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# Functional dissociation of anterior cingulate cortex and intraparietal sulcus in visual working memory



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## ABSTRACT

Previous electrophysiological studies of lateralized visual working memory (VWM) identified an ERP component, defined as contralateral delay activity (CDA), directly modulated by the number of items held in memory. One of the main candidate as the cortical source of this ERP component is the inferior intraparietal sulcus (IPS). Moreover, previous neuroimaging studies put forth evidence for the presence of a distributed VWM network involving also prefrontal areas and in particular the anterior cingulate cortex (ACC). Nonetheless, the understanding of the functional role of ACC is still debated. We recorded the high-density EEG in 20 healthy participants undergoing a VWM and a control task. Explorative cluster-based permutation statistics confirmed the posterior memory load dependent CDA modulation, but also identified an additional anterior cluster of electrodes whose amplitude was modulated by memory load. The source reconstruction revealed a memory load dependent activation in the IPS but also in the ACC, suggesting that these two areas might be nodes of a fronto-parietal circuit underlying VWM maintenance. Crucially, parietal and prefrontal areas showed a temporal dissociation, since IPS was more engaged in the early phase of visual information storage while the ACC was more active during the late phase. This pattern suggests a functional dissociation between the parietal cortex, which is involved in encoding and storage of information, and prefrontal areas, subserving cognitive control processes, including the boosting and protection of information from decay. Remarkably, the connection strength between IPS and ACC predicted the individual number of items held in memory. These findings are discussed within the theoretical account of a neural distributed model of VWM.

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# 1. Introduction

Working memory (WM) involves the ability to maintain and manipulate information over short periods of time (Baddeley & Hitch, 1974). It has been consistently shown that humans possess a limited capacity for visual WM (VWM), since information about only three/four items can be retained at one time (Cowan, 2001; Luck & Vogel, 1997). In a pioneering study, Vogel and Machizawa (2004) first recorded the event-related potential (ERP) during a lateralized change-detection task, reporting an increased negativity at the posterior scalp regions contralateral to the visual hemifield of the memoranda relative to the ipsilateral side. This slow negative wave, defined as contralateral delay activity (CDA), was obtained by subtracting ipsilateral from contralateral activity over occipito-parietal scalp sites. One important feature of CDA is that, starting from about 300 ms from stimulus onset, its amplitude increases monotonically with the number of to-bememorized items, showing a plateau when individual's WM capacity is reached. Further evidence supporting these results came from neuroimaging studies showing an almost linear increase in hemodynamic activity in neurons located in the intra-parietal sulcus (IPS) as the number of items encoded in VWM increased, but levelling off after individual VWM capacity was reached (Brigadoi et al., 2017; Todd & Marois, 2004; Xu & Chun, 2006). These findings suggested a central role of posterior cortical areas in the storage of visual information (Todd & Marois, 2004).

Most recently, neuroimaging studies provided additional evidence of a fronto-parietal network in VWM (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017). One of these studies (Linden et al., 2003) reported the presence of a distributed circuit during the VWM retention period, involving IPS, frontal eye fields (FEF), the dorsolateral pre-frontal cortex (DLPFC) and pre-supplementary motor area (pre-SMA). In particular, they found a monotonic increase of activity over frontal areas (DLPFC and pre-SMA) in relation to the number of items to be encoded. By contrast, the activity in IPS and FEF peaked when subjects had to maintain only two or three items and decreased in the highest load condition. Based on these results, they theorized that the operations performed by the DLPFC and pre-SMA could support an integrated representation of the encoded visual information, helping subjects to maintain an efficient performance in the highest load condition. The engagement of frontal areas in VWM tasks was also supported by Ester, Sprague, and Serences (2015). They reconstructed highfidelity representations of the memorized orientation of a visual stimulus, hinging on the activation patterns of voxels located in the ventro-lateral and dorsolateral pre-frontal cortex (PFC). Frontal areas are also involved in the flexible maintenance of content-specific information, suggesting the presence of a hierarchical network ranging from early visual cortex to PFC involved in VWM maintenance (Serences, 2016).

