainstorm. The EEG head model was then derived by using the three-layer boundary element method (BEM) from OpenMEEG, also via Brainstorm (Kybic, Clerc, Faugeras, Keriven, & Papadopoulos, 2005; Gramfort, Papadopoulos, Olivi, & Clerc, 2011). The source space was constrained to the cortex and modelled as a grid of 15002 orthogonal current dipole triplets. SLORETA was used as a source model with Brainstorm's default parameter settings. The empirical noise covariance model was obtained from the average of baseline EEG signals. The sources were projected to the standard anatomical template (MNI), and their activity was transformed into Z scores relative to the baseline.

3.2.7 Functional connectivity

Functional connectivity was estimated using the phase-locking value (PLV) measure (Lachaux et al., 1999). Functional connectivity was computed by calculating the PLV between pairs of regions of interest (ROIs) over the memory maintenance period (i.e., 300-1200 ms from memory array onset). Regions of interest (ROIs) were derived from the atlas of the Destrieux parcellation (Destrieux, Fischl, Dale, & Halgren, 2010) available on the ICBM152 template of Brainstorm. The ROIs comprised the IPS and ACC, ipsilateral and contralateral to the cued hemifield. The PLV was computed both contralateral and ipsilateral to the cued visual hemifield. For each condition and

participant, the contralateral connectivity was computed by averaging the PLV of the contralateral hemispheres (right hemisphere for left cued hemifield, left hemisphere for right cued hemifield, respectively). Ipsilateral connectivity was estimated by averaging the PLV over the ipsilateral hemispheres.

In line with the hypothesis of increased frontoparietal functional connectivity with increasing memory load, significant differences in PLV across memory set sizes was tested by using paired one-tailed t tests.

3.3 Results

3.3.1 Behavioural results

The average K was 1.73 (SD = .17), 2.38 (SD = .52) and 2.39 (SD = .68) for two, four and five items, respectively. The difference between two and four as well as between two and five items was statistically significant [2 vs. 5 $t(19) = -4.63, p < .001$; 2 vs. 4 $t(19) = -6.50, p < .001$]. No significant difference was found between four and five items [4 vs. 5 $t(19) = .022, p = .983$]. Cowan's K was calculated only for the VSTM task, since in the control task the amount of information to be maintained in memory did not change. The mean sensitivity index d' was 3.19 (SD = .52), 1.82 (SD = .42) and 1.40 (SD = .44) for two, four and five items, respectively. The mean sensitivity index d' in the control task was 3.7 (SD = .65), 3.71 (SD = .67) and 3.74 (SD = .66) for two, four and five items, respectively. No effects related to the increase in the number of items were detected in the control task [2 vs. 5 $t(19) = -0.57, p = .57$; 2 vs. 4 $t(19) = -0.20, p = .84$].

3.3.2 ERP results

The EEG scalp maps showed a clear load-dependent increase in posterior negativity in the VSTM task, which was more pronounced over posterior electrodes contralateral to the cued hemifield (Fig. 12A). By contrast, no appreciable topographical effects were observed in the control task (Fig. 12B).

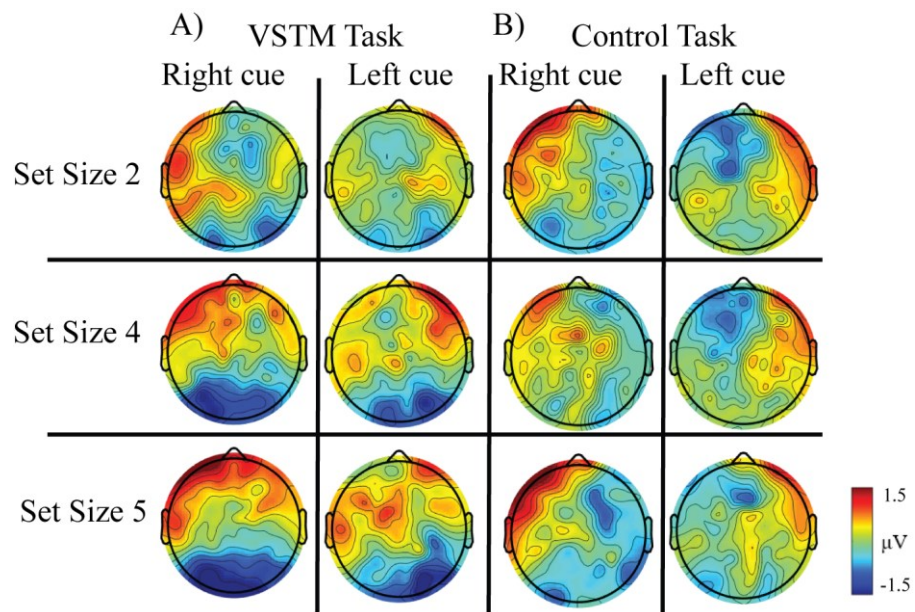


Fig.12. Scalp Maps. Grand-average scalp maps of the mean voltage amplitude during the memory maintenance interval (300-1200 ms) in the VSTM task (A) and control task (B) for both cued visual hemifields (right and left) and for all set size conditions.

The load-dependent increase in this contralateral negativity was confirmed by statistical testing. A significant posterior negative cluster contralateral to the cued hemifield was found when comparing the mean activity during memory maintenance of five vs. two items for both cued directions (Fig. 13) (Right cue: Negative cluster $p = .002$, cluster statistic = -103, cluster size = 62; Left cue: Negative cluster $p = .009$, cluster statistic = -37, cluster size = 24). The posterior contralateral negative cluster also emerged when contrasting the activity of 4 vs. 2 items to be memorized (Right cue: Negative cluster $p = .0079$, cluster statistic = -59, cluster size = 40; Left cue: Negative cluster, $p = .016$, cluster statistic = -56, cluster size = 40). No significant differences emerged when comparing 5 vs. 4 items for both cued hemifields. No statistically significant effects were observed in the control task.