From a theoretical perspective, frontal activity in VWM task has been usually interpreted as an element of general domain cognitive control, mainly related to Baddeley's executive central system (Baddeley, 1996), whereas the posterior regions, such as IPS, may be responsible of VWM storage (Christophel, Hebart, & Haynes, 2012).

Within this picture, it can be hypothesized that the communication between frontal and parietal regions may play a key functional role in the retention of visual information in WM. Electrophysiological measures of fronto-parietal connectivity, mostly in the theta band (4–7 Hz), have been for example proposed as a communication mechanism sustaining WM maintenance (Albouy, Weiss, Baillet, & Zatorre, 2017; Babiloni et al., 2004; Klimesch, Schack, & Sauseng, 2005; Salazar, Dotson, Bressler, & Gray, 2012; Sauseng et al., 2005).

Another fundamental hub of the memory network has been identified in the anterior cingulate cortex (ACC). In line with previous studies claiming a core role of 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 subtend the executive processes necessary to allow the maintenance of information into the short-term storage. ACC was identified as a key generator of frontal midline theta (FMT; Gevins, Smith, McEvoy, & Yu, 1997), which showed a power increase with memory load during a WM task (Jensen & Tesche, 2002). These results point to a possible functional involvement of ACC in WM (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). ACC activity was found to be stronger in high compared to low WM capacity individuals (Osaka et al., 2003), further suggesting a direct link between this area and WM. 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).

Yet, the actual functional role of ACC in the WM network remains unclear. A first hypothesis is that it is limited to a domain-general supervision, supporting cognitive control over the entire maintenance process. In line with this account, we may predict that ACC should exhibit a sustained, rather than phasic, activation over the whole delay period. Alternatively, ACC might be specifically involved in boosting information maintenance and/or in the protection from the memory trace decay. If this was the case, its engagement in WM tasks should result in a functional pattern characterized by a precise temporal dynamic. Since information trace decays with time in short term memory (Phillips & Baddeley, 1971), we should expect a boost of information in the late phase of retention. Therefore, 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 WM distributed brain network engaged during WM maintenance, we may also expect its functional connectivity with other regions of the fronto-parietal network to be modulated with task demand.

The present research aimed at clarifying the functional role of ACC as a core node of the fronto-parietal network entailed in VWM. More specifically, by using time-resolved ERP source imaging, we intended to investigate the spatiotemporal dynamics of ACC activation with the purpose to shed light on how this structure interacts with the posterior parietal areas. To this purpose we measured high-resolution EEG activity of 20 healthy participants whilst performing a VWM task. Firstly, we expected to confirm the memory loaddependent modulation of electrophysiological activity both in the parietal cortex and ACC. Secondly, we hypothesized that the functional connectivity between the ACC and posterior parietal areas would be enhanced as a function of memory load increase. To better enucleate the contribution of each cortical region as being specifically associated to VWM, we 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 VWM task in both perceptual and motor demand, but without involving memory load modulations. This comparison was planned to specifically address how fronto-parietal areas are functionally shaped by VWM demand removing the effect of other confounds such as perceptual or motor processes.

# 2. Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/ exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

# 2.1. Participants

Data were collected from 30 healthy adult participants (mean age = 22.5 years [SD = 2], range 20–25, 12 males). Only participants with at least 60% of accuracy in the VMW 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 was of 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). No part of the study procedures and analysis was pre-registered prior to the research being conducted.

#### 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 2 tasks, explained below. Experimental design was task-wise delivered, and task order was counterbalanced across participants. Before EEG data acquisition, participants 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.

#### 2.2.1. Working memory task

In the WM task participants performed the cued memory probe task illustrated in Fig. 1. Each trial began with the presentation of a fixation point at the center 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 color 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 WM task, the shape of the stimuli was taskirrelevant, since participants were asked to remember colours only. We used two different shapes to equate the perceptual features across the WM task and the Control Task (which will be 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), gray (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/right



Fig. 1 – Experimental paradigm. In the VWM task participants were instructed to memorize the colors of either two, four or five colored patches displayed in the cued visual hemifield (left or right). The probe array consisted of one centrally displayed colored patch, which could be ("same") or not be ("different") of the same color as one of the to-be-remembered colored patches. In the control task, participants had to remember only the stimulus shape of the items in the cued hemifield.

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 colors of the patches presented in the cued visual hemifield while ignoring those presented in the opposite hemifield. A single probe color patch was then presented at fixation after a blank retention interval of 900 ms. Participants had to indicate within 2000 ms, by pressing one of two keys on a response box, whether the probe color matched one of the to-be-memorized colors. 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 color of the probe matched one of the colors displayed in the cued hemifield, whereas on the other half of trials the probe color was randomly selected among the set of non-displayed colors. Following the response, an intertrial 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).

# 2.2.2. Control task

The temporal and stimulus structure of the control task was identical to that of the WM task (Fig. 1), 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 the numerosity of 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, as for the WM task). The number of trials was identical to the WM task. The experimental paradigm and the behavioural data are available on Figshare public repository (10.6084/m9.figshare.9249530).

# 2.3. EEG recordings

We used 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 $\Omega$  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. The EEG data are available on Figshare public repository (10.6084/ m9.figshare.9225476; 10.6084/m9.figshare.9227495).

#### 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 colors stored in VWM, S is the number of colors 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 accuracy for all set sizes and both tasks. The sensitivity index d' was also computed: d' = Z(hit rate) – Z(false alarm rate) (Green & Swets, 1966). Trials associated with an incorrect response were excluded from EEG analyses.

# 2.5. ERP analysis

The continuous EEG signals were bandpass filtered (.1-45 Hz) using a Hamming windowed sinc finite impulse response filter (filter order = 16500) and downsampled 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 obtained with independent component analysis (Stone, 2002). The resulting independent components were visually inspected in topography and timeseries, and those related to eye blinks, eye movements and muscle artifacts 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  $(\pm 100 \,\mu V$  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 (Ferree, 2006; Perrin, Pernier, Bertrand, & Echallier, 1989). The data were then rereferenced 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 WM 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).

Table 1 — Mean "hit" and "false alarm" rate and standard deviation (between brackets) for each sets size and task.

		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)	

We applied a whole-brain analysis approach 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). We derived 1,000 Monte-Carlo permutations with cluster-based correction over all 128 electrode locations using the Fieldtrip functions (Oostenveld, Fries, Maris, & Schoffelen, 2011), accessible via Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 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 & Jolicœur, 2007), one set of analyses was performed 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 rearranged 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, & Jolicœur, 2011).

Statistical analyses on the CDA component were conducted using a linear-mixed-model approach implemented in R, defining as 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, 2014) and *lmertest* (Kuznetsova, Brockhoff, & Christensen, 2017). In order to test the statistical significance of the predictors, we used *Car* package (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.

#### 2.6. Source modelling

Baseline-corrected epochs were imported in Brainstorm (Tadel et al., 2011) to model their cortical generators. We used the ICBM152 anatomical template to approximate the individual anatomy of each participant (Evans, Janke, Collins, & Baillet, 2012) and warped it to the digitized EEG sensor positions GSN Hydrocel 128 E1 available in Brainstorm. We then derived an EEG head model using the three-layer boundary element method (BEM) from OpenMEEG, also via Brainstorm (Gramfort, Papadopoulo, Olivi, & Clerc, 2011; Kybic, Clerc, Faugeras, Keriven, & Papadopoulo, 2005). The source space was constrained to the cortex and modeled as a grid of 15002 orthogonal current dipole triplets. We used sLORETA 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 in Z scores relative to the baseline.

# 2.6.1. Functional connectivity

Functional connectivity was estimated using the phaselocking value (PLV) measure (Lachaux, Rodriguez, Martinerie, & Varela, 1999). We computed PLV between pairs of regions of interest (ROIs) over the memory maintenance period (i.e., 300–1200 ms from memory array onset). We defined the ROIs 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, ipsilaterally and contralaterally to the cued hemifield. We calculated both contralateral and ipsilateral connectivity. For each condition and participant, the contralateral connectivity was computed by averaging PLV of the contralateral hemispheres (right hemisphere for left cued hemifield, left hemisphere for right cued hemifield, respectively). Ipsilateral connectivity was estimated by averaging PLV over the ipsilateral hemispheres.