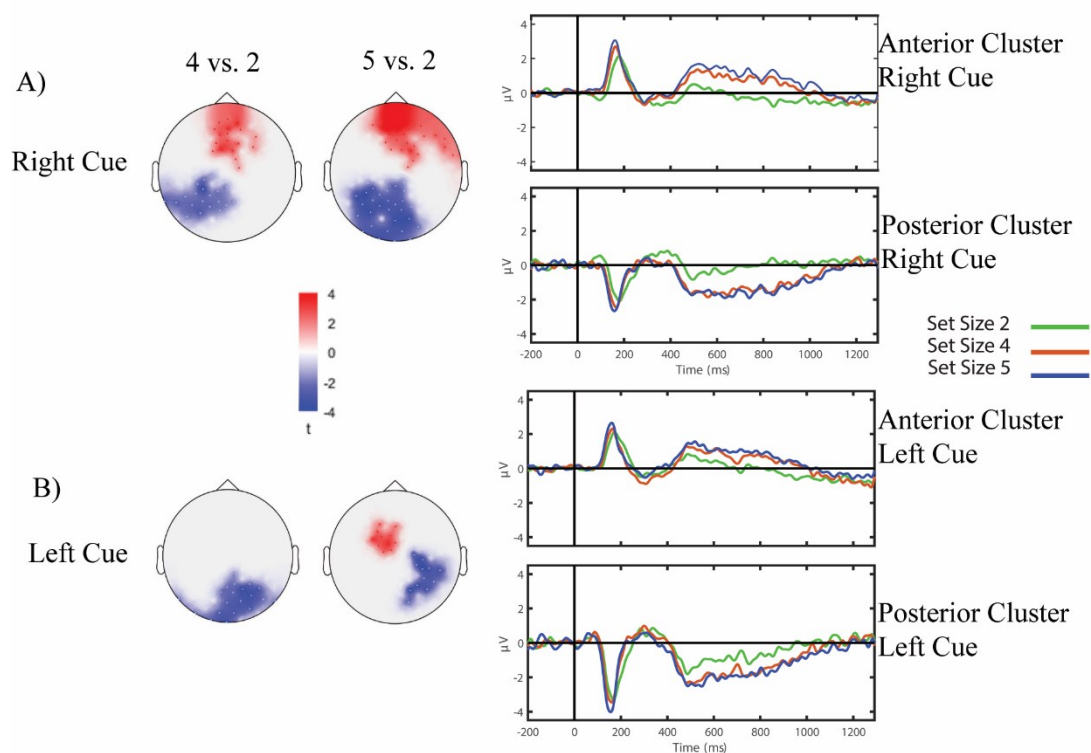


Fig.13. Cluster-based maps for the comparisons between ERP activities at different set sizes in the VSTM task. Statistically significant electrodes ($p < .05$) are displayed in reddish or bluish colours, depending on the direction of the t-test. A) The left side shows the comparison between set size 4 vs. 2 and 5 vs. 2 when stimuli were presented in the right visual hemifield. The right

side shows the time series of the significant anterior and posterior clusters. B) The left side shows the comparison between set size 4 vs. 2 and 5 vs. 2 when stimuli were presented in the left visual hemifield. The right side shows the time series of the significant anterior and posterior clusters.

The whole-brain analysis also identified a fronto-central positive cluster with increased activity both when 5 vs. 2 items had to be remembered [Right cue: Positive cluster $p = .002$, cluster statistic = 86, cluster size = 56; Left cue: Positive cluster $p = .026$, cluster statistic = 29, cluster size = 22], and when 4 vs. 2 items had to be remembered, although for the latter, only when the right hemifield was cued [Right cue: Positive cluster $p = .01$, cluster statistic = 55, cluster size = 36]. However, the cluster based results did not show the anterior cluster in the comparison 4 vs. 2 items for the left cue. This could be due to the conservative statistical approach, namely the contrast of the activity for 4 vs. 2 items for the left cue did not survive the multiple comparison correction. Overall, these scalp topographical results suggest putative increased activation of frontal regions as memory load increases during the maintenance phase.

To confirm observations from previous studies (Robitaille, Jolicoeur Dell'Acqua & Sessa, 2007; Lefebvre et al. 2011), the CDA difference wave was computed specifically from PO7/PO8 electrode signals. The CDA is usually computed by averaging the contralateral activity measured at PO7 (i.e., the activity elicited when stimuli are presented in the right hemisphere) and the contralateral activity measured at PO8 (i.e., the activity elicited when stimuli are presented in the left hemisphere) and subtracting the average ipsilateral activity between PO7 and PO8. This provides one CDA for each condition. As expected, memory load-dependent increases in ERP negativity was observed during the memory maintenance phase (300-1200 ms) in the VSTM task but not in the control task (Fig. 14).

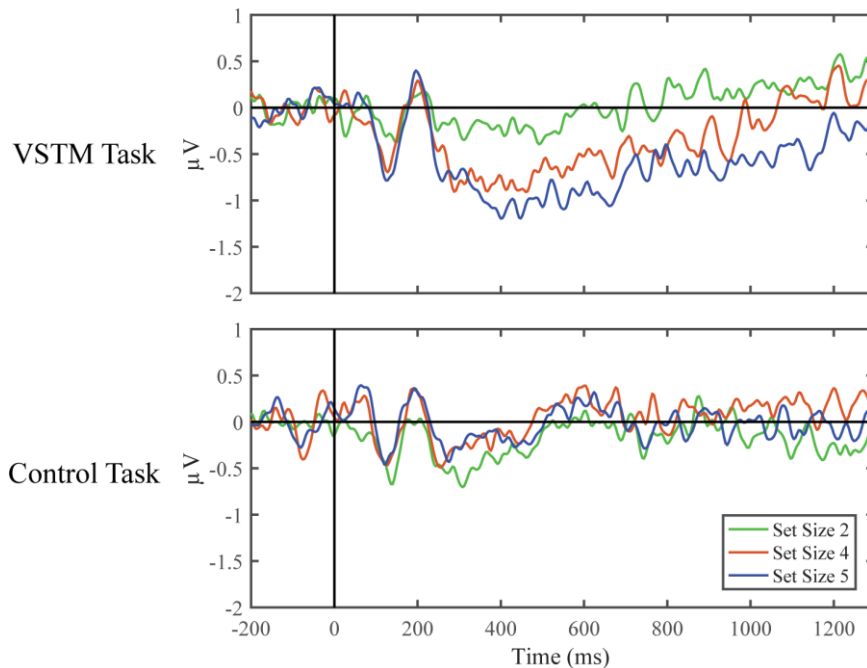


Fig.14. CDA difference wave. The upper panel shows the memory load-dependent amplitude modulations for the CDA. The green line refers to set size 2, red line to set size 4 and blue line to set size 5. The lower panel reports the CDA measured in the control task where memory load was constant among conditions, thus leading to no amplitude modulations of this component as the number of displayed items increased. It is worth remembering that CDA was computed as the difference between the average contralateral and ipsilateral activity between PO7 and PO8.

Considering set size (2 vs. 4 vs. 5) and task (VSTM vs. control task) as predictors, a linear mixed model of the mean amplitude of the CDA activity between 300-1200 ms and subjects as the random effect revealed a significant main effect of the task factor [$F(1,95) = 14.887, p = .00021$] and a significant interaction between task and set-size factors [$F(2,95) = 4.68, p = .0115$]. The helmert contrasts showed a significant increase in negativity when 4 vs. 2 items had to be memorized ($t(95) = 2.38, p = .04$) and when 5 vs. 2 items had to be remembered ($t(95) = 3.63, p = .0056$) for the WM task. No experimental effects were found in the control task.

3.3.3.1 Whole-brain source model

The EEG source maps relative to the VSTM task showed a memory load-dependent increase of cortical activity over both parietal and prefrontal brain regions.

3.3.3.2 Parietal Activity

ERP source reconstruction during the maintenance interval showed a memory-load-dependent increase of activity in the posterior parietal cortex spreading over the inferior parietal lobule (IPL) and IPS contralateral to the cued hemifield (Fig. 15). Critically, no memory load-related modulation of the posterior parietal cortices emerged in the control task.