In line with the hypothesis of increased of fronto-parietal functional connectivity with memory load, we tested the significance of differences in PLV across memory set sizes, using paired one-tailed t tests. The EEG analysis pipeline, with all the computational steps and the functions used from EEGLAB (Delorme & Makeig, 2004) and Brainstorm (Tadel et al., 2011), is available on Figshare (10.6084/m9.figshare.9249695).

# 3. Results

#### 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 WM 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) = -.57, p = .57; 2 vs 4 t(19) = -.20, p = .84].

#### 3.2. ERP results

The EEG scalp maps showed a clear load-dependent increase of posterior negativity in the WM task, which was more pronounced over posterior electrodes contralateral to the cued hemifield (Fig. 2A). By contrast, no appreciable topographical effects were observed in the control task (Fig. 2B).

The load-dependent increase of this contralateral negativity was confirmed by statistical testing. We found a significant posterior negative cluster contralateral to the cued hemifield when comparing the mean activity during memory



Fig. 2 – Scalp Maps. Grand-average scalp maps of the mean voltage amplitude during the memory maintenance interval (300–1200 ms) in WM task (A) and control Task (B) for both cued visual hemifields (right and left) and for all set size conditions.

maintenance of five vs two items, for both cued directions (Fig. 3) [Right cue: Negative cluster p = .002, cluster statistic = -103, cluster size = 62; Left cue: Negative cluster p = .009, cluster statistic = -37, cluster size = 24]. We also found a more pronounced posterior contralateral negativity when 4 vs 2 items had 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 comparting 5 vs 4 items for both cued hemifields. No statistically significant effects were found in the control task.

We 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 4 vs 2 items for the left cue did not survive the multiple comparison correction. Overall, these scalp topographical results suggest a 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) we computed the CDA difference wave specifically from PO7/PO8 electrode signals. 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, we found memory load-dependent increases in ERP negativity during the memory maintenance phase (300–1200 ms) in the WM task, but not in the control task (Fig. 4).

The linear mixed model of the mean amplitude of the CDA activity between 300 and 1200 ms, considering set-size (2 vs 4 vs 5) and task (WM vs control task) as predictors, 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. Whole-brain source model

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

#### 3.3.1. Parietal activity

ERP source reconstruction during the maintenance interval showed a memory-load-dependent increase of activity in posterior parietal cortex spreading over inferior parietal lobule



Fig. 3 – Cluster-based maps for the comparisons between ERP activities at different set-sizes in the WM task. Statistically significant electrodes (p < .05) are displayed in reddish or bluish colours, depending on the direction of the t-test. A) On the left side the comparison between set size 4 vs 2 and 5 vs 2 when stimuli were presented in the right visual hemifield. On the right side the time series of the significant anterior and posterior clusters. B) On the left side the comparison between set size 4 vs 2 and 5 vs 2 when stimuli hemifield. On the right side the time series of the significant anterior and posterior clusters. B) On the left side the time series of the significant anterior and posterior clusters.

(IPL) and IPS contralateral to the cued hemifield (Fig. 5). Critically, no memory-load-related modulation of the posterior parietal cortices emerged in the control task.

#### 3.3.2. Prefrontal activity

We also found frontal activity involving ACC in both tasks. Akin to IPS/PPC, ACC also displayed a memory-loaddependent activity modulation in the WM task. However, there was no lateralization to the hemisphere contralateral to the cued visual hemifield (Fig. 6).

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 of a specific role of prefrontal areas in the WM task.

# 3.4. Functional connectivity

Contralateral functional connectivity between IPS and ACC showed a significant increase in the theta [4–7 Hz; one-tailed t(19) = 2.65, p = .008, Cohen's d = .155] and alpha [8–12 Hz; one-tailed t(19) = 2.23, p = .019, Cohen's d = .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 = .043, Cohen's d = .11]

(Fig. 7, Supplementary Fig.2). No significant effects were identified in the ipsilateral connectivity in the WM task (setsize 5 vs 2, theta band, one-tailed t(19) = -.7, p = .75; alpha band, one-tailed t(19) = -.47, p = .68; set-size 4 vs 2, theta band t(19) = -.44, p = .66; alpha band t(19) = -.58, p = .71).

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 = .51, p = .021; Fig. 8). The robust correlation was computed with WRS package (Wilcox, 2012) of R software.