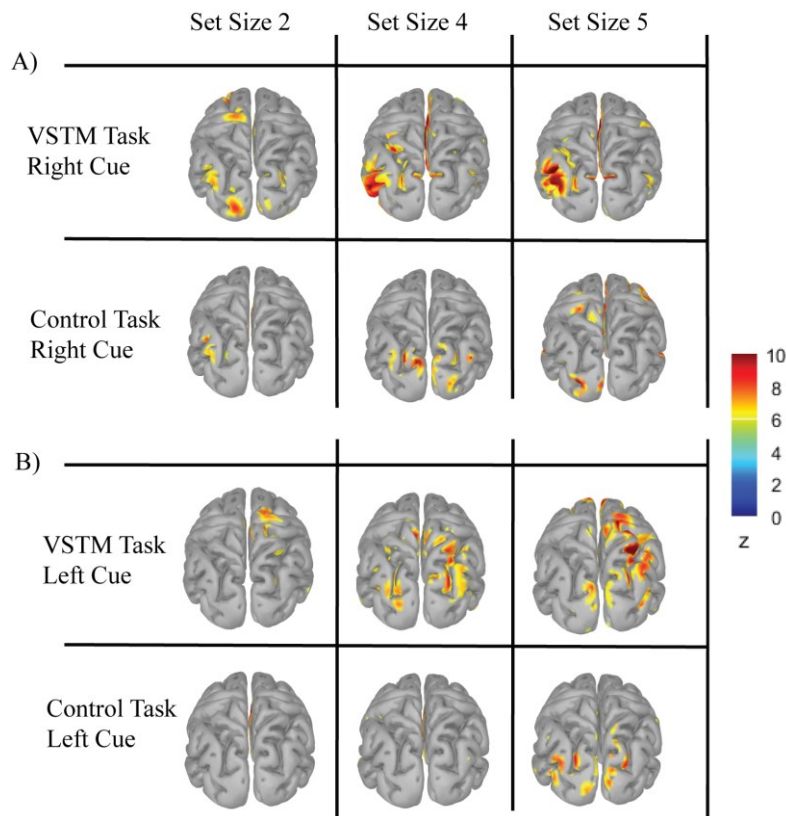


Fig.15. Source-reconstructed parietal activation. A) The upper row reports the source-reconstructed mean activity during the memory maintenance phase (300-1200 ms) for the VSTM task when to-be-memorized stimuli were delivered in the right visual hemifield, showing a clear involvement of IPL/IPS brain areas. The bottom row reports the same source reconstructions but for the control task. Source activations are plotted as Z scores and are adjusted using a threshold

of 60% of the maximum amplitude and a size of at least 10 vertices. B) This figure shows the source activation when to-be-memorized stimuli were delivered in the left visual hemifield.

To investigate correlations between K and parietal and/or prefrontal activity given the different time-courses of parietal and prefrontal activity (see Fig.16), the correlation was computed in three different time windows of the maintenance period: 300-600 ms, 600-900 ms and 900-1200 ms. The increase in the differential (contralateral-ipsilateral) response in both parietal and prefrontal areas from 2 to 5 items was correlated with the K for 5 items, similar to the procedure used to compute the correlation of the connectivity measures (see section 3.3.3.4). The results showed a significant correlation between the increase in parietal activity (Setsize5-Setsize2) with the K for 5 items ($r = .49, p = .032$; see Fig.16) only in the 600-900 ms time window (300-600 ms: $r = .28, p = .23$; 900-1200 ms: $r = .29, p = .20$). Considering that the activation stems from the Z scores (in absolute values) of the reconstructed sources, the negative values of the parietal activation might be plausibly interpreted in terms of an inverse effect, namely lower activation for those participants with a limited memory capacity for the larger set size (Luria, Sessa, Gotler, Jolicoeur & Dell'Acqua, 2010). It is indeed conceivable that participants with smaller Cowan's K reached their VSTM limit already in the lower load condition, which prevented a memory-load-dependent increase in activation for larger set sizes.

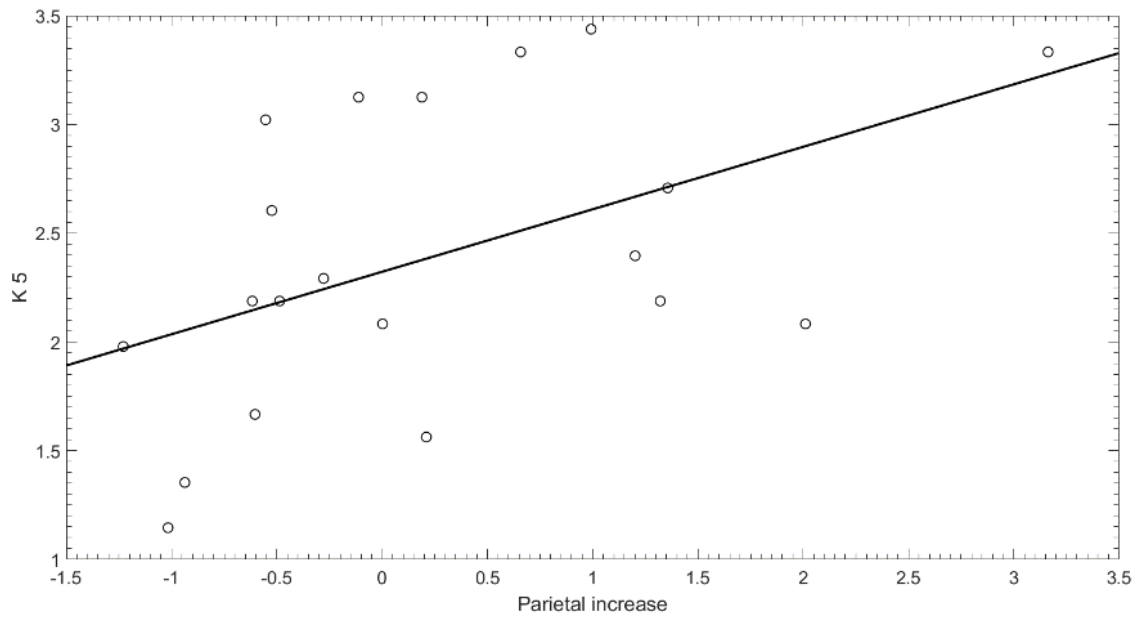


Fig.16. Correlation between memory capacity and parietal activation. The figure shows the correlation between the parietal (IPS) increase in activation (measured as the activity difference of 5 minus 2 items) and the Cowan's K when 5 items had to be remembered.

3.3.3.3 Prefrontal Activity.

The results evidenced also a frontal activity involving ACC in both tasks. Similar to the IPS/PPC, the ACC also displayed a memory load-dependent activity modulation only in the VSTM task. However, there was no lateralization to the hemisphere contralateral to the cued visual hemifield (Fig. 17).

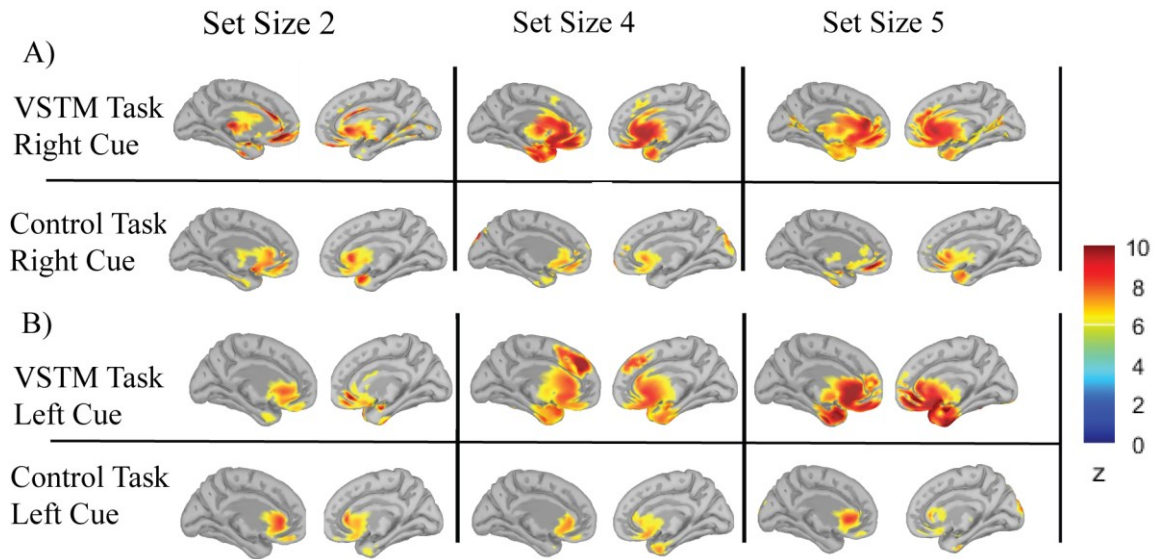


Fig.17. Source-reconstructed ACC activity. A) The upper row reports the source-reconstructed mean activity during the late part of the memory maintenance phase (700-1200 ms) for the VSTM task when to-be-memorized stimuli were delivered in the right visual hemifield. This time window has been extracted based on the ACC temporal evolution (see Fig. 18) ramping from 700 ms and showing a memory load-related modulation. The bottom row reports the same source reconstructions but for the control task. Source activations are plotted as Z scores and are adjusted using a threshold of 60% of the maximum amplitude and a size of at least 10 vertices. B) The figure shows the source activity when to-be-memorized stimuli were delivered in the left visual hemifield.

Activations in the control task did not show any changes in mean activity during the maintenance period depending on the number of displayed items, supporting the hypothesis for a specific role of prefrontal areas in the WM task. No significant correlation between prefrontal (ACC) activity and the Cowan's K for 5 items emerged in

any of the three windows of interest during maintenance (300-600 ms: $r = .11, p = .50$; 600-900 ms: $r = .02, p = .90$; 900-1200 ms: $r = .05, p = .82$).

3.3.3.4 Functional connectivity

Contralateral functional connectivity between the IPS and ACC showed a significant increase in the theta (4-7 Hz; one-tailed $t(19) = 2.65, p = 0.008$, Cohen's $d=0.155$) and alpha (8-12 Hz; one-tailed $t(19) = 2.23, p = 0.019$, Cohen's $d=0.125$) frequency bands when comparing set size 5 to set size 2 in the WM task. Connectivity was also increased between set size 4 and 2 in the theta band (one tailed $t(19) = 1.8, p = 0.043$, , Cohen's $d=0.11$) (Fig. 18). No significant effects were identified in ipsilateral connectivity in the WM task (set size 5 vs.2, theta band, one-tailed $t(19) = -0.7, p = 0.75$; alpha band, one-tailed $t(19) = -0.47, p = 0.68$; set size 4 vs.2, theta band $t(19) = -0.44, p = 0.66$; alpha band $t(19) = -0.58, p = 0.71$).

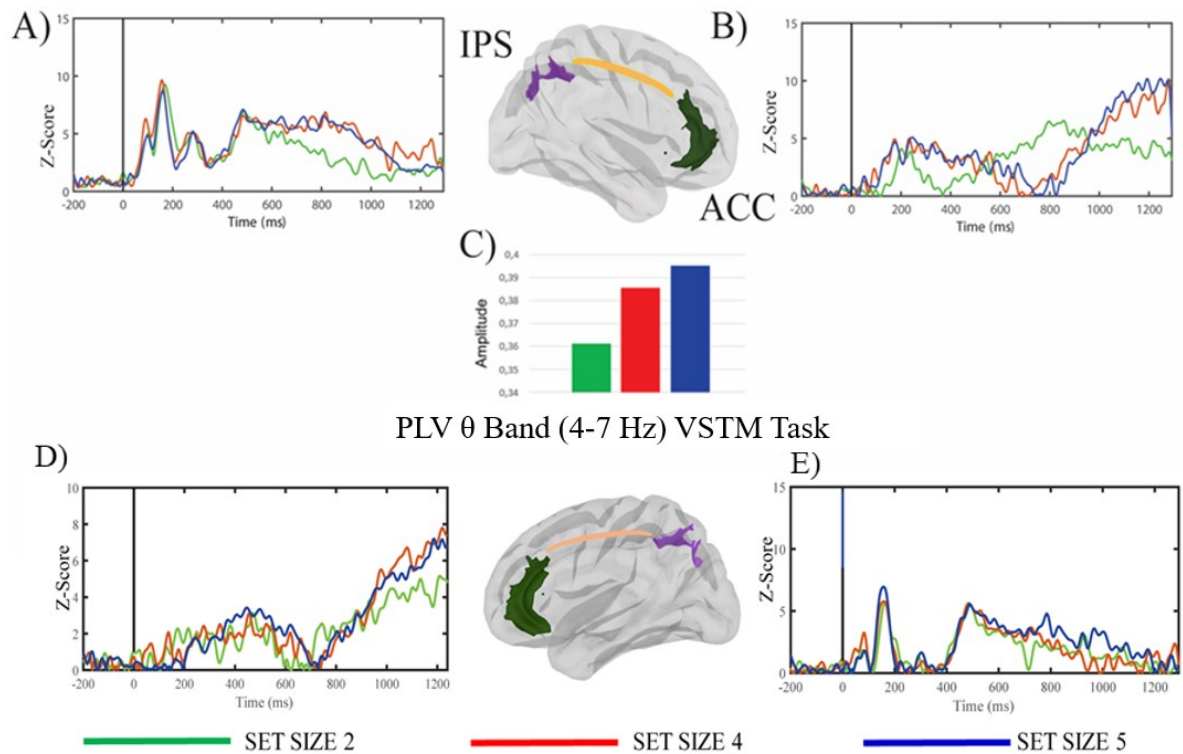


Fig.18. Functional connectivity in the VSTM task. Time-course of source-reconstructed IPS (A, E) and ACC (B, D) activity in the contralateral hemisphere to the cued visual hemifield. C) Memory load-dependent modulation of the contralateral PLV.

The augmentation of theta-band connectivity in the contralateral hemisphere between 5 and 2 items was positively correlated with Cowan's K with 5 items ($r = 0.51, p = 0.021$; Fig. 19). The robust correlation was computed with the WRS package (Wilcox, 2012) of R software.