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) = .54, p = .30; alpha band, one-tailed t(19) = .62, p = .68; set-size 4 vs 2, theta band t(19) = .62, p = .27; alpha band t(19) = .11, p = .45; ipsilateral connectivity: set-size 5 vs 2, theta band, one-tailed t(19) = 1.14, p = .13; alpha band, one-tailed t(19) = .62, p = .27; alpha band t(19) = .21; set-size 4 vs 2, theta band t(19) = .62, p = .27; alpha band t(19) = .21; set-size 4 vs 2, theta band t(19) = .62, p = .27; alpha band t(19) = .82, p = .21).

#### 3.5. Regional dynamics

The temporal evolution of the source-reconstructed activity of the cortical ROIs in the WM task is shown in Fig. 7.



Fig. 4 – CDA difference wave. The upper panel shows the memory load-dependent amplitude modulations for the CDA. 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.

Interestingly, IPS activity contralateral to the cued hemifield was similar to the morphology of the ERP observed at the contralateral electrodes (Supplementary Fig. 1). Pairwise statistical comparisons of the IPS contralateral time-series between set sizes for the WM task, estimated with the permutation approach, revealed a memory-load-dependent activation increase 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 = -.7 p = .78), mirroring the modulations of the CDA. Activity in ACC for the WM task, instead, showed a steep increase after around 700 ms from memory array onset until the end of the maintenance period (Fig. 7B), presenting, in this time window, a memory-load related modulation. More 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 = -.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 WM task (Supplementary Fig. 3).

# 4. Discussion

The main purpose of the present study was to investigate the modulations of the neurophysiological activity within and the interactions between the main regional nodes of WM brain networks, specifically targeting fronto-parietal connections (Christophel et al., 2017). We recorded the high-density EEG activity while healthy participants performed a standard memory-probe WM task that required participants to encode and maintain in WM 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 WM load. Our ERP data confirmed the 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 is compatible with the hypothesized activation of prefrontal cortical regions during VWM retention.

The brain source reconstruction allowed us to estimate the cortical generators underlying the ERP effects observed over the scalp. A first cortical region that showed a 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 a functional activity contralateral to the target presentation side that increased with the number of memoranda. The involvement of the IPS has been consistently reported in VWM tasks (Todd & Marois, 2004; Xu & Chun, 2006). Specifically, in a previous functional resonance imaging study, adopting the same task of the present work, it was identified a



Fig. 5 – Source reconstructed parietal activation. A) The upper row reports the source reconstructed mean activity during the memory maintenance phase (300–1200 ms) for the WM 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) The figure shows the source activation when to-be-memorized stimuli were delivered in the left visual hemifield.

neural population in the inferior portion of IPS as a candidate source of the electromagnetic contralateral responses to working memory load (Brigadoi et al., 2017). Noteworthy, compared to our previous results here we report a more diffuse parietal activity around IPS that extended over adjacent parietal regions, including IPL. This difference may be related to the limited spatial resolution offered by the source reconstruction as well as by the application of smoothed spatial filters (Pascual-Marqui, 2002) that make difficult the localization of sources originating from sulcal structures (Luck, 2014). Nevertheless, to provide a more direct comparison with previous literature, we purposely focused on IPS as a cortical area of interest to run connectivity analyses. Crucially, the reconstructed source localized in IPS exhibited a 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. 7 and Supplementary Fig. 1). Overall, the source data are in line with

the hypothesis that the IPS is a core regional contributor to CDA.

Remarkably, our results further revealed the involvement of anterior brain areas, namely ACC, during the retention phase of the WM task. The ACC showed a memory-load related activity modulation. At odds with posterior areas, the functional activity of the ACC was mainly occurring in the later phase of memory retention, starting from 700 ms after the onset of the memory array. A central role of prefrontal cortex in VWM 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 VWM 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 VWM maintenance was also supported by Ester et al. (2015), who extracted voxel-based cortical representations during the



Fig. 6 – 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 WM 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. 7) 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.