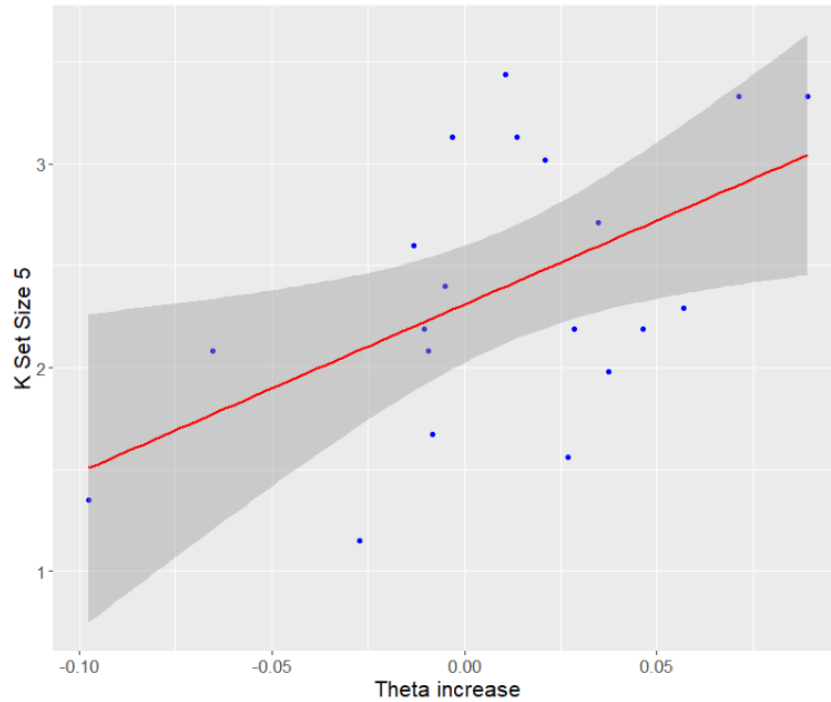


Fig.19. Correlation between memory capacity and connectivity. Correlation between individual theta increase in PLV value between set size 5 and 2, and individual memory capacity measured with Cowan’s K when 5 items had to be remembered. The shaded area represents the confidence interval of 95%.

No modulatory effects on contralateral and ipsilateral connectivity were detected due to the set size increase in the control task (contralateral connectivity: set size 5 vs.2, theta band, one-tailed $t(19) = 0.54, p = 0.30$; alpha band, one-tailed $t(19) = 0.62, p = 0.68$; set size 4 vs.2, theta band $t(19) = 0.62, p = 0.27$; alpha band $t(19) = 0.11, p = 0.45$; ipsilateral connectivity: set size 5 vs.2, theta band, one-tailed $t(19) = 1.14, p = 0.13$; alpha band, one-tailed $t(19) = 0.49, p = 0.31$; set size 4 vs.2, theta band $t(19) = 0.62, p = 0.27$; alpha band $t(19) = 0.82, p = 0.21$).

3.3.3.5 Regional dynamics:

The temporal evolution of the source-reconstructed activity of the cortical ROIs in the VSTM task is shown in Fig. 7. Interestingly, IPS activity contralateral to the cued hemifield was similar to the morphology of the ERP observed at the contralateral electrodes (Fig. 20).

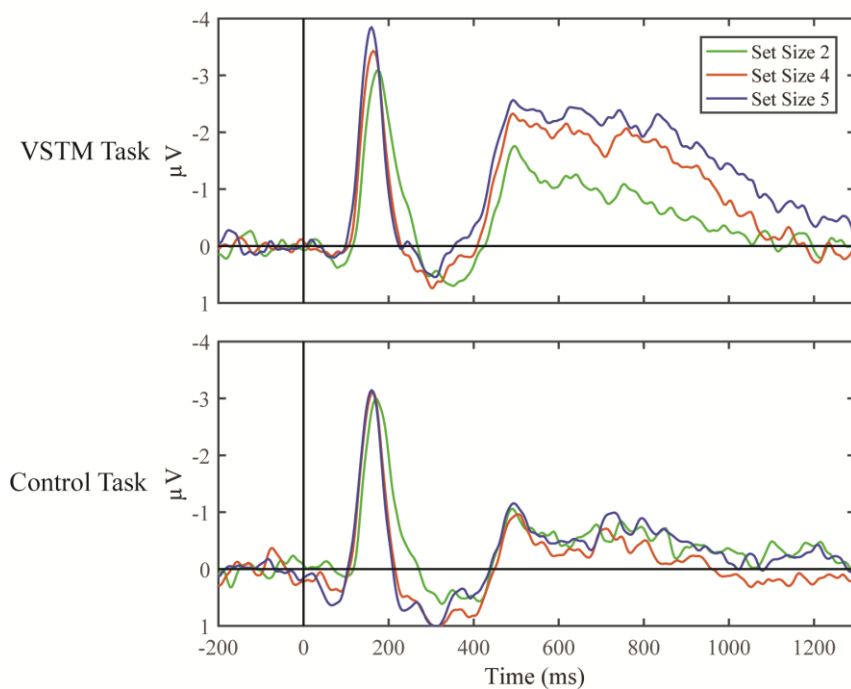


Fig. 20. Contralateral activity in the electrodes space. This figure shows modulation in the grand average of the contralateral activity in the PO7/PO8 electrodes, while no modulation is evident in the control task.

Pairwise statistical comparisons of the IPS contralateral time-series between set sizes for the VSTM task, estimated with the permutation approach, revealed a memory load-dependent increase in activation in the 700-1000 ms time window (5 vs. 2 items: $t = 1.84$,

$p = .033$; 4 vs. 2 items: $t = 1.95$, $p = .034$; 5 vs. 4 items: $t = -0.7$ $p = .78$), mirroring the CDA modulations. Activity in the ACC for the WM task, in contrast, showed a steep increase around 700 ms from memory array onset until the end of the maintenance period (Fig. 18B), revealing memory load-related modulation in this time window. Specifically, pairwise statistical comparisons with the permutation approach demonstrated that this load-related modulation was statistically significant in the late part of this temporal window, between 950 and 1200 ms (5 vs. 2 items: $t = 3.13$, $p = .003$; 4 vs. 2 items: $t = 2.01$, $p = .032$; 5 vs. 4 items: $t = -0.01$ $p = .50$). Temporal evolution of IPS and ACC activation in the control task did not show a memory load modulation as expressed in the contralateral hemispheres in the VSTM task (Fig. 21).

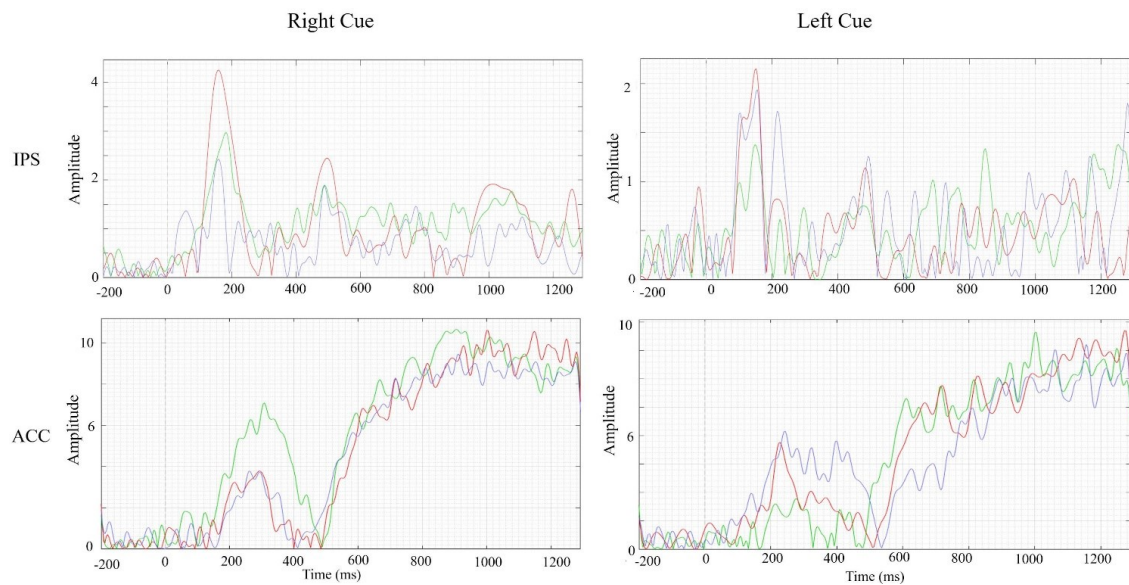


Fig. 21. IPS and ACC temporal dynamics in the control task. This figure shows the temporal dynamics of the IPS and ACC contralateral to the cued visual hemifield (right and left) in the control task.

3.4 Discussion of the second experiment

The main purpose of this second study was to investigate modulation of neurophysiological activity as well as interactions between two main regional nodes of VSTM maintenance brain networks, specifically targeting frontoparietal connections (ACC and IPS) identified in the first experiment. High-density EEG activity was recorded while healthy participants performed a standard memory-probe VSTM task that required participants to encode and maintain in short-term memory a variable set of coloured items (i.e., 2, 4 or 5 items) and a control task that was matched in perceptual and motor demand but did not manipulate memory load. The ERP data confirmed CDA load-related amplitude modulation, with increased voltage negativity as memory load increased during the maintenance of memory information in the hemisphere contralateral to the cued hemifield (Vogel & Machizawa, 2004). Interestingly, the analysis of the EEG scalp topography further revealed a positive anterior central cluster of electrodes that showed a memory-load amplitude modulation. This result matches the hypothesized activation of prefrontal cortical regions during VSTM retention. Brain source reconstruction allowed for estimating the cortical generators underlying the ERP effects observed over the scalp. A first cortical region that showed clear memory-load dependent activity was identified over the posterior brain areas. Specifically, a large portion of the posterior parietal cortex spreading over the inferior parietal lobule (IPL) and IPS displayed functional activity contralateral to the target presentation side, which increased with the number of memoranda. The involvement of the IPS has been consistently reported in VSTM tasks (Xu and Chun, 2006; Todd and Marois, 2004). Specifically, in a previous functional resonance imaging study using the same task adopted by this work, a neural population in the inferior portion of IPS was identified as a candidate source of the electromagnetic

contralateral responses to working memory load (Brigadoi et al., 2017). Notably, compared to previous results, the present data evidenced more diffuse parietal activity around the IPS that extended over adjacent parietal regions including the IPL. This difference may be related to the limited spatial resolution offered by the source reconstruction as well as by the smoothed source reconstruction provided by the LORETA inverse solution (Pascual-Marqui, 2002) that make it difficult to localize sources originating from sulcal structures (Luck, 2014). Nevertheless, to provide a more direct comparison with previous literature, the focus was placed on the IPS as a cortical area of interest to run connectivity analyses. Crucially, the reconstructed source localized in the IPS exhibited memory load-related activation, with a temporal dynamic mirroring the modulatory pattern consistently observed in the parietal electrodes contralateral to the cued hemifield (see Fig. 8 and Supplementary Fig. 1). Interestingly, the IPS activity was correlated with the number of elements held in memory. Overall, the source data are in line with the hypothesis that the IPS is a core regional contributor to the CDA. Remarkably, the present findings further revealed the involvement of anterior brain areas, namely the ACC, during the retention phase of the VSTM task. The ACC showed memory-load related activity modulation. In contrast to posterior areas, the functional activity of the ACC mainly occurred in the later phase of memory retention, starting from 700 ms after the onset of the memory array. A central role for the prefrontal cortex in the VSTM has been previously proposed by Liesefeld, Liesefeld, and Zimmer (2014), who hypothesized that the interaction between prefrontal and parietal brain regions may play a protective role in defending VSTM from sensory interference. They proposed a model in which prefrontal activation prevents subsequent unnecessary parietal storage of distractors. The overall relevance of frontal areas during VSTM maintenance was also

supported by Ester et al. (2015), who extracted voxel-based cortical representations during maintenance of stimulus orientation in both dorsal and ventral portions of the lateral PFC. More specifically, several studies reported a direct involvement of the ACC in visual working memory, in agreement with the current results. A clinical study on Attention Deficit Hyperactivity Disorder (ADHD) reported that improvements in a Sternberg task in patients treated with psychostimulant drugs were positively related to the functional connectivity between the ACC, vIPFC and precuneus (Wong & Stevens, 2012). Ma et al. (2012) used dynamic causal modelling to identify a connection pattern similar to the one presented by Lenartowicz et al. (2005), where the amplitude of ACC activation and connectivity patterns were directly influenced by memory load modulations in a numeric VSTM task.

Crucially, here the data shows that the IPS and ACC display distinct neurophysiological dynamics during VSTM maintenance. Specifically, the IPS exhibited a temporal pattern that mirrored the evolution of the CDA component, with the peak amplitude reaching its maximum in the early phase of the maintenance time window (around 600ms) and progressively decreasing while approaching probe onset. By contrast, the ACC showed an opposite temporal dynamic, with the amplitude increase occurring in the late maintenance phase around 700 ms after the onset of the memory array. Remarkably, it was only in this late window that the data displayed an ACC load-dependent modulation. Noteworthy, this area exhibited an increase in functional activity that mimicked the memory task demand, with larger engagement depending on the set size. In other words, the higher the memory task demand, the larger the involvement of both parietal and prefrontal areas, with both these areas showing an activity plateau when the VSTM capacity limit was reached.