Fig. 7 – Functional connectivity in the WM task. Time course of source reconstructed IPS (A) and ACC (B) activity in the left hemisphere (the one contralateral to the right visual hemifield). C) Memory load-dependent modulation of the contralateral PLV.

maintenance of a stimulus orientation, in both dorsal and ventral portions of the lateral PFC. More specifically, several studies reported a direct involvement of ACC in VWM, in line with our 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 ACC, vlPFC and precuneus (Wong & Stevens, 2012). Ma et al. (2012) used dynamic causal modelling to identify a very similar connection pattern to the one presented by



Fig. 8 – 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%.

Lenartowicz & McIntosh, (2005), where the amplitude of ACC activation and connectivity pattern were directly influenced by memory load modulations in a numeric WM task.

Crucially, here we show that IPS and ACC display distinct neurophysiological dynamics during WM 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 and progressively decreasing while approaching probe onset. By contrast, the ACC showed an opposite temporal dynamic, with amplitude increase occurring in the late maintenance phase, that is around 700 ms after the onset of the memory array. Remarkably, it was only in this late window that we were able to identify an ACC load-dependent modulation. Noteworthy, this area exhibited an increase of functional activity that mimicked the memory task demand, with a larger engagement depending on the set size. In other words, the higher was the memory task demand, the larger was the involvement of both parietal and prefrontal areas, with both these areas showing an activity plateau when the WM 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 WM processes. While the activity of posterior areas has been more reliably associated to memory encoding and storage by itself (Todd & Marois, 2004), the exact role of prefrontal areas is still debated.

As argued by Jolicœur and Dell'Acqua (1998), storage by itself is not sufficient to preserve the sensory information consolidated in VWM. 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 the decay in the late phase of maintenance. In order to prevent the trace decay, an activity boost of the brain areas sustaining information representation might be then required. In this scenario, the ramping activity of the ACC arising in the late phase of the maintenance window might be related to the boosting/protection of memory trace from decay. In line with this account, some researchers have specifically argued for the critical role of attention in the maintenance of visual items encoded in VWM. In this framework, attention would cycle through each of the encoded items, refreshing them to prevent passive decay and forgetting (Cowan, 1999; Cowan et al., 2005). Attentional involvement in the VWM maintenance phase has been also theorized by Shimi and Scerif (2017), who described two dissociable attentional contributions to VWM maintenance: a general attentional scanning and reactivation mechanism and a specialised visuo-spatial 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. Our 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 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) can be observed. This theoretical model finds neurophysiological support in the Stable Code model of WM 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 interferences. 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 IPS and ACC suggests a possible spatiotemporal dissociation of WM maintenance processes in 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 a predominant involvement of 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 areas, it is possible to relate the early phase of the Barbosa's model to the dynamic changes of neurons configuration in the IPS. By contrast, in the later phase the ACC may be keeping memoranda representation in a more stable code. In this theoretical framework, communication between ACC and IPS could be a fundamental mechanism for WM information stabilization. Distal network nodes are thought to interact via slow rhythmic fluctuations; theta synchronization has been shown in cortical networks involved in different subprocesses of complex WM functions (Klimesch et al., 2005; Sauseng, Griesmayr, Freunberger, & Klimesch. 2010). The causal role of theta activity in fronto-parietal networks engaged by WM has been recently demonstrated by Albouy et al. (2017). They showed that theta fronto-parietal connectivity could be rhythmically entrained using transcranial magnetic stimulations (TMS) during maintenance, which resulted in improved WM performances. Additionally, theta fronto-parietal connectivity increase due to memory load increment was found with a VWM 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).

The above presented results are in line with the role of theta oscillatory activity in fronto-parietal networks for WM maintenance, further suggesting that functional connectivity modulations might be relevant mechanisms of VWM maintenance predicting individual memory capacity. We found augmentations of theta-band synchronization between IPS and ACC with increasing memory load, specifically in the hemisphere contralateral to the cued visual hemifield, reaching a plateau when memory capacity is reached. In line with the previously proposed interpretation, the communication between IPS and ACC would play a key role in the active maintenance of information. As the task demand (in terms of set size) increases, ACC is engaged in order to prevent information decay. Results showed that memory-load-dependent modulation of the synchronization between theta rhythmic fluctuations of IPS and ACC was significantly correlated with individual memory capacity (Cowan's K), although, due to the small sample size here available, further confirmatory studies are required to corroborate this finding. The absence of modulatory effects of memory load related increase of source activation and connectivity in the control task ensured that the involvement of the fronto-parietal network is more specifically linked to the proactive maintenance of information in WM. The dynamical increase of fronto-parietal connection may provide further functional evidence supporting the hypothesis that decay is prevented by a reactivation/attentionrefreshing process, in line with Cowan's theoretical model and the one proposed by Shimi and Scerif (Cowan, 1999; Shimi & Scerif, 2017).