On the basis of the specular temporal dynamics showed by the IPS and the ACC over the maintenance interval, it may be hypothesized that posterior and frontal cortical areas may play a distinct functional role in VSTM processes. While the activity of posterior areas has been more reliably associated with memory encoding and storage (Todd and Marois, 2004, Xu & Chun, 2006, Brigadoi et al. 2017), the exact role of prefrontal areas is still under debate. As argued by Jolicoeur and Dell'Acqua (1998), storage by itself is not sufficient to preserve the sensory information consolidated in VSTM. It is well known that information decays after encoding in short term memory (Phillips & Baddeley, 1971). Therefore, the memory trace representation is more susceptible to decay in the late phase of maintenance. In order to prevent decay of the trace, a boost in activity in brain areas sustaining information representation might be important. In this scenario, ramping activity of the ACC arising in the late phase of the maintenance window might be related to the boosting/protection of the memory trace from decay. In support of this hypothesis, some researchers have specifically argued for the critical role of attention in the maintenance of visual items encoded in VSTM. In this framework, attention cycles through each of the encoded items, refreshing them to prevent passive decay and forgetting (Cowan, 1999; Cowan et al., 2005). Attentional involvement in the VSTM maintenance phase has been also theorized by Shimi & Scherif (2017), who described two dissociable attentional contributions to maintenance process: a general attentional scanning and reactivation mechanism and a specialised visuospatial refreshment mechanism. The former is responsible for transferring information across memory systems and for retaining information when no cues are available, while the latter operates in a top-down manner by refreshing a spatially selected internal part of the memory trace. The current results, according to both Cowan's (1999) and Shimi and Scerif's (2017)

theories, might be interpreted within the framework of the attentional reactivation mechanism, where the ACC has a significant role in refreshing the memorized items stored in IPS: as the number of memorized items increases, an increase in the recruitment of resources (both at the neural and connectivity level) is observed. This theoretical model finds neurophysiological support in the Stable Code model of working memory proposed by Barbosa (2017), which divides the retention period into an early and late phase. The early phase, when memories are still being encoded and susceptible to distractors, is characterized by transient dynamics. In this dynamic phase, information is more sensitive to interference. During the late period, when the neural network sustaining information representation reaches a stable functional configuration, information representation is stabilized. Our interpretation is therefore compatible with Barbosa's model, in a larger theoretical framework. Indeed, the distinct neurophysiological dynamics of the IPS and ACC suggest a possible spatiotemporal dissociation of VSTM maintenance processes into two distinct phases involving different brain regions and timing. The early part of the maintenance interval, which may be related to storage processes, might be characterized by predominant involvement of the IPS while the late phase may require the recruitment of prefrontal brain areas, with ACC potentially playing a protective role against information decay. In other words, based on the temporal dissociation of the temporal evolution of parietal and prefrontal activation, the early phase of the Barbosa's model may be related to the dynamic changes of neurons configuration in the IPS. By contrast, in the later phase the ACC may be keeping representation of memoranda in a more stable code. In this theoretical framework, communication between the ACC and IPS could be a fundamental mechanism for VSTM information stabilization. Distal network nodes are thought to interact via slow rhythmic fluctuations; theta synchronization has been shown

in cortical networks involved in different sub-processes of complex WM functions (Sauseng, Griesmayr, Freunberger, & Klimesch. 2010, Klimesch et al., 2005). The causal role of theta activity in frontoparietal networks engaged by WM has been recently demonstrated by Albouy et al. (2017). They showed that theta frontoparietal connectivity could be rhythmically entrained using transcranial magnetic stimulations (TMS) during maintenance, resulting in improved WM performances. Additionally, theta frontoparietal connectivity increase due to memory load increment was observed with a visual working memory task in the electrodes space by Zhang, Zhao, Bai and Tian (2016). They showed that frontoparietal connectivity increases until memory capacity is reached, and then decreases as memory load further increases. They also found an increase in frontal mid-line theta connectivity, which crucially has been related to ACC activity as shown by Gevins et al. (1997).

These results are consistent with the role of theta oscillatory activity in frontoparietal networks for short-term memory maintenance, further suggesting that functional connectivity modulation might be a relevant mechanism of VSTM maintenance predicting individual memory capacity. The results from Experiment 2 show augmentations of theta-band synchronization between IPS and ACC with increasing memory load specifically in the hemisphere contralateral to the cued visual hemifield, plateauing when memory capacity is reached. In line with the previously proposed interpretation, communication between the IPS and ACC might play a key role actively maintaining information. As the task demand (in terms of set size) increases, the ACC is engaged in order to prevent information decay. The present findings show that memory load-dependent modulation of synchronization between theta rhythm fluctuations of the IPS and ACC was significantly correlated with individual memory capacity (Cowan's K);

however, due to the small sample size, further confirmatory studies are required to corroborate this finding. The absence of modulatory effects on the memory load-related increase in source activation and connectivity in the control task ensured that the involvement of the frontoparietal network is more specifically linked to proactive maintenance of information in VSTM. The dynamic increase in frontoparietal connections may provide further functional evidence supporting the hypothesis that decay is prevented by a reactivation/attention-refreshing process, consistent with Cowan's theoretical model as well as the one proposed by Shimi and Scerif (Cowan, 1999, Shimi & Scerif, 2017).

Recently, Pinotsis, Buschman and Miller (2019) employed a VSTM change detection task in non-human primate model to show that the connectivity strength between the PFC and the lateral intraparietal area (LIP) increases in relation to the memory load increment. Examining the temporal dynamics of connectivity strength, they also showed that the connection from PFC to LIP was mainly expressed in the late phase of maintenance. Although the current analysis did not compute time-resolved connectivity, the results and the neurophysiological dynamic observed in the ACC seem to be in line with the findings provided by Pinotsis et al. (2019).

Nevertheless, it is possible that there may be additional interpretations of the present results. The experimental paradigm employed in this investigation possesses some features that can be exploited to possibly depict some interpretative hypotheses as highly unlikely. It is unlikely to attribute the measured frontal activity to an active search of the probe position in the memory trace (Klingberg, 2006; Monosov, Trageser & Thompson, 2008), since the task requires a colour match/no match response for a centrally positioned probe. Participants were not required to memorize any spatial information, although this

possibility cannot be totally excluded. It is also unlikely that ACC activation could be due to response selection or conflict monitoring processes (Pardo, Pardo, Janer, & Raichle, 1990; Braver, Barch, Gray, Molfese, & Snyder, 1999), since the target brain activity occurred between memory array offset and probe presentation, and no response was required until probe presentation. Previous literature has suggested that frontal ramping activity might be a consequence of the fixed retention interval among trials; participants could have rapidly learnt when the probe was supposed to be presented and therefore started to refresh memorized items earlier than probe presentation (Stokes, 2015). In this sense, while it has been suggested that WM maintenance in prefrontal areas is not always related to sustained activity (Sreenivasan, Curtis and D'Esposito, 2014; Shafi et al., 2007), most of the studies investigating implicit temporal expectancy induced by fixed preparatory intervals showed different anticipatory ERP patterns. For example, Mento et al. (2013) reported sustained rather than ramping Contingent Negative Variation activity elicited by a fixed temporal structure in the absence of any task demand. This sustained pattern was also observed when response preparation was implicitly prompted by sequential effects in a temporal orienting task (Mento, 2017). On the basis of this evidence, prefrontal activity cannot simply be ascribed to response preparation induced by a fixed temporal expectancy. Finally, memory load modulatory effects on the ACC, IPS and their connectivity are specifically expressed in the VSTM task, indicating a specific relationship of the frontal areas (ACC) with memory processes (storage, rehearsal and attention-refreshing).

Chapter 4 - General Discussion

The main aim of the present thesis was to investigate the interaction between selective attention and information maintenance in visual short-term memory, focusing on temporal orienting of attention. This study was motivated by the fact that the role of selective temporal attention over controlled processes is a relevant issue that still needs to be clarified.

From a broad theoretical perspective, temporal orienting can be defined as the attentional product of the capacity to generate, implement and update expectancy in the temporal dimension (Mento and Vallesi, 2016). Indeed, the possibility to anticipate when a stimulus will appear is translated into a better chance to produce an efficient behavioural response. In fact, anticipation allows the system to generate preparatory strategies in order to optimize cognitive resources dedicated to adjusting action preparation and execution to upcoming stimuli. From an evolutionary point of view, refining the ability to implement a strategy results in a greater chance of survival. Additionally, from a cognitive point of view, the capacity to generate temporal prediction also imply the possibility to implement strategic processes to keep active the representation needed to accomplish behaviourally relevant goals. In this scenario, the main goal of the present thesis was to deepen the comprehension of the neurocognitive mechanisms at the basis of the interplay between these two important functions.

To this purpose, two experiments were performed. In the first experiment, it was examined the effect of temporal orienting (TO) on visual information encoding (Experiment 1a) and maintenance (Experiment 1b). The second experiment was focused to understand the neural mechanisms at the basis of the interaction between TO and VSTM by unravelling the functional contributions of prefrontal areas on posterior brain

regions. Indeed, while the role of anterior and posterior regions has been consistently reported in literature as being associated with the control and storage of information in VSTM, respectively, it is not clear yet whether and to what extent the functional coupling of these two nodes (rather than their single contributions) may represent a neurophysiological mechanism driving behavioural performance.

A key finding of the first experiment was that TO elicits a complex functional effect on VSTM, depending on the relative duration of the information retention interval. Indeed, the possibility to predict the onset of either the memory array (Experiment 1a) or the memory test (Experiment 1b) conferred a clear behavioural benefit in terms of accuracy only for short intervals. By contrast, prediction of a long interval before the onset of both the memory array and the memory test resulted in disruption of behavioural performance. From a functional point of view, this behavioural trade-off between cue informativeness and interval durations was supported by a different neurophysiological pattern during both the preparatory (pre-array) and the maintenance (pre-memory test) of short and long intervals. Specifically, providing a temporal informative cue generated an increase of the CNV for both short and long cued compared to uncued trials. However, greater posterior activity in response to memory array and memory test was observed exclusively in the short-cued trials. This neural modulation, consisting of an increase in the P3 component for predicted rather than unpredicted items, is likely the functional mechanism at the basis of the behavioural advantage conferred by TO on VSTM for short intervals. Consistent with previous source imaging studies that investigated the effect of TO on motor preparation (Mento et al., 2015; Mento, 2017), the cortical activity elicited during both the post-cue and post-array intervals mainly involved a frontoparietal network. Specifically, this circuit included two important memory nodes, namely the ACC and

posterior parietal cortex (PPC). The similarity of the network involved during anticipation and memory maintenance suggests that TO induces feedforward pre-activation of the network that will successively be involved for the encoding, maintenance and retrieval of forthcoming items. This pre-allocation of neural resources translates, at least in the short interval, into improving the behavioural outcome. Concerning the long intervals, even though similar network activation was found during the preparatory process in the long intervals compared to the short intervals, this preparation was not extended during the maintenance period.

In other words, the possibility to predict the memory array onset prompted strong frontoparietal anticipatory activity for both short and long cued maintenance intervals. However, this pre-activation was actually transferred over the period of information retention and further to information retrieval only with short duration interval. In contrast, when the predicted duration was long, no beneficial effects of neural activity were observed on behavioural performance. While the reason for this duration-dependent TO effect on VSTM is not entirely clear, it may be speculated that it is due to interference effect arising from competition for executive resources required by both working memory and temporal preparation tasks. Furthermore, prefrontal areas might play a crucial role for mastering cognitive control in complex tasks. Several studies have related cingulate activation to the implementation of feed-forward cognitive control (Chein & Schneider, 2005; Kondo et al., 2004; MacDonald et al., 2000; Paus, 2001). However, the role of the ACC during visual information maintenance it is still not clear. In Experiment 1, it may be speculated that the ACC is functionally affected by increasing cognitive load due to the integration of dual information, i.e., orienting attention in time and maintaining information in short term memory. On the other hand, the ACC may be a region important

not only for cognitive control but also for information maintenance in VSTM. Crucially, Todd & Marois (2004) evidenced activation of the ACC and IPS during VSTM maintenance, even though only IPS hemodynamic activity seemed to be sensitive to memory load. In light of this, we hypothesized a functional coupling between prefrontal and parietal areas (ACC and IPS), with a possible different functional role for these two nodes. The results of the second experiment corroborated this hypothesis, revealing a dissociation of the role of the ACC and IPS within visual information maintenance in short term memory. Indeed, both of these areas showed memory load-dependent activity modulation, displaying an activation increase in relation to the increase of the number of items to be remembered. Additionally, based on the different temporal dynamics of their source-reconstructed activity, it was found that prefrontal and posterior areas exhibited a spatiotemporal dissociation during information retention into VSTM. Specifically, the IPS was mainly active during the early phase of the maintenance, this pattern suggested greater involvement of this area during temporary storage of information in the early phase of maintenance. On the other hand, the ACC displayed a specific increase in activation during the late phase of the maintenance period, which might be linked with protection or boosting of the information to be retained. Remarkably, the strength of the coupling in the theta oscillatory frequency between these two areas showed a memory load-dependent increase, in accordance with the modulation of the ERP and source activity. Furthermore, the connectivity between ACC and IPS was positively correlated with individual memory capacity. Altogether, the results of Experiment 2 provide additional evidence for an integrated interpretation regarding the frontoparietal network involvement of the first experiment findings. In fact, this network was clearly engaged only during the maintenance of information for a short interval, this pattern being

accompanied by a concurrent behavioural benefit. In contrast, clear frontoparietal neural activity during long retention intervals was not observed. Here, the results of Experiment 1b suggest the speculation that cognitive overload due to the conjunction of top-down attentional orienting and maintenance in the long interval may have resulted in down-regulation of prefrontal engagement, failing to subserve the increased demand for item storage over posterior areas. While this hypothesis remains to be fully tested, the findings of the present thesis provide promising starting points for further future exploration. In fact, this study is the first to provide empirical evidence investigating spatiotemporal dynamics of prefrontal and posterior areas in spatial and temporal orienting. Thus, this work paves the way for others to follow up these initial data. For example, to further unravel the timing of the interplay between the ACC and IPS from a causal point of view, it could be useful to exploit transcranial magnetic stimulation (TMS). Using this approach, it could be possible to inhibit prefrontal or parietal areas during a specific phase of information maintenance (early or late phase) and consequently examine this effect on the behavioural outcome. These results would allow for further clarification of the role of ACC and IPS in VSTM retention. Using TMS, it could be also possible to more directly explore the functional dynamics of frontoparietal network nodes in a temporal cueing experimental context. Moreover, other experiments may consider combining the first and the second experiment of this thesis by eliciting attentional orienting in time with increasing memory load, providing additional information about the incoming memory load. This would allow direct investigation of how the cognitive control system administers resources allocation to forthcoming stimuli in time based on their complexity. Furthermore, this examination could shed light on the fundamental relationship between executive functions and temporal orienting.

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