Recently, Pinotsis, Buschman, and Miller (2018) employed a VWM change detection task with a non-human primate model to show that the connectivity strength between PFC and lateral intraparietal area (LIP) increased 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 we did not compute a time resolved connectivity analysis, our results and the neurophysiological dynamic of ACC seem to be in line with the findings provided by Pinotsis et al. (2018).

Notwithstanding the abovementioned interpretation, it should be recognized that the present results may be susceptible to additional interpretations. The experimental paradigm employed in the present investigation possesses some features that can be exploited to possibly depict some interpretative hypotheses as highly unlikely. It is difficult 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 our task required a colour match/no match response for a centrally positioned probe. Participants were not required to memorize any spatial information, although we cannot exclude this possibility. 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, 2001), since we analysed brain activity between memory array offset and probe presentation, and no response was required until probe presentation. It has been suggested that frontal ramping activity might be a consequence of the fixed retention interval among trials; participants could have soon learnt when the probe was supposed to be presented, therefore starting to refresh memorized items some time 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 a sustained activity (Sreenivasan, Curtis, & 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. (2018) reported a 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 effect in a temporal orienting task (Mento, 2017). On the basis of this evidence prefrontal activity cannot be simply ascribed to response preparation induced by a fixed temporal expectancy. Finally, the presence of memory load modulatory effects over ACC, IPS and their connectivity are specifically expressed in the WM task, indicating a specific relation of the frontal areas (ACC) with memory processes (storage and/or rehearsal/attention-refreshing).

The present work shows some limitations for its exploratory nature, mainly regarding the involvement of ACC in change detection tasks targeting VWM, and also for the low spatial resolution of the source reconstructed EEG. It should be underlined that the main aim was not to provide a punctual functional localization of the brain maintenance network, but rather to exploit the high temporal resolution of the EEG to investigate the temporal evolution of two of the main nodes of the VWM network. Notwithstanding the above possible methodological limitations, the present findings provide relevant information regarding the neural signature related to the maintenance of memory information in VWM, providing new insights about the fronto-parietal nodes involved and their possible roles in memory maintenance. Future experiments might be planned to deepen the understanding of the relationship between the ACC-IPS network and storage/ attention-refresh processes in VWM.

# 5. Conclusion

Our study provides evidence in support of the distributed nature of VWM. Both the IPS and the ACC showed memoryload dependent activity modulations. Their distinct temporal dynamics provide evidence of a functional dissociation between parietal and prefrontal areas in their contribution to the memory retention process. We propose that during memory maintenance IPS might be mainly involved in storage processes while ACC may be more probably engaged in the attentional effort needed to protect information from decay and boost memory trace. Crucially, we identified in the strength of theta-band functional connectivity between IPS and ACC a possible neurophysiological mechanism able to predict individual visual working memory capacity.

# Open practices

The study in this article earned Open Materials and Open Data badges for transparent practices. The experimental paradigm and the behavioural data are available on Figshare public repository (https://10.6084/m9.figshare. 9249530), p10. The EEG data are available on Figshare public repository (https://10.6084/m9.figshare.9225476; https:// 10.6084/m9.figshare.9227495), p10.

#### **CRediT** authorship contribution statement

Gian Marco Duma: Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. Giovanni Mento: Supervision, Methodology, Investigation, Writing - original draft, Writing - review & editing. Simone Cutini: Supervision, Conceptualization, Writing - original draft, Writing - review & editing. Paola Sessa: Conceptualization, Writing - review & editing. Sylvain Baillet: Methodology, Writing - original draft, Writing - review & editing. Sabrina Brigadoi: Supervision, Conceptualization, Writing original draft, Writing - review & editing. Roberto Dell'Acqua: Investigation, Project administration, Resources, Writing review & editing.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2019.09.009.

